

SULFOXIMINE COMPOUND HAVING FGFR INHIBITORY EFFECT, PHARMACEUTICAL COMPOSITION COMPRISING SAME, AND USE THEREOF

TECHNICAL FIELD

5 The present invention relates to the field of medicinal chemistry, and specifically provides a structurally novel FGFR inhibitor.

BACKGROUND

10 Fibroblast growth factor receptor (FGFR) is a receptor for fibroblast growth factor (FGF) signaling, and its family consists of four members (FGFR1, FGFR2, FGFR3, FGFR4), which are glycoproteins consisting of extracellular immunoglobulin (Ig) like domains, hydrophobic transmembrane regions, and intracellular portion including tyrosine kinase regions. The binding of FGF ligands induces receptor dimerization and conformational changes in the intracellular domain, which cause intermolecular phosphorylation of the kinase domain and intracellular tail.
15 Phosphorylated residues act as docking sites for attachment proteins, which promote downstream signaling cascades that lead to cellular behavior including proliferation, survival, differentiation, migration, and angiogenesis. FGFRs signal abnormalities involve a variety of cancer types, including liver cancer, intrahepatic cholangiocarcinoma, bladder cancer, endometrial cancer, breast cancer and lung cancer, and disease progression occurs through overexpression, point
20 mutation and/or chromosomal translocation.

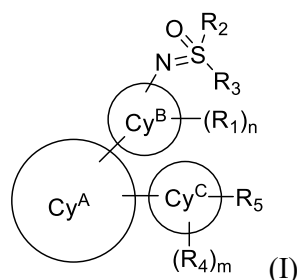
 With the continuous deepening of research, pan FGFR1-3 inhibitors have shown clinical responses to various cancers with altered FGFR, but also exhibit target-limited toxicity, which lead to adverse side effects such as hyperphosphatemia and tissue mineralization, which originate from the fact that the regulation of phosphate reabsorption is mediated by FGFR1 and FGFR3.
25 Some studies have summarized that FGFR2 translocation occurred in 14% of intrahepatic cholangiocarcinoma; FGFR2 mutations occurred in 12-14% of endometrial cancers and 5% of squamous non-small cell lung cancers; FGFR2 was amplified in 12-14% of gastric cancer and 4% of breast cancer. FGFR2 plays a role in promoting acquired resistance to human epidermal growth factor receptor 2 (HER2) targeted therapy by indirectly overactivating FGFR2 in tumor associated
30 fibroblasts.

 Therefore, based on the clinical needs to be met, the development of FGFR2 selective inhibitors for treatment has great value and prospects.

SUMMARY OF THE INVENTION

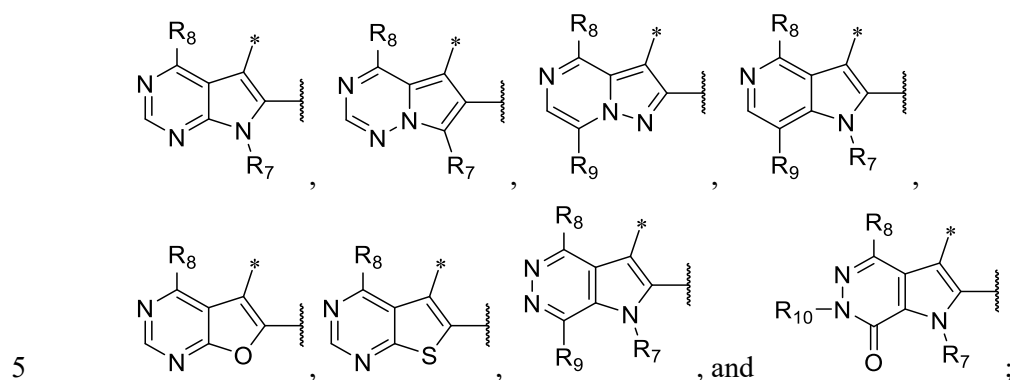
35 The purpose of the present invention is to develop a small molecule compound as FGFR inhibitor.

 In the first aspect of the present invention, provided is a compound as shown in formula (I), a tautomer, a stereoisomer, a hydrate, a solvate, or a pharmaceutically acceptable salt thereof:



wherein, n and m are each independently 0, 1, 2, or 3;

Cy^A is selected from the group consisting of:



wherein denotes a bond connected to Cy^B, and denotes a bond connected to Cy^C;

Cy^B is selected from the group consisting of: C₆₋₁₀ aryl and 5-12 membered heteroaryl;

10 Cy^C is selected from the group consisting of: C₆₋₁₀ aryl, 5-12-membered heteroaryl, saturated or partially unsaturated C₃₋₆ carbocyclyl, saturated or partially unsaturated 4-12-membered heterocyclyl;

15 R₁ is selected from the group consisting of: H, D, halogen, CN, OH, NH₂, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkyl, C₁₋₆ haloalkoxy, C₁₋₆ alkylamino, C₂₋₄ alkenyl, C₁₋₄ haloalkenyl, C₂₋₄ alkynyl, C₁₋₄ haloalkynyl, C₃₋₆ saturated or partially unsaturated carbocyclyl, C₃₋₆ halogenated saturated or partially unsaturated carbocyclyl, C₃₋₆ saturated or partially unsaturated carbocyclyl-O-, SF₅ and 4-12 membered heterocyclyl;

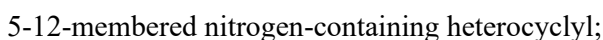
R₂ and R₃ are each independently selected from the group consisting of: C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkyl, C₁₋₆ haloalkoxy, C₁₋₆ alkylamino, C₃₋₆ saturated or partially unsaturated carbocyclyl, and 4-12-membered heterocyclyl; wherein R₂ and R₃ can be the same or different;

20 or R₂ and R₃ together with the sulfur atom to which they are connected form a 4-12-membered heterocyclyl;

25 R₄ is selected from the group consisting of: H, D, halogen, CN, OH, NH₂, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkyl, C₁₋₆ haloalkoxy, C₁₋₆ alkylamino, C₂₋₄ alkenyl, C₁₋₄ haloalkenyl, C₂₋₄ alkynyl, C₁₋₄ haloalkynyl, C₃₋₆ saturated or partially unsaturated carbocyclyl, C₃₋₆ halogenated saturated or partially unsaturated carbocyclyl, C₃₋₆ carbocyclyl-O-, SF₅ and 4-12-membered heterocyclyl;

R₅ is -L-R_w, wherein L is selected from the group consisting of: covalent bond, -C₁₋₄ alkyl-, -NR₆-, and -C₁₋₄ alkyl NR₆-;

R₆ is selected from the group consisting of: H, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkyl and C₁₋₆ haloalkoxy;



or R₆ and R_w together form a ring; and the ring is selected from the group consisting of: 5-12 membered heteroaryl and 4-12 membered heterocyclyl;

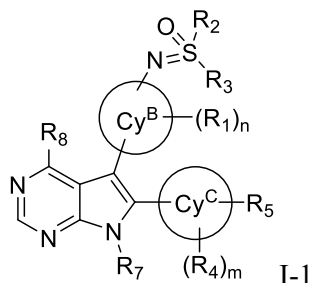
R₈ is selected from the group consisting of: H, OH, NH₂, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkyl, C₁₋₆ haloalkoxy and C₁₋₆ alkylamino;

unless otherwise specified, each of the above-mentioned alkyl, alkoxy, haloalkyl, haloalkoxy, alkylamino, alkenyl, haloalkenyl, alkynyl, haloalkynyl, saturated or partially unsaturated carbocyclyl, halogenated saturated or partially unsaturated carbocyclyl, saturated or partially unsaturated heterocyclyl, aryl and heteroaryl can be substituted with one or more Ra;

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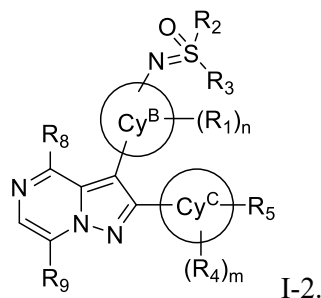
wherein, the heterocyclyl is a saturated or partially unsaturated non-aromatic group; the carbocyclyl or heterocyclyl can be optionally in the form of a monocycle, bridged ring, spirocycle, or fused ring.

In some embodiments, the compound has a structure as shown in formula (I-1):



wherein, R₁, R₂, R₃, R₄, R₅, R₇, R₈, Cy^B, and Cy^C have the definitions as claimed in claim 1; or R₇, R₄, and atoms to which they connected together form a 5-12 membered carbocyclyl or heterocyclyl.

In some embodiments, the compound has a structure as shown in formula (I-2):



In another preferred embodiment, R₈ is selected from the group consisting of: H, NH₂, C₁₋₆ alkyl, and C₁₋₆ alkylamino.

In another preferred embodiment, R₉ is selected from the group consisting of: H, D, halogen, CN, C₁₋₆ alkyl and C₁₋₆ haloalkyl.

In some embodiments, Cy^B is selected from the group consisting of: phenyl and 5-7 membered heteroaryl.

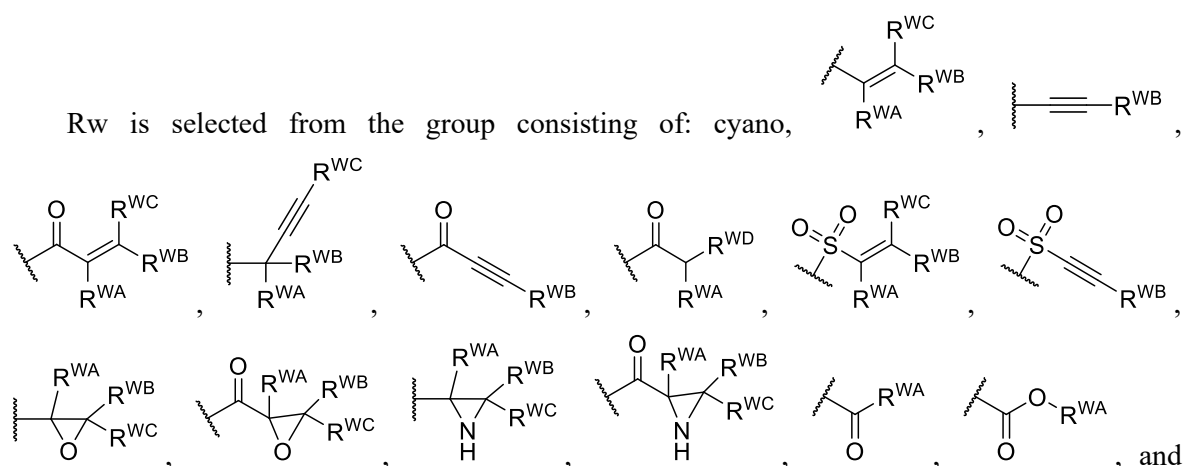
In another preferred embodiment, Cy^B is selected from the group consisting of: phenyl, pyridyl, pyrimidinyl, pyridazinyl, pyrrolyl, furanyl, thiophenyl, imidazolyl, pyrazolyl, thiazolyl, triazolyl, and oxazolyl.

In some embodiments, Cy^C is selected from the group consisting of: phenyl, 5-7 membered heteroaryl, saturated or partially unsaturated C₃₋₆ saturated or partially unsaturated carbocyclyl, and saturated or partially unsaturated 4-7 membered heterocyclyl.

In another preferred embodiment, Cy^C is selected from the group consisting of: phenyl, pyridyl, pyrimidinyl, pyridazinyl, pyrrolyl, furanyl, thiophenyl, imidazolyl, pyrazolyl, thiazolyl, triazolyl, oxazolyl, 5-7 membered saturated or partially unsaturated heterocyclyl.

In some embodiments, R₅ is -L-R_w, wherein L is selected from the group consisting of: covalent bonds, -C₁₋₄ alkyl, -NR₆-;

R₆ is selected from the group consisting of: H, C₁₋₆ alkyl;



5-7 membered nitrogen-containing heterocyclyl;

- 5 R^{WA}, R^{WB}, and R^{WC} are each independently selected from the group consisting of: H, D, halogen, C₁₋₆ alkyl and C₁₋₆ haloalkyl; and R^{WA}, R^{WB}, and R^{WC} can each be independently substituted with 1, 2, or 3 substituents selected from the group consisting of: C₁₋₆ alkylamino, and C₁₋₆ alkoxy;

- 10 or R₆ and R_w together form a ring; and the ring is selected from the group consisting of: 5-7 membered heteroaryl and 4-7 membered heterocyclyl.

In some embodiment,

R₁ is selected from the group consisting of: H, D, halogen, CN, OH, NH₂, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkyl, C₁₋₆ haloalkoxy, C₁₋₆ alkylamino, C₂₋₄ alkenyl, C₁₋₄ haloalkenyl, C₂₋₄ alkynyl, C₁₋₄ haloalkynyl and SF₅;

- 15 R₂ and R₃ are each independently selected from the group consisting of: C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkyl, C₁₋₆ haloalkoxy and C₁₋₆ alkylamino; wherein, R₂ and R₃ can be the same or different;

or R₂ and R₃ together with the sulfur atom to which they are connected form a 3-7 membered heterocyclyl (preferably a 4-6 membered heterocyclyl);

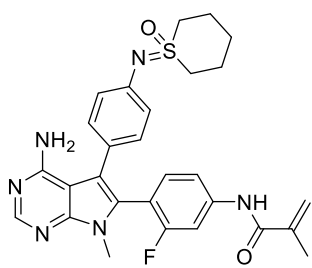
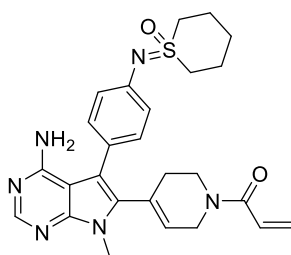
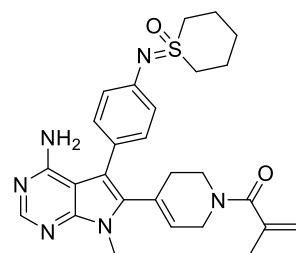
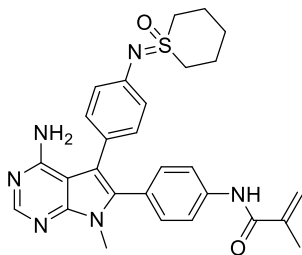
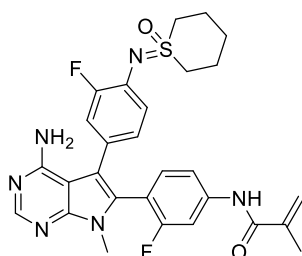
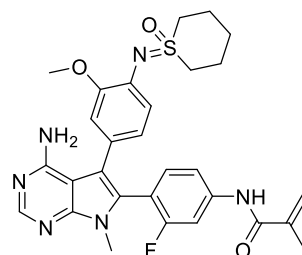
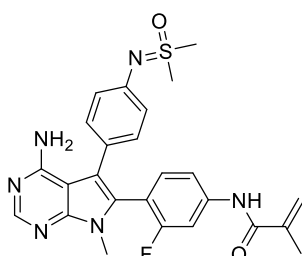
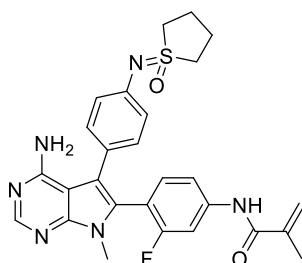
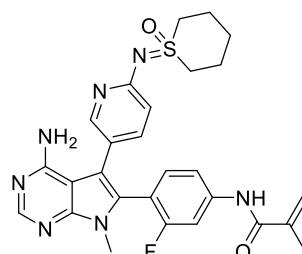
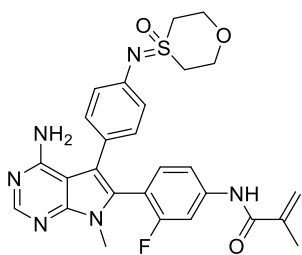
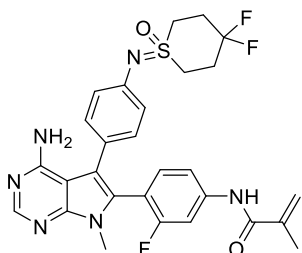
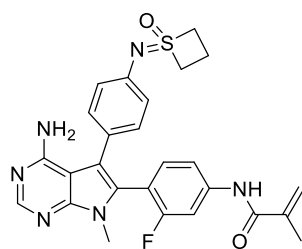
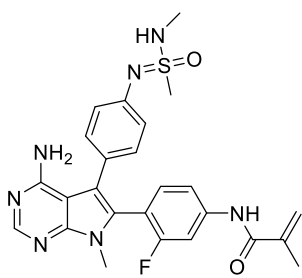
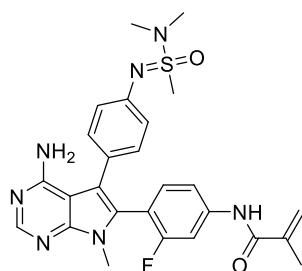
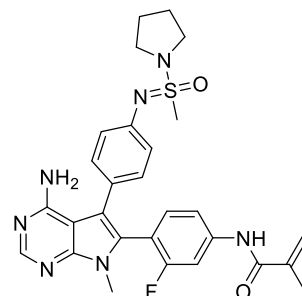
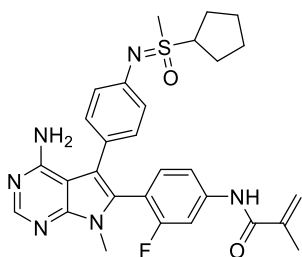
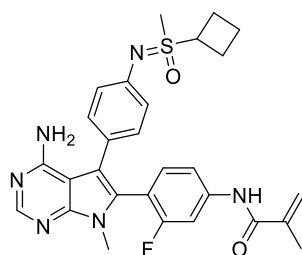
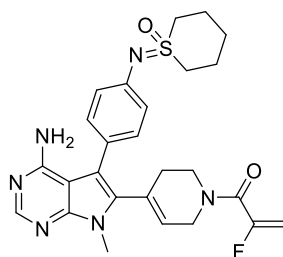
- 20 R₄ is selected from the group consisting of: H, D, halogen, CN, OH, NH₂, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkyl, C₁₋₆ haloalkoxy and C₁₋₆ alkylamino.

In another preferred embodiment, R₁ is selected from the group consisting of: H, D, halogen, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkyl and C₁₋₆ haloalkoxy;

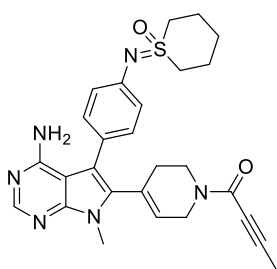
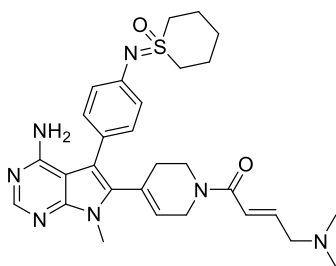
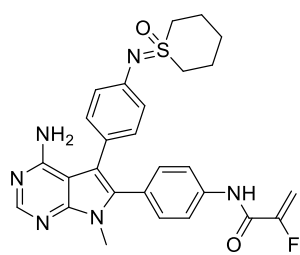
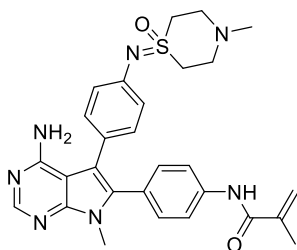
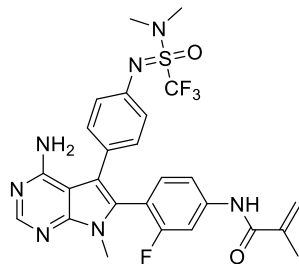
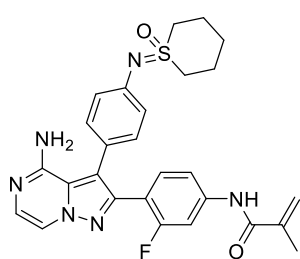
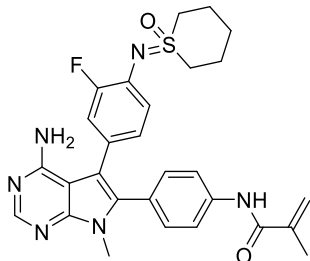
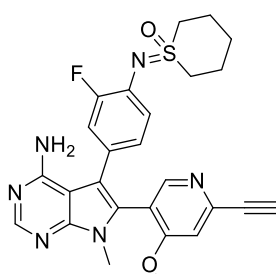
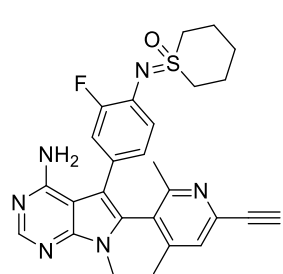
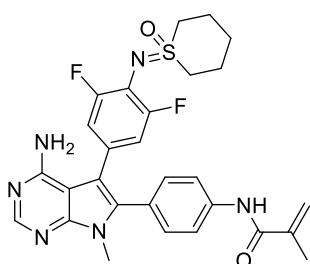
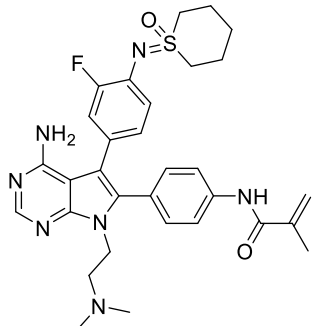
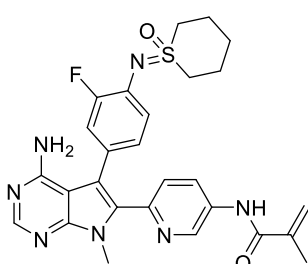
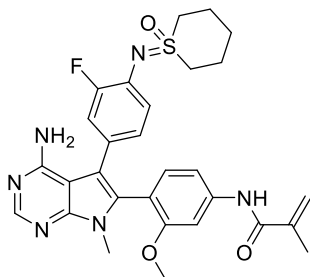
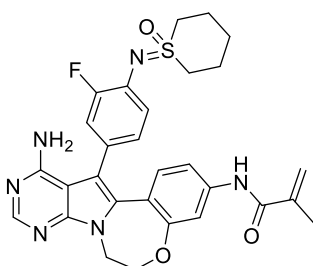
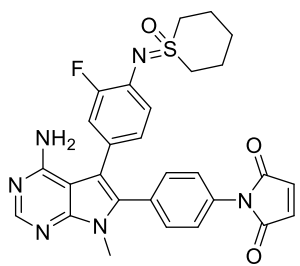
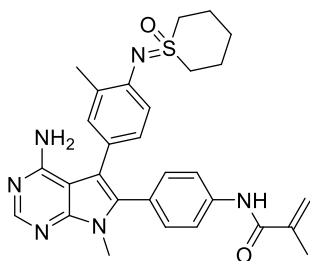
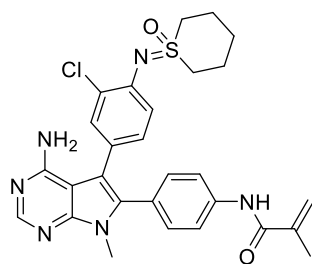
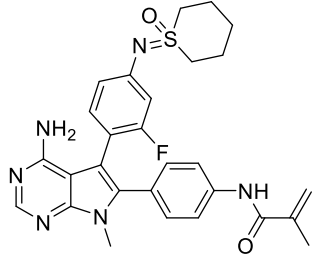
- 25 R₂ and R₃ are each independently selected from the group consisting of: C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₁₋₆ alkylamino and C₁₋₆ haloalkylamino; wherein, R₂ and R₃ can be the same or different; or R₂ and R₃ together with the sulfur atom to which they are connected form a 4-8 membered heterocyclyl;

R₄ is selected from the group consisting of: H, D, halogen, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkyl and C₁₋₆ haloalkoxy.

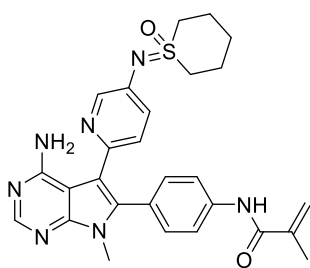
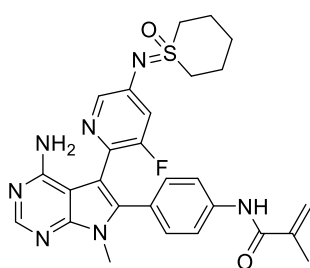
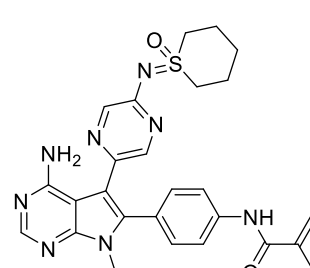
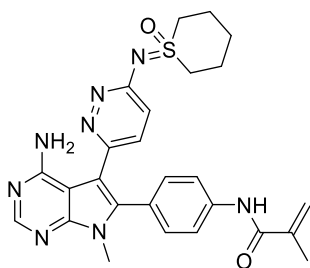
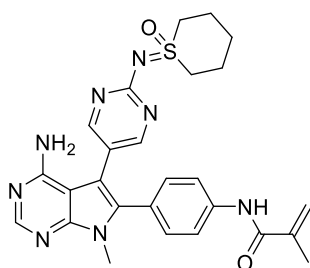
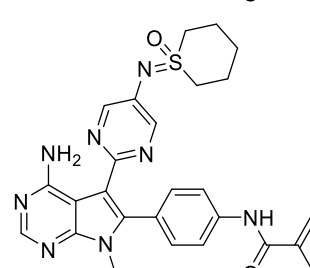
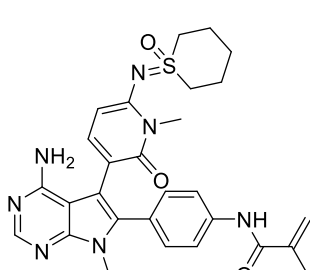
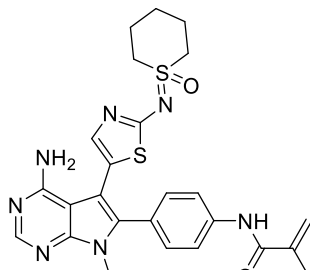
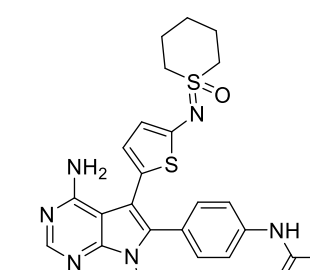
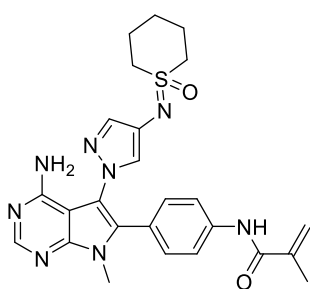
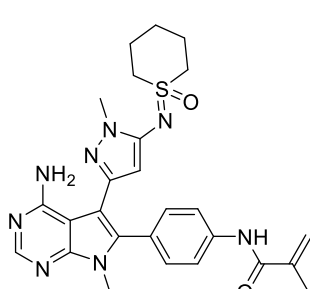
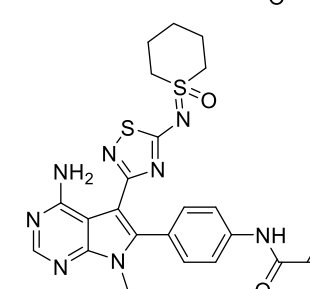
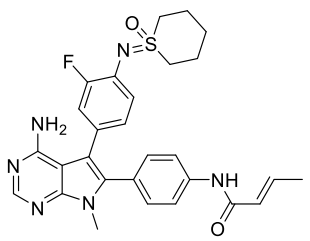
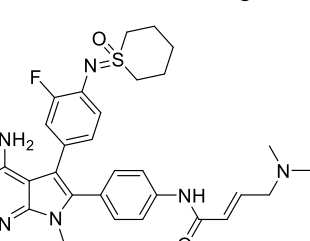
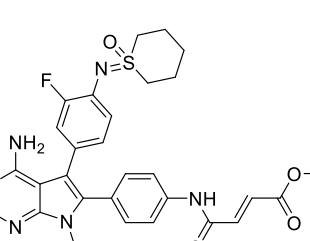
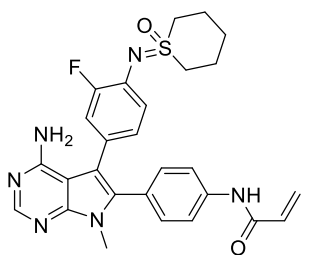
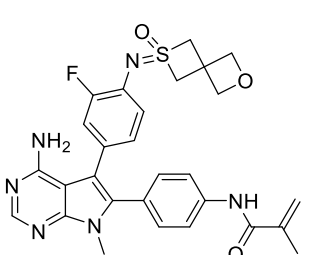
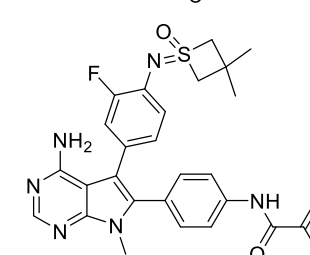
- 30 In some embodiments, the compound is selected from the group consisting of:



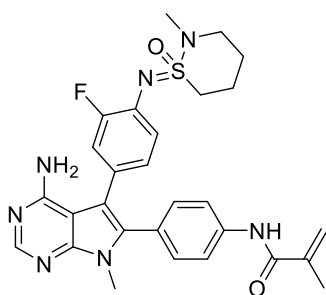
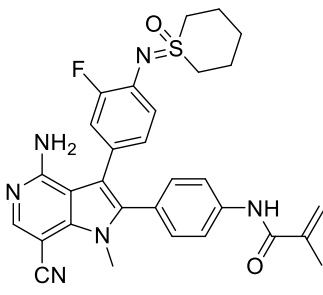
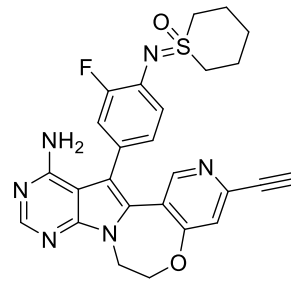
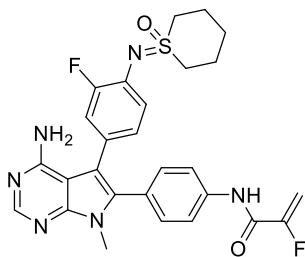
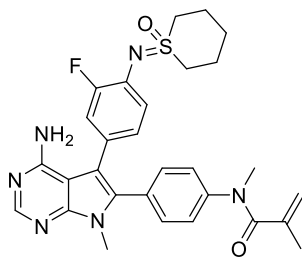
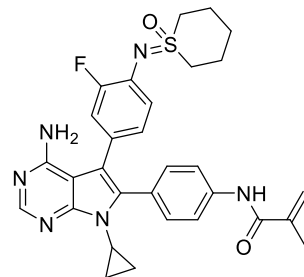
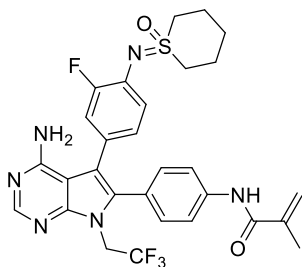
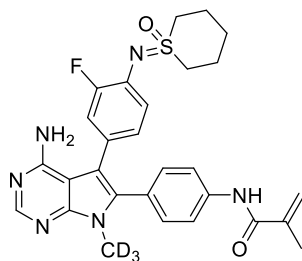
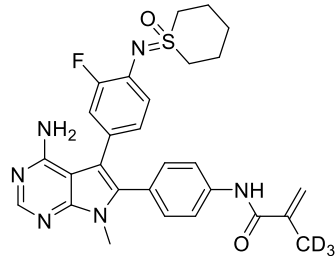
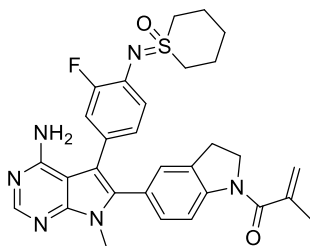
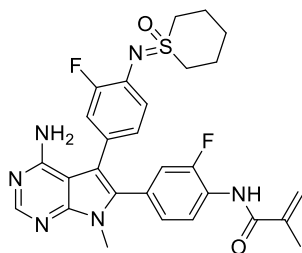
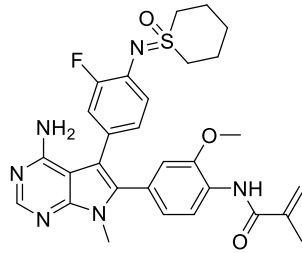
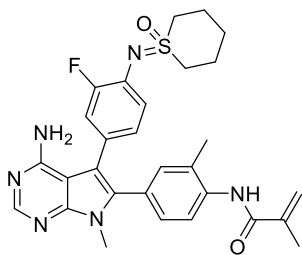
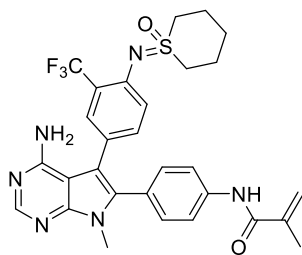
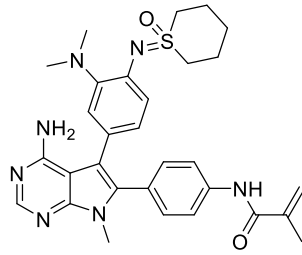
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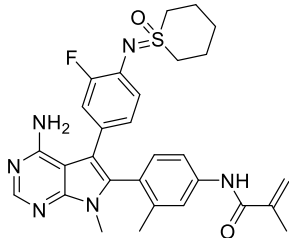
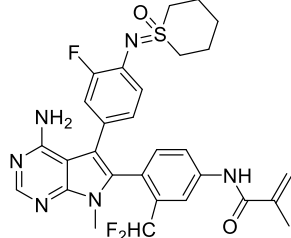
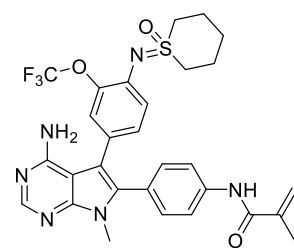
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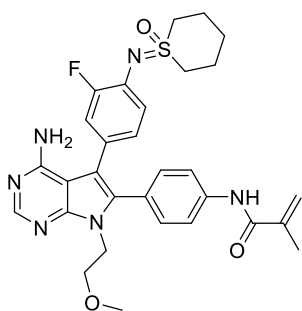
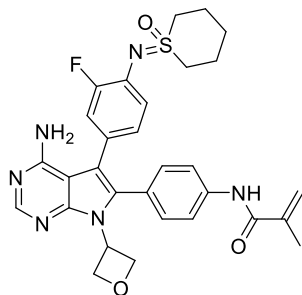
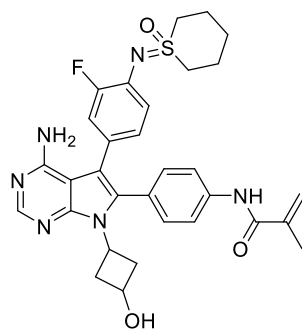
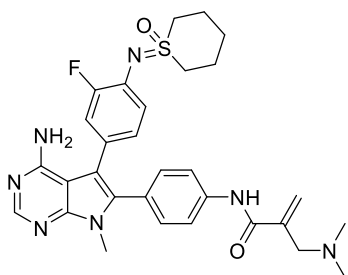
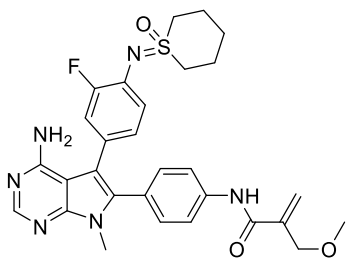
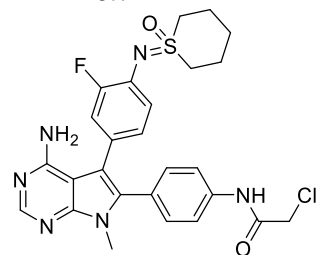
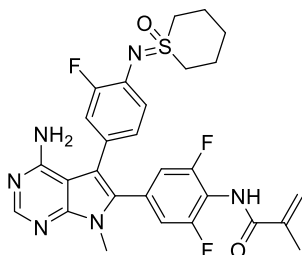
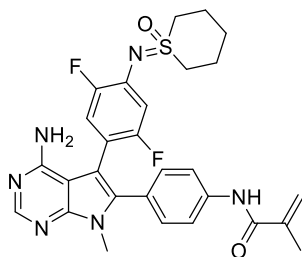
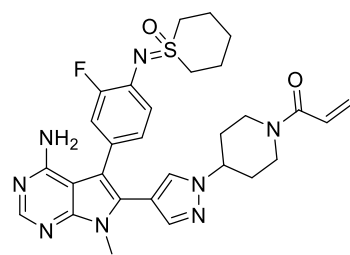
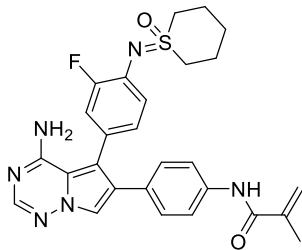
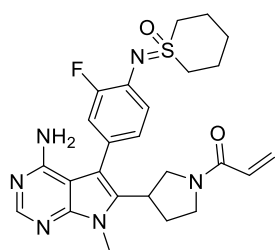
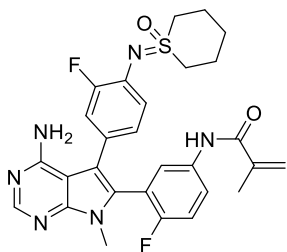
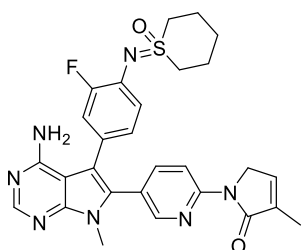
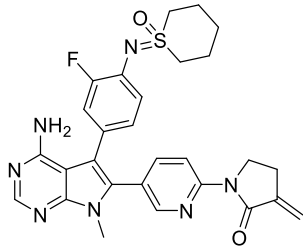
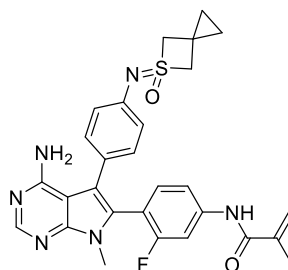


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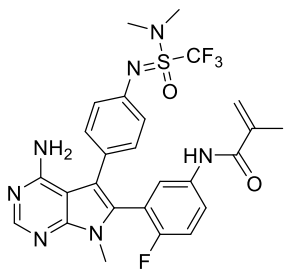
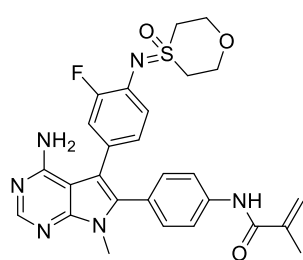
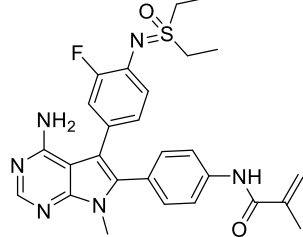


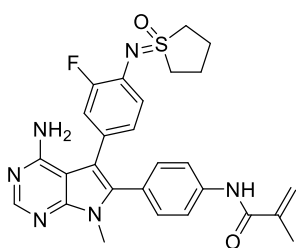
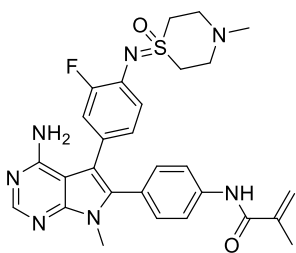
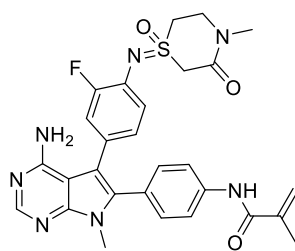
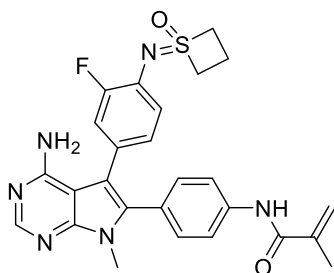
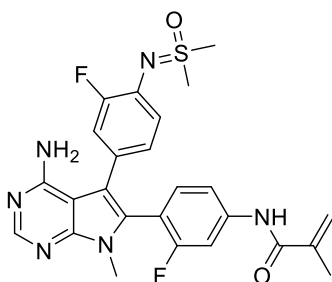
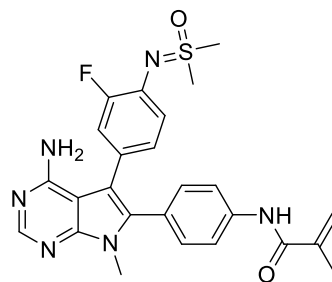
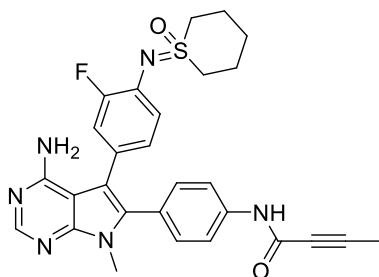
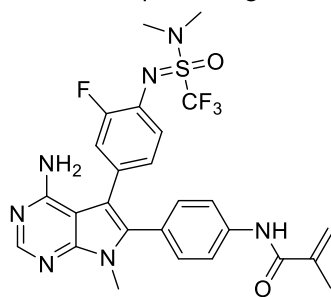
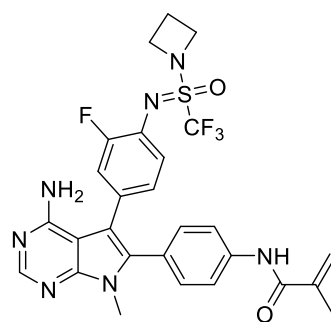
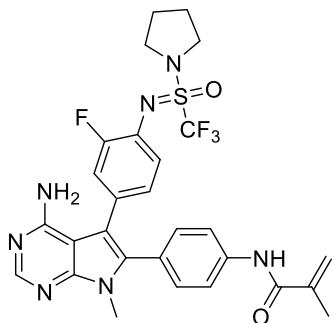
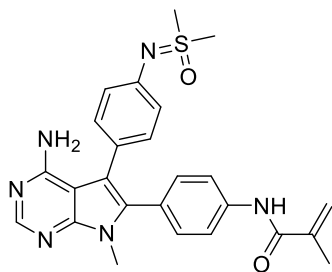
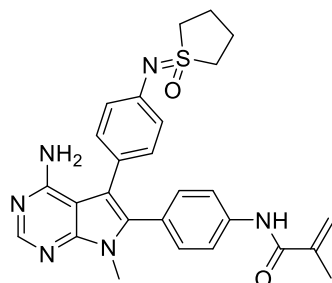
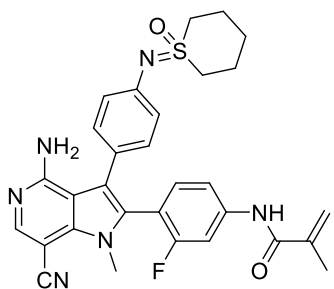
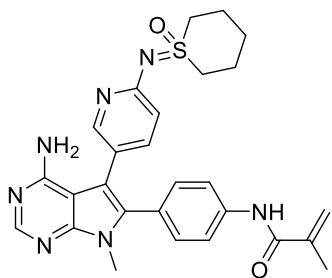
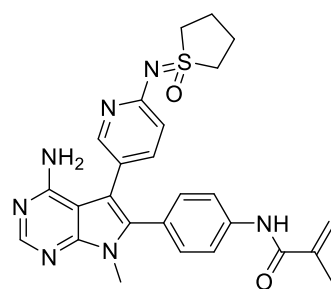
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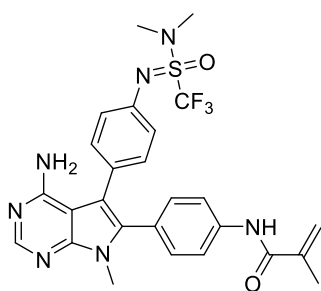
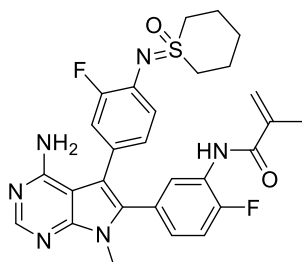
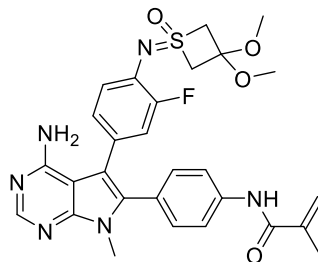
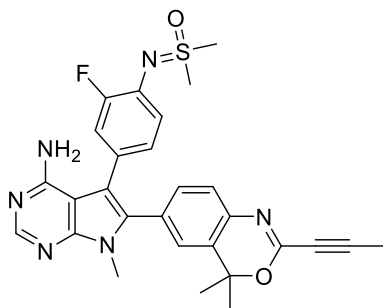
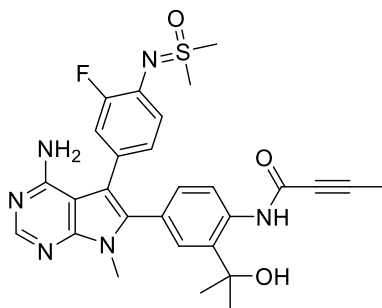
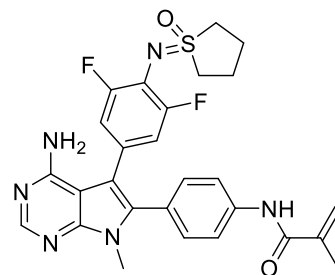
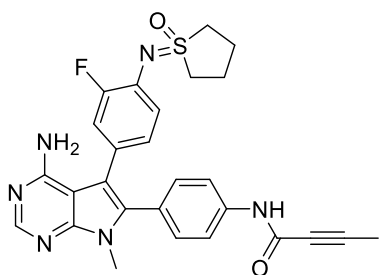
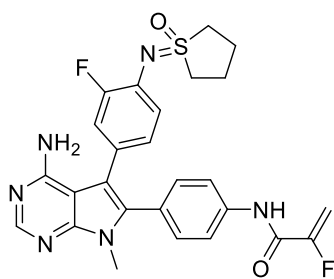
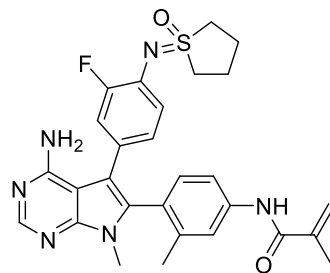
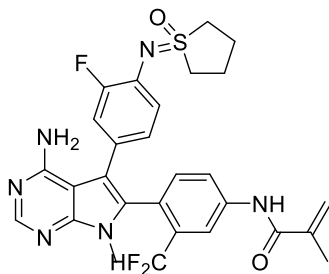
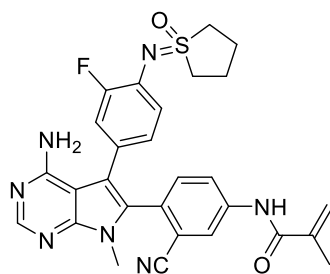
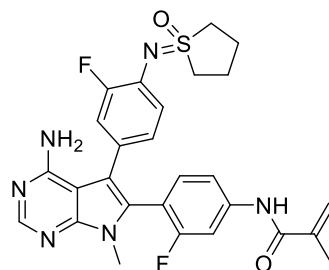
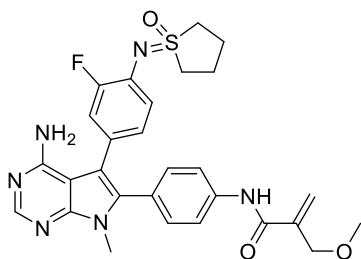
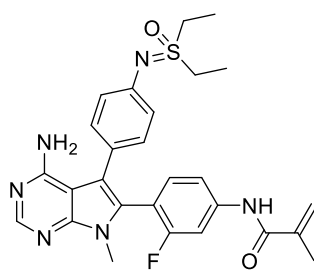
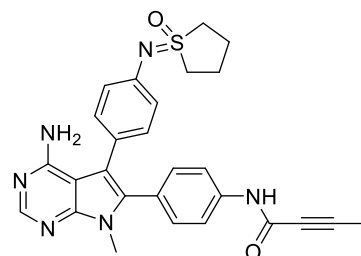


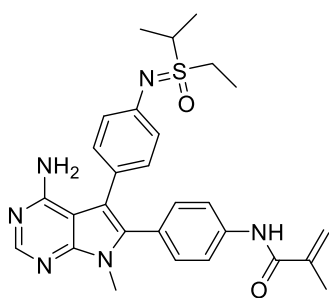
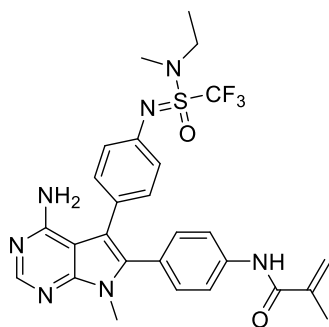
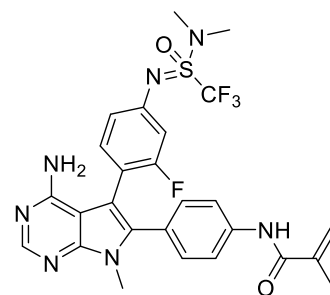
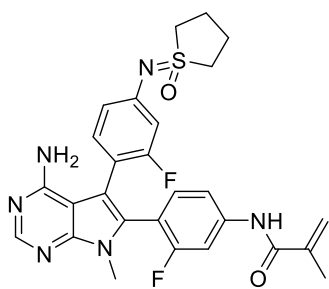
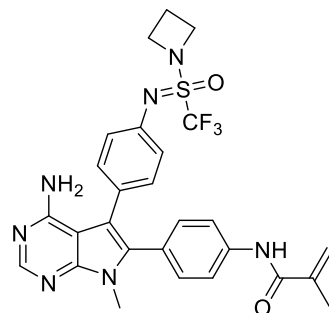
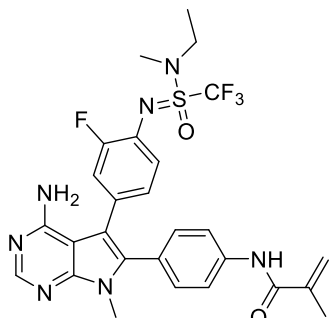
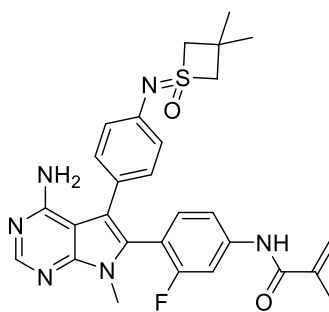
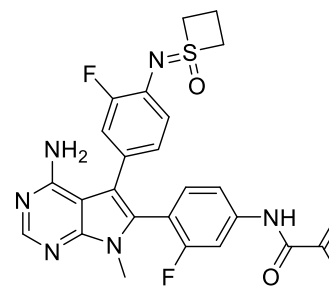
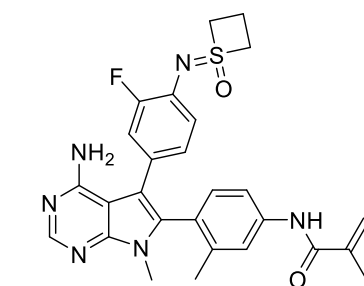
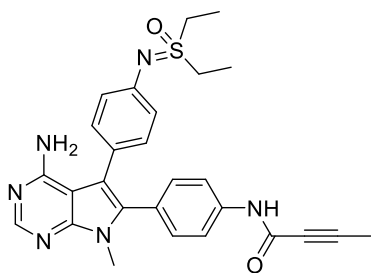
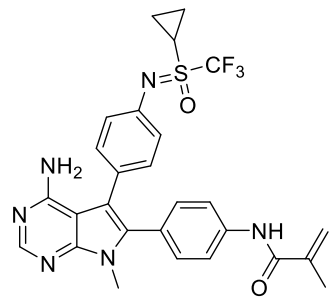
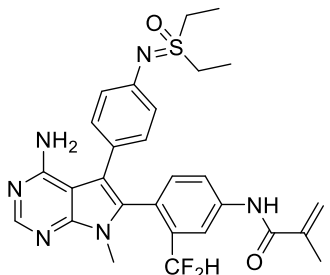
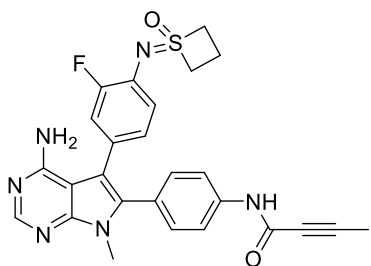
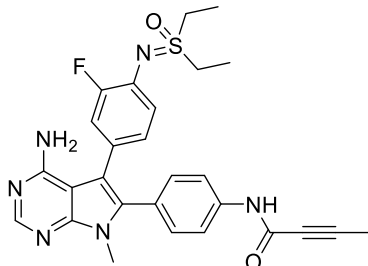
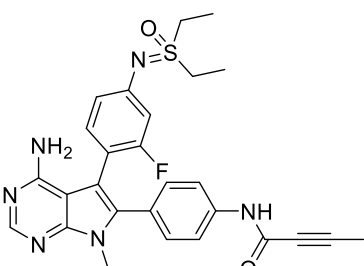
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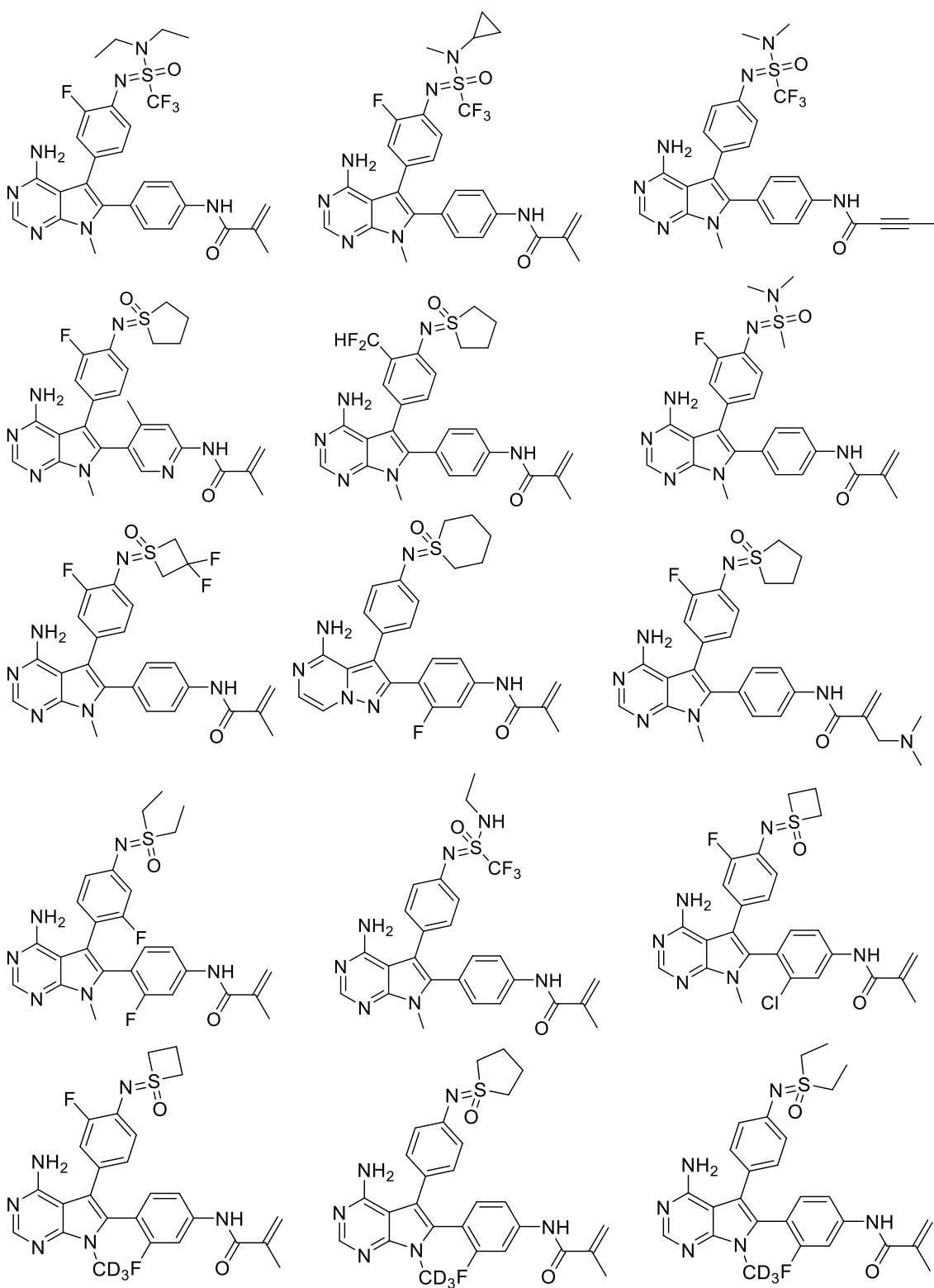




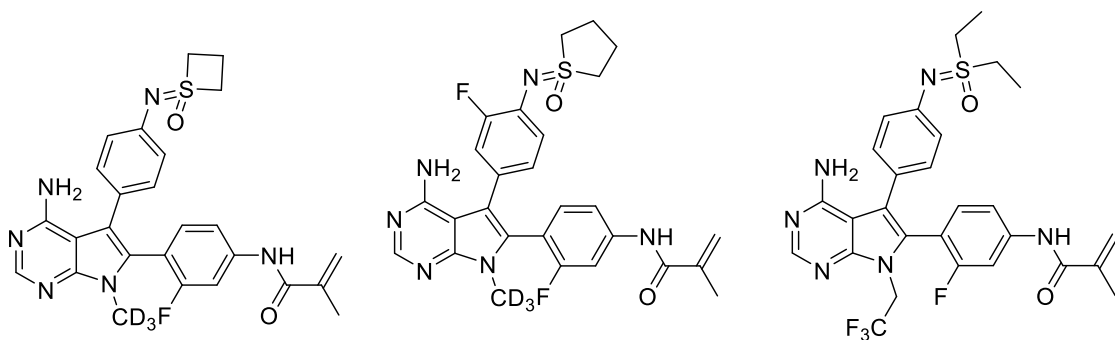
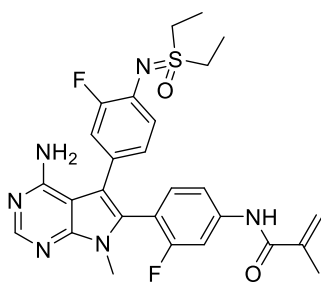
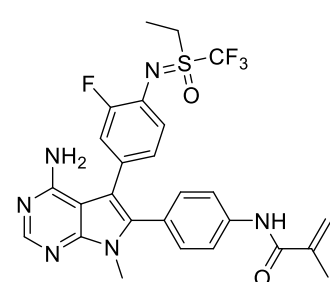
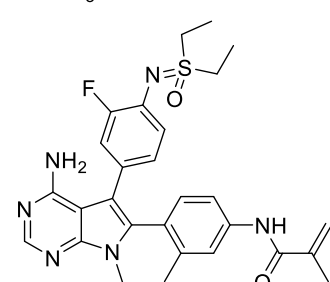
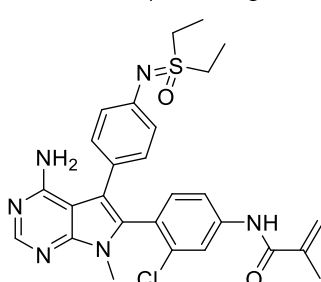
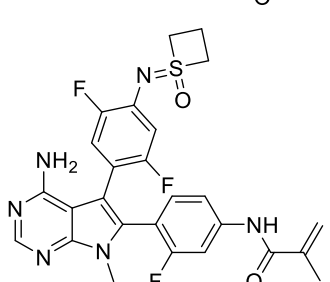
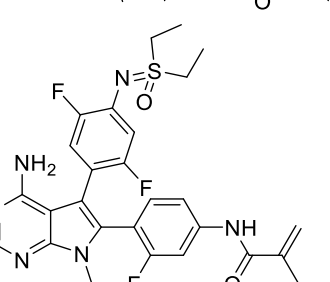
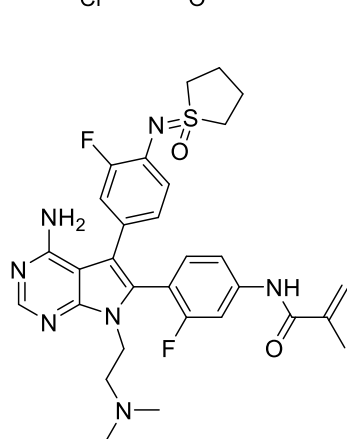
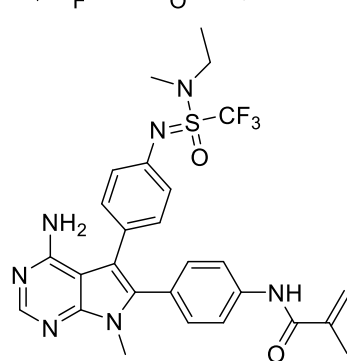
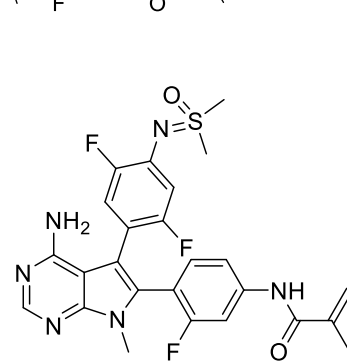
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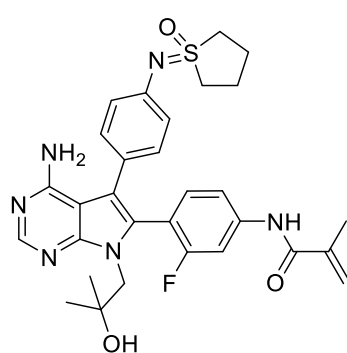
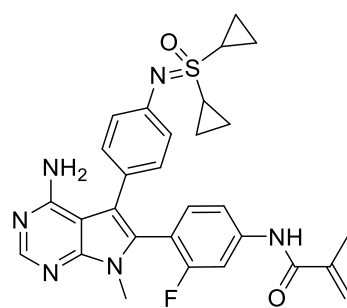
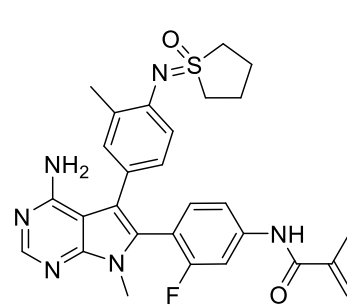


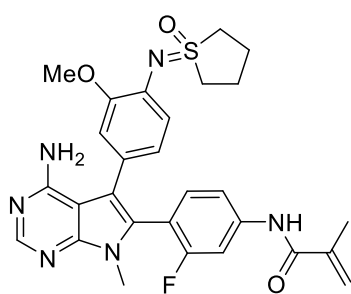
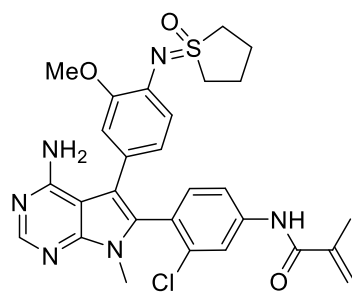
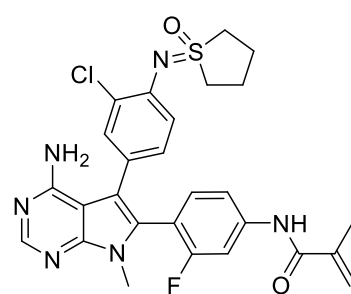
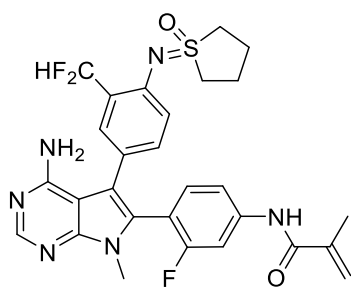
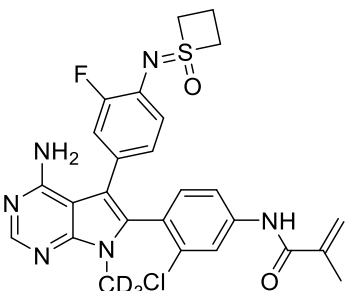
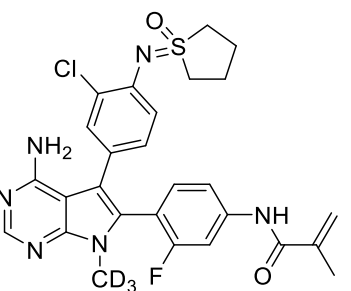
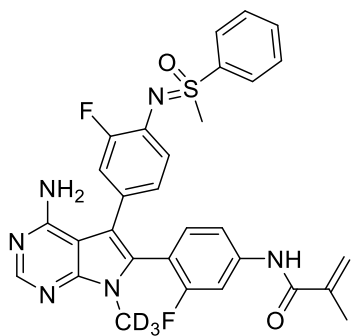
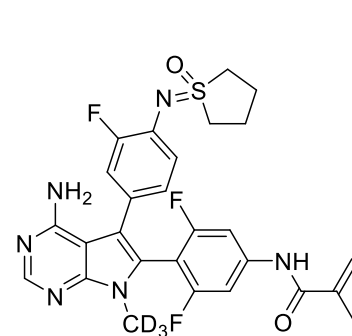
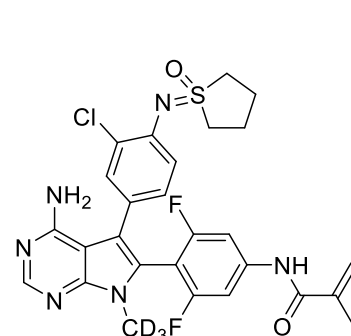


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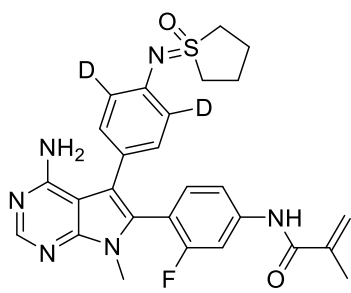
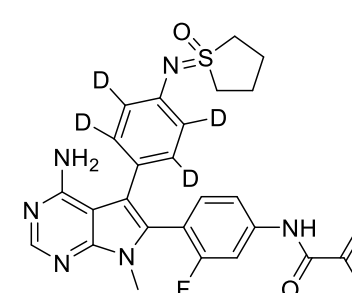
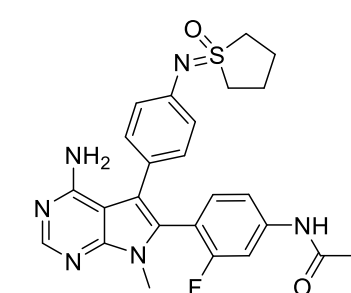
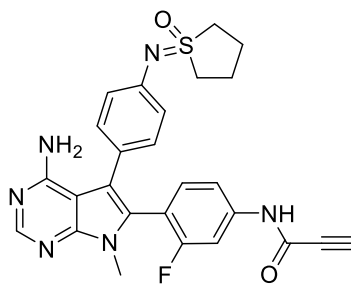
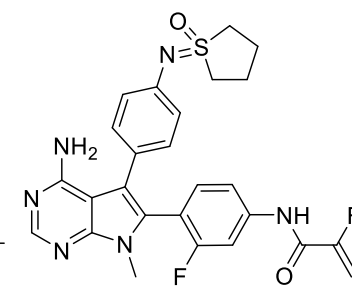
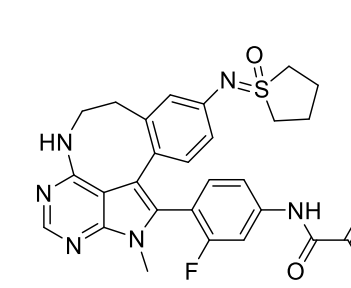


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In the second aspect of the present invention, provided is a pharmaceutical composition comprising:

(1) one or more the compound as described in the first aspect of the present invention, a tautomer, a stereoisomer, a hydrate, a solvate, or a pharmaceutically acceptable salt thereof,

5 (2) one or more pharmaceutically acceptable carriers, excipients, adjuvants, excipients, and/or diluents.

In another preferred embodiment, the pharmaceutical composition is used for treating or preventing diseases or condition associated with abnormal activity or expression levels of FGFR; preferably, the disease or condition is selected from the group consisting of: cholangiocarcinoma, hepatic carcinoma, breast carcinoma, prostate carcinoma, lung carcinoma, thyroid carcinoma, 10 gastric carcinoma, ovarian carcinoma, rectal carcinoma, endometrial carcinoma and uroepithelial carcinoma.

In another preferred embodiment, the cholangiocarcinoma is intrahepatic cholangiocarcinoma.

15 In another preferred embodiment, the hepatic carcinoma is hepatocellular carcinoma.

In another preferred embodiment, the lung carcinoma is squamous cell carcinoma or non-small cell lung carcinoma.

In the third aspect of the present invention, provided is a use of the compound as described in 20 the first aspect of the present invention, a tautomer, a stereoisomer, a hydrate, a solvate, or a pharmaceutically acceptable salt thereof, or mixture thereof, or a pharmaceutical composition as described in the second aspect of the present invention in the preparation a pharmaceutical composition for treating or preventing diseases or conditions associated with abnormal activity or expression levels of FGFR.

25 In another preferred embodiment, the disease or condition is specifically associated with a subtype of FGFR; preferably, the FGFR subtype is selected from the group consisting of: FGFR2.

It should be understood that, within the scope of the present invention, each of the above-mentioned technical features of the present invention and each of the technical features 30 specifically described in the following (such as the examples) can be combined with each other to form new or preferred technical solutions. Due to space limitations, it will not be elaborated herein.

EMBODIMENTS FOR CARRYING OUT THE INVENTION

35 After long-term and intensive research, the inventors provided a sulfoximine derivative with FGFR inhibitory activity, which has good FGFR inhibitory activity and can be used for preventing, treating, and/or alleviating indications associated with FGFR dysregulation. Based on the above discoveries, the inventors have completed the present invention.

40 DEFINITION

As used herein, the term “alkyl” includes straight or branched alkyl. For example, a C₁-C₈ alkyl refers to a straight or branched alkyl with 1 to 8 carbon atoms, such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, etc.

As used herein, the term “alkenyl” includes straight or branched alkenyl. For example, C₂-C₆ alkenyl refers to a straight or branched alkenyl with 2-6 carbon atoms, such as vinyl, allyl, 1-propenyl, isopropenyl, 1-butenyl, 2-butenyl, or similar groups.

As used herein, the term “alkynyl” includes straight or branched alkynyl. For example, C₂-C₆ alkynyl refers to a straight or branched alkynyl with 2-6 carbon atoms, such as ethynyl, propynyl, butynyl, or similar groups.

As used herein, the term “carbocyclyl” refers to a cyclic saturated or partially unsaturated aliphatic hydrocarbyl with a specific number of carbon atoms. For example, C₃-C₁₀ carbocyclyl refers to a cyclic saturated or partially unsaturated aliphatic hydrocarbyl with 3-10 carbon atoms. It can be a monocyclic group, such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, or similar groups. It can also be in the form of a bicyclic group, such, bridged ring or a spiro.

As used herein, the term “alkylamino” refers to an amine group substituted with alkyl. For example, “C₁-C₈ alkylamino” refers to an amino group substituted with a C₁-C₈ alkyl, which can be monosubstituted or disubstituted; for example, methylamino, ethylamino, propylamino, isopropylamino, butylamino, isobutylamino, tert-butylamino, dimethylamino, diethylamino, dipropylamino, diisopropylamino, dibutylamino, diisobutylamino, di tert-butylamino, etc.

As used herein, the term “alkoxy” refers to a group with a structure of alkyl-O-. For example, “C₁-C₈ alkoxy” refers to a straight or branched alkoxy with 1-8 carbon atoms, including methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, tert-butoxy, etc.

As used herein, the term “haloalkyl” refers to an alkyl in which one or more hydrogen atoms are substituted with halogens, wherein, the definition of alkyl is described above.

As used herein, the term “haloalkoxy” refers to an alkoxy in which one or more hydrogen atoms are substituted with halogens, wherein, the definition of alkoxy is described above.

As used herein, the term “heterocyclyl” or “heterocyclic alkyl” refers to a saturated or partially saturated cyclic group with a specific number of ring atoms (such as 3-10 ring atoms), wherein 1-3 atoms are heteroatoms selected from N, S, and O. It can be in the form of a monocyclic ring, a bicyclic ring, or a multiple ring, such, bridged ring or a spirocycle. Specific examples can include oxetanyl, azetidiny, tetrahydro-2H-pyranyl, piperidiny, tetrahydrofuranyl, morpholinyl, and pyrrolidinyl.

As used herein, the term “aryl” refers to an aromatic ring group with a specific number of carbon atoms, such as C₆-C₁₀ aryl refers to an aromatic ring group with 6-10 carbon atoms, such as phenyl, naphthyl, and the like.

As used herein, the term “heteroaryl” refers to a cyclic aromatic group with a specific number of atoms, wherein 1-3 atoms are heteroatoms selected from N, S, and O. For example, a 5-12 membered heteroaryl refers to an aromatic ring group with 5-12 carbon atoms. It can be in the form of a monocyclic ring or a fused ring. Specific examples can include pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl, pyrrolyl, pyrazolyl, imidazolyl, (1,2,3)-triazolyl, and (1,2,4)-triazolyl, tetrazolyl, furanyl, thiophenyl, imidazolyl, thiazolyl, oxazolyl, etc.

Unless otherwise specified as “substituted or unsubstituted”, the groups of the present invention may be substituted with substituents selected from the group consisting of: halogen, cyano, nitro, hydroxyl, amino, C₁-C₆ alkyl-amino, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ alkoxy, halogenated C₁-C₆ alkyl, halogenated C₂-C₆ alkenyl, halogenated C₂-C₆ alkynyl, halogenated C₁-C₆ alkoxy, allyl, benzyl, C₆-C₁₂ aryl, C₁-C₆ alkoxy-C₁-C₆ alkyl, C₁-C₆-alkoxy

carbonyl, phenoxy carbonyl, C₂-C₆ alkynyl-carbonyl, C₂-C₆ alkynyl carbonyl, C₃-C₆ carbocyclyl-carbonyl, C₁-C₆ alkyl-sulfonyl, etc.

As used herein, "halogen" or "halogen atom" refers to F, Cl, Br, and I. More preferably, the halogen or halogen atom is selected from F, Cl, and Br. "Halogenated" refers to being substituted with atoms selected from F, Cl, Br, and I.

Unless otherwise specified, the structural formulas described in the present invention are intended to include all isomeric forms (such as enantiomers, diastereomers, and geometric isomers (or conformational isomers)), such as R and S configurations with asymmetric centers, (Z) and (E) isomers with double bonds, etc. Therefore, the individual stereoisomers or enantiomers, diastereomers, or geometric isomers (or conformational isomers) of the compounds of the present invention, or the combination thereof are within the scope of the present invention.

As used herein, the term "tautomer" refers to structural isomers with different energies that can be transformed into each other by exceed the low energy barrier. For example, proton tautomers (i.e. proton shift) include interconversion through proton transfer, such as 1H-indazole and 2H-indazole. Valence tautomers include interconversion through recombination of some bonding electrons.

As used herein, the term "solvate" refers to a complex formed by the coordination of a compound of the present invention with a solvent molecule in a specific ratio.

As used herein, the term "hydrate" refers to a complex formed by the coordination of a compound of the present invention with water.

ACTIVE INGREDIENT

In the present invention, an active ingredient that can effectively inhibit FGFR is provided. The active ingredient is a compound represented by formula (I), which can effectively prevent, treat, and/or alleviate FGFR related diseases.

Experiments have shown that the active ingredients of the present invention can effectively inhibit FGFR kinase proteins, thereby preventing, treating, and/or alleviating FGFR related diseases.

It should be understood that the active ingredients of the present invention include compounds represented by formula (I), or pharmaceutically acceptable salts, or prodrugs thereof. It should be understood that the active ingredients of the present invention also include crystal forms, amorphous compounds, and deuterated compounds of compounds of formula (I).

The term "pharmaceutically acceptable salt" refers to a salt formed by the compound of the present invention with an acid or base that is suitable for pharmaceutical use. Pharmaceutically acceptable salts include inorganic salts and organic salts. A preferred type of salt is the salt formed by the compound of the present invention with an acid. Suitable acids for salt formation include but are not limited to inorganic acids such as hydrochloric acid, hydrobromic acid, hydrofluoric acid, sulfuric acid, nitric acid, phosphoric acid, etc; organic acids such as formic acid, acetic acid, trifluoroacetic acid, propionic acid, oxalic acid, malonic acid, succinic acid, fumaric acid, maleic acid, lactic acid, malic acid, tartaric acid, citric acid, picric acid, benzoic acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, benzenesulfonic acid, naphthalene sulfonic acid, etc; and amino acids such as proline, phenylalanine, aspartic acid, glutamic acid, etc. Another preferred type of salt is the salt formed by the compound of the present invention with a base,

such, alkali metal salts (e.g. sodium or potassium salts), alkaline earth metal salts (e.g. magnesium or calcium salts), ammonium salts (e.g. lower alkyl alcohol ammonium salts and other pharmaceutically acceptable amine salts), such as methylamine salt, ethylamine salt, propylamine salt, dimethylamine salt, trimethylamine salt, diethylamine salt, triethylamine salt, tert-butylamine salt, ethylenediamine salt, hydroxyethyl amine salt, dihydroxyethylamine salt, trihydroxyethylamine salt and amine salts formed by morpholine, piperazine, and lysine, respectively.

PHARMACEUTICAL COMPOSITION AND MODE OF ADMINISTRATION

Due to the excellent FGFR kinase inhibitory activity of the compounds of the present invention, the compounds of the present invention and various crystal forms, pharmaceutically acceptable inorganic or organic salts, hydrates or solvates thereof, as well as pharmaceutical compositions containing the compounds of the present invention as the main active ingredient, can be used for preventing, treating and/or alleviating FGFR related diseases, such as treating cancer.

The pharmaceutical composition of the present invention comprises a safe and effective amount of the compound of the present invention and a pharmaceutically acceptable excipient or carrier. The term "safe and effective amount" refers to the amount of a compound that is sufficient to significantly improve the condition without causing serious side effects. Generally, pharmaceutical compositions contain 1-2000mg of the compound of the present invention per dose, and more preferably 10-200mg of the compound of the present invention per dose. Preferably, the "one dose" is a capsule or tablet.

"Pharmaceutically acceptable carrier" refers to one or more compatible solid or liquid fillers or gel substances, which are suitable for human use and must have sufficient purity and low toxicity. "Compatible" here refers to each component in the composition can be blended with the compound of the present invention and with each other without significantly reducing the efficacy of the compound. Examples of pharmaceutically acceptable carriers include cellulose and derivatives thereof (such as sodium carboxymethyl cellulose, sodium ethyl cellulose, cellulose acetate, etc.), gelatin, talc, solid lubricants (such as stearic acid, magnesium stearate), calcium sulfate, vegetable oils (such as soybean oil, sesame oil, peanut oil, olive oil, etc.), polyols (such as propylene glycol, glycerol, mannitol, sorbitol, etc.), emulsifiers (such as Tween®), wetting agents (such as sodium dodecyl sulfate), coloring agents, flavoring agents, stabilizers, antioxidants, preservatives, pyrogen-free water, etc.

There is no special limitation of mode of administration of the compound or pharmaceutical combination of the present invention, and representative mode of administration include (but are not limited to): oral, parenteral (intravenous, intramuscular, or subcutaneous).

Solid dosage forms for oral administration include capsules, tablets, pills, powders, and granules. In these solid dosage forms, the active compound is mixed with at least one conventional inert excipient (or carrier), such as sodium citrate or dicalcium phosphate, or with the following components: (a) fillers or compatibilizers, such as starch, lactose, sucrose, glucose, mannitol, and silica; (b) binders, such as hydroxymethylcellulose, alginate, gelatin, polyvinylpyrrolidone, sucrose, and arabic gum; (c) humectants, such as glycerin; (d) disintegrants, such as, calcium carbonate, potato starch or cassava starch, alginic acid, certain composite

silicates, and sodium carbonate; (e) dissolution-retarding agents, such as paraffin; (f) absorption accelerators, such as quaternary ammonium salt; (g) wetting agents, such as cetyl alcohol and glycerol monostearate; (h) adsorbents, such as kaolin; and (i) lubricants, such as talc, calcium stearate, magnesium stearate, solid polyethylene glycol, sodium dodecyl sulfate, or mixtures thereof. In capsules, tablets, and pills, the dosage form may also contain buffering agents.

Solid dosage forms such as tablets, sugar pills, capsules, pills, and granules can be prepared by coating and shell materials, such as enteric coatings and other materials known in the art. They may contain opaque agents, and the active compounds or compounds in this combination can be released in a delayed mode in a certain part of the digestive tract. Examples of usable embedding components are polymeric substances and wax based substances. When necessary, the active compound and one or more of the above-mentioned excipients can form microcapsule.

Liquid dosage forms for oral administration include pharmaceutically acceptable emulsion, solutions, suspensions, syrups or tinctures. In addition to active compounds, liquid formulations may include conventional inert diluents used in this art, such as water or other solvents, solubilizers, and emulsifiers, such as ethanol, isopropanol, ethyl carbonate, ethyl acetate, propylene glycol, 1,3-butanediol, dimethylformamide, as well as oils, particularly cottonseed oil, peanut oil, corn germ oil, olive oil, castor oil, and sesame oil, or the combination thereof.

In addition to these inert diluents, the composition may also contain adjuvants such as humectants, emulsifiers and suspensions, sweeteners, corrigens, and spices.

In addition to the active compounds, the suspensions may contain suspensions, such as ethoxylated isooctadecanol, polyoxyethylene sorbitol and dehydrated sorbitol esters, microcrystalline cellulose, methanol aluminum and agar, or the combination thereof.

The compositions for parenteral injection may include physiologically acceptable sterile aqueous or anhydrous solutions, dispersions, suspensions or emulsions, and sterile powders for being re-dissolved into sterile injectable solutions or dispersions. Suitable aqueous and non-aqueous carriers, diluents, solvents, or excipients include water, ethanol, polyols, and suitable combination thereof.

The compound of the present invention can be administered alone or in combination with other pharmaceutically acceptable therapeutic agents.

When administered in combination, the pharmaceutical composition further comprises one or more (2, 3, 4, or more) other pharmaceutically acceptable therapeutic agents. One or more of the other pharmaceutically acceptable therapeutic agents (2, 3, 4, or more) can be used simultaneously, separately, or sequentially with the compound of the present invention for preventing, treating, and/or alleviating FGFR mediated diseases.

When using a pharmaceutical composition, a safe and effective dosage of the compound of the present invention is applied to a mammal (such, human) in need of treatment, wherein the dosage of administration is a pharmaceutically effective dosage, for a person weighed 60 kg, the daily dosage is usually 1-2000 mg, preferably 20-500 mg. Of course, the specific dosage should also consider factors such as the route of administration and the patient's health condition, which are within the skill range of skilled physicians.

BENEFICIAL EFFECTS

According to embodiments of the present invention, the present invention provides novel structurally, metabolically stable, and highly effective FGFR inhibitors, which can be used for effectively treating FGFR related diseases and conditions.

5 The compound of the present invention has a good inhibitory effect on FGFR and good in vitro efficacy. In addition, the results of mouse experiments showed that the compounds of the present invention exhibited excellent pharmacokinetic properties and good druggability.

The following will explain the solution of the present invention in conjunction with the examples. Technicians in this art will understand that the following examples are only used to illustrate the present invention and should not be considered as limiting the scope of the present invention. The specific technology or conditions with no description in the examples are performed under the technology or conditions described in the literature in this art or according to manufacturer's instructions. The reagents or instruments used without specifying the manufacturer are conventional products that can be obtained through commercial purchase.

15 Unless otherwise specified, the structures of the compounds of the present invention are determined by nuclear magnetic resonance (NMR) and/or mass spectrometry (MS). The unit of NMR shift is 10^{-6} ppm. The solvents used for NMR determination are deuterated dimethyl sulfoxide, deuterated chloroform, deuterated methanol, etc. The internal standard is tetramethylsilane (TMS).

The abbreviation definition of the present invention is as follows:

20 M: molar concentration, such as 1M hydrochloric acid refers to 1 mol/L hydrochloric acid solution

HATU: O-(7-azabenzotriazole-1-yl)-N,N,N,N-tetramethylurea hexafluorophosphate

T3P: 1-propylphosphamide

DIPEA: also known as DIEA, diisopropylethylamine, i.e. N, N-diisopropylethylamine

25 NIS: N-iodosuccinimide

NBS: N-bromosuccinimide

EA: ethyl acetate

TFA: trifluoroacetic acid

DMF: N, N-dimethylformamide

30 THF: tetrahydrofuran

PE: petroleum ether

LC-MS: liquid chromatography-mass spectrometry

DMSO: dimethyl sulfoxide

Xantphos: 4,5-diphenylphosphine-9,9-dimethyloxaanthracene

35 TLC: thin layer chromatography

IC50: half inhibitory concentration, which refers to the concentration at which half of the maximum inhibitory effect is achieved.

Unless otherwise indicated, the compounds listed herein are named and numbered using ChemBioDraw Ultra 14.0.

40

Intermediate 1g 5-iodo-7-methyl-7H-pyrrolo [2,3-d] pyrimidin-4-amine

Compound **1j-1** (5.0 g, 26.3 mmol) and triethylamine (8.0 g, 11 ml) were dissolved in DCM (50 ml), at 0 °C, 2-methylacryloyl chloride (3.03 g, 2.8 ml) was added dropwise to the reaction solution, and stirred for 1 h. The reaction solution was diluted with water (100 ml), and extracted with DCM (100 ml) three times. The organic phase was washed with saturated saline solution, dried over anhydrous Na₂SO₄, and concentrated under reduced pressure, the obtained crude product was purified by silica gel column chromatography (EA/PE=1/4) to obtain compound **1j-2** (4.9 g, 72%), pale yellow white solid.

MS (ESI) *m/z* 258, 260 [M + H]⁺.

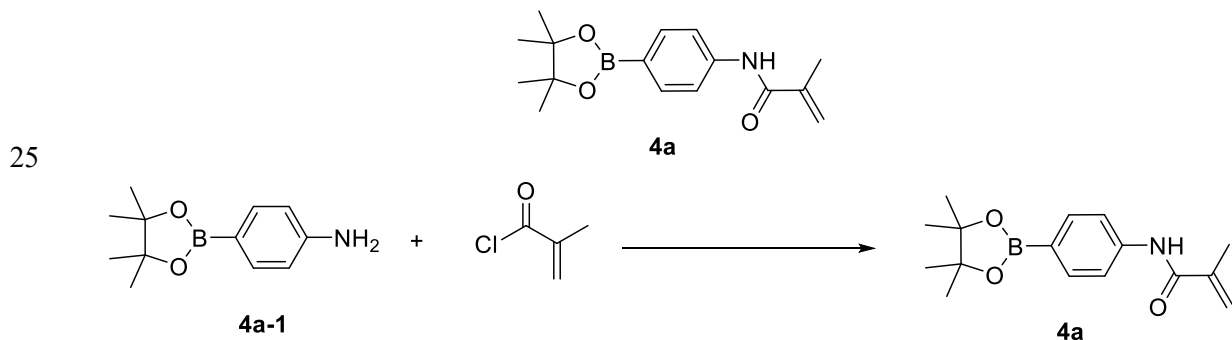
Step 2: *N*-(3-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl) methacrylamide **1j**

To a sealed tube was added Compound **1j-2** (2.0 g, 7.75 mmol), bis(pinacolato)diboron (3.94 g, 15.5 mmol), Pd(dppf)Cl₂ (567 mg, 0.77 mmol), AcOK (2.28 g, 23.25 mmol), and 1,4-dioxane (20 ml), and replaced with argon gas three times. The mixture reacted at 90 °C for 5 h. The reaction was then quenched with water and extracted with DCM. The organic phase was washed with saturated saline solution, dried over anhydrous Na₂SO₄, and concentrated under reduced pressure. The obtained crude product was purified by silica gel column chromatography (EA/PE=1/8 to 1/4) to obtain compound **1j** (1.52 g, 64%), yellow solid.

MS (ESI) *m/z* 306 [M + H]⁺.

¹H NMR (500 MHz, CDCl₃) δ 7.70-7.65 (m, 2H), 7.53 (dd, *J* = 11.5, 1.9 Hz, 1H), 7.20 (dd, *J* = 8.2, 1.9 Hz, 1H), 5.78 (s, 1H), 5.48 (d, *J* = 1.7 Hz, 1H), 2.04 (s, 3H), 1.34 (s, 12H).

Intermediate **4a** *N*-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl) methacrylamide

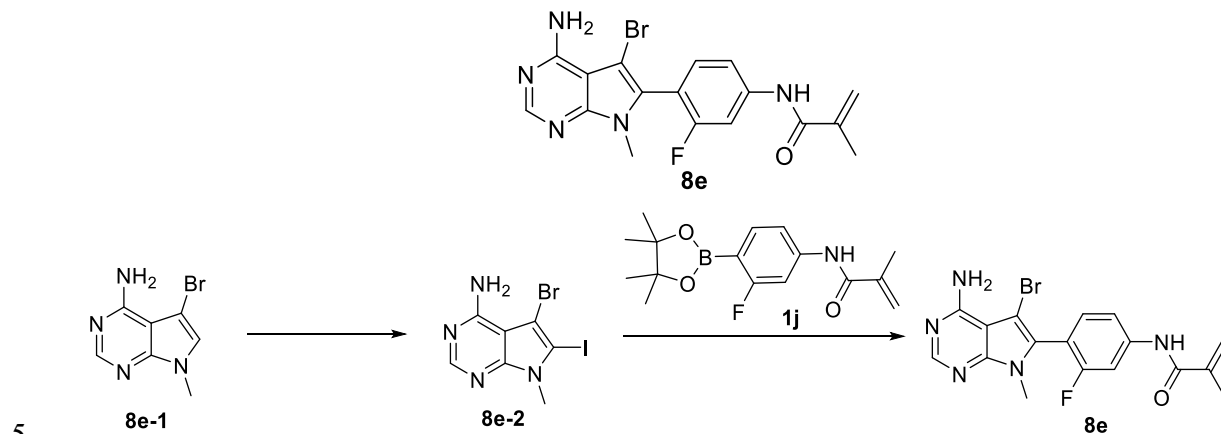


Compound **4a-1** (2.0 g, 9.12 mmol) was dissolved in ultra dry DCM (50 mL), triethylamine (2.77g, 27.36 mmol) was added, and stirred at 0 °C for 5 min. The 2-methylacrylamide was diluted with ultra dry DCM (30 mL), slowly dropwise added to the reaction solution and reacted at 0 °C for 2 h. The reaction solution was poured into water, and extracted with DCM three times. The organic layers were combined and washed with saturated salt once, the organic phase was dried over anhydrous sodium sulfate, concentrated under reduced pressure, and purified by column chromatography (PE/EA=2/1) to obtain compound **4a** (2.15 g), white solid.

MS (ESI) *m/z* 288 [M + H]⁺.

¹H NMR (400 MHz, DMSO-*d*₆) δ 9.87 (s, 1H), 7.71 (d, *J*=8.5 Hz, 2H), 7.61 (d, *J*=8.6 Hz, 2H), 5.81 (t, *J*=1.0 Hz, 1H), 5.55-5.51 (m, 1H), 1.95 (s, 3H), 1.28 (s, 12H).

Intermediate 8e *N*-(4-(4-amino-5-bromo-7-methyl-7*H*-pyrrolo [2,3-*d*] pyrimidin- 6-yl) -3-fluorophenyl) methacrylamide



Step 1: 5-bromo-6-iodo-7-methyl-7*H*-pyrrolo [2,3-*d*] pyrimidin-4-amino 8e-2

Compound **8e-1** (10.6 g 0.0466 mol) was dissolved in dichloromethane (100 mL) and trifluoroacetic acid (26.7 g 0.2334 mol), at 10 °C, N-iodosuccinimide (10.5 g 0.0466 mol) was added in batches to react for 4 h. After the reaction was completed, saturated sodium bicarbonate aqueous solution (150 mL) was added slowly at 10 °C, then a solid was precipitated, filtered and dried to obtain compound **8e-2** (13.4 g), purple solid.

MS (ESI) *m/z* 352.6 [M+H]⁺.

¹H NMR (400 MHz, CDCl₃) δ 8.22 (s, 1H), 5.61 (s, 2H), 3.80 (s, 3H).

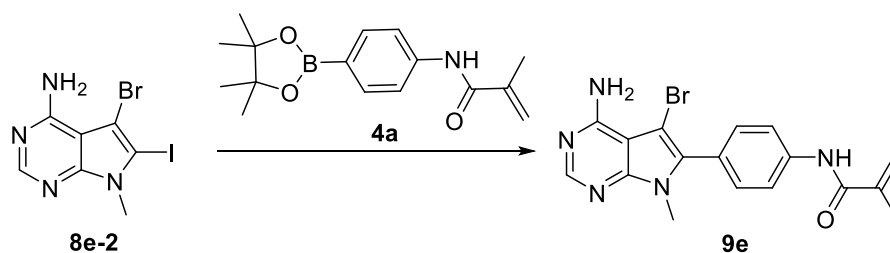
Step 2: *N*-(4-(4-amino-5-bromo-7-methyl-7*H*-pyrrolo [2,3-*d*] pyrimidin-6-yl) -3-fluorophenyl) methacrylamide 8e

Compound **1j** (2 g, 6.5 mmol), compound **8e-2** (2.3 g, 6.5 mmol), tetrakis (triphenylphosphine) palladium (0.65 g, 0.56 mmol), and potassium phosphate (3.6 g, 0.017 mol) were added into a reaction flask, and replaced with nitrogen gas three times, then DMF (35 mL) and water (5 mL) were added, and stirred at 50 °C for 16 h. After the reaction was completed, water (150 mL) and dichloromethane (200 mL) were added to extract the solution, the organic phase was washed with saturated saline and concentrated to obtain a crude product. The crude product was purified by column chromatography to obtain compound **8e** (1.1 g), light yellow solid.

MS (ESI) *m/z* 404.2 [M+H]⁺.

¹H NMR (400 MHz, CDCl₃) δ 8.35 (s, 1H), 7.82 (dd, *J* = 11.7, 2.1 Hz, 1H), 7.69 (s, 1H), 7.44 – 7.33 (m, 2H), 5.87 (s, 1H), 5.66 (s, 2H), 5.58 (q, *J* = 1.5 Hz, 1H), 3.66 (d, *J* = 1.1 Hz, 3H), 2.12 (dd, *J* = 1.6, 0.9 Hz, 3H).

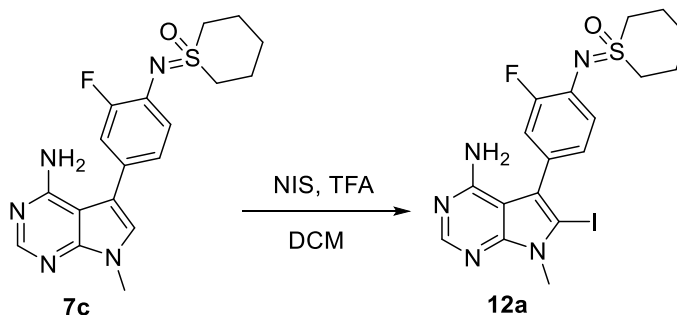
Intermediate 9e *N*-(4-(4-amino-5-bromo-7-methyl-7*H*-pyrrolo [2,3-*d*] pyrimidin -6-yl) phenyl) methacrylamide



Intermediate **9e** was synthesized with reference to intermediate **8e**. MS (ESI) m/z 386.32 $[M+H]^+$.

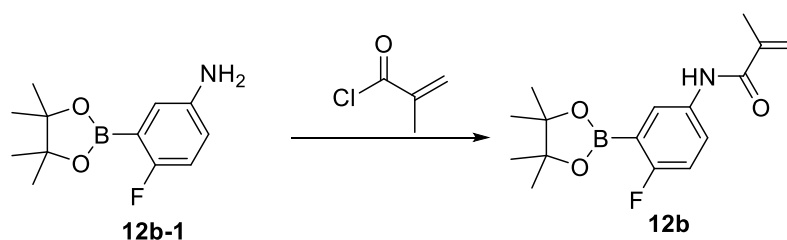
^1H NMR (400 MHz, $CDCl_3$) δ 8.32 (s, 1H), 7.77 – 7.71 (m, 2H), 7.62 (s, 1H), 7.48 – 7.41 (m, 2H), 5.90 – 5.82 (m, 1H), 5.63 (s, 2H), 5.53 (q, J = 1.6 Hz, 1H), 3.67 (s, 3H), 2.10 (dd, J = 1.6, 0.9 Hz, 3H).

Intermediate 12a 1-(4-(4-amino-6-iodo-7-methyl-7H-pyrrolo [2,3-*d*] pyrimidin -5-yl) -2-fluorophenyl) imino) hexahydro-1 λ^6 -thiopyran-1-oxide



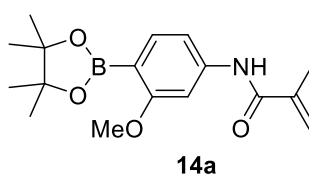
Intermediate **12a** was synthesized with reference to intermediate **84b**, MS (ESI) m/z 500 $[M+H]^+$.

Intermediate 12b *N*-(4-fluoro-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) phenyl) methacrylamide



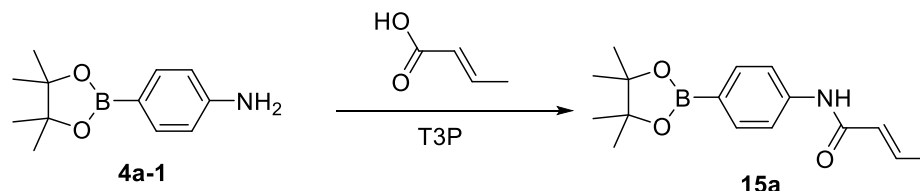
Intermediate **12b** was synthesized with reference to compound **4a**, MS (ESI) m/z 306 $[M+H]^+$.

Intermediate 14a *N*-(3-methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) phenyl) methacrylamide



Intermediate **14a** was synthesized with reference to WO2020231990A1.

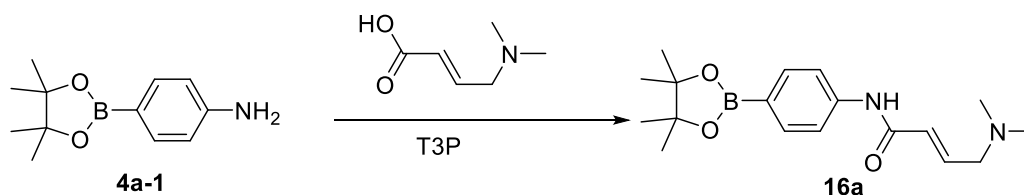
Intermediate 15a (E)-N-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)but -2-enamide



Intermediate **15a** was synthesized with reference to compound **21a**, MS (ESI) m/z 289 $[M+H]^+$.

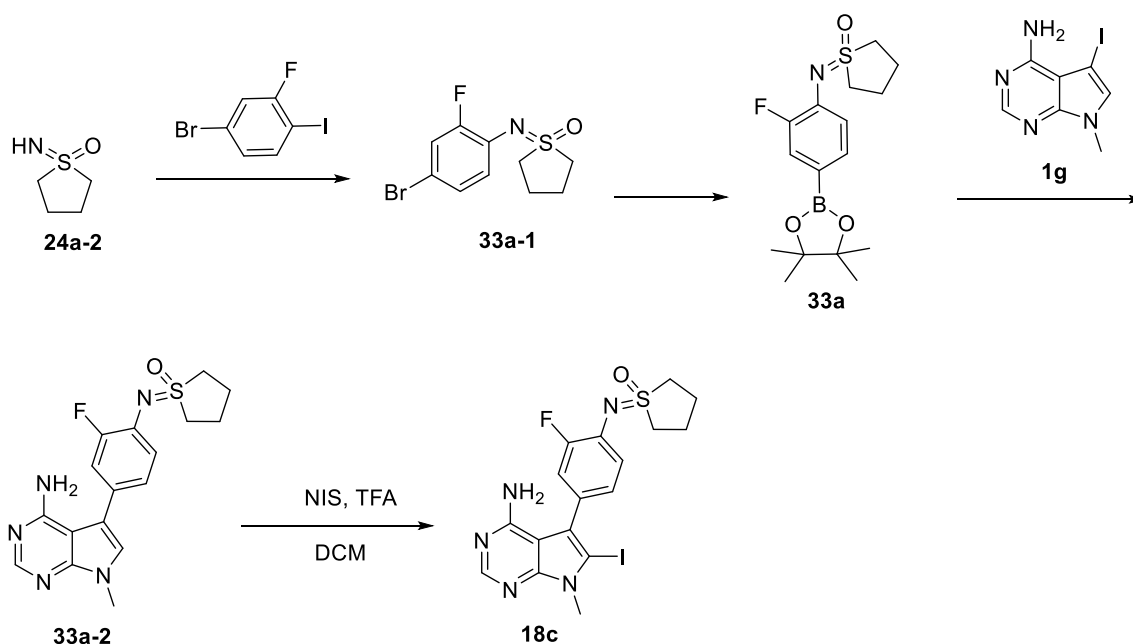
^1H NMR (400 MHz, CDCl_3) δ 7.80 – 7.73 (m, 2H), 7.57 (d, J = 8.1 Hz, 2H), 7.28 (s, 1H), 6.99 (dq, J = 15.2, 6.9 Hz, 1H), 5.94 (dq, J = 15.0, 1.7 Hz, 1H), 1.90 (dd, J = 6.9, 1.7 Hz, 3H), 1.33 (s, 12H).

Intermediate 16a (E)-4-(dimethylamino)-N-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)but-2-enamide



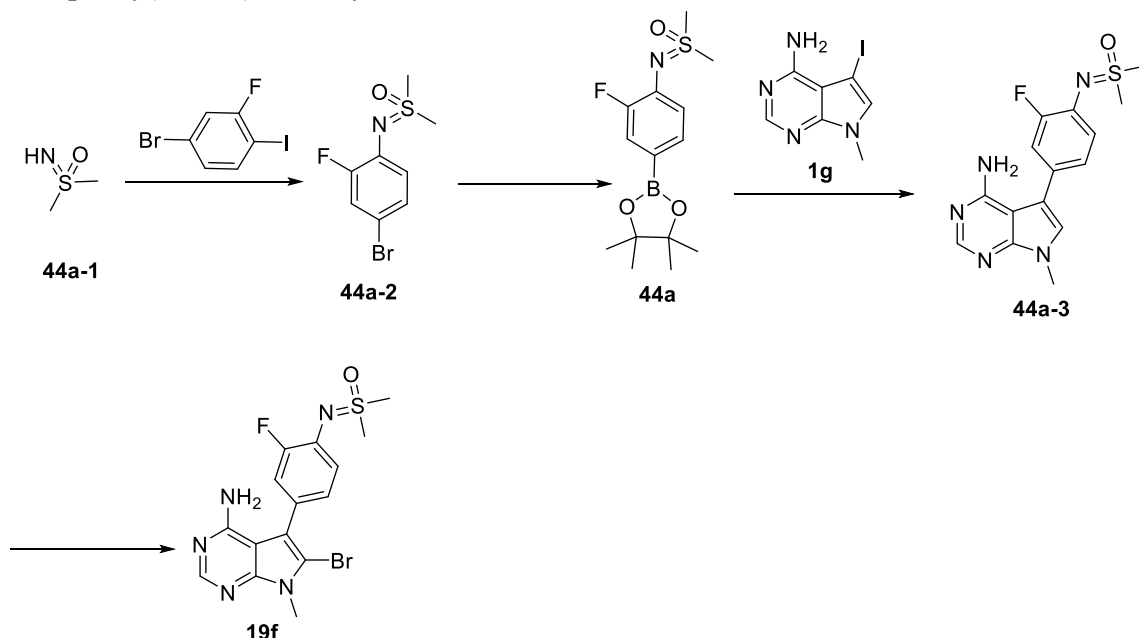
Intermediate **16a** was synthesized with reference to compound **21a**, MS (ESI) m/z 331 $[M+H]^+$.

Intermediate 18c 1-((4-(4-amino-6-iodo-7-methyl-7H-pyrrolo [2,3-d] pyrimidin -5-yl)-2-fluorophenyl) imino) tetrahydro-1H-1 λ^6 -thiophene-1-oxide



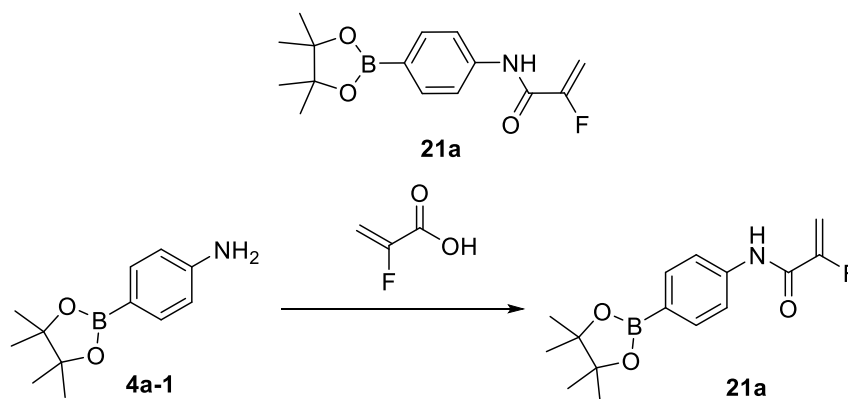
Intermediate **18c** was synthesized with reference to intermediate **77d**, MS (ESI) m/z 486 $[M+H]^+$.

5 **Intermediate 19f** ((4-(4-amino-6-bromo-7-methyl-7H-pyrrolo [2,3-*d*] pyrimidin -5-yl)-2-fluorophenyl) imino) dimethyl - λ^6 -sulfone



Intermediate **19f** was synthesized with reference to compound **5d**, MS (ESI) m/z 413 $[M+H]^+$.

10 **Intermediate 21a** 2-fluoro-*N*-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) phenyl) acrylamide



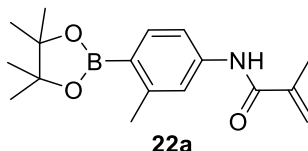
15 Compound **4a-1** (500 mg, 2.28 mmol), 2-fluoroacrylic acid (246.6 mg, 2.74 mmol), and triethylamine (1.38 g, 13.68 mmol) were dissolved in DMF (20 mL), and T3P (1.09 g, 3.42 mmol) was added dropwise at 0 °C to react overnight. After the reaction was completed, H₂O (100 mL) was added and extracted with ethyl acetate (50 mL $\times$ 3) three times. The organic layers were combined, washed with saturated saline solution, the organic layer was dried over anhydrous sodium sulfate, concentrated under reduced pressure, and purified by column chromatography (PE/EA=3/1) to obtain compound **21a** (480 mg), yellow solid.

20

MS (ESI) m/z 292.1 $[M+H]^+$.

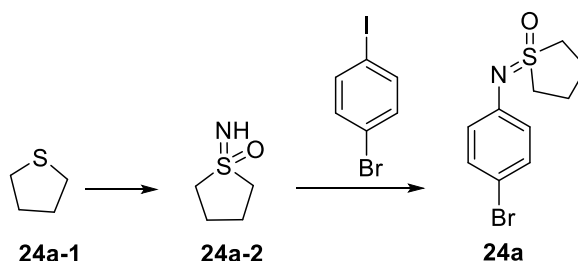
^1H NMR (400 MHz, CDCl_3) δ 7.97 (s, 1H), 7.81 (d, $J = 8.5$ Hz, 2H), 7.61 (d, $J = 8.5$ Hz, 2H), 5.83 (dd, $J = 47.9, 3.4$ Hz, 1H), 5.26 (dd, $J = 15.3, 3.4$ Hz, 1H), 1.34 (s, 12H).

5 **Intermediate 22a** *N*-(3-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) phenyl) methacrylamide



Intermediate **22a** was synthesized with reference to WO2022109577 A1.

10 **Intermediate 24a** 1-((4-bromophenyl)imino)tetrahydro-1*H*-1 λ^6 -thiophene-1-oxide



Step 1: 1-iminotetrahydro-1*H*-1 λ^6 -thiophene-1-oxide 24a-2

At room temperature, tetrahydrothiophene (1 g, 11.34 mmol) and ammonium carbamate (1.33 g, 17.01 mmol) were added to a round bottom flask and dissolved in methanol (10 mL). It was cooled to 0 °C in an ice water mixture, and iodobenzene diethyl ester (7.67 g, 23.82 mmol) was added in batches. After the addition was completed, the temperature was raised up slowly to room temperature, and the reaction was stirred for 16 h. After the reaction was completed, the mixture was concentrated under reduced pressure to obtain a crude product. The crude product was filtered under reduced pressure, the filtrate was diluted with water (3 mL), and then sodium bicarbonate solid was added slowly to the diluted filtrate to adjust the pH to 7. The mixture was filtered under reduced pressure, and the filtrate was concentrated under reduced pressure to obtain a crude product. The crude product was purified by column chromatography (DCM/MeOH=20/1) to obtain compound **24a-2** (0.7 g), orange yellow oil.

MS (ESI) m/z 120 $[M + H]^+$.

^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 3.00-2.92 (m, 4H), 2.14-2.01 (m, 4H).

Step 2 1-((4-bromophenyl) imino) tetrahydro-1*H*-1 λ^6 -thiophene-1-oxide 24a

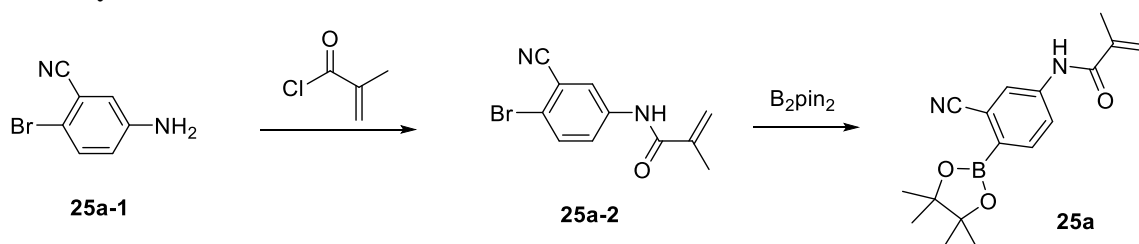
At room temperature, compound **24a-2** (3 g, 25.2 mmol), p-bromoiodobenzene (7.83 g, 27.72 mmol), tris (dibenzylideneacetone) dipalladium (0.46 g, 0.5 mmol), 4,5- bisdiphenyl phosphine-9,9-dimethylxanthene (0.875 g, 1.51 mmol), cesium carbonate (9.86 g, 30.24 mmol), and 1,4-dioxane (30 mL) were sequentially added to a round bottom flask, followed by vacuum pumping and nitrogen gas purging three times, then heated up to 100 °C and stirred for 16 h. After the reaction was completed, the mixture was cooled down to room temperature and filtered under

reduced pressure. The filter cake was washed with dichloromethane three times, and all filtrates were combined and concentrated under reduced pressure to obtain a crude product. The crude product was purified by column chromatography (PE/EtOAc=4/1) to obtain compound **24a** (5.3 g), yellow solid.

MS (ESI) m/z 273 $[M + H]^+$.

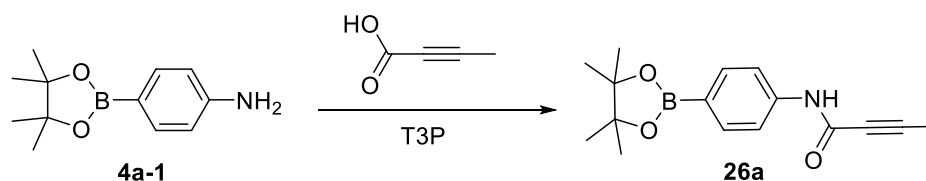
^1H NMR (400 MHz, DMSO- d_6) δ 7.35 (d, $J=8.0$ Hz, 2H), 6.87 (d, $J=8.0$ Hz, 2H), 3.33-3.17 (m, 4H), 2.14-2.04 (m, 4H).

Intermediate 25a N-(3-cyano-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) phenyl) methacrylamide



Intermediate **25a** was synthesized with reference to compound **1j**, MS (ESI) m/z 313 $[M+H]^+$.

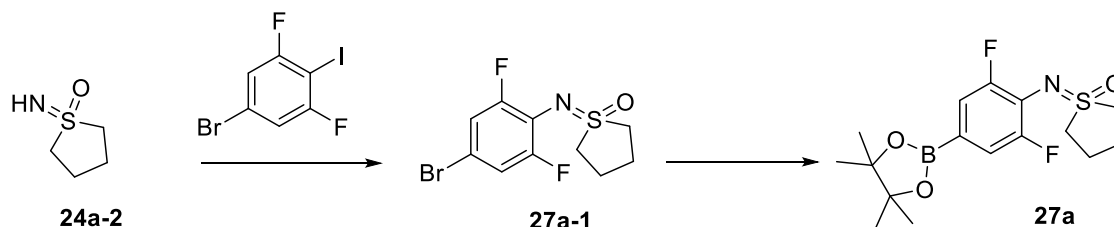
Intermediate 16a N-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)but-2-ynamide



Intermediate **26a** was synthesized with reference to compound **1a**, MS (ESI) m/z 286 $[M+H]^+$.

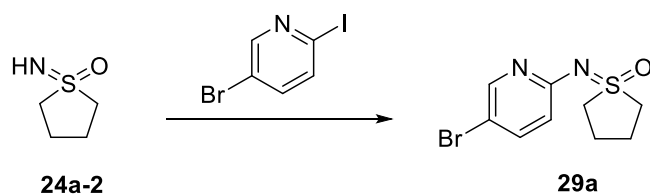
20

Intermediate 27a 1-((2,6-difluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) phenyl) imino) tetrahydro-1H-1 λ^6 -thiophene-1-oxide



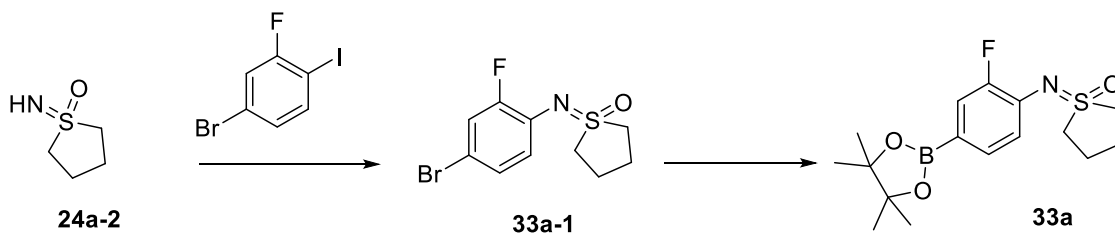
Intermediate **27a** was synthesized with reference to compound **1f**, MS (ESI) m/z 358 $[M + H]^+$.

Intermediate 29a 1- ((5-bromopyridin-2-yl) imino) tetrahydro-1H-1 λ^6 -thiophene -1-oxide



Intermediate **29a** was synthesized with reference to compound **1d**, MS (ESI) m/z 276 $[M + H]^+$.

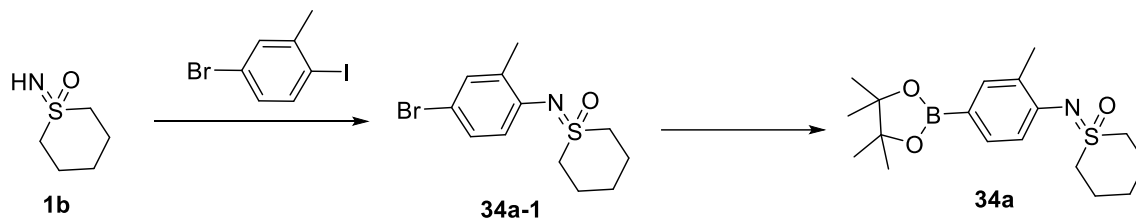
5 **Intermediate 33a 1-((2-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) phenyl) imino) tetrahydro-1*H*-1 λ^6 -thiophene-1-oxide**



Intermediate **33a** was synthesized with reference to compound **1f**, MS (ESI) m/z 340 $[M + H]^+$

10

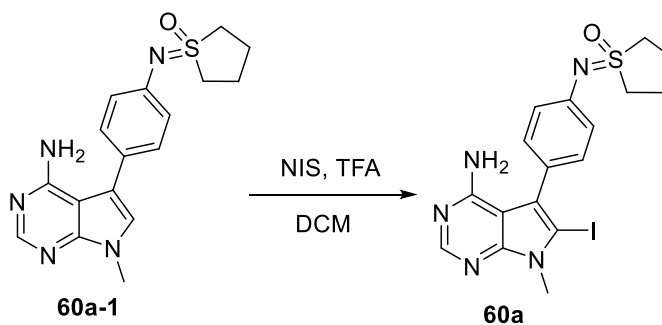
Intermediate 34a 1-((2-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) phenyl) imino) hexahydro-1 λ^6 -thiopyran-1-oxide



Intermediate **34a** was synthesized with reference to compound **1f**, MS (ESI) m/z 350 $[M + H]^+$.

15

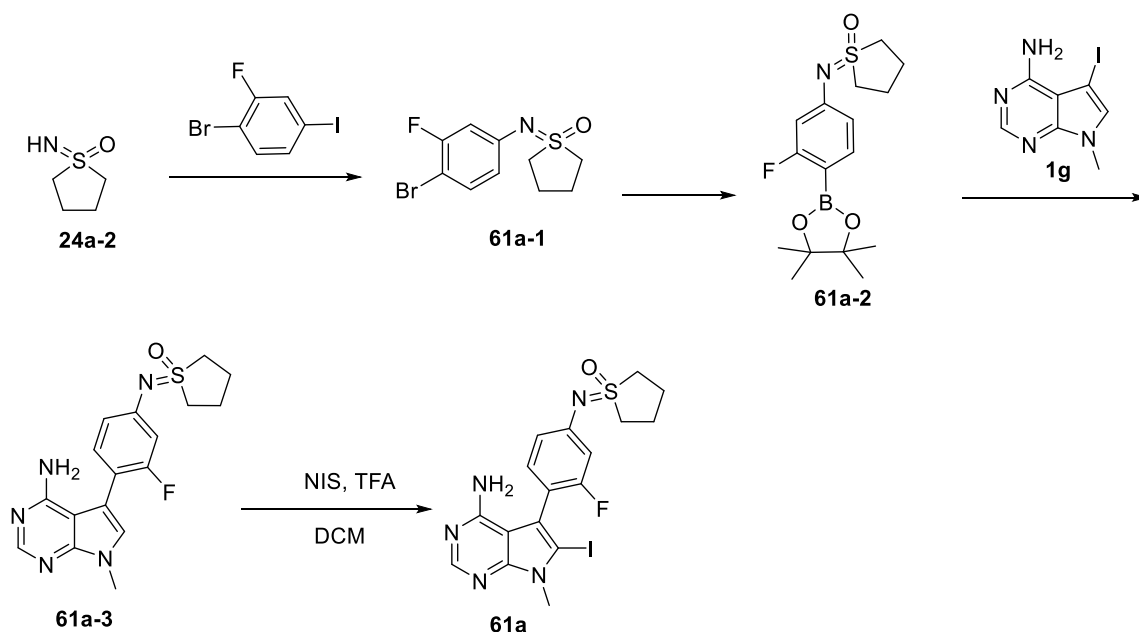
Intermediate 60d 1-(4-(4-amino-6-iodo-7-methyl-7*H*-pyrrolo [2,3-*d*] pyrimidin-5- yl) phenyl) imino) tetrahydro-1*H*-1 λ^6 -thiophene-1-oxide



Intermediate **60a** was synthesized with reference to intermediate **84b**, MS (ESI) m/z 468 $[M+H]^+$.

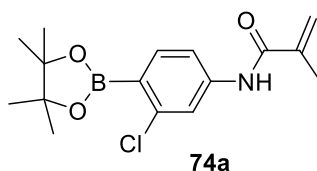
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Intermediate 61a 1-(4-(4-amino-6-iodo-7-methyl-7*H*-pyrrolo [2,3-*d*] pyrimidin-5-yl)-3-fluorophenyl) imino) tetrahydro-1*H*-1λ-thiophene-1-oxide



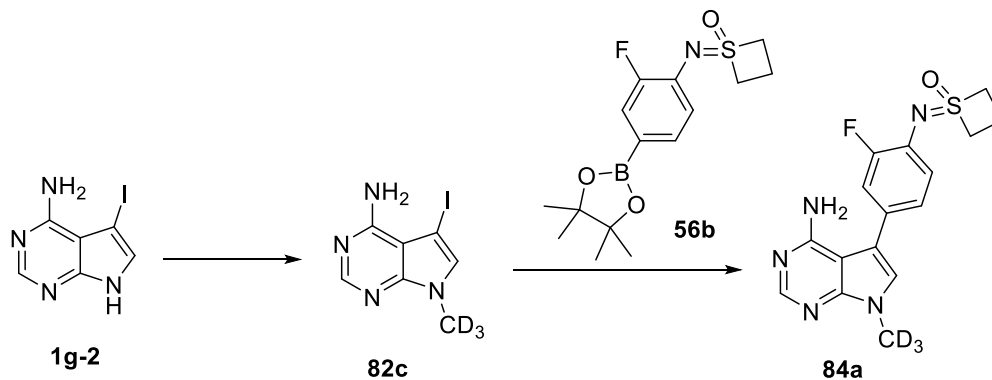
Intermediate **61a** was synthesized with reference to intermediate **77d**, MS (ESI) m/z 486 [M+H]⁺.

Intermediate 74a *N*-(3-chloro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) phenyl) methacrylamide



Intermediate **74a** was synthesized with reference to WO2023046117 A1.

Intermediate 84a 1-((4-(4-amino-7-(methyl-*d*₃)-7*H*-pyrrolo [2,3-*d*] pyrimidin-5-yl) -2-fluorophenyl) imino)-1 λ⁶-thiophene-1-oxide



Step 1 5-iodo-7-(methyl-*d*₃) -7*H*-pyrrole [2,3-*d*] pyrimidin-4-amine **82c**

Compound **1g-2** (10.0 g, 38.5 mmol) was dissolved in N,N-dimethylformamide (50 mL), cesium carbonate (18.8 g, 57.8 mmol) was added at room temperature, then cooled down to 0 °C, deuterated iodomethane (6.70 g, 46.1 mmol) was added to react at room temperature for 1 h. After the reaction was completed, it was extracted with dichloromethane (100 mL × 3), and the organic phases were combined and concentrated under reduced pressure to obtain a crude product. To the crude product was added water (100 mL × 3), a brown solid was precipitated. The brown solid was collected by filtration to obtain compound **82c** (5.80 g), brown solid.

MS (ESI) m/z 277.70 $[M + H]^+$.

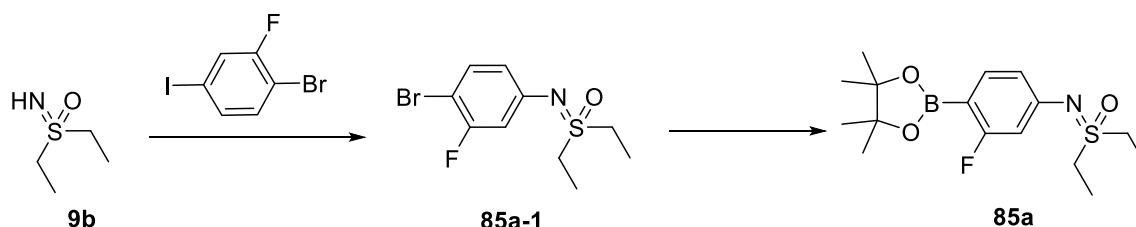
^1H NMR (400 MHz, DMSO) δ 8.10(s, 1H), 7.45 (s, 1H), 6.85 - 6.35 (m, 2H).

Step 2 1- ((4-(4-amino-7-(methyl- d_3) -7H-pyrrolo [2,3- d] pyrimidin-5-yl) -2-fluorophenyl) imino) -1 λ^6 thiophene-1-oxide **84a**

Compound **82c** (0.50 g, 1.80 mmol) was dissolved in 1,4-dioxane (10 mL) and H₂O (2 mL), compound **56b** (0.65 g, 2.00 mmol), potassium phosphate (1.15 g, 5.40 mmol), and tetrakis (triphenylphosphine) palladium (0.21 g, 0.18 mmol) were added, and reacted at 90 °C for 14 h under N₂ protection. After TLC monitored the completion of the reaction, it was extracted with ethyl acetate (50 mL × 3), and the organic phases were combined and concentrated under reduced pressure to obtain a crude product. The crude product was purified by column chromatography (DCM/MeOH=10/1) to obtain compound **84a** (420 mg).

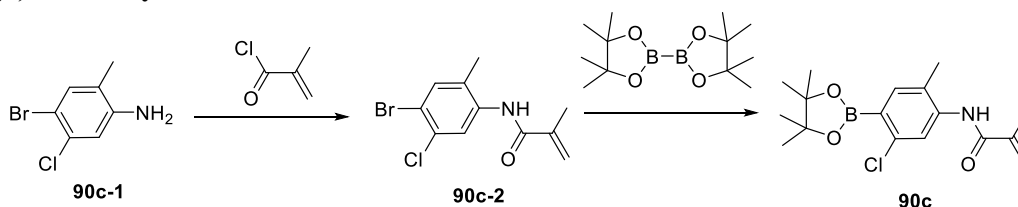
MS (ESI) m/z 349.10 $[M + H]^+$.

Intermediate 85a diethyl ((3-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) phenyl) imino) - λ^6 -sulfone



Intermediate **85a** was synthesized with reference to compound **1f**, MS (ESI) m/z 342 $[M+H]^+$.

Intermediate 90c N-(5-chloro-2-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) phenyl) methacrylamide



Step 1: N-(4-bromo-5-chloro-2-methylphenyl) methacrylamide 90c-2

The **90c-1** (500 mg, 2.27 mmol) and Et₃N (459 mg, 4.54 mmol) were dissolved in DCM (5 mL), methacryloyl chloride (357 mg, 3.41 mmol) was added to the reaction solution at 0 °C to react for 1 h at 0 °C, then concentrated under reduced pressure, extracted with added H₂O (20 mL)

and dichloromethane, the organic phase was washed with saturated saline solution, dried over anhydrous sodium sulfate, concentrated under reduced pressure, and purified by column chromatography to obtain compound **90c-2** (509 mg, 2.27), white solid.

MS (ESI) m/z 288 $[M+H]^+$

5

Step 2: *N*-(5-chloro-2-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) phenyl) methacrylamide **90c**

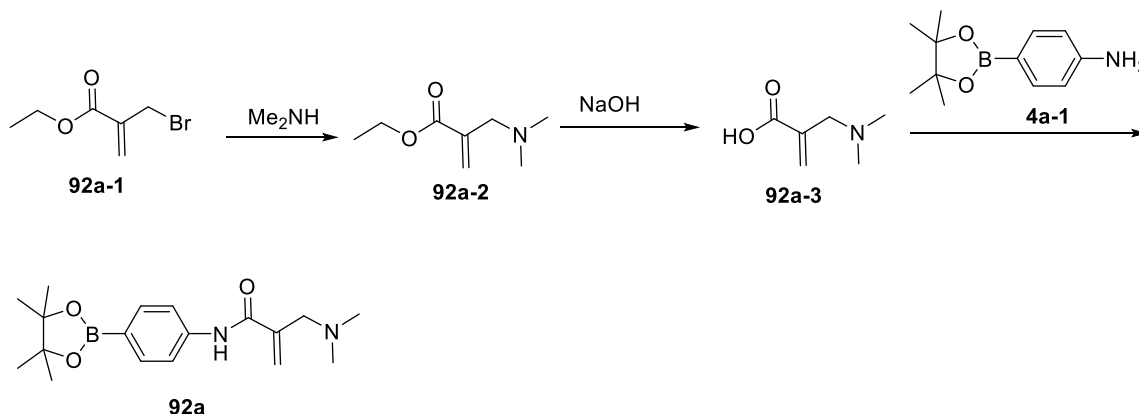
Compound **90c-2** (457 mg, 1.29 mmol), anhydrous 1,4-dioxane (6 mL), bis(pinacolato)diboron (606 mg, 2.39 mmol), potassium acetate (468 mg, 4.77 mmol), and Pd(dppf)Cl₂ (115 mg, 0.16 mmol) were added to the reaction flask in sequence, after replaced with nitrogen three times, heated up to 90 °C to react for 4 h. TLC showed the formation of new dots. After the reaction was completed, the reaction solution was cooled down to room temperature, diluted with EA and H₂O, filtered through diatomaceous earth, extracted with ethyl acetate, and the organic phase was washed with saturated saline solution, dried over anhydrous sodium sulfate, concentrated under reduced pressure, and purified by column chromatography (PE/EA=1/1) to obtain compound **90c** (350 mg), light yellow oil.

15

MS (ESI) m/z 336 $[M+H]^+$

Intermediate **92a 2-((dimethylamino)methyl)-*N*-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) phenyl) acrylamide**

20



Step 1 2-((dimethylamino) methyl) ethyl acrylate **92a-2**

Compound **92a** (5 g, 26.04 mmol) was dissolved in tetrahydrofuran (20 mL) at room temperature. After it was cooled down to 0 °C, the dimethylamine (1.40 g, 31.2 mmol) dissolved in tetrahydrofuran (10 mL) was added slowly dropwise to the above solution to react at room temperature for 6 h. After TLC monitored the completion of the reaction, the mixture was filtered through a Buchner funnel, and the filtrate was collected and concentrated under reduced pressure to obtain crude product compound **92a-2** (2 g), yellow oily liquid.

25

MS (ESI) m/z 158 $[M + H]^+$.

30

Step 2 2-((dimethylamino) methyl) acrylic acid **92a-3**

At room temperature, compound **92a-2** (2 g, 12.7 mmol) was dissolved in tetrahydrofuran (5 mL) and water (5 mL), and lithium hydroxide (365.76 mg, 15.24 mmol) was added in batches. The reaction was stirred at room temperature for additional 4 h. After TLC monitored the

completion of the reaction, the mixture was concentrated under reduced pressure to obtain crude product compound **92a-3** (1.2 g), yellow solid.

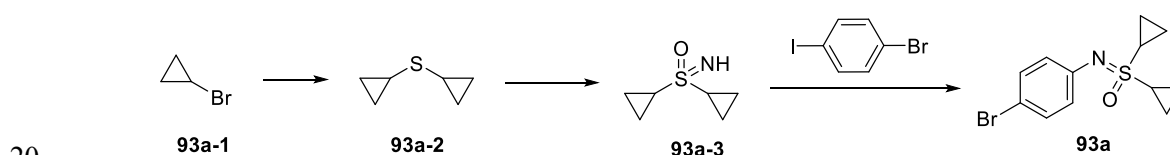
MS (ESI) m/z 130 $[M + H]^+$.

5 **Step 3 2-(dimethylamino)methyl)-N-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) phenyl) acrylamide 92a**

At room temperature, compound **92a-3** (500 mg, 3.88 mmol) and 4-aminophenylboronic acid pinacol ester (679.34 mg, 3.10 mmol) were dissolved in dichloromethane (5 ml), and triethylamine (1.18 g, 11.64 mmol) was added. After it was cooled down to 0 °C, a solution of 1-propylphosphonic anhydride in 50% ethyl acetate (1.85 g, 5.82 mmol) was added slowly dropwise to react at room temperature for 4 h. The reaction solution was diluted with water, extracted with dichloromethane (5 mL $\times$ 3), washed with saturated saline solution (10 mL), and the organic phases were combined, dried over anhydrous sodium sulfate, and concentrated under reduced pressure to obtain a crude product. The crude product was purified by column chromatography (DCM/MeOH=15/1) to obtain compound **92a** (130 mg), light yellow solid.

MS (ESI) m/z 331 $[M + H]^+$.

Intermediate 93a ((4-bromophenyl) imino) dicyclopropyl- λ^6 - sulfone



Step 1 dicyclopropyl sulfide 93a-2

Compound **93a-1** (2.0 g, 16.7 mmol) was dissolved in DMF (5 mL), Na₂S (640 mg, 8.2 mmol) was added to react in a sealed tube at 100 °C for 16 h. After the reaction was completed, 30mL of ethyl acetate was added, and the organic phase was washed with saline solution (10 mL $\times$ 3), concentrated under reduced pressure to obtain a brown crude product **93a-2**, which was directly used in the next step.

Step 2 dicyclopropyl sulfoximine 93a-3

The crude product **93a-2** from the previous step was dissolved in methanol (15 mL), NH₄CO₂NH₂ (1.3 g, 16.7 mmol) and PhI(OAc)₂ (6.7 g, 20.8 mmol) was added in sequence. The reaction solution was left to react at room temperature for 16 h. After TLC monitored the completion of the reaction, it was cooled down to room temperature, the spun-dried crude product was purified by column chromatography (DCM/MeOH=10/1) to obtain compound **93a-3** (264 mg), brown oily substance.

MS (ESI) m/z 146.1 $[M + H]^+$.

¹H NMR (400 MHz, CDCl₃) δ 2.54 (m, 2 H), 1.20 (m, 4 H), 1.02 (m, 4 H).

Step 3 ((4-bromophenyl) imino) dicyclopropyl - λ^6 -sulfone 93a

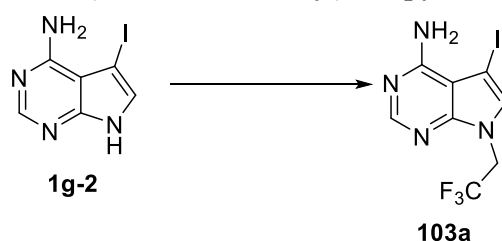
Compound **93a-3** (264.0 mg, 1.82 mmol) was dissolved in 1,4-dioxane (5 mL), p-bromoiodobenzene (566 mg, 2.0 mmol), Pd₂(dba)₃ (50 mg, 0.05 mmol), xantphos (60 mg, 0.10

mmol), and cesium carbonate (1180 mg, 3.64 mmol) were added at room temperature. The reaction was heated up to 90 °C to react for 4 h, after TLC monitored the completion of the reaction, it was cooled down to room temperature, ethyl acetate (30 mL) and saturated sodium bicarbonate solution (10 mL) was added, and it was extracted with ethyl acetate (20 mL × 3), and the organic phases were combined, washed with saturated saline solution (50 mL), concentrated under reduced pressure to obtain a crude product, and the crude product was purified by column chromatography (PE/EtOAc=3/1) to obtain compound **93a** (60 mg).

MS (ESI) m/z 300.0 $[M + H]^+$.

¹H NMR (400 MHz, CDCl₃) δ 7.30-7.25 (m, 2H), 6.97 - 6.92 (m, 2H), 2.54-2.44 (m, 2H), 1.38-1.24 (m, 4H), 1.09 – 0.95 (m, 4H).

Intermediate 103a 5-iodo-7-(2,2,2-trifluoroethyl)-7H-pyrrolo [2,3-*d*] pyrimidin -4-amine

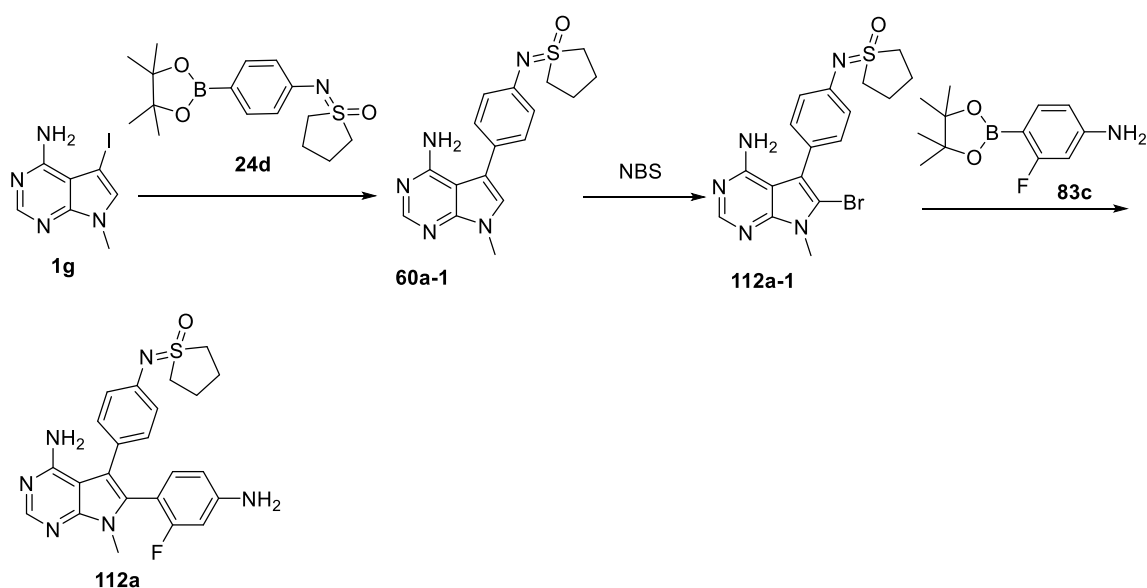


Compound **1g-2** (1.0 g, 3.85 mmol), 2,2,2-trifluoroethyl trifluoromethane sulfonate (1.34 g, 5.78 mmol), and cesium carbonate (2.5 g, 7.7 mmol) was dissolved in DMF (10 mL) to react at room temperature for 3 h, and it was concentrated under reduced pressure to remove the solvent, extracted with H₂O (100 mL) and DCM three times, the organic layers were combined, washed with saturated sodium chloride once, dried over anhydrous sodium sulfate, concentrated under reduced pressure, and purified by column chromatography (PE/EA=1/2) to obtain compound **103a** (850 mg), white solid.

MS (ESI) m/z 343.1 $[M + H]^+$.

¹H NMR (400 MHz, DMSO-*d*₆) δ 8.16 (s, 1H), 7.50 (s, 1H), 6.79 (s, 2H), 5.03 (q, J = 9.3 Hz, 2H).

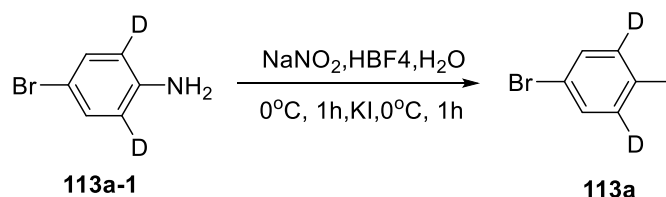
Intermediate 112a 1-(4-(4-amino-6-(4-amino-2-fluorophenyl)-7-methyl-7H-pyrrolo [2,3-*d*] pyrimidin 3-5-yl) phenyl) imino) tetrahydro-1H-1 λ^6 -thiophene-1-oxide



Compound **112a** was synthesized with reference to the similar synthetic route and steps of compound **83d**, wherein the compound **82c** was replaced with compound **1g** in first step, MS (ESI) m/z 451.2 $[M + H]^+$.

5

Intermediate **113a** 1-bromo-4-iodobenzene-3,5- d_2

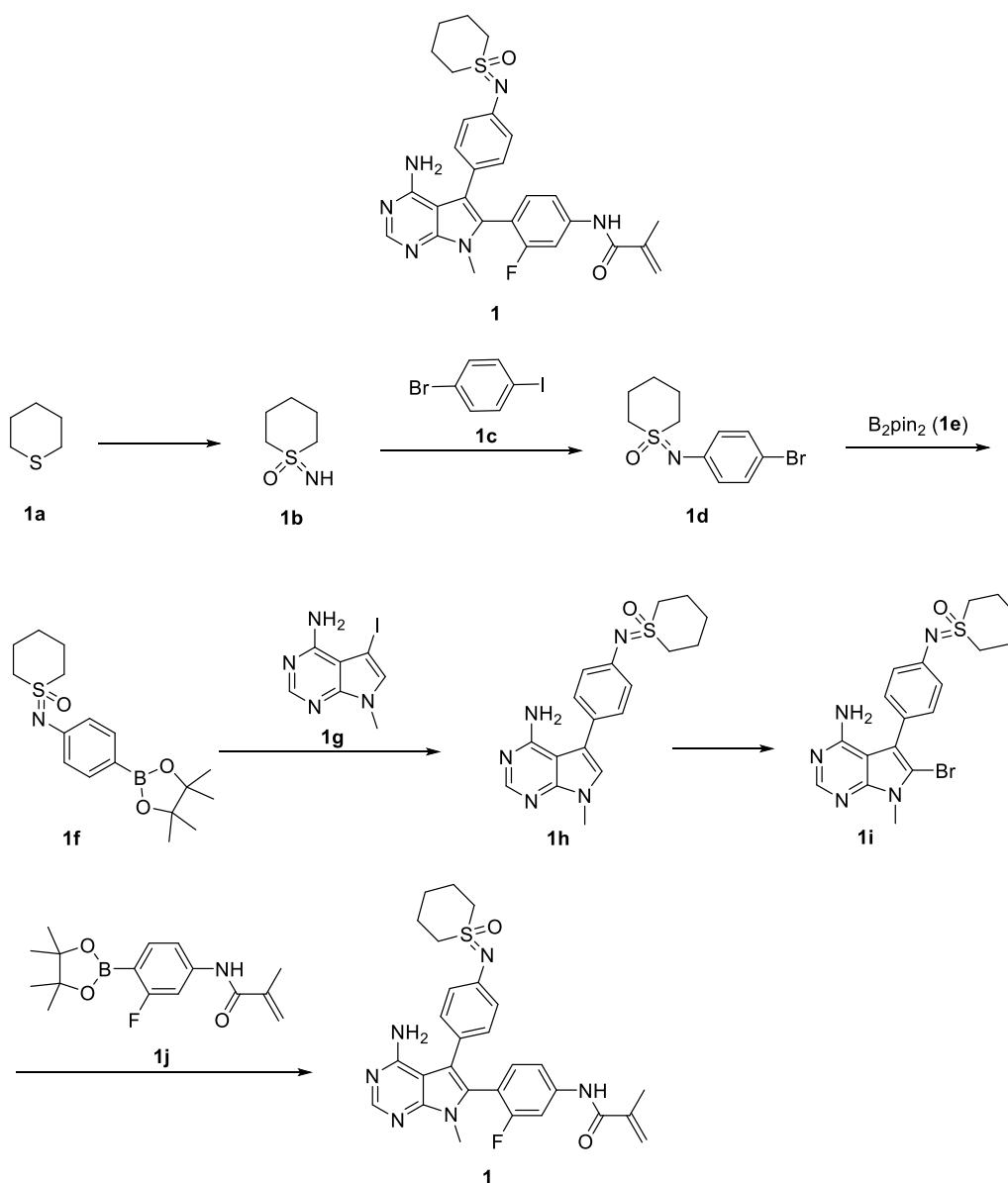


Compound **113a-1** was synthesized with reference to ACS Catalysis (2016), 6 (11), 7814-7823. Compound **113a-1** (724 mg, 4.16 mmol), H_2O (33 mL), and 40% HBF_4 (2.28 g, 913 mg, 10.40 mmol) were added into the reaction flask in sequence, and it was cooled in an ice salt water bath for 10 min. NaNO_2 (344 mg, 4.99 mmol)- H_2O (5.7 mmol) solution was added in the ice salt water bath to react in the ice salt water bath for 1 h. NaI (1.24 g, 8.24 mmol)- H_2O (5.8 mmol) solution was added slowly to the above reaction solution to react in the ice salt water bath for additional 1 h. Then saturated NaHSO_3 aqueous solution (20 mL) was added and stirred for additional 10 min, and H_2O and EA were added for extraction, the organic phase was washed with saturated saline solution, dried over anhydrous sodium sulfate, concentrated under reduced pressure, and purified by column chromatography to obtain compound **113a** (225 mg), yellow solid.

MS (GC) m/z 284.1 $[M]^+$

20

Example 1 *N*-(4-(4-amino-7-methyl-5-(4-(1-oxotetrahydro-2*H*-1 λ^6 -thiopyran-1- imino) phenyl) -7*H*-pyrrolo [2,3-*d*] pyrimidin-6-yl) -3-fluorophenyl) methacrylamide



Step 1 1-iminohexahydro-1 λ^6 -thiopyran-1-oxide **1b**

Tetrahydro-2H-pyran **1a** (2.00 g, 19.6 mmol) and ammonium carbamate (2.29 g, 29.4 mmol) were added into a flask in sequence, then MeOH (40 mL) and iodobenzene diethyl ester (13.24 g, 41.1 mmol) were added. The reaction solution was stirred open at room temperature for 30 min, and then it was concentrated under reduced pressure to remove the solvent to obtain a crude product. The crude product was purified by column chromatography (MeOH/DCM=1/80) to obtain compound **1b** (1.62 g), white solid.

MS (ESI) m/z 134 $[M + H]^+$.

Step 2 1-((4-bromophenyl) imino) hexahydro-1 λ^6 -thiopyran-1-oxide **1d**

Compound **1b** (282 mg, 2.12 mmol), cesium carbonate (806 mg, 2.47 mmol), 1-bromo-4-iodobenzene **1c** (500 mg, 1.77 mmol), $Pd_2(dba)_3$ (40 mg, 0.05 mmol), and Xantphos (77 mg, 0.13 mmol) were added to 1,4-dioxane (10 mL), and the reaction solution was heated up

to 105 °C for 13 h. The reaction solution was filtered through diatomaceous earth, the filter cake was washed with ethyl acetate (50 mL), and saturated saline solution (50 mL) was used for washing. The organic phase was dried over anhydrous sodium sulfate and concentrated under reduced pressure to obtain a crude product. The crude product was purified by column chromatography (PE/EtOAc=4/1 to 1/1) to obtain compound **1d** (410 mg), yellow oily liquid.

MS (ESI) m/z 288 $[M + H]^+$.

Step 3 1-(4-(4,4,5,5-methyl-1,3,2-dioxaborolan-2-yl)phenyl)imino)hexahydro-1 λ^6 -thiopyran-1-oxide **1f**

Compound **1d** (350 mg, 1.22 mmol), bis(pinacolato)diboron **1e** (372 mg, 1.46 mmol), Pd(dppf)Cl₂ (179 mg, 0.24 mmol), potassium acetate (359 mg, 3.66 mmol), and 1,4-dioxane (10 mL) was added into a sealed tube, after replaced with argon gas three times, sealed, and the reaction solution was heated up to 90 °C and stirred for 12 h. Water (10 mL) was added, and it was extracted with DCM (20 mL $\times$ 3). The organic phase was washed with saturated saline solution (20 mL), dried over anhydrous sodium sulfate, and concentrated under reduced pressure to obtain a crude product. The crude product was purified by column chromatography (PE/EtOAc=4/1) to obtain compound **1f** (356 mg), yellow solid.

MS (ESI) m/z 336 $[M + H]^+$.

Step 4 1-(4-(4-amino-7-methyl-7*H*-pyrrolo [2,3-*d*] pyrimidin-5-yl)phenyl)imino)hexahydro-1 λ^6 -thiopyran-1-oxide **1h**

Compound **1f** (302 mg, 0.9 mmol), 5-iodo-7-methyl-7*H*-pyrrolo [2,3-*d*] pyrimidin-4-amine **1g** (206 mg, 0.75 mmol), Pd(PPh₃)₄ (66 mg, 0.075 mmol), and K₃PO₄ (302 mg, 1.88 mmol) were added into a sealed tube, after replaced with argon gas three times, and 1,4-dioxane (5 mL) and H₂O (0.5 mL) were added. The reaction solution was heated up to 90 °C and stirred for 5 h. Then water (30 mL) was added, and extracted with DCM (60 mL $\times$ 3). The organic phase was washed with saturated saline solution (50 mL), dried over anhydrous sodium sulfate, and concentrated under reduced pressure to obtain a crude product. The crude product was purified by column chromatography (MeOH/DCM=1/50) to obtain compound **1h** (184 mg), light yellow solid.

MS (ESI) m/z 356 $[M + H]^+$.

¹H NMR (500 MHz, CDCl₃) δ 8.31 (s, 1H), 7.33-7.29 (m, 2H), 7.21-7.17 (m, 2H), 6.91 (s, 1H), 5.50 (s, 2H), 3.83 (s, 3H), 3.43-3.35 (m, 2H), 3.14 (ddd, J =13.9, 8.9, 5.0 Hz, 2H), 2.15-2.04 (m, 4H), 1.78 (ddd, J =12.3, 6.5, 3.8 Hz, 1H), 1.62 (dt, J =13.6, 9.0, 4.6 Hz, 1H).

Step 5 1-(4-(4-amino-6-bromo-7-methyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl) phenyl) imino) hexahydro-1 λ^6 -thiopyran-1-oxide **1i**

Compound **1h** (150 mg, 0.42 mmol) was dissolved in DMF (3 mL), NBS (83 mg, 0.46 mmol) was added at 0 °C, and the reaction solution was stirred at 0 °C for 1 h. Then DCM (30 mL) was added, and washed with saturated saline solution (10 mL $\times$ 3), the organic phase was dried over anhydrous sodium sulfate, and concentrated under reduced pressure to obtain a crude product. The crude product was purified by column chromatography (MeOH/DCM=1/50) to obtain compound **1i** (99 mg), white solid.

MS (ESI) m/z 434 $[M + H]^+$.

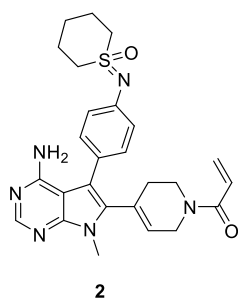
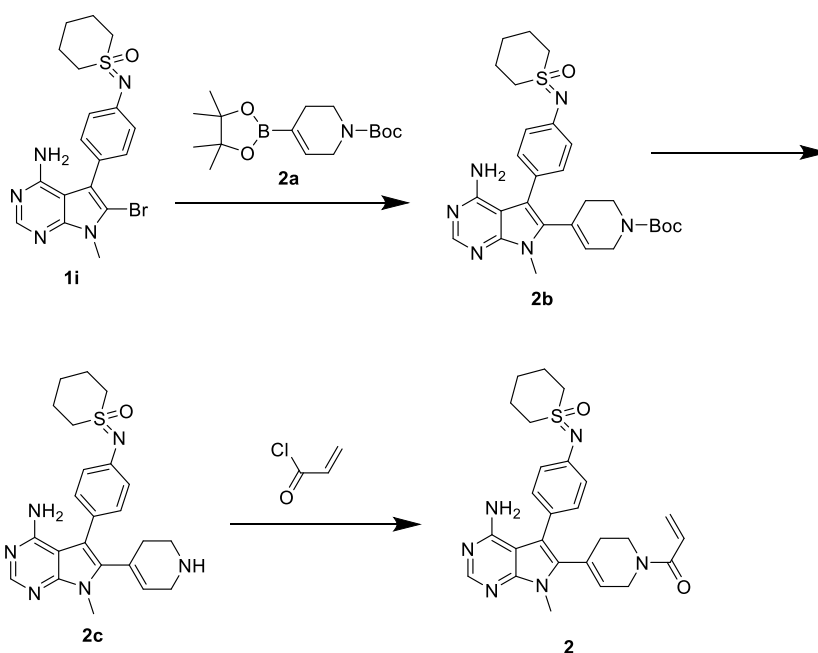
Step 6 *N*-(4-(4-amino-7-methyl-5-(4-(1-oxotetrahydro-2*H*-1 λ^6 -thiopyran-1-imino)phenyl)-7*H*-pyrrolo [2,3-*d*] pyrimidin-6-yl) 3-fluorophenyl) methacrylamide **1**

Compound **1i** (50 mg, 0.12 mmol), *N*-(3-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) methacrylamide **1j** (42 mg, 0.14 mmol), Pd(PPh₃)₄ (28 mg, 0.024 mmol), and K₃PO₄ (76 mg, 0.36 mmol) were added into a sealed tube, after replaced with argon gas three times, and 1,4-dioxane (1 mL) and H₂O (0.2 mL) were added, sealed, and the reaction solution was heated up to 100 °C and stirred for 12 h. Then ethyl acetate (20 mL) and saturated saline solution (10 mL) were added to extract, the organic phase was dried over anhydrous sodium sulfate, and concentrated under reduced pressure to obtain a crude product. The crude product was purified by column chromatography (MeOH/DCM=1/40) to obtain compound **1** (24 mg), light yellow solid.

MS (ESI) *m/z* 356 [M + H]⁺.

¹H NMR (500 MHz, CDCl₃) δ 8.30 (s, 1H), 7.95 (s, 1H), 7.71 (dd, *J*=11.6, 2.1 Hz, 1H), 7.12-6.97 (m, 6H), 5.79 (s, 1H), 5.47 (s, 1H), 5.37 (s, 2H), 3.63 (s, 3H), 3.31 (dt, *J*=11.7, 5.0 Hz, 2H), 3.15-3.07 (m, 2H), 2.10-2.03 (*m*, 4H), 2.03 (s, 3H), 1.72 (dp, *J*=15.2, 5.2 Hz, 1H), 1.60 (ddt, *J*=15.2, 11.9, 5.6 Hz, 1H).

Example 2 1- (4-(4-amino-7-methyl-5-(4-(1-oxotetrahydro-2*H*-1 λ^6 -thiopyran-1-imino)phenyl)-7*H*-pyrrolo [2,3-*d*] pyrimidin-6-yl)-3,6-dihydropyridine-1(2*H*)-yl)prop-2-enyl-1-one



Step 1 4- (4-amino-7-methyl-5-(4-((1-oxotetrahydro-2*H*-1λ⁶-thiopyran-1-imino)phenyl)- 7*H*-pyrrolo [2,3-*d*] pyrimidin-6-yl) -3,6-dihydropyridine-1 (2*H*) – tert-butyl carbonate **2b**

Compound **1i** (345 mg, 0.8 mmol), compound **2a** (295.6 mg, 0.96 mmol), Pd(PPh₃)₄ (184 mg, 0.16 mmol), and potassium phosphate (509.5 mg, 2.4 mmol) were dissolved in anhydrous 1,4-dioxane (8 mL) and H₂O (2 mL), after replaced with nitrogen gas three times, the reaction was refluxed at 100 °C for 12 h. After the reaction was completed, the reaction solution was cooled down to room temperature, filtered through diatomaceous earth, concentrated under reduced pressure to remove the solvent, and it was extracted with EA/H₂O three times, the organic layers were combined, washed with saturated saline solution once, dried over anhydrous sodium sulfate, concentrated under reduced pressure, and purified by column chromatography (DCM/MeOH=40/1) to obtain compound **2b** (312 mg), yellow brown solid.

MS (ESI) *m/z* 537 [M + H]⁺.

Step 2 1- (4-(4-amino-7-methyl-6-(1,2,3,6-tetrahydropyridine-4-yl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)phenyl)imino)hexahydro-1λ⁶-thiopyran-1-oxide **2c**

Compound **2b** (310 mg, 0.58 mmol) was dissolved in dichloromethane (10 mL), trifluoroacetic acid (2 mL) was added dropwise at room temperature to react for 5 h. After the

reaction was completed, it was concentrated under reduced pressure to obtain a crude product **2c** (250 mg).

MS (ESI) m/z 437 $[M + H]^+$.

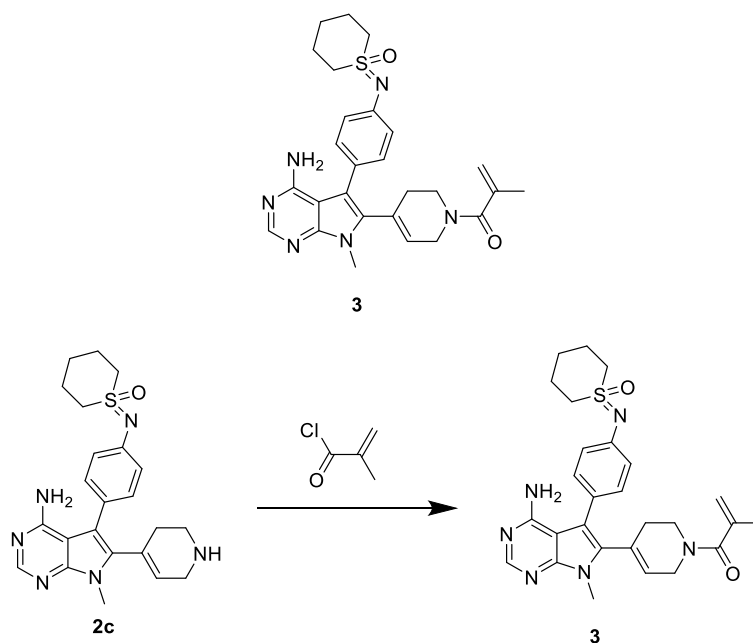
5 Step 3 1-(4-(4-amino-7-methyl-5-(4-(1-oxotetrahydro-2H-1 λ^6 -thiopyran-1-imino) phenyl)-7H-pyrrolo[2,3-*d*]pyrimidin-6-yl)-3,6-dihydropyridine-1(2H)-yl)prop-2-enyl-1-one **2**

Compound **2c** (125 mg, 0.29 mmol) was dissolved in ultra dry DCM (3 mL), TEA (232 mg, 2.29 mmol) was added at 0 °C and stirred for 5 min. A solution of acryloyl chloride (28.5 mg, 0.32 mmol) in dichloromethane (2 mL) was added slowly dropwise to the above reaction solution to react at 0 °C for 1 h. After the reaction was completed, it was extracted with DCM/H₂O three times, the organic layers were combined, washed with saturated saline solution, dried over anhydrous sodium sulfate, concentrated under reduced pressure, and purified by column chromatography (DCM/MeOH=30/1) to obtain compound **2** (103 mg), white powdery solid.

MS (ESI) m/z 491 $[M + H]^+$.

15 ¹H NMR (400 MHz, MeOD-*d*₄) δ 8.13 (s, 1H), 7.26 (dd, J =8.5, 2.9 Hz, 2H), 7.16 (dd, J =8.3, 1.3 Hz, 2H), 6.84-6.65 (m, 1H), 6.29-6.14 (m, 1H), 6.04-5.88 (m, 1H), 5.86-5.67 (m, 1H), 4.32-4.19 (m, 2H), 3.72 (s, 3H), 3.70 (t, J =5.3 Hz, 2H), 3.47-3.36 (m, 2H), 3.30-3.21 (m, 2H), 2.22-2.14 (m, 2H), 2.12-2.01 (m, 4H), 1.81-1.73 (m, 1H), 1.72-1.61 (m, 1H).

20 Example 3 1-(4-(4-amino-7-methyl-5-(4-(1-oxotetrahydro-2H-1 λ^6 -thiopyran-1-imino) phenyl)-7H-pyrrolo[2,3-*d*]pyrimidin-6-yl)-3,6-dihydropyridine-1(2H)-yl)2-methylprop-2-enyl-1-one



25 Step 1 1-(4-(4-amino-7-methyl-5-(4-(1-oxotetrahydro-2H-1 λ^6 -thiopyran-1-imino) phenyl)-7H-pyrrolo[2,3-*d*]pyrimidin-6-yl)-3,6-dihydropyridine-1(2H)-yl)2-methylprop-2-enyl-1-one

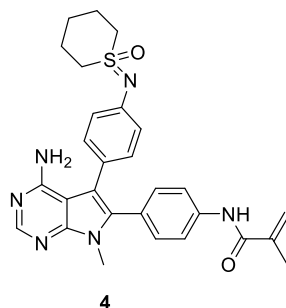
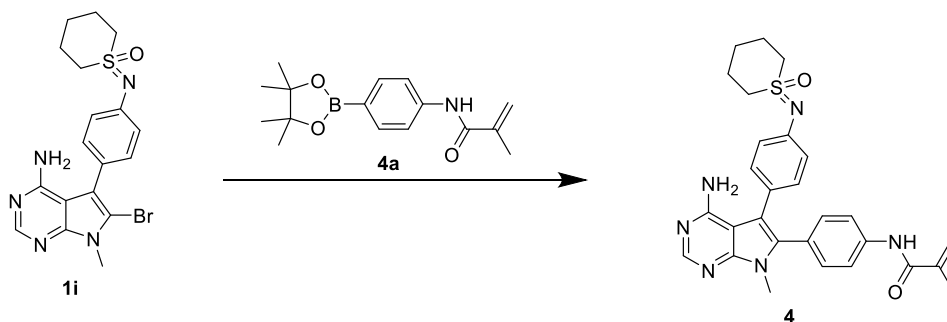
Compound **2c** (125 mg, 0.29 mmol) was dissolved in ultra dry DCM (3 mL), TEA (232 mg, 2.29 mmol) was added at 0 °C and stirred for 5 min. A solution of methacryloyl chloride (32.8 mg,

0.32 mmol) in dichloromethane (2 mL) was added dropwise to the above reaction solution to react at 0 °C for 1 h. After the reaction was completed, it was extracted with DCM/H₂O three times, the organic layers were combined, washed with saturated saline solution, dried over anhydrous sodium sulfate, concentrated under reduced pressure, and purified by column chromatography (DCM/MeOH=30/1) to obtain compound **3** (67.8 mg), white powdery solid.

MS (ESI) m/z 505 [M + H]⁺.

¹H NMR (400 MHz, MeOD-d₄) δ 8.13 (s, 1H), 7.27 (d, J =8.0 Hz, 2H), 7.16 (d, J =8.4 Hz, 2H), 5.93 (d, J =31.5 Hz, 1H), 5.24 (d, J =13.4 Hz, 1H), 5.02 (s, 1H), 4.20 (d, J =3.5 Hz, 2H), 3.77-3.6 (m, 5H), 3.48-3.37 (m, 2H), 3.29-3.22 (m, 2H), 2.25-2.14 (m, 2H), 2.13-1.99 (m, 4H), 1.93 (t, J =1.4 Hz, 3H), 1.82-1.72 (m, 1H), 1.71-1.61 (m, 1H).

Example 4 *N*-(4-(4-amino-7-methyl-5-(4-(1-oxotetrahydro-2H-1 λ ⁶-thiopyran-1-imino) phenyl) -7H-pyrrolo [2,3-*d*] pyrimidin-6-yl) phenyl) methacrylamide



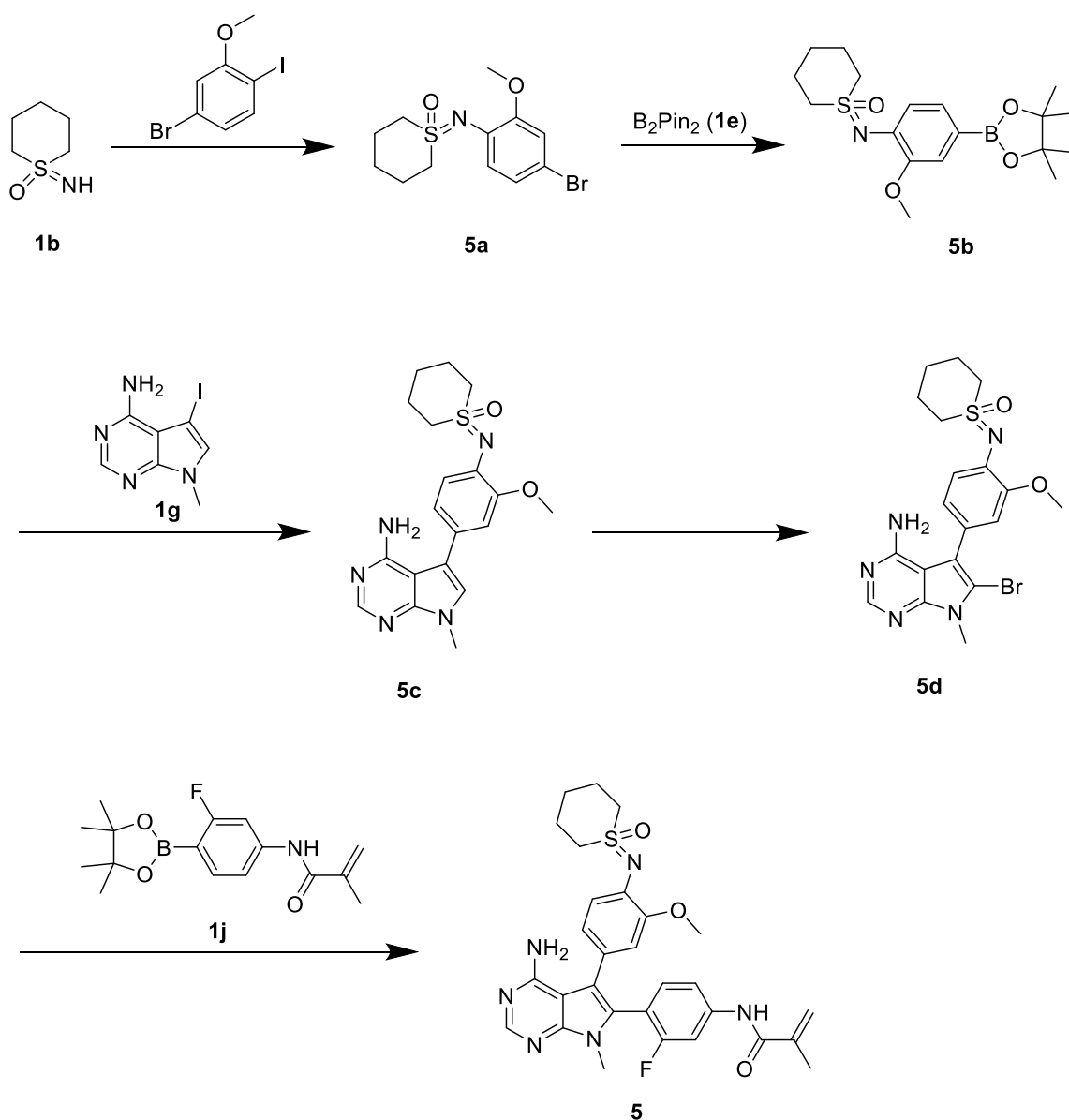
Step 1 *N*-(4-(4-amino-7-methyl-5-(4-(1-oxotetrahydro-2H-1 λ ⁶-thiopyran-1-imino) phenyl) -7H-pyrrolo [2,3-*d*] pyrimidin-6-yl) phenyl) methacrylamide **4**

Compound **1i** (180 mg, 0.42 mmol), compound **4a** (143.2 mg, 0.5 mmol), Pd(PPh₃)₄ (97.1 mg, 0.08 mmol), and potassium phosphate (267.5 mg, 1.26 mmol) were dissolved in anhydrous 1,4-dioxane (4 mL) and H₂O (1 mL), after replaced with nitrogen gas three times, heated up to 100 °C, and the reaction was refluxed for 12 h. After the reaction was completed, the reaction solution was cooled down to room temperature, filtered through diatomaceous earth, concentrated under reduced pressure to remove the solvent, and it was extracted with EA/H₂O three times, the organic layers were combined, washed with saturated salt once, dried over anhydrous sodium sulfate, concentrated under reduced pressure, and purified by column chromatography (DCM/MeOH=40/1) to obtain compound **4** (128 mg), light yellow solid.

MS (ESI) m/z 515 [M + H]⁺.

5 **Example 5** *N*-(4-(4-amino-5-(3-methoxy-4-(1-oxotetrahydro-2H-1λ⁶-thiopyran-1-imino) phenyl)-7-methyl-7*H*-pyrrolo [2,3-*d*] pyrimidin-6-yl)-3-fluorophenyl) methacrylamide





Step 1 1- ((4-bromo-2-methoxyphenyl) imino) hexahydro-1 λ^6 -thiopyran-1-oxide **5a**

Compound **1b** (638 mg, 4.79 mmol), 4-bromo-1-iodo-2-methoxybenzene (1.79 g, 5.75 mmol), $Pd_2(dba)_3$ (109.7 mg, 0.12 mmol), Xantphos (208 mg, 0.36 mmol), cesium carbonate (2.3 g, 7.19 mmol) were sequentially added to the reaction flask, after replaced with nitrogen gas three times, anhydrous 1,4-dioxane (25 mL) was added, the temperature was raised to 100 °C, and the reaction was refluxed for 6 h. After the reaction was completed, the reaction solution was filtered through diatomaceous earth, concentrated under reduced pressure, and purified by column chromatography (PE/EA=5/1) to obtain compound **5a** (650 mg), light yellow oil.

MS (ESI) m/z 318 $[M + H]^+$.

Step 2 1- ((2-methoxy-4- (4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) phenyl) imino) hexahydro-1 λ^6 -thiopyran-1-oxide **5b**

Compound **5a** (650 mg, 2.05 mmol), bis(pinacolato)diboron **1e** (624.8 mg, 2.46 mmol), potassium acetate (603.6 mg, 6.15 mmol), and $Pd(dppf)Cl_2$ (300 mg, 0.41 mmol) were added into

a reaction flask in sequence, after replaced with nitrogen gas three times, anhydrous 1,4-dioxane (15 mL) was added to dissolve, and the reaction solution reacted overnight at 90 °C. After the reaction was completed, the reaction solution was cooled down to room temperature, filtered through diatomaceous earth, concentrated under reduced pressure, extracted with DCM/H₂O three times, the organic layers were combined, washed with saturated salt once, dried over anhydrous sodium sulfate, concentrated and purified by silica gel column chromatography (PE/EA=4/1) to obtain compound **5b** (405 mg), yellow solid.

MS (ESI) *m/z* 366 [M + H]⁺.

Step 3 1- (4- (4-amino-7-methyl-7*H*-pyrrolo [2,3-*d*] pyrimidin-5-yl) -2-methoxyphenyl) imino) hexahydro-1 λ⁶-thiopyran-1-oxide **5c**

Compound **5b** (401 mg, 1.1 mmol), compound **1g** (274 mg, 1.0 mmol), Pd(PPh₃)₄ (116 mg, 0.1 mmol), and potassium phosphate (530.7 mg, 2.5 mmol) were dissolved in 1,4-dioxane (12 mL) and water (3 mL), after replaced with nitrogen gas three times, the reaction was carried out overnight at 90 °C. It was filtered through diatomaceous earth, concentrated under reduced pressure to remove the solvent, extracted with EA/H₂O three times, the organic layers were combined and washed with saturated salt water once, dried over anhydrous sodium sulfate, concentrated under reduced pressure and purified by column chromatography (DCM/MEOH=30/1) to obtain compound **5c** (180 mg), light yellow solid.

MS (ESI) *m/z* 382 [M + H]⁺.

Step 4 1- (4-(4-amino-6-bromo-7-methyl-7*H*-pyrrolo [2,3-*d*] pyrimidin-5-yl)-2-methoxyphenyl) imino) hexahydro-1 λ⁶-thiopyran-1-oxide **5d**

Compound **5c** (174 mg, 0.45 mmol) was dissolved in anhydrous DMF (4 mL), NBS (88 mg, 0.50 mmol) was added at 0 °C to react for 1 h. After the reaction was complete, sodium thiosulfate solution was added to quench the reaction, and it was extracted with EA/H₂O 4 times, the organic layers were combined, washed with saturated salt water once, dried over anhydrous sodium sulfate, concentrated under reduced pressure, and purified by column chromatography (DCM/MEOH=30/1) to obtain compound **5d** (107 mg), yellow solid.

MS (ESI) *m/z* 464 [M + H]⁺.

¹H NMR (400 MHz, CDCl₃) δ 8.28 (s, 1H), 7.31 (d, *J*=7.7 Hz, 1H), 6.92 (d, *J*=8.4 Hz, 2H), 5.53 (s, 2H), 3.87 (s, 3H), 3.85 (s, 3H), 3.43-3.34 (m, 2H), 3.28-3.16 (m, 2H), 2.16-2.03 (m, 4H), 1.79-1.62 (m, 2H).

Step 5 *N*- (4- (4-amino-5- (3-methoxy-4- (1-oxotetrahydro-2*H*-1 λ⁶-thiopyran-1-imino) phenyl) -7-methyl-7*H*-pyrrolo [2,3-*d*] pyrimidin-6-yl) -3-fluorophenyl) methacrylamide **5**

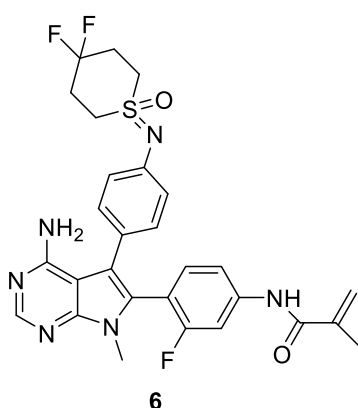
Compound **5d** (101 mg, 0.22 mmol), compound **1j** (99.8 mg, 0.33 mmol), Pd(PPh₃)₄ (50.4 mg, 0.04 mmol), and potassium phosphate (138.9 mg, 0.65 mmol) were dissolved in 1,4-dioxane (8 mL) and water (2 mL), after replaced with nitrogen gas three times, the reaction was refluxed at 100 °C for 12 h. After the reaction was completed, the reaction solution was cooled down to room temperature, filtered through diatomaceous earth, concentrated under reduced pressure to remove the solvent, and it was extracted with DCM/H₂O three times, the organic layers were combined, washed with saturated salt water once, dried over anhydrous sodium sulfate, concentrated under

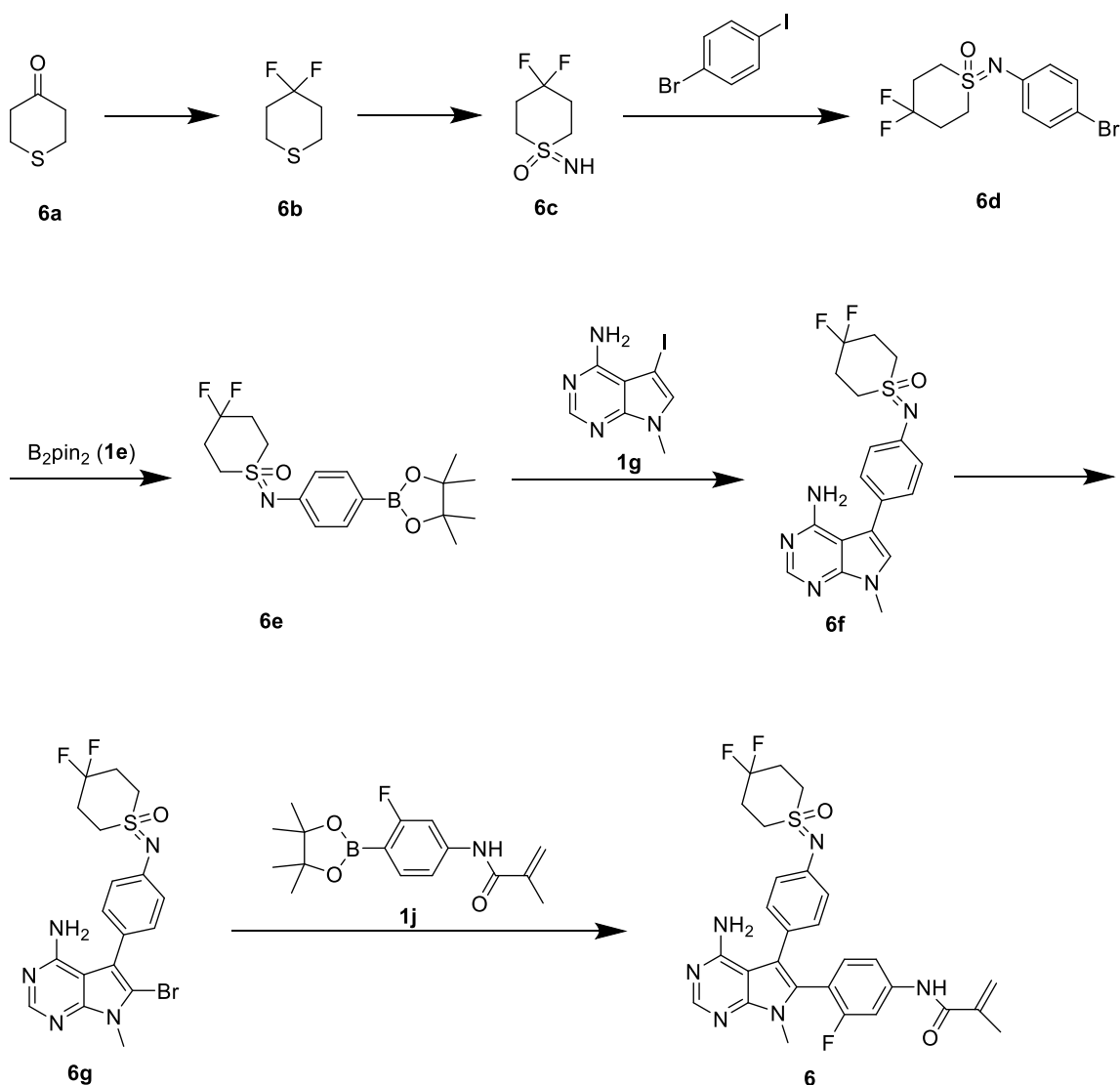
reduced pressure, and purified by column chromatography (DCM/MEOH=40/1) to obtain compound **5** (63 mg), light yellow solid.

MS (ESI) m/z 563 $[M + H]^+$.

¹H NMR (400 MHz, Methanol-d₄) δ 8.40 (s, 1H), 7.77 (dd, $J=12.2, 2.1$ Hz, 1H), 7.44 (dd, $J=8.5, 2.1$ Hz, 1H), 7.25 (dd, $J=9.9, 8.1$ Hz, 2H), 6.98-6.82 (m, 2H), 5.82 (s, 1H), 5.57 (q, $J=1.6$ Hz, 1H), 3.75 (s, 3H), 3.73 (s, 3H), 3.69-3.59 (m, 2H), 3.57-3.43 (m, 2H), 2.18-2.07 (m, 4H), 2.02 (s, 3H), 1.84-1.65 (m, 2H).

Example 6 N-(4-(4-amino-5-(4-(4,4-difluoro-1-oxotetrahydro-2H-1 λ^6 -thiopyran-1-imino) phenyl) -7-methyl-7H-pyrrolo [2,3-*d*] pyrimidin-6-yl) -3-fluorophenyl) methacrylamide





Step 1 4,4-difluorotetrahydro-2H-pyran **6b**

Compound **6a** (2.0 g, 17.24 mmol) was dissolved in ultra dry DCM (100 mL), stirred at 0 °C for 5 min, BAST (5.6 g, 34.47 mmol) was added to react for additional 4 h. After the reaction was completed, the reaction solution was poured into a cold NaHCO₃ aqueous solution, and it was extracted with DCM three times, the organic layers were combined, and washed with saturated salt water once, dried over anhydrous sodium sulfate, concentrated and dried to obtain compound **6b** (2.38 g), oily liquid, which were used directly for the next reaction step without purification.

MS (ESI) m/z 139 [M + H]⁺.

Step 2 4,4-difluoro-1-imino-tetrahydro-1λ⁶-thiopyran-1-oxide **6c**

Compound **6b** (2.38 g, 17.24 mmol) was dissolved in anhydrous methanol (100 mL), ammonium carbonate (2.49 g, 25.86 mmol) and iodobenzoic acid (13.9 g, 43.1 mmol) were added to the above reaction solution sequentially, and reacted at room temperature for 4 h. It was concentrated under reduced pressure to remove the solvent, and extracted with DCM/H₂O three times, the organic layers were combined, washed with saturated salt water once, dried over

anhydrous sodium sulfate, concentrated and purified by column chromatography (DCM/MeOH=40/1) to obtain compound **6c** (1.07 g), yellow liquid.

MS (ESI) m/z 170 $[M + H]^+$.

5 Step 3 1- ((4-bromophenyl)imino)-4,4-difluorotetrahydro-1 λ^6 -thiopyran-1-oxide **6d**

Compound **6c** (1.07 g, 6.33 mmol), p-bromoiodobenzene (2.14 g, 7.60 mmol), Pd₂(dba)₃ (144.9 mg, 0.16 mmol), Xantphos (274.7 mg, 0.47 mmol), and cesium carbonate (3.09 g, 9.49 mmol) were added to a reaction flask sequentially, after replaced with nitrogen gas three times, anhydrous 1,4-dioxane (35 mL) was added, the temperature was raised up to 100 °C, and the
10 reaction was refluxed for 6 h. The reaction solution was filtered through diatomaceous earth, concentrated under reduced pressure, and purified by column chromatography (PE/EA=5/1) to obtain compound **6d** (228 mg), yellow solid.

MS (ESI) m/z 324 $[M + H]^+$.

15 Step 4 4,4-difluoro-1-((4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)imino) hexahydro-1 λ^6 -thiopyran-1-oxide **6e**

Compound **6d** (224 mg, 0.69 mmol), compound **1e** (211.3 mg, 0.83 mmol), potassium acetate (203 mg, 2.07 mmol), and Pd(dppf)Cl₂ (101 mg, 0.14 mmol) were added to the reaction flask in sequence, after replaced with nitrogen three times, anhydrous 1,4-dioxane (8 mL) was
20 added to dissolve, and then heated up to 90 °C and reacted overnight. It was filtered through diatomaceous earth, concentrated under reduced pressure, extracted with DCM/H₂O three times, the organic layers were combined, washed with saturated salt once, dried over anhydrous sodium sulfate, concentrated and purified by column chromatography (PE/EA=3/1) to obtain compound **6e** (164 mg), yellow solid.

25 MS (ESI) m/z 372 $[M + H]^+$.

Step 5 1- (4-(4-amino-7-methyl-7H-pyrrolo [2,3-*d*] pyrimidin-5-yl) phenyl) imino)-4,4-difluorohexahydro-1 λ^6 -thiopyran-1-oxide **6f**

Compound **6e** (158 mg, 0.43 mmol), compound **1g** (106 mg, 0.39 mmol), Pd(PPh₃)₄ (45 mg, 0.039 mmol), and potassium phosphate (207 mg, 0.88 mmol) were dissolved in 1,4-dioxane (4 mL) and water (1 mL), after replaced with nitrogen three times, heated up to 90 °C and reacted overnight. It was filtered through diatomaceous earth, concentrated under reduced pressure to remove the solvent, extracted three times with DCM/H₂O, the organic layers were combined, and washed with saturated sodium chloride once, dried over anhydrous sodium sulfate, concentrated
35 under reduced pressure and purified by column chromatography (DCM/MeOH=30/1) to obtain compound **6f** (155 mg), light yellow solid.

MS (ESI) m/z 392 $[M + H]^+$.

¹H NMR (400 MHz, CDCl₃) δ 8.31 (s, 1H), 7.34 (d, J =8.4 Hz, 2H), 7.19 (d, J =8.4 Hz, 2H), 6.93 (s, 1H), 5.61 (s, 2H), 3.85 (s, 3H), 3.56-3.46 (m, 2H), 3.45-3.35 (m, 2H), 2.65-2.45 (m, 4H).

40

Step 6 1- (4- (4-amino-6-bromo-7-methyl-7H-pyrrolo [2,3-*d*] pyrimidin-5-yl) phenyl) imino) -4,4-difluorohexahydro-1 λ^6 -thiopyran-1-oxide **6g**

Compound **6f** (150 mg, 0.38 mmol) was dissolved in anhydrous DMF (4 mL), NBS (75.1 mg, 0.42 mmol) was added at 0 °C to react for 1 h. Sodium thiosulfate solution was added to quench the reaction, and it was extracted with EA/H₂O 4 times, the organic layers were combined, and washed with saturated salt water once, the organic phase was dried over anhydrous sodium sulfate, concentrated under reduced pressure, and purified by column chromatography (DCM/MEOH =30/1) to obtain compound **6g** (52 mg), yellow solid.

MS (ESI) *m/z* 470, 472 [M + H]⁺.

¹H NMR (400 MHz, CDCl₃) δ 8.28 (s, 1H), 7.35 (d, *J*=8.4 Hz, 2H), 7.20 (d, *J*=8.4 Hz, 2H), 5.12 (s, 2H), 3.83 (s, 3H), 3.56-3.48 (m, 2H), 3.46-3.38 (m, 2H), 2.65-2.52 (m, 4H).

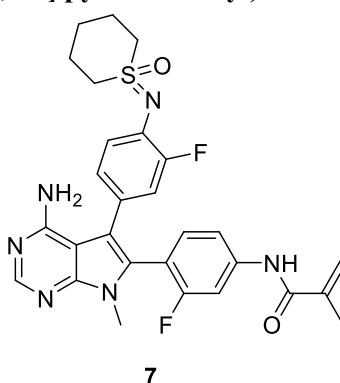
Step 7 *N*-(4-(4-amino-5-(4-(4,4-difluoro-1-oxotetrahydro-2*H*-1λ⁶-thiopyran-1-imino) phenyl) -7-methyl-7*H*-pyrrolo [2,3-*d*] pyrimidin-6-yl) -3-fluorophenyl) methacrylamide **6**

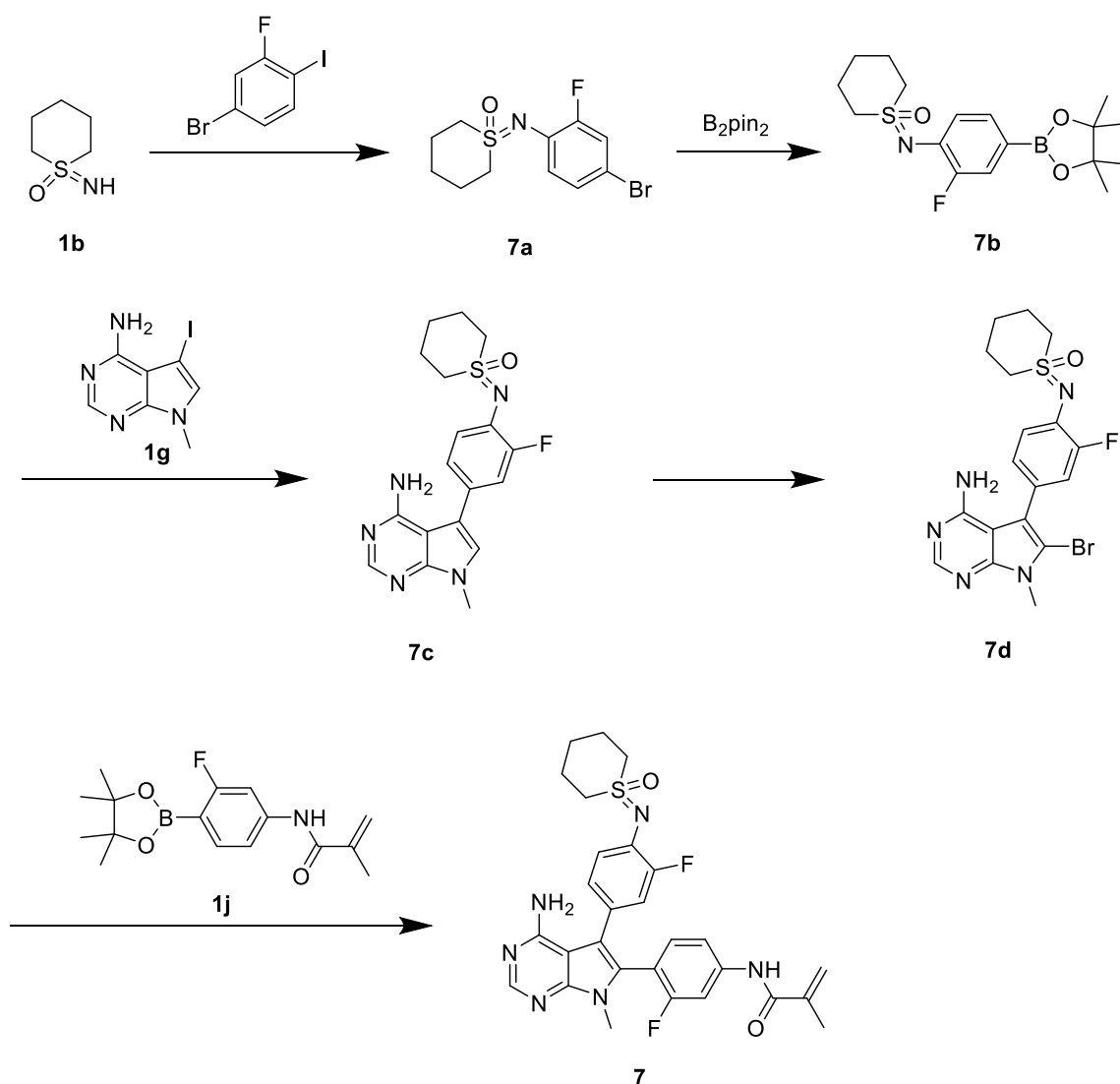
Compound **6g** (40 mg, 0.09 mmol), compound **1j** (39 mg, 0.13 mmol), Pd(PPh₃)₄ (19.7 mg, 0.02 mmol), and potassium phosphate (54.3 mg, 0.26 mmol) were dissolved in 1,4-dioxane (4 mL) and water (1 mL), after replaced with nitrogen three times, the reaction was refluxed at 100 °C for 12 h. After the reaction solution was cooled down to room temperature, it was filtered through diatomaceous earth, concentrated under reduced pressure to remove the solvent, and extracted with DCM/H₂O three times, the organic layers were combined, washed with saturated salt water once, dried over anhydrous sodium sulfate, concentrated under reduced pressure, and purified by column chromatography (DCM/MEOH=40/1) to obtain compound **6** (18 mg), white solid.

MS (ESI) *m/z* 569 [M + H]⁺.

¹H NMR (400 MHz, MeOD-*d*₄) δ 8.37 (s, 1H), 7.76 (dd, *J* = 12.3, 2.0 Hz, 1H), 7.41 (dd, *J* = 8.5, 2.1 Hz, 1H), 7.26-7.15 (m, 3H), 7.10 (d, *J* = 8.8 Hz, 2H), 5.82 (s, 1H), 5.57 (q, *J* = 1.5 Hz, 1H), 3.73 (s, 3H), 3.61-3.41 (m, 4H), 2.61-2.40 (m, 4H), 2.02 (dd, *J* = 1.6, 1.0 Hz, 3H).

Example 7 *N*-(4-(4-amino-5-(3-fluoro-4-((1-oxotetrahydro-2*H*-1λ⁶-thiopyran-1-imino) phenyl) -7-methyl-7*H*-pyrrolo [2,3-*d*] pyrimidin-6-yl) -3-fluorophenyl) methacrylamide





Step 1- ((4-bromo-2-fluorophenyl) imino) hexahydro-1 λ^6 -thiopyran-1-oxide **7a**

Compound **1b** (104 mg, 0.78 mmol), 1-bromo-3-fluoro-4-iodobenzene (281.2 mg, 0.94 mmol), $Pd_2(dba)_3$ (17.9 mg, 0.02 mmol), Xantphos (33.8 mg, 0.06 mmol), and cesium carbonate (381.2 mg, 1.2 mmol) were added to a reaction flask sequentially, after replaced with nitrogen three times, anhydrous 1,4-dioxane (8 mL) was added, the temperature was raised up to 100 °C, and the reaction was refluxed for 6 h. It was filtrated through diatomaceous earth, concentrated under reduced pressure, and purified by column chromatography (PE/EA=5/1) to obtain compound **7a** (181 mg), light yellow oil.

MS (ESI) m/z 305 $[M + H]^+$.

Step 2 1- ((2-Fluoro-4- (4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) phenyl) imino) hexahydro-1 λ^6 -thiopyran-1-oxide **7b**

Compound **7a** (181 mg, 0.59 mmol), bis(pinacolato)diboron (181 mg, 0.71 mmol), potassium acetate (173.7 mg, 1.77 mmol), and $Pd(dppf)Cl_2$ (86.3 mg, 0.12 mmol) were added to the reaction flask in sequence, after replaced with nitrogen three times, anhydrous 1,4-dioxane (8 mL) was

added to dissolve, and heated up to 90 °C to react overnight. After the reaction was completed, the reaction solution was cooled down to room temperature, filtered through diatomaceous earth, concentrated under reduced pressure, extracted with DCM/H₂O three times, the organic layers were combined, washed with saturated salt once, the organic phase was dried over anhydrous sodium sulfate, concentrated and purified by column chromatography (PE/EA=4/1) to obtain compound **7b** (231 mg), yellow liquid.

MS (ESI) m/z 354 [M + H]⁺.

¹H NMR (400 MHz, CDCl₃) δ 7.20 (dd, J =10.1, 2.1 Hz, 1H), 7.14 (t, J =8.3 Hz, 1H), 7.10 (dd, J =8.7, 2.1 Hz, 1H), 3.39-3.29 (m, 2H), 3.18-3.07 (m, 2H), 2.18-2.01 (m, 4H), 1.79-1.71 (m, 1H), 1.68-1.53 (m, 1H).

Step 3 1- (4- (4-amino-7-methyl-7H-pyrrolo [2,3-d] pyrimidin-5-yl) -2-fluorophenyl) imino) hexahydro-1 λ^6 -thiopyran-1-oxide 7c

Compound **7b** (231 mg, 0.65 mmol), compound **1g** (149 mg, 0.55 mmol), Pd(PPh₃)₄ (62.8 mg, 0.06 mmol), and potassium phosphate (292 mg, 1.38 mmol) were dissolved in 1,4-dioxane (8 mL) and water (2 mL), after replaced with nitrogen three times, the reaction was carried out at 90 °C overnight. After the reaction was completed, it was cooled down to room temperature, filtered through diatomaceous earth, concentrated under reduced pressure to remove the solvent, extracted with DCM/H₂O three times, the organic layers were combined, washed with saturated sodium chloride once, dried over anhydrous sodium sulfate, concentrated under reduced pressure and purified by column chromatography (DCM/MeOH=30/1) to obtain compound **7c** (132 mg), yellow solid.

MS (ESI) m/z 374 [M + H]⁺.

¹H NMR (400 MHz, CDCl₃) δ 8.32 (s, 1H), 7.33 (t, J =8.4 Hz, 1H), 7.16 (dd, J =11.3, 2.1 Hz, 1H), 7.09 (dd, J =8.3, 1.9 Hz, 1H), 6.92 (s, 1H), 5.37 (s, 2H), 3.83 (s, 3H), 3.45-3.33 (m, 2H), 3.23-3.08 (m, 2H), 2.22-2.13 (m, 4H), 1.86-1.73 (m, 1H), 1.70-1.57 (m, 1H).

Step 4 1- (4-(4-amino-6-bromo-7-methyl-7H-pyrrolo [2,3-d] pyrimidin-5-yl) -2-fluorophenyl) imino) hexahydro-1 λ^6 -thiopyran-1-oxide 7d

Compound **7c** (132 mg, 0.35 mmol) was dissolved in anhydrous DMF (4 mL), NBS (69.2 mg, 0.39 mmol) was added at 0 °C, and the reaction was quenched with sodium thiosulfate solution after 2 h of reaction, and it was extracted with EA/H₂O 4 times, the organic layers were combined, washed with saturated salt water once, the organic phase was dried over anhydrous sodium sulfate, concentrated under reduced pressure, and purified by column chromatography (DCM/MeOH=30/1) to obtain compound **7d** (60 mg), yellow solid.

MS (ESI) m/z 452 [M + H]⁺.

¹H NMR (400 MHz, CDCl₃) δ 8.28 (s, 1H), 7.36 (t, J =8.5 Hz, 1H), 7.17 (dd, J =11.3, 2.1 Hz, 1H), 7.07 (dd, J =8.2, 2.2 Hz, 1H), 5.30 (s, 2H), 3.84 (s, 3H), 3.47-3.34 (m, 2H), 3.25-3.15 (m, 2H), 2.23-2.08 (m, 4H), 1.82-1.73 (m, 1H), 1.72-1.60 (m, 1H).

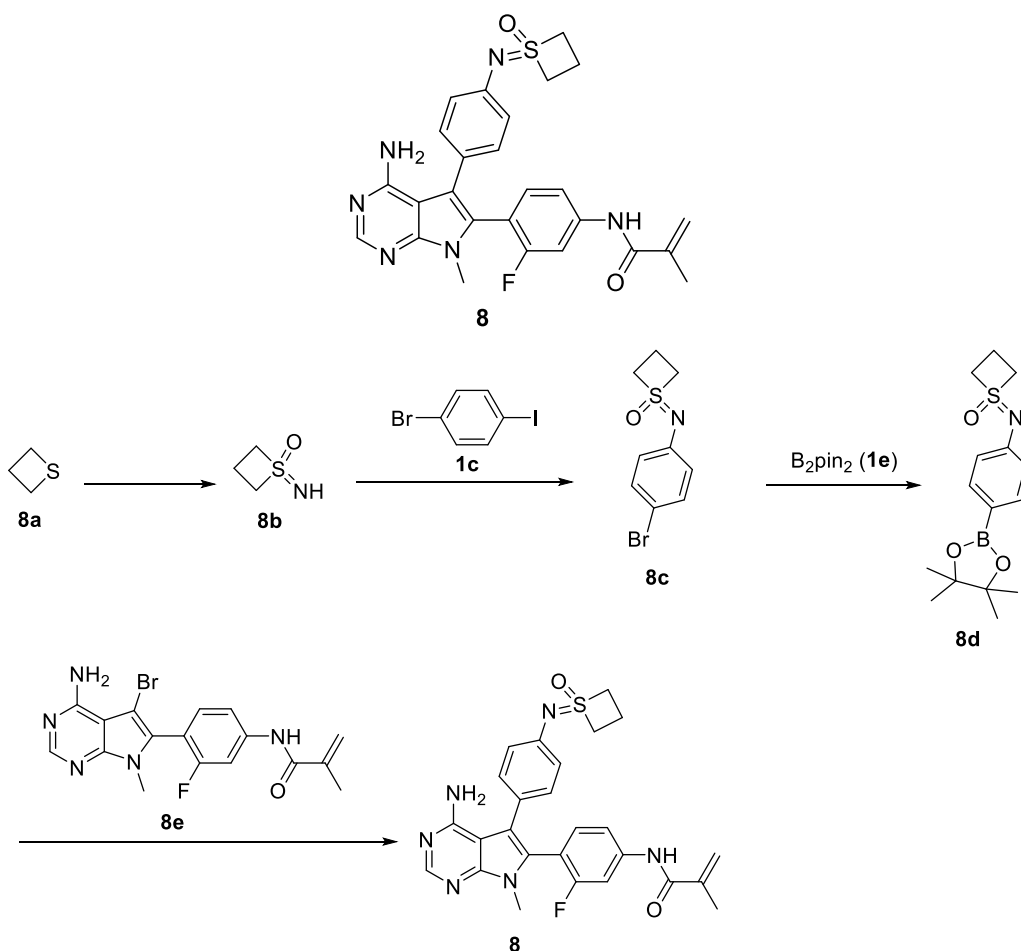
Step 5 N-(4-(4-amino-5- (3-fluoro-4- ((1-oxotetrahydro-2H-1 λ^6 -thiopyran-1-imino) phenyl) -7-methyl-7H-pyrrolo [2,3-d] pyrimidin-6-yl)-3-fluorophenyl) methacrylamide 7

Compound **7d** (60 mg, 0.13 mmol), compound **1j** (61 mg, 0.20 mmol), Pd(PPh₃)₄ (30 mg, 0.03 mmol), and potassium phosphate (82.8 mg, 0.39 mmol) were dissolved in 1,4-dioxane (4 mL) and water (1 mL), after replaced with nitrogen three times, the reaction was refluxed at 100 °C for 12 h. The reaction solution was cooled down to room temperature, filtered through diatomaceous earth, concentrated under reduced pressure to remove the solvent, extracted with DCM/H₂O three times, and the organic layers were combined, washed with saturated saline solution, dried over anhydrous sodium sulfate, concentrated under reduced pressure, purified by column chromatography (DCM/MeOH =40/1) to obtain compound **7** (57 mg), light yellow solid.

MS (ESI) *m/z* 551 [M + H]⁺.

¹H NMR (400 MHz, MeOD-*d*₄) δ 8.19 (s, 1H), 7.73 (dd, *J*=12.1, 2.1 Hz, 1H), 7.38 (dd, *J*=8.4, 2.1 Hz, 1H), 7.25-7.14 (m, 2H), 7.01-6.88 (m, 2H), 5.82 (s, 1H), 5.55 (q, *J*=1.6 Hz, 1H), 3.62 (s, 3H), 3.42-3.33 (m, 2H), 3.29-3.20 (m, 2H), 2.11-1.98 (m, 7H), 1.79-1.70 (m, 1H), 1.69-1.70 (m, 1H) 1.58 (m, 1H).

Example 8 N-(4- (4-amino-7-methyl-5-(4-(1-oxo-1λ⁶-thietan-1-ylidene) amino) phenyl) -7H-pyrrolo [2,3-*d*] pyrimidin-6-yl) -3-fluorophenyl) methacrylamide



Step 1 1-Amino-1 λ⁶-thietane-1-oxide **8b**

Thietane **8a** (5 g, 67.5 mmol) and ammonium carbamate (7.85 g, 101 mmol) were added to a flask sequentially, and then MeOH (100 mL) and iodobenzene diethyl ester (43.5 g, 135 mmol)

were added. The reaction solution was stirred open at room temperature for 30 min, and then concentrated under reduced pressure to remove the solvent to obtain a crude product. The crude product was purified by column chromatography (MeOH/DCM=1/20) to obtain compound **8b** (3.6 g), colorless oil.

5 ^1H NMR (400 MHz, CDCl_3) δ 4.12-3.98 (m, 4H), 3.39 (brs, 1H), 2.24-2.14 (m, 2H).

Step 2 1-((4-bromophenyl) imino) -1 λ^6 -thietane-1-oxide **8c**

Compound **8b** (210 mg, 2.0 mmol), cesium carbonate (0.99 g, 3.0 mmol), 1-bromo-4-iodobenzene **1c** (0.688 g, 2.4 mmol), $\text{Pd}_2(\text{dba})_3$ (55 mg, 0.06 mmol), and Xantphos (104 mg, 0.18 mmol) were added to 1,4-dioxane (6 mL), and the reaction solution was heated up to 100 °C to react for 16 h. The reaction solution was filtered through diatomaceous earth, and the filter cake was washed with ethyl acetate (100 mL) and saturated saline solution (50 mL). The organic phase was dried over anhydrous sodium sulfate and concentrated under reduced pressure to obtain a crude product. The crude product was purified by column chromatography (PE/EtOAc=4/1 to 3/2) to obtain compound **8c** (470 mg), light yellow solid.

15 ^1H NMR (400 MHz, CDCl_3) δ 7.33 (d, J = 8.8 Hz, 2H), 6.90 (d, J = 8.8 Hz, 2H), 4.18 (d, J = 8.0 Hz, 4H), 2.40-2.28 (m, 2H).

Step 3 1- (4- (4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) phenyl) imino) -1 λ^6 -thietane-1-oxide **8d**

Compound **8c** (260 mg, 1.0 mmol), bis(pinacolato)diboron **1e** (305 mg, 1.2 mmol), $\text{Pd}(\text{dppf})\text{Cl}_2$ (146 mg, 0.2 mmol), potassium acetate (294 mg, 3.0 mmol), and 1,4-dioxane (5 mL) were added into a sealed tube, after replaced with argon gas three times, sealed, and the reaction solution was heated up to 90 °C and stirred for 16 h. Then water (10 mL) was added, and extracted with DCM (20 mL $\times$ 3). The organic phase was washed with saturated saline solution (20 mL), dried over anhydrous sodium sulfate, and concentrated under reduced pressure to obtain a crude product. The crude product was purified by column chromatography (PE/EtOAc=3/2) to obtain compound **8d** (256 mg), white solid.

25 ^1H NMR (400 MHz, CDCl_3) δ 7.66 (d, J = 8.4 Hz, 2H), 6.95 (d, J = 8.4 Hz, 2H), 4.10 (t, J = 8.0 Hz, 4H), 2.27-2.19 (m, 2H), 1.28 (s, 12H).

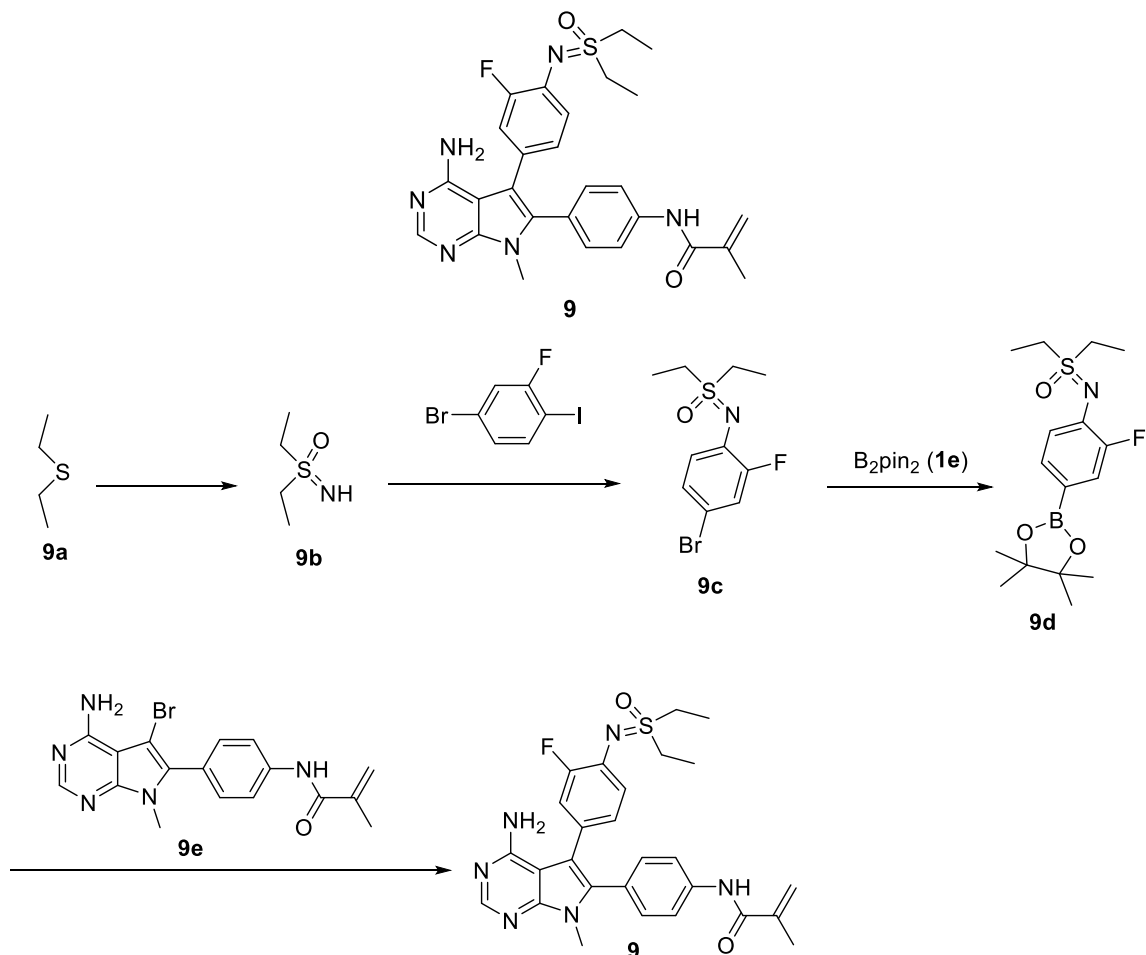
Step 4 *N*-(4-(4-amino-7-methyl-5- (4- (1-oxo-1 λ^6 -thiocyclobutan-1-ylidene) amino) phenyl) -7*H*-pyrrolo [2,3-*d*] pyrimidin-6-yl) -3-fluorophenyl) methacrylamide **8**

Compound **8e** (60 mg, 0.15 mmol), compound **8d** (55 mg, 0.18 mmol), $\text{Pd}(\text{PPh}_3)_4$ (17 mg, 0.015 mmol), and K_3PO_4 (95 mg, 0.45 mmol) were added into a sealed tube, after replaced with argon gas three times, 1,4-dioxane (2 mL) and H_2O (0.2 mL) were added, sealed, the reaction solution was heated up to 100 °C and stirred for 16 h. then dichloromethane (20 mL) and saturated saline solution (10 mL) were added to extract, the organic phase was dried over anhydrous sodium sulfate, and concentrated under reduced pressure to obtain a crude product. The crude product was purified by column chromatography (MeOH/DCM=1/10) to obtain compound **8** (12 mg), white solid.

40 MS (ESI) m/z 505 $[\text{M} + \text{H}]^+$.

¹H NMR (400 MHz, CDCl₃) δ 8.36 (s, 1H), 7.70 (dd, *J* = 11.6, 1.9 Hz, 1H), 7.58 (s, 1H), 7.14-7.03 (m, 4H), 6.94 (d, *J* = 8.4 Hz, 2H), 5.80 (s, 1H), 5.51 (d, *J* = 1.6 Hz, 1H), 5.00 (s, 2H), 4.21 (dd, *J* = 9.4, 7.3 Hz, 4H), 3.65 (s, 3H), 2.40-2.32 (m, 2H), 2.07 (s, 3H).

5 **Example 9** *N*-(4-(4-amino-5-methyl-1H-pyrrolo[2,3-*d*]pyrimidin-6-yl)-phenyl)-2-methylmethacrylamide-7-fluorophenyl)-1- λ^6 -sulfonyl-diethylsulfide



Step 1 imine-1 λ^6 -diethylsulfoxide 9b

10 Diethylthioether **9a** (4.5 g, 50 mmol) and ammonium carbamate (5.85 g, 75 mmol) were added into a flask in sequence, then MeOH (100 mL) and iodobenzene diethyl ester (32.2 g, 100 mmol) were added. The reaction solution was stirred open at room temperature for 30 min and then concentrated under reduced pressure to remove the solvent to obtain a crude product. The crude product was purified by column chromatography (MeOH/DCM=1/20) to obtain compound

15 **9b** (3.6 g), colorless oil.

¹H NMR (400 MHz, CDCl₃) δ 3.12-2.93 (q, *J* = 7.5 Hz, 4H), 2.66 (s, 1H), 1.38 (t, *J* = 7.5 Hz, 6H).

Step 2 1-((4-bromo-2-fluorophenyl) imino)-1 λ^6 -diethylsulfoxide 9c

20 Compound **9b** (400 mg, 3.3 mmol), cesium carbonate (1.6 g, 5 mmol), 1-bromo-3-fluoro-4-iodobenzene (1.2 g, 4 mmol), Pd₂(dba)₃ (92 mg, 0.1 mmol), and Xantphos

(173 mg, 0.3 mmol) were added to 1,4-dioxane (12 mL), the reaction solution was heated up to 100 °C to react for 16 h. The reaction solution was filtered through diatomaceous earth, the filter cake was washed with ethyl acetate (100 mL), and saturated saline solution (50 mL) was used for washing. The organic phase was dried over anhydrous sodium sulfate and concentrated under reduced pressure to obtain a crude product. The crude product was purified by column chromatography (PE/EtOAc=4/1 to 3/2) to obtain compound **9c** (0.8 g), brownish yellow oil.

¹H NMR (400 MHz, CDCl₃) δ 7.18 ((dd, *J* = 10.0, 2.4 Hz, 1H), 7.15 (t, *J* = 8.4 Hz, 1H), 7.09 (dd, *J* = 8.4, 2.4 Hz, 1H), 3.27-3.12 (m, 4H), 1.41 (t, *J* = 7.4 Hz, 6H).

Step 3 1- (4- (4,4,5,5-methyl-1,3,2-dioxaborolan-2-yl) -3-fluorophenyl) imino)-1 λ⁶-diethylsulfoxide 9d

Compound **9c** (500 mg, 1.7 mmol), bis(pinacolato)diboron **1e** (518 mg, 2.0 mmol), Pd(dppf)Cl₂ (249 mg, 0.34 mmol), potassium acetate (500 mg, 5.1 mmol), and 1,4-dioxane (10 mL) were added into a sealed tube, after replaced with argon gas three times, sealed, the reaction solution was heated up to 90 °C and stirred for 16 h. Water (10 mL) was added, and it was extracted with DCM (20 mL × 3). The organic phase was washed with saturated saline solution (20 mL), dried over anhydrous sodium sulfate, and concentrated under reduced pressure to obtain a crude product. The crude product was purified by column chromatography (PE/EtOAc=3/2) to obtain compound **9d** (360 mg), white solid.

MS (ESI) *m/z* 342 [M + H]⁺.

¹H NMR (400 MHz, CDCl₃) δ 7.45 (dd, *J* = 11.2, 1.6 Hz, 1H), 7.41 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.27 (t, *J* = 8.0 Hz, 1H), 3.31-3.16 (m, 4H), 1.41 (t, *J* = 7.4 Hz, 6H), 1.32 (s, 12H).

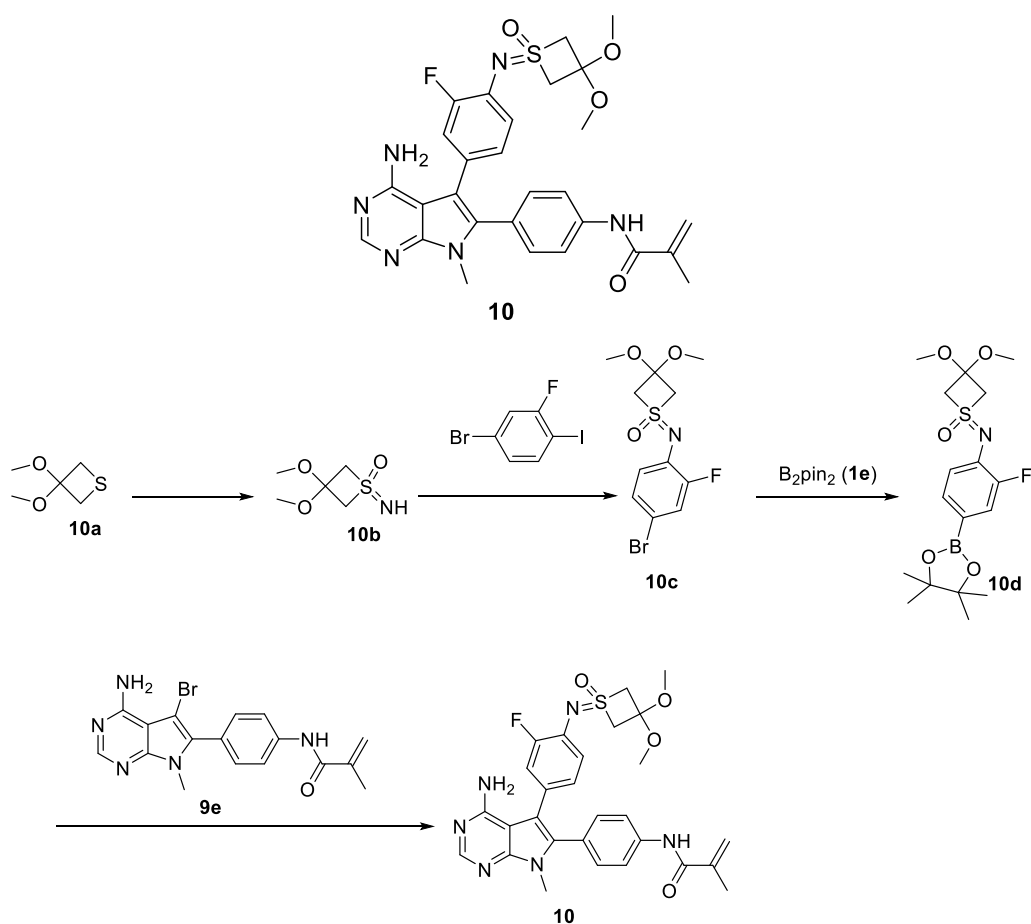
Step 4 N- (4- (4-amino-5- (4- (diethyl (oxo) 1 λ⁶-sulfanylidene) -3-fluorophenyl) -7-methyl 7H-pyrrolo [2,3-*d*] pyrimidin-6-yl) - phenyl) methacrylamide 9

Compound **9e** (300 mg, 0.88 mmol), compound **9d** (283 mg, 0.73 mmol), Pd(PPh₃)₄ (84 mg, 0.072 mmol), and K₃PO₄ (464 mg, 2.2 mmol) were added into a sealed tube, after replaced with argon gas three times, 1,4-dioxane (10 mL) and H₂O (1 mL) was added, sealed, the reaction solution was heated up to 100 °C and stirred for 16 h. Dichloromethane (20 mL) and saturated saline solution (10 mL) were added, and it was extracted, the organic phase was dried over anhydrous sodium sulfate, and concentrated under reduced pressure to obtain a crude product. The crude product was purified by column chromatography (MeOH/DCM=1/10) to obtain compound **9** (52 mg), white solid.

MS (ESI) *m/z* 521 [M + H]⁺.

¹H NMR (400 MHz, CDCl₃) δ 8.26 (s, 1H), 7.56-7.42 (m, 3H), 7.20-7.12 (m, 3H), 6.82 (*d*, *J* = 10.5 Hz, 2H), 5.74 (s, 1H), 5.43 (s, 1H), 5.27 (brs, 2H), 3.63 (s, 3H), 3.20-3.09 (m, 4H), 2.01 (s, 3H), 1.37 (t, *J* = 7.4 Hz, 6H).

Example 10 N-(4-(4-amino-5-(4-(3,3-dimethoxy-1-oxo-1λ⁶-thiocyclobutan-1-ylidene) amino)-3-fluorophenyl) -7-methyl-7H-pyrrolo [2,3-*d*] pyrimidin-6-yl)- phenyl) methacrylamide



Step 1 1-imino-3,3-dimethoxy-1λ⁶-thietane-1-oxide **10b**

3,3-dimethoxythietane **10a** (2.68 g, 20 mmol) and ammonium carbamate (2.34 g, 30 mmol) were added to a flask sequentially, and then MeOH (80 mL) and iodobenzene diethyl ester (12.9 g, 40 mmol) were added. The reaction solution was stirred open at room temperature for 30 min and then concentrated under reduced pressure to remove the solvent to obtain a crude product. The crude product was purified by column chromatography (MeOH/DCM=1/20) to obtain compound **10b** (0.9 g), colorless oil.

¹H NMR (400 MHz, CDCl₃) δ 4.15 (s, 4H), 3.25 (s, 6H).

Step 2 1-((4-bromo-2-fluorophenyl) imino)-3,3-dimethoxy-1λ⁶-thietan-1- oxide **10c**

Compound **10b** (380 mg, 2.3 mmol), cesium carbonate (1.13 g, 3.45 mmol), 1-bromo-3-fluoro-4-iodobenzene (832 mg, 2.76 mmol), Pd₂(dba)₃ (105 mg, 0.12 mmol), and Xantphos (200 mg, 0.36 mmol) were added to 1,4-dioxane (10 mL), and the reaction solution was heated up to 100 °C to react for 16 h. The reaction solution was filtered through diatomaceous earth, and the filter cake was washed with ethyl acetate (100 mL) and saturated saline solution (50 mL). The organic phase was dried over anhydrous sodium sulfate and concentrated under reduced pressure to obtain a crude product. The crude product was purified by column chromatography (PE/EtOAc=4/1 to 3/2) to obtain compound **10c** (0.4 g), light yellow solid.

¹H NMR (400 MHz, CDCl₃) δ 7.20 (dd, *J* = 10.4, 2.4 Hz, 1H), 7.14 (dd, *J* = 8.6, 2.4 Hz, 1H), 6.95 (t, *J* = 8.6 Hz, 1H), 4.35 (d, *J* = 13.2 Hz, 1H), 4.27 (d, *J* = 13.2 Hz, 1H), 3.28 (s, 3H), 3.26 (s, 3H).

Step 3 1-((2-fluoro-4- (4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) phenyl) imino) -3,3-dimethoxy-1 λ⁶-thietane-1-oxide 10d

Compound **1d** (600 mg, 1.77 mmol), bis(pinacolato)diboron (541 mg, 2.13 mmol), Pd(dppf)Cl₂ (259 mg, 0.35 mmol), potassium acetate (520 mg, 5.31 mmol), and 1,4-dioxane (10 mL) were added into a sealed tube, it was replaced with argon gas three times, sealed, the reaction solution was heated up to 90 °C and stirred for 16 h. Water (10 mL) was added and it was extracted with DCM (20 mL × 3). The organic phase was washed with saturated saline solution (20 mL), dried over anhydrous sodium sulfate, and concentrated under reduced pressure to obtain a crude product. The crude product was purified by column chromatography (PE/EtOAc=3/2) to obtain compound **10d** (580 mg), brownish yellow solid.

¹H NMR (400 MHz, CDCl₃) δ 7.50-7.45 (m, 1H), 7.45 (s, 1H), 7.05 (t, *J* = 7.9 Hz, 1H), 4.41-4.25 (m, 4H), 3.28 (s, 3H), 3.25 (s, 3H), 1.32 (s, 12H).

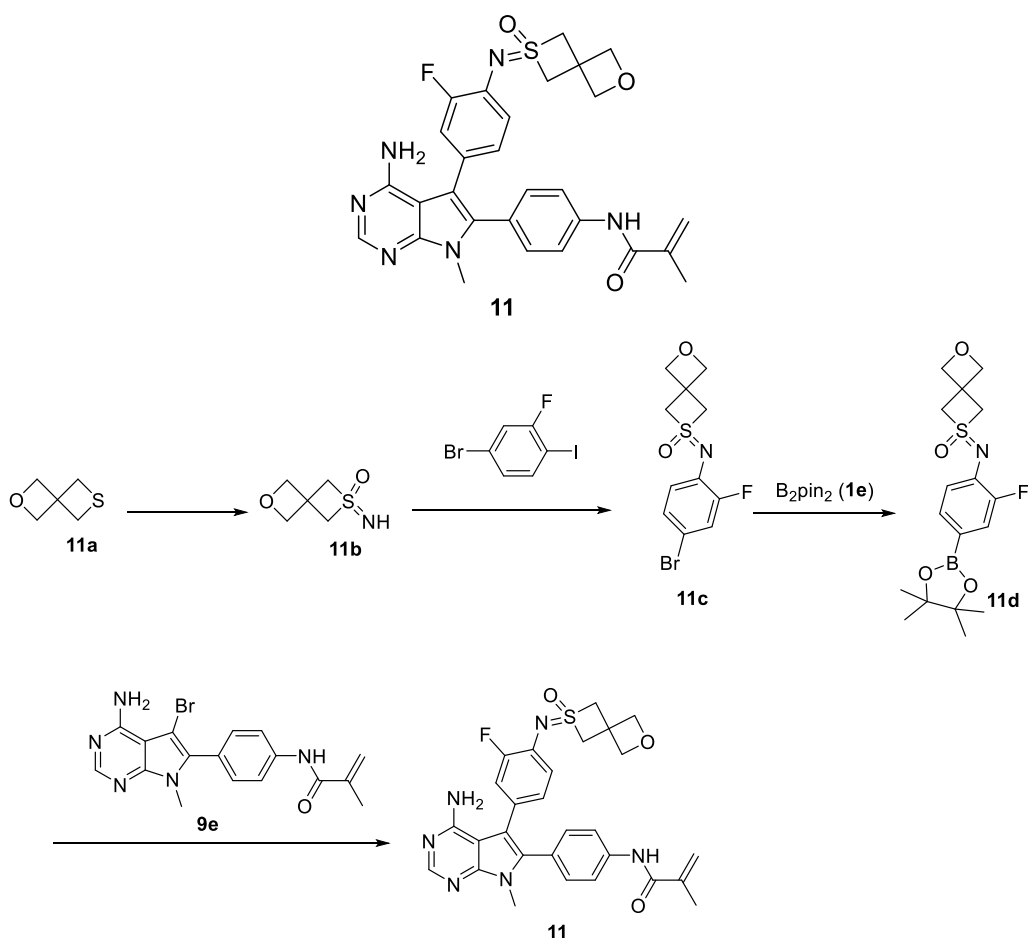
Step 4 N- (4- (4-amino-5- (4- (3,3-dimethoxy-1-oxo-1 λ⁶-thiocyclobutan-1-ylidene) amino) -3-fluorophenyl) -7-methyl-7H-pyrrolo [2,3-*d*] pyrimidin-6-yl) - phenyl) methacrylamide 10

Compound **9e** (185 mg, 0.48 mmol), compound **10d** (154 mg, 0.4 mmol), Pd(PPh₃)₄ (46 mg, 0.04 mmol), and K₃PO₄ (254 mg, 1.2 mmol) were added into a sealed tube, after replaced with argon gas three times, 1,4-dioxane (5 mL) and H₂O (0.5 mL) were added, sealed, the reaction solution was heated up to 100 °C and stirred for 16 h. Dichloromethane (20 mL) and saturated saline solution (10 mL) were added to extract, the organic phase was dried over anhydrous sodium sulfate, and concentrated under reduced pressure to obtain a crude product. The crude product was purified by column chromatography (MeOH/DCM=1/10) to obtain compound **10** (19 mg), white solid.

MS (ESI) *m/z* 565 [M + H]⁺.

¹H NMR (400 MHz, CDCl₃) δ 8.34 (s, 1H), 7.65 (s, 1H), 7.57 (d, *J* = 8.6 Hz, 2H), 7.20 (d, *J* = 8.6 Hz, 2H), 7.00 (dd, *J* = 9.2, 7.6 Hz, 1H), 6.95-6.88 (m, 2H), 5.79 (s, 1H), 5.47 (d, *J* = 1.6 Hz, 1H), 5.07 (brs, 2H), 4.37 (d, *J* = 13.6 Hz, 2H), 4.29 (d, *J* = 13.6 Hz, 2H), 3.68 (s, 3H), 3.28 (s, 3H), 3.26 (s, 3H), 2.06 (s, 3H).

Example 11 N-(4- (4-amino-5- (3-fluoro-4- (6-oxo-2-oxa-6 λ⁶-thiaspiro [3.3] heptan-6-ylidene) amino) phenyl) -7-methyl-7H-pyrrolo [2,3-*d*] pyrimidin-6-yl) - phenyl) methacrylamide



Step 1 6-amino-2-oxo-6 λ^6 -thiaspiro [3.3] heptane-6-oxide **11b**

Compound **11a** (1.74 g, 15 mmol) and ammonium carbamate (1.75 g, 22.5 mmol) were added to a flask sequentially, and then MeOH (100 mL) and iodobenzene diethyl ester (9.66 g, 30 mmol) were added. The reaction solution was stirred open at room temperature for 30 min and then concentrated under reduced pressure to remove the solvent to obtain a crude product. The crude product was purified by column chromatography (MeOH/DCM=1/20) to obtain compound **11b** (0.7 g), colorless oil.

^1H NMR (400 MHz, CDCl_3) δ 4.85 (s, 2H), 4.81 (s, 2H), 4.28 (s, 4H), 2.04 (s, 1H).

Step 2 6- ((4-bromo-2-fluorophenyl) imino) -2-oxo-6 λ^6 -thiaspiro [3.3] heptane-6-oxide **11c**

Compound **11b** (480 mg, 3.3 mmol), cesium carbonate (1.59 g, 4.9 mmol), 1-bromo-3-fluoro-4-iodobenzene (1.2 g, 3.9 mmol), $\text{Pd}_2(\text{dba})_3$ (92 mg, 0.1 mmol), and Xantphos (174 mg, 0.3 mmol) were added to 1,4-dioxane (15 mL), and the reaction solution was heated up to 100 °C for 16 h. The reaction solution was filtered through diatomaceous earth, and the filter cake was washed with ethyl acetate (100 mL) and saturated saline solution (50 mL). The organic phase was dried over anhydrous sodium sulfate and concentrated under reduced pressure to obtain a crude product. The crude product was purified by column chromatography (PE/EtOAc=4/1 to 3/2) to obtain compound **11c** (0.6 g), brownish yellow solid.

¹H NMR (400 MHz, CDCl₃) δ 7.20 (dd, *J* = 10.4, 2.4 Hz, 1H), 7.13 (ddd, *J* = 8.4, 2.4, 1.0 Hz, 1H), 6.93 (t, *J* = 8.8 Hz, 1H), 4.84 (s, 2H), 4.82 (s, 2H), 4.45 (d, *J* = 14.0 Hz, 2H), 4.39 (d, *J* = 14.0 Hz, 2H).

Step 3 6- ((2-fluoro-4- (4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) phenyl) imino) -2-oxo-6 λ⁶-thiaspiro [3.3] heptane-6-oxide 11d

Compound **11c** (260 mg, 0.81 mmol), bis(pinacolato)diboron (248 mg, 0.98 mmol), Pd(dppf)Cl₂ (119 mg, 0.16 mmol), potassium acetate (238 mg, 2.43 mmol), and 1,4-dioxane (5 mL) were added into a sealed tube, after replaced with argon gas three times, sealed, the reaction solution was heated up to 90 °C and stirred for 16 h. Water (10 mL) was added and extracted with DCM (20 mL × 3). The organic phase was washed with saturated saline solution (20 mL), dried over anhydrous sodium sulfate, and concentrated under reduced pressure to obtain a crude product. The crude product was purified by column chromatography (PE/EtOAc=3/2) to obtain compound **11d** (230 mg), brownish yellow solid.

¹H NMR (400 MHz, CDCl₃) δ 7.47 (dd, *J* = 5.2, 1.2 Hz, 1H), 7.45 (s, 1H), 7.04 (t, *J* = 8.0 Hz, 1H), 4.86 (s, 2H), 4.85 (s, 2H), 4.50 (d, *J* = 14.0 Hz, 2H), 4.42 (d, *J* = 14.0 Hz, 2H), 1.32 (s, 12H).

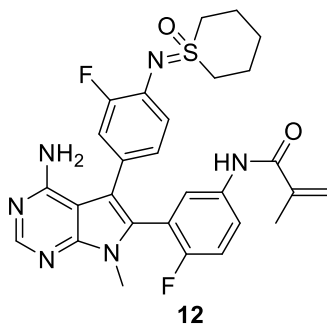
Step 4 N- (4- (4-amino-5- (3-fluoro-4- (6-oxo-2-oxa-6 λ⁶-thiaspiro [3.3] heptan-6-ylidene) amino) phenyl) -7-methyl-7H-pyrrolo [2,3-*d*] pyrimidin-6-yl) - phenyl) methacrylamide 11

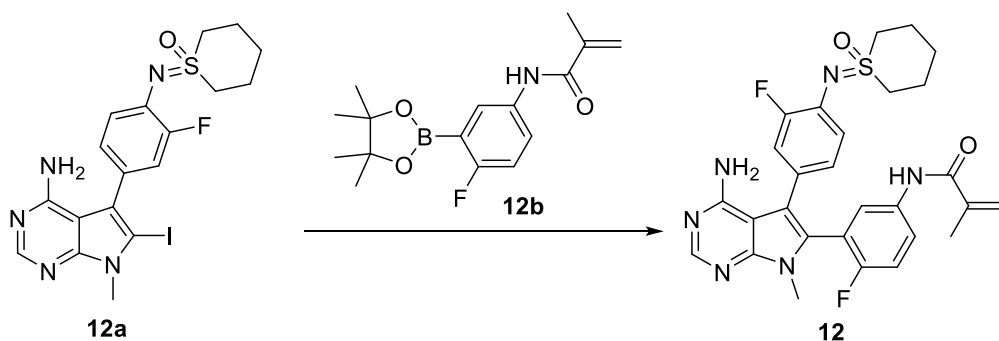
Compound **8e** (150 mg, 0.4 mmol), compound **11d** (143 mg, 0.37 mmol), Pd(PPh₃)₄ (43 mg, 0.037 mmol), and K₃PO₄ (235 mg, 1.1 mmol) were added into a sealed tube, after replaced with argon gas three times, 1,4-dioxane (4 mL) and H₂O (0.4 mL) were added, sealed, and the reaction solution was heated up to 100 °C and stirred for 16 h. Dichloromethane (20 mL) and saturated saline solution (10 mL) were added to extract, the organic phase was dried over anhydrous sodium sulfate, and concentrated under reduced pressure to obtain a crude product. The crude product was purified by column chromatography (MeOH/DCM=1/10) to obtain compound **11** (15 mg), white solid.

MS (ESI) *m/z* 547 [M + H]⁺.

¹H NMR (400 MHz, CDCl₃) δ 8.29 (s, 1H), 7.58-7.43 (m, 3H), 7.15 (d, *J* = 8.6 Hz, 2H), 6.98-6.80 (m, 3H), 5.73 (s, 1H), 5.42 (d, *J* = 1.6 Hz, 1H), 4.92 (s, 2H), 4.82 (s, 2H), 4.79 (s, 2H), 4.45 (d, *J* = 14.1 Hz, 2H), 4.37 (d, *J* = 14.1 Hz, 2H), 3.62 (s, 3H), 2.00 (s, 3H).

Example 12 N-(3- (4-amino-5- (3-fluoro-4- ((1-oxotetrahydro-2H-1 λ⁶-thiopyran-1-ylidene) amino) phenyl) -7-methyl-7H-pyrrolo [2,3-*d*] pyrimidin-6-yl) -4-fluorophenyl) methacrylamide



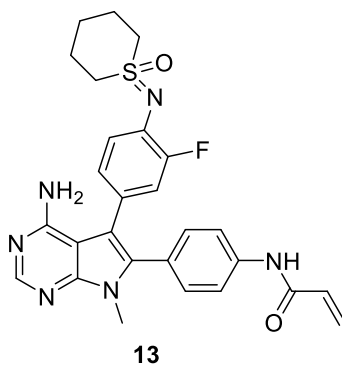


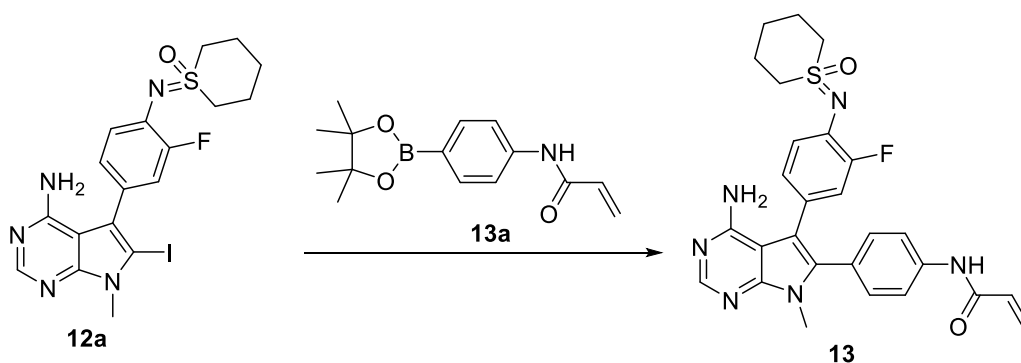
Compound **12a** (150 mg, 0.3 mmol), compound **12b** (105 mg, 0.36 mmol), Pd(PPh₃)₄ (35 mg, 0.03 mmol), and K₃PO₄ (192 mg, 0.9 mmol) were added into a sealed tube, after replaced with argon gas three times, 1,4-dioxane (3 mL) and H₂O (0.3 mL) was added, sealed, and the reaction solution was heated up to 90 °C and stirred for 16 h. Dichloromethane (40 mL) and saturated saline solution (10 mL) were added to extract, the organic phase was dried over anhydrous sodium sulfate, and concentrated under reduced pressure to obtain a crude product. The crude product was purified by column chromatography (MeOH/DCM=1/10) to obtain compound **12** (10 mg), white solid.

MS (ESI) *m/z* 551 [M + H]⁺.

¹H NMR (400 MHz, CDCl₃) δ 8.36 (s, 1H), 7.65 (ddd, *J* = 8.8, 4.4, 2.8 Hz, 1H), 7.45 (s, 1H), 7.30 (dd, *J* = 6.0, 2.8 Hz, 1H), 7.19 (t, *J* = 8.8 Hz, 1H), 7.12 (t, *J* = 8.8 Hz, 1H), 7.00-6.88 (m, 2H), 5.76 (s, 1H), 5.46 (d, *J* = 1.6 Hz, 1H), 5.11 (brs, 2H), 3.65 (s, 3H), 3.36-3.28 (m, 2H), 3.17-3.10 (m, 2H), 2.18-2.10 (m, 4H), 2.03 (s, 3H), 1.66-1.58 (m, 2H).

Example 13 *N*- (4- (4-amino-5- (3-fluoro-4- ((1-oxotetrahydro-2*H*-1 λ⁶-thiopyran-1-ylidene) amino) phenyl) -7-methyl-7*H*-pyrrolo [2,3-*d*] pyrimidin-6-yl) phenyl) acrylamide



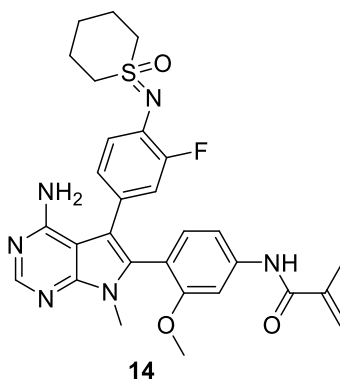


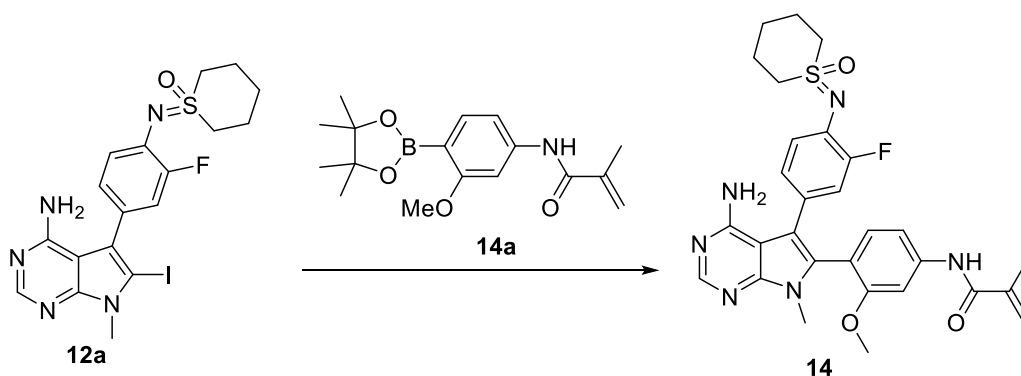
Compound **12a** (150 mg, 0.3 mmol), compound **13a** (107 mg, 0.39 mmol), Pd(PPh₃)₄ (69 mg, 0.06 mmol), and K₃PO₄ (192 mg, 0.9 mmol) were added into a sealed tube, after replaced with argon gas three times, 1,4-dioxane (6 mL) and H₂O (0.6 mL) were added, sealed, and the reaction solution was heated up to 90 °C and stirred for 16 h. Dichloromethane (40 mL) and saturated saline solution (10 mL) were added to extract, the organic phase was dried over anhydrous sodium sulfate, and concentrated under reduced pressure to obtain a crude product. The crude product was purified by column chromatography (MeOH/DCM=1/10) to obtain compound **13** (13 mg), white solid.

MS (ESI) *m/z* 519 [M + H]⁺.

¹H NMR (400 MHz, CDCl₃) δ 8.28 (s, 1H), 7.76 (s, 1H), 7.59 (d, *J* = 8.4 Hz, 2H), 7.19 (d, *J* = 8.4 Hz, 2H), 7.17 (m, 1H), 6.90-6.84 (m, 2H), 6.44 (dd, *J* = 16.8, 1.2 Hz, 1H), 6.28 (dd, *J* = 16.8, 10.0 Hz, 1H), 5.77 (dd, *J* = 10.0, 1.2 Hz, 1H), 5.60 (*brs*, 2H), 3.68 (s, 3H), 3.35-3.29 (m, 2H), 3.18-3.11 (m, 2H), 2.13-2.06 (m, 4H), 1.79-1.70 (m, 1H), 1.66-1.58 (m, 1H).

Example 14 *N*-(4-(4-amino-5-(3-fluoro-4-((1-oxotetrahydro-2H-1λ⁶-thiopyran-1-ylidene)amino)phenyl)-7-methyl-7H-pyrrolo[2,3-*d*]pyrimidin-6-yl)-3-methoxyphenyl) methacrylamide



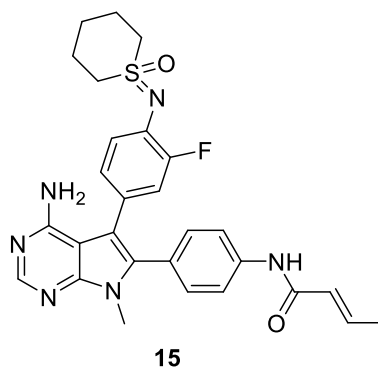


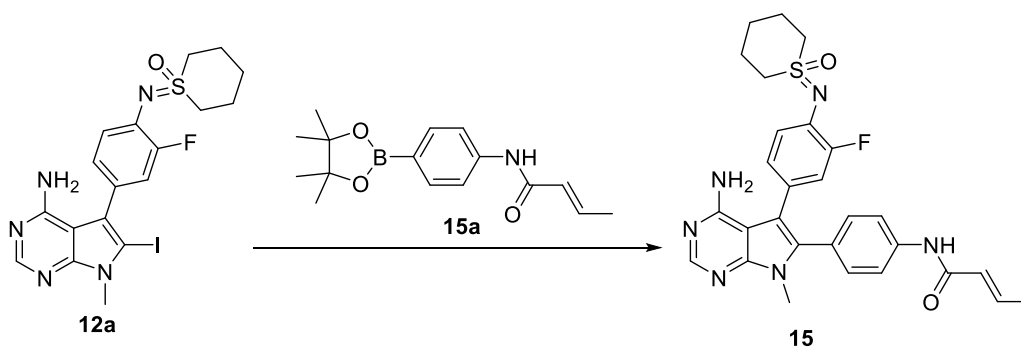
Compound **12a** (50 mg, 0.1 mmol), compound **14a** (38 mg, 0.12 mmol), Pd(PPh₃)₄ (23 mg, 0.02 mmol), and K₃PO₄ (64 mg, 0.3 mmol) were added into a sealed tube, after replaced with argon gas three times, 1,4-dioxane (2 mL) and H₂O (0.2 mL) were added, sealed, and the reaction solution was heated up to 90 °C and stirred for 16 h. Dichloromethane (20 mL) and saturated saline solution (10 mL) were added to extract, the organic phase was dried over anhydrous sodium sulfate, and concentrated under reduced pressure to obtain a crude product. The crude product was purified by column chromatography (MeOH/DCM=1/10) to obtain compound **14** (10 mg), white solid.

MS (ESI) m/z 563 [M + H]⁺.

¹H NMR (400 MHz, CDCl₃) δ 8.27 (s, 1H), 7.71 (d, J = 2.0 Hz, 1H), 7.62 (s, 1H), 7.16 (t, J = 8.0 Hz, 1H), 6.93 (d, J = 8.0 Hz, 2H), 6.91-6.85 (m, 1H), 6.76 (dd, J = 8.0, 2.0 Hz, 1H), 5.81 (s, 1H), 5.81 (brs, 2H), 5.50 (s, 1H), 3.79 (s, 3H), 3.58 (s, 3H), 3.30 (m, 2H), 3.14 (m, 2H), 2.14-2.06 (m, 4H), 2.07 (s, 3H), 1.78-1.69 (m, 1H), 1.66-1.56 (m, 1H).

Example 15 (*E*)-*N*-(4-(4-amino-5-(3-fluoro-4-((1-oxotetrahydro-2H-1λ⁶-thiopyran-1-ylidene) amino) phenyl)-7-methyl-7H-pyrrolo [2,3-*d*] pyrimidin -6-yl) -phenyl)-2-butenamide



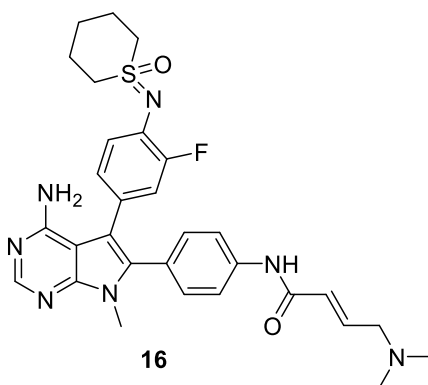


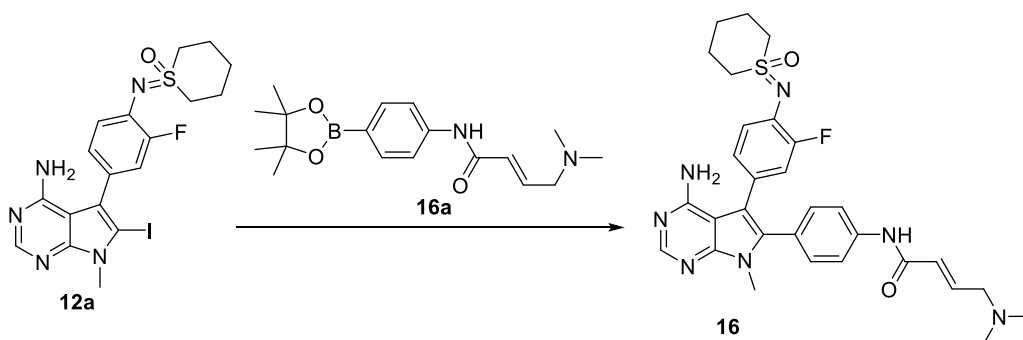
Compound **12a** (150 mg, 0.3 mmol), compound **15a** (103 mg, 0.36 mmol), Pd(PPh₃)₄ (35 mg, 0.03 mmol), and K₃PO₄ (192 mg, 0.9 mmol) were added into a sealed tube, after replaced with argon gas three times, 1,4-dioxane (5 mL) and H₂O (0.5 mL) were added, sealed, and the reaction solution was heated up to 90 °C and stirred for 16 h. Dichloromethane (40 mL) and saturated saline solution (10 mL) were added to extract, the organic phase was dried over anhydrous sodium sulfate, and concentrated under reduced pressure to obtain a crude product. The crude product was purified by column chromatography (MeOH/DCM=1/10) to obtain compound **15** (7 mg), white solid.

MS (ESI) m/z 533 [M + H]⁺.

¹H NMR (400 MHz, CDCl₃) δ 8.36 (s, 1H), 7.56 (d, J = 8.5 Hz, 2H), 7.21-7.16 (m, 4H), 7.05-6.96 (m, 1H), 6.92-6.87 (m, 2H), 5.96 (dd, J = 15.1, 1.8 Hz, 1H), 4.98 (s, 2H), 3.69 (s, 3H), 3.38-3.28 (m, 2H), 3.20-3.11 (m, 2H), 2.15-2.06 (m, 4H), 1.93 (dd, J = 6.9, 1.7 Hz, 3H), 1.79-1.71 (m, 1H), 1.69-1.61 (m, 1H).

Example 16 (*E*)-*N*-(4-(4-amino-5-(3-fluoro-4-((1-oxotetrahydro-2H-1λ⁶-thiopyran-1-ylidene) amino) phenyl) -7-methyl-7H-pyrrolo [2,3-*d*] pyrimidin-6-yl) - phenyl) -4-(dimethylamino) -2-butenamide



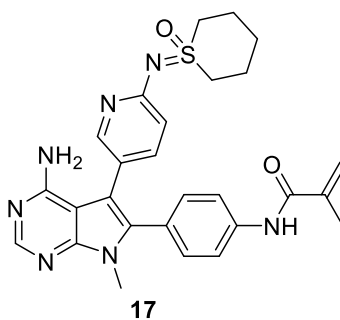


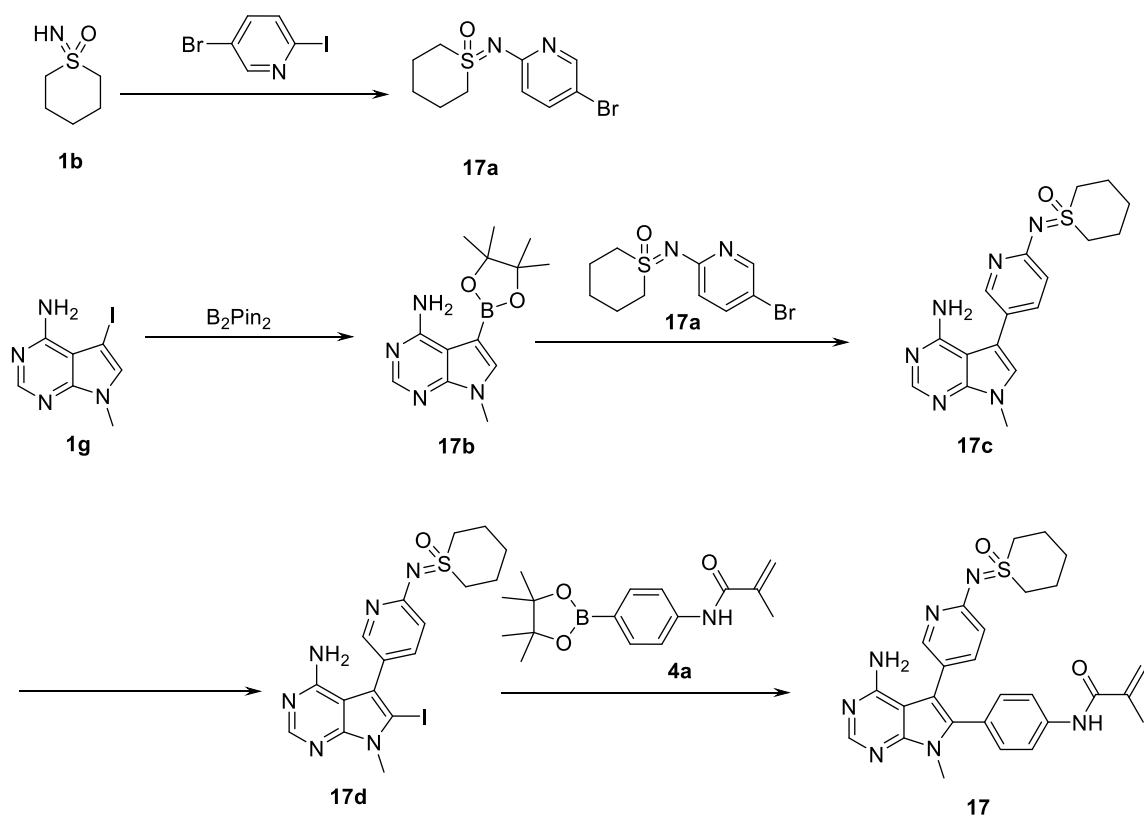
Compound **12a** (100 mg, 0.2 mmol), compound **16a** (77 mg, 0.24 mmol), Pd(PPh₃)₄ (23 mg, 0.02 mmol), and K₃PO₄ (127 mg, 0.6 mmol) were added into a sealed tube, after replaced with argon gas three times, 1,4-dioxane (3 mL) and H₂O (0.3 mL) were added, sealed, and the reaction solution was heated up to 90 °C and stirred for 16 h. Dichloromethane (40 mL) and saturated saline solution (10 mL) were added to extract, the organic phase was dried over anhydrous sodium sulfate, and concentrated under reduced pressure to obtain a crude product. The crude product was purified by column chromatography (MeOH/DCM=1/10) to obtain compound **16** (16 mg), white solid.

MS (ESI) *m/z* 574 [M - H]⁻.

¹H NMR (400 MHz, CDCl₃) δ 8.44 (s, 1H), 7.68-7.60 (m, 3H), 7.36-7.28 (m, 3H), 7.11-7.04 (m, 1H), 6.99 (d, *J* = 9.5 Hz, 2H), 6.23 (d, *J* = 15.6 Hz, 1H), 5.15 (s, 2H), 3.78 (s, 3H), 3.45-3.40 (m, 2H), 3.26-3.20 (m, 4H), 2.37 (s, 6H), 2.28-2.16 (m, 4H), 1.86-1.79 (m, 1H), 1.78-1.66 (m, 1H).

Example 17 *N*-[4- (4-amino-7-methyl-5- (6- ((1-oxotetrahydro-2H-1 λ⁶-thiopyran-1-ylidene) amino) pyridin-3-yl) pyrrolo [2,3-*d*] pyrimidin-6-yl) phenyl) methacrylamide





Step 1 1-[(5-bromopyridin-2-yl) imino]-1,1,6,6-tetrahydro-2H-thiopyran-2-oxide 17a

At room temperature, compound **1b** (1 g, 7.52 mmol), 5-bromo-2-iodopyridine (2.35 g, 8.27 mmol), tris (dibenzylideneacetone) dipalladium (173.99 mg, 0.19 mmol), 4,5-diphenylphosphine-9,9-dimethyloxanthracene (324.03 mg, 0.56 mmol), cesium carbonate (3.43 g, 10.53 mmol), 1,4-dioxane (20 ml), and a stirrer were added to a round bottom flask sequentially, followed by vacuum pumping and nitrogen gas purging three times. The reaction was heated up to 100 °C and stirred for 16 h. After the reaction was completed, the mixture was cooled down to room temperature and concentrated under reduced pressure to obtain a crude product. The crude product was purified by column chromatography (PE/EtOAc=1/1) to obtain compound **17a** (700 mg), light yellow solid.

MS (ESI) m/z 289 $[M + H]^+$.

^1H NMR (400 MHz, DMSO- d_6) δ 8.16 (d, $J = 4.0$ Hz, 1H), 7.72 (dd, $J = 4.0, 4.0$ Hz, 1H), 6.67 (d, $J = 8.0$ Hz, 1H), 3.63-3.62 (m, 2H), 3.43-3.42 (m, 2H), 2.02-1.81 (m, 4H), 1.62-1.59 (m, 2H).

Step 2 7-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) pyrrolo [2,3-d] pyrimidin-4-amine

At room temperature, compound **1g** (5 g, 18.25 mmol), bis(pinacolato)diboron (6.95 g, 27.37 mmol), potassium acetate (5.34 g, 54.75 mmol), of 1,1'- biphenylphosphine ferrocene palladium chloride (1.34 mg, 1.83 mmol), and dimethyl sulfoxide (25 mL) were added to a round bottom flask sequentially, followed by vacuum pumping and nitrogen gas purging three times. The reaction was heated up to 100 °C and stirred for 1 h. After the reaction was completed, the mixture was cooled down to room temperature, diluted with water, extracted with ethyl acetate (20 mL $\times$

3), washed with saturated saline (30 mL), and the organic phases were combined, dried over anhydrous sodium sulfate and concentrated under reduced pressure to obtain a crude product. The crude product was purified by column chromatography (DCM/MeOH=15/1) to obtain compound **7b** (700 mg), reddish brown solid.

5 MS (ESI) m/z 275 $[M + H]^+$.

Step 3 1-((5-(4-amino-7-methyl-7H-pyrrolo [2,3-*d*] pyrimidin-5-yl) pyridin-2-yl) imino) hexahydro-1 λ^6 -thiopyran-1-oxide 17c

At room temperature, compound **7b** (500 mg, 1.82 mmol), compound **17a** (471.74 mg, 1.64 mmol), 1,1'- bis (ditert-butylphosphine) ferrocene palladium dichloro (117.68 mg, 0.18 mmol), cesium fluoride (829.37 mg, 5.46 mmol), N, N-dimethylformamide (10 mL), and water (2.5 mL) were added to a round bottom flask in sequence, followed by vacuum pumping and nitrogen gas purging three times. The reaction was heated up to 100 °C and stirred for 1 h. After the reaction was completed, the mixture was cooled down to room temperature, diluted with water, extracted with ethyl acetate (15 ml $\times$ 3), washed with saturated saline (20 ml), and the organic phases were combined, dried over anhydrous sodium sulfate and concentrated under reduced pressure to obtain a crude product. The crude product was purified by column chromatography (DCM/MeOH=10/1) to obtain compound **17c** (400 mg), brown solid.

MS (ESI) m/z 357 $[M + H]^+$.

20 ^1H NMR (400 MHz, DMSO- d_6) δ 8.17-8.16 (m, 2H), 7.61 (dd, J = 4.0, 4.0 Hz, 1H), 7.28 (s, 1H), 6.79 (d, J = 8.0 Hz, 1H), 6.07 (s, 2H), 3.74 (s, 3H), 3.69-3.64 (m, 2H), 3.47-3.41 (m, 2H), 1.96-1.94 (m, 4H), 1.64-1.61 (m, 2H).

Step 4 1-(5-(4-amino-6-iodo-7-methyl-7H-pyrrolo [2,3-*d*] pyrimidin-5-yl) pyridine -2-yl) imino) hexahydro-1 λ^6 -thiopyran-1-oxide 17d

Compound **17c** (300 mg, 0.84 mmol), dichloromethane (3 ml), and trifluoroacetic acid (287.33 mg, 2.52 mmol) were added to a round bottom flask at room temperature. After it was cooled down to 0 °C, N-iodosuccinimide (283.47 mg, 1.26 mmol) was added in batches, and the reaction was warmed up to room temperature naturally and stirred for additional 2 h. After TLC monitored the completion of the reaction, the mixture was concentrated under reduced pressure to obtain a crude product. The crude product was purified by column chromatography (DCM/MeOH=10/1) to obtain compound **17d** (65 mg), white solid.

MS (ESI) m/z 483 $[M + H]^+$.

35 ^1H NMR (400 MHz, DMSO- d_6) δ 8.10-8.09 (m, 2H), 7.55 (dd, J = 4.0, 4.0 Hz, 1H), 6.81 (d, J = 8.0 Hz, 1H), 5.95 (s, 2H), 3.74 (s, 3H), 3.70-3.66 (m, 1H), 3.51-3.45 (m, 2H), 3.17 (d, J = 4.0 Hz, 1H), 1.97-1.96 (m, 4H), 1.66-1.62 (m, 2H).

Step 5 N-[4-(4-amino-7-methyl-5-(6-(1-oxotetrahydro-2H-1 λ^6 -thiopyran-1-ylidene) amino) pyridin-3-yl) pyrrolo [2,3-*d*] pyrimidin-6-yl) phenyl] methacrylamide 17

40 At room temperature, compound **17d** (65 mg, 0.13 mmol), compound **4a** (40.20 mg, 0.14 mmol), chlorine[(*n*-butyl di (1-adamantanyl) phosphine) -2- (2- aminobiphenyl)] palladium (II) (8.69 mg, 0.013 mmol), potassium phosphate (55.12 mg, 0.26 mmol), N, N-dimethylacetamide (2 mL)/water (0.5 mL) were added to a round bottom flask sequentially, followed by vacuum

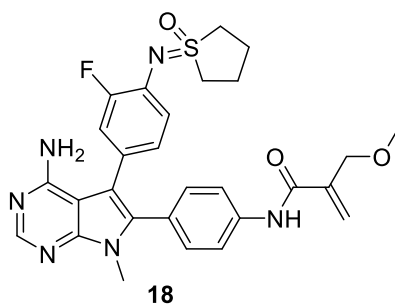
pumping and nitrogen gas purging three times. The reaction was heated up to 80 °C and stirred for 3 h. After the reaction was completed, the mixture was cooled down to room temperature and concentrated under reduced pressure to obtain a crude product. The crude product was purified by column chromatography (DCM/MeOH=10/1) to obtain compound **17** (11.2 mg), white solid.

5 MS (ESI) m/z 516 $[M + H]^+$.

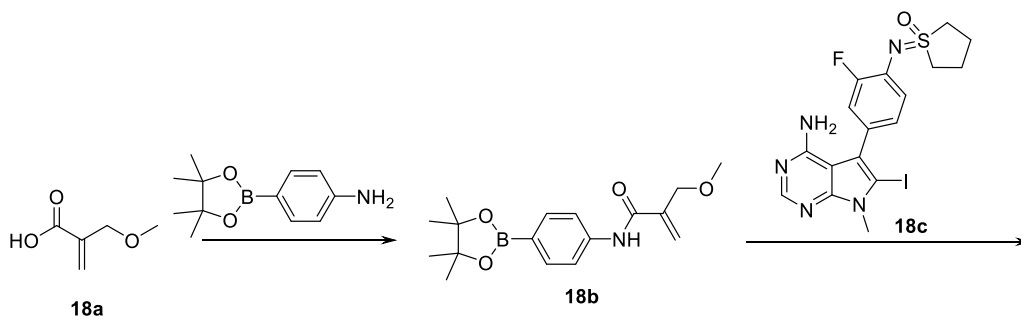
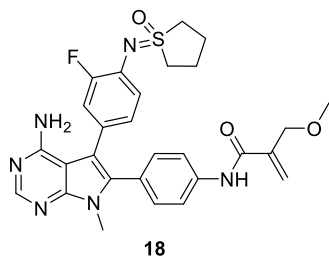
^1H NMR (400 MHz, DMSO- d_6) δ 9.93 (s, 1H), 8.19 (s, 1H), 7.90 (d, $J = 4.0$ Hz, 1H), 7.73 (d, $J = 8.0$ Hz, 2H), 7.40 (dd, $J = 4.0, 4.0$ Hz, 1H), 7.28 (d, $J = 8.0$ Hz, 2H), 6.67 (d, $J = 8.0$ Hz, 1H), 5.88 (s, 2H), 5.82 (s, 1H), 5.53 (s, 1H), 3.62 (s, 1H), 3.60 (s, 3H), 3.34-3.41 (m, 1H), 3.18-3.17 (m, 2H), 1.96 (s, 3H), 1.95-1.93 (m, 4H), 1.61-1.58 (m, 2H).

10

Example 18 N- (4- (4-amino-5- (3-fluoro-4- ((1-oxotetrahydro-1 λ^6 -thiophene-1- ylidene) amino) phenyl) -7-methyl-7H-pyrrolo [2,3-*d*] pyrimidin-6-yl) phenyl) -2- (methoxymethyl) acrylamide



15



Step 1 7-methyl-5- (4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) pyrrolo [2,3-*d*] pyrimidin-4-amine 18b

20 Compound **18a** (150 mg, 1.29 mmol) and 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan -2-yl) aniline (197.23 mg, 0.90 mmol) were dissolved in N, N-dimethylformamide (3 mL), and then triethylamine (391.6 mg, 3.87 mmol) was added. It was cooled down to 0 °C, a solution of

1-propylphosphonic anhydride in 50% ethyl acetate (820.90 mg, 1.93 mmol) was added slowly dropwise, and heated up to room temperature and stirred to react for 4 h. After the reaction was completed, the mixture was diluted with water, extracted with ethyl acetate (5 ml $\times$ 3), washed with saturated saline solution (10 mL), and the organic phases were combined and dried over anhydrous sodium sulfate. The crude product was concentrated under reduced pressure and purified by column chromatography (DCM/MeOH=15/1) to obtain compound **18b** (60 mg), light yellow solid.

MS (ESI) m/z 275 $[M + H]^+$.

^1H NMR (400 MHz, DMSO- d_6) δ 10.00 (s, 1H), 7.71 (d, $J = 8.0$ Hz, 2H), 7.62 (d, $J = 8.0$ Hz, 2H), 5.97 (s, 1H), 5.70 (s, 1H), 4.16 (s, 2H), 3.30 (s, 3H), 1.29 (s, 12H).

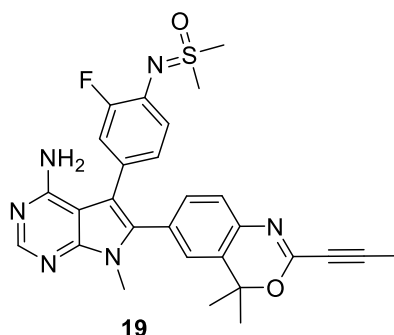
Step 2 N- (4- (4-amino-5- (3-fluoro-4- ((1-oxotetrahydro-1 λ^6 -thiophene-1-ylidene) amino) phenyl) -7-methyl-7H-pyrrolo [2,3- d] pyrimidin-6-yl) phenyl) -2- (methoxymethyl) acrylamide **18**

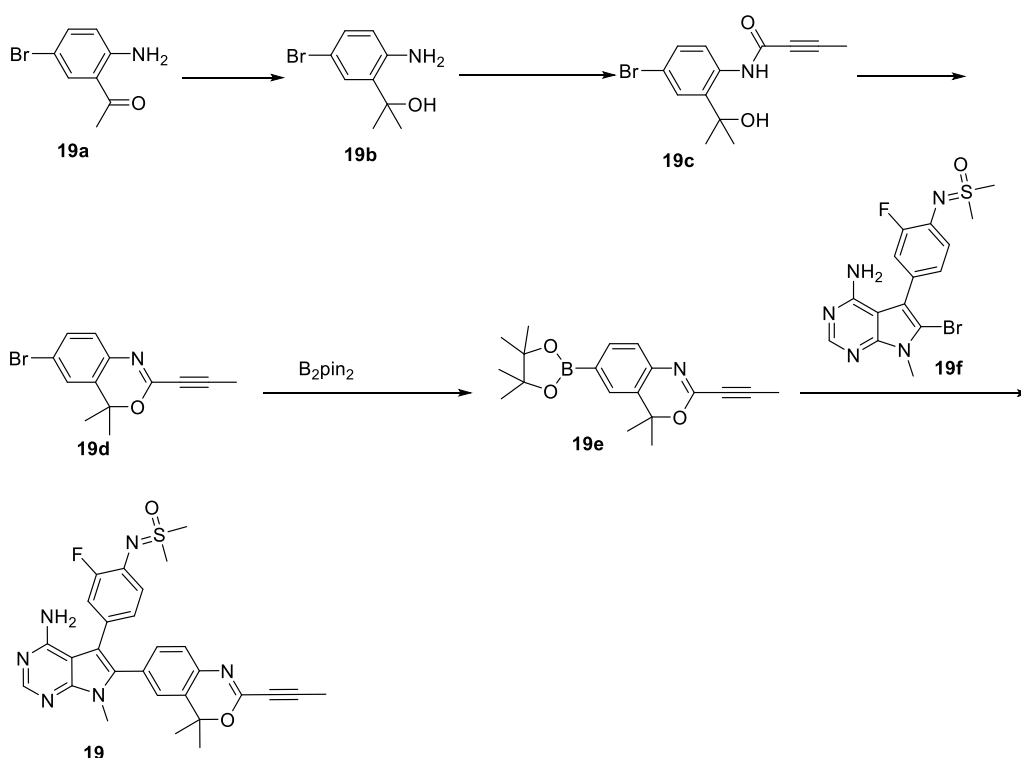
At room temperature, compound **18b** (60.00 mg, 0.19 mmol), compound **18c** (82.50 mg, 0.17 mmol), chlorine [(*n*-butyl di (1-adamantanyl) phosphine) -2- (2-aminobiphenyl)] palladium (II) (12.70 mg, 0.019 mmol), potassium phosphate (80.56 mg, 0.38 mmol), N, N-dimethylacetamide (2 mL), and water (0.5 mL) were sequentially added to a round bottom flask, followed by vacuum pumping and nitrogen gas purging three times, then heat up to 80 $^\circ\text{C}$ and stirred for 3 h. After the reaction was completed, the mixture was cooled to room temperature and concentrated under reduced pressure to obtain a crude product. The crude product was purified by column chromatography (DCM/MeOH=15/1) to obtain compound **18** (12.3 mg), white solid.

MS (ESI) m/z 549 $[M + H]^+$.

^1H NMR (400 MHz, DMSO- d_6) δ 10.09 (s, 1H), 8.24 (s, 1H), 7.77 (d, $J = 8.0$ Hz, 2H), 7.35 (d, $J = 8.0$ Hz, 2H), 7.10 (t, $J = 20.0$ Hz, 1H), 6.99-6.95 (m, 2H), 6.02 (s, 1H), 5.76 (s, 1H), 4.22 (s, 2H), 3.65 (s, 3H), 3.42 (s, 2H), 3.37 (s, 3H), 2.29-2.06 (m, 4H), 1.31 (s, 1H).

Example 19 (4- (4-amino-6- (4,4-dimethyl-2- (propyl-1-yn-1-yl) -4H benzo [d] [1,3] oxazin-6-yl) -7-methyl-7H-pyrrolo [2,3- d] pyrimidin-5-yl) -2-fluorophenyl) imino) dimethyl - λ^6 -sulfoxide





Step 1 2-(2-amino-5-bromophenyl) propan-2-ol **19b**

Compound **19a** (1 g, 4.67 mmol) was dissolved in tetrahydrofuran (5 mL), and it was cooled to around 0 °C, a solution of methyl magnesium bromide in tetrahydrofuran (1 M, 7 mL) was added, and then the temperature was restored to room temperature to react for 2 h. The reaction solution was quenched by added saturated amine chloride solution (20 mL), extracted with ethyl acetate (20 mL × 3), and the organic phases were combined, dried over anhydrous sodium sulfate and concentrated. The crude product was purified by column chromatography (PE/EtOAc=10/1) to obtain compound **19b** (0.7 g), white solid.

MS (ESI) m/z 230 $[M + H]^+$.

Step 2 *N*-(4-bromo-2-(2-hydroxypropyl-2-yl) phenyl) but-2-amide **19c**

Compound **19b** (200 mg, 0.87 mmol) and 2-butyne acid (73 mg, 0.87 mmol) were dissolved in dry dichloromethane (5 mL), after cooled down to around 0 °C, 1-ethyl - (3-dimethylaminopropyl) carbodiimide hydrochloride (183 mg, 0.95 mmol) was added, and then the temperature was restored to room temperature to react for 3 h. The reaction solution was concentrated, and the crude product was purified by column chromatography (PE/EtOAc=10/1) to obtain compound **19c** (200 mg), yellow oil.

MS (ESI) m/z 296 $[M + H]^+$.

¹H NMR (400 MHz, DMSO-*d*₆) δ 10.90 (s, 1H), 8.04 (d, J = 9.2 Hz, 1H), 7.52 – 7.35 (m, 2H), 6.38 (s, 1H), 2.04 (s, 3H), 1.53 (s, 6H).

Step 3 6-bromo-4,4-dimethyl-2-(propyl-1-acetyl-1-yl) -4*H* benzo [*d*] [1,3] oxazine **19d**

Compound **19c** (540 mg, 1.82 mmol) was dissolved in dry dichloromethane (5 mL), methanesulfonic acid (876 mg, 9.13 mmol) was added, and under nitrogen protection, it was

heated up to 45 °C to react for 16 h, and then cooled down to room temperature, concentrated to dry solvent. Saturated sodium bicarbonate solution (20 mL) was added and extracted with ethyl acetate (20 mL × 3), and the organic phases were combined, washed with saturated saline water (50 mL), and concentrated under reduced pressure to obtain a crude product. The crude product was purified by column chromatography (PE/EtOAc=50/1) to obtain compound **19d** (240 mg), yellow oil.

MS (ESI) m/z 278 [M + H]⁺.

¹H NMR (400 MHz, DMSO-*d*₆) δ 7.52 (d, J = 2.2 Hz, 1H), 7.49 – 7.45 (m, 1H), 7.01 (d, J = 8.3 Hz, 1H), 2.05 (s, 3H), 1.58 (s, 6H).

Step 4 4,4-dimethyl-2-(propyl-1-yn-1-yl)-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-4H benzo [d] [1,3] oxazine **19e**

Compound **19d** (270 mg, 0.97 mmol) was dissolved in dry 1,4-dioxane (10 mL), bis(pinacolato)diboron (370 mg, 1.46 mmol), 1,1'-biphenylphosphine ferrocene palladium chloride (71 mg, 0.097 mmol), and potassium acetate (285 mg, 2.91 mmol) were added sequentially, after replaced with nitrogen three times, heated up to 90 °C under nitrogen protection to react for 18 h. Then cooled down to room temperature, filtered, concentrated, and the crude product was purified by column chromatography (PE/EtOAc =50/1) to obtain compound **19e** (140 mg), yellow oil.

MS (ESI) m/z 325 [M + H]⁺.

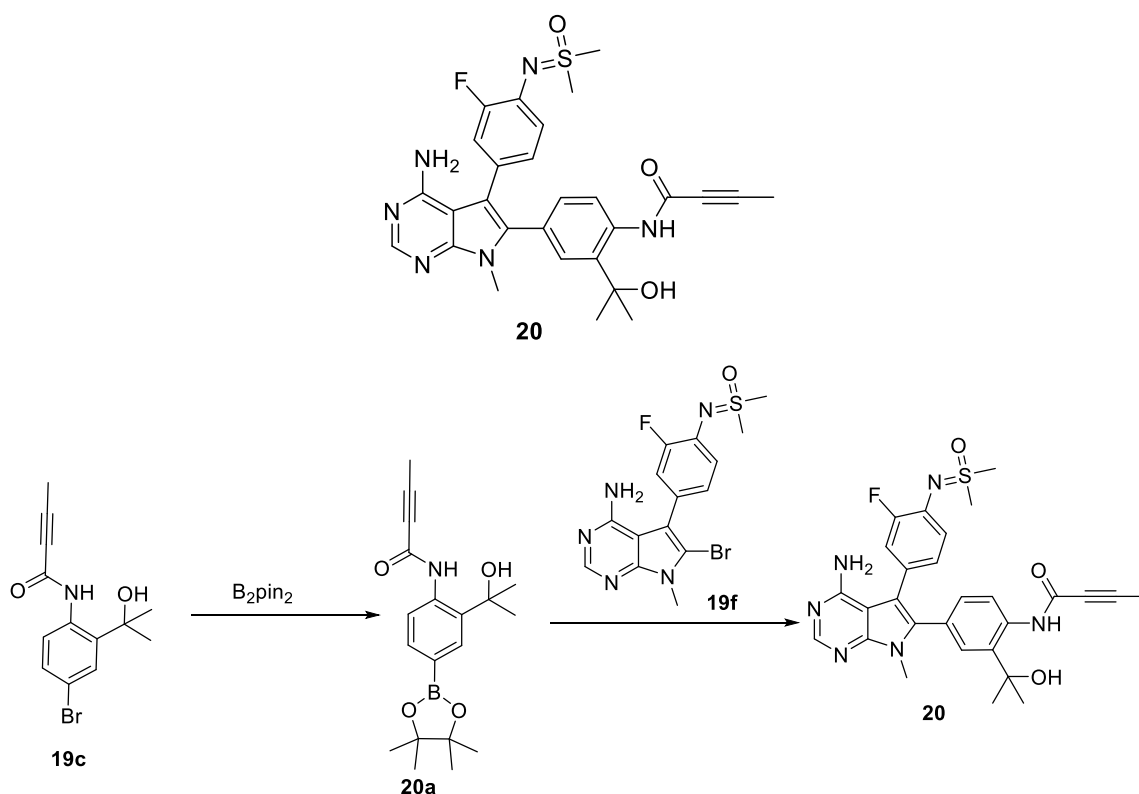
Step 5 4-(4-amino-6-(4,4-dimethyl-2-(propyl-1-yn-1-yl)-4H benzo [d] [1,3] oxazine -6-yl)-7-methyl-7H-pyrrolo [2,3-*d*] pyrimidin-5-yl)-2-fluorophenyl imino) dimethyl - λ^6 -sulfoxide **19**

Compound **19e** (66 mg, 0.20 mmol), ((4-(4-amino-6-bromo-7-methyl-7H-pyrrolo [2,3-*d*] pyrimidin-5-yl)-2-fluorophenyl) imino) dimethyl- λ^6 -sulfone **19f** (70 mg, 0.17 mmol) were dissolved in 1,4-dioxane (7 mL) and water (1.5 mL), tetrakis (triphenylphosphine) palladium (39.2 mg, 0.034 mmol), K₃PO₄ (108 mg, 0.51 mmol) were added, after replaced with nitrogen gas three times, heated up to 90 °C to react for 2 h. Then cooled down to room temperature, diluted with water (10 mL), extracted with dichloromethane (10 mL × 3), and the organic phases were combined, dried with anhydrous sodium sulfate, concentrated, and the crude product was separated by high-performance liquid chromatography (preparation column: YMCC18, mobile phase A: 0.05% ammonia solution in H₂O, mobile phase B: acetonitrile, 30%~60% acetonitrile, 40mL/min) to obtain compound **19** (13 mg), white solid.

MS (ESI) m/z 531 [M + H]⁺.

¹H NMR (400 MHz, DMSO-*d*₆) δ 8.20 (s, 1H), 7.29 (dd, J = 8.0, 1.8 Hz, 1H), 7.12 (dd, J = 15.3, 5.1 Hz, 2H), 7.04 (d, J = 8.0 Hz, 1H), 6.96 – 6.86 (m, 2H), 6.00 (*brs*, 2H), 3.66 (s, 3H), 3.26 (s, 6H), 2.04 (s, 3H), 1.44 (s, 6H).

Example 20 N-(4-(4-amino-5-(4-(dimethyl (oxo) - λ^6 -sulfanylidene) amino)-3-fluorophenyl)-7-methyl-7H-pyrrolo [2,3-*d*] pyrimidin-6-yl)-2-(2-hydroxypropan-2-yl)phenyl) but-2-amide



Step 1 *N*-(2- (2-hydroxypropan-2-yl) -4- (4,4,5,5-tetramethyl-1,3,2- dioxaborolan - 2-yl) phenyl) but-2-amide 20a

Compound **19c** (270 mg, 0.97 mmol) was dissolved in dry 1,4-dioxane (10 mL), bis(pinacolato)diboron (370 mg, 1.46 mmol), Pd(dppf)Cl₂ (71 mg, 0.097 mmol), and potassium acetate (285 mg, 2.91 mmol) were added sequentially, after replaced with nitrogen three times, heated up to 90 °C under nitrogen protection, and reacted for 18 h. Then cooled to room temperature, filtered, concentrated, and the crude product was purified by column chromatography (PE/EtOAc=50/1) to obtain compound **20a** (140 mg), yellow oil.

MS (ESI) *m/z* 343 [M + H]⁺.

Step 2 *N*-(4- (4-amino-5- (4- (dimethyl (oxo) - λ⁶-sulfanylidene) amino) -3-fluorophenyl) -7-methyl-7*H*-pyrrolo [2,3-*d*] pyrimidin-6-yl) -2- (2-hydroxypropan-2-yl) phenyl) but-2-amide 20

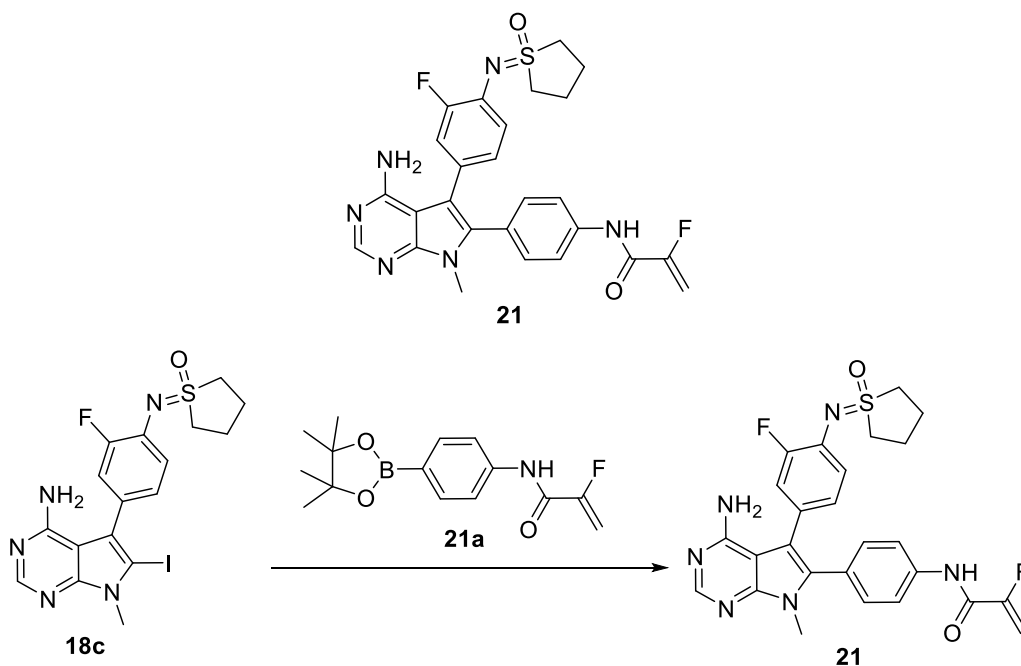
Compound **20a** (70 mg, 0.20 mmol), (4- (4-amino-6-bromo-7-methyl-7*H*-pyrrolo [2,3-*d*] pyrimidin-5-yl) -2-fluorophenyl) imino) dimethyl - λ⁶-sulfone **19f** (66 mg, 0.16 mmol) were dissolved in 1,4-dioxane (7 mL) and water (1.5 mL), tetrakis (triphenylphosphine) palladium (39.2 mg, 0.034 mmol), K₃PO₄ (108 mg, 0.51 mmol) were added, after replaced with nitrogen gas three times, heated up to 90 °C and reacted for 2 h. Then cooled down to room temperature, diluted with water (10 mL), extracted with dichloromethane (10 mL × 3), and the organic phases were combined, dried with anhydrous sodium sulfate, concentrated, and the crude product was separated by high-performance liquid chromatography (preparation column: YMCC18, mobile phase A: 0.05% ammonia solution in H₂O, mobile phase B: acetonitrile, 30%~60% acetonitrile, 40mL/min) to obtain compound **20** (7.6 mg), white solid.

MS (ESI) m/z 549 $[M + H]^+$.

^1H NMR (400 MHz, DMSO- d_6) δ 12.71 (s, 1H), 8.21 (s, 1H), 7.34 (d, $J = 8.2$ Hz, 1H), 7.21 – 7.10 (m, 3H), 6.92 (dd, $J = 16.5, 11.0$ Hz, 2H), 6.07 (brs, 2H), 5.02 (s, 1H), 3.66 (s, 3H), 3.26 (s, 6H), 2.00 (s, 3H), 1.49 (s, 6H).

5

Example 21 *N*-(4-(4-amino-5-(3-fluoro-4-((1-oxotetrahydro-1 λ^6 -thiophene-1-ylidene) amino) phenyl) -7-methyl-7H-pyrrolo [2,3-*d*] pyrimidin-6-yl) phenyl) -2-fluoroacrylamide



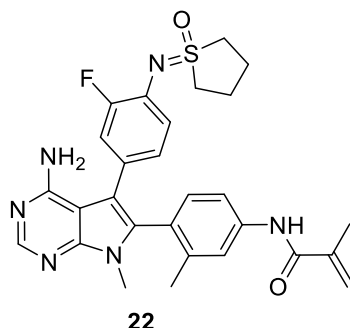
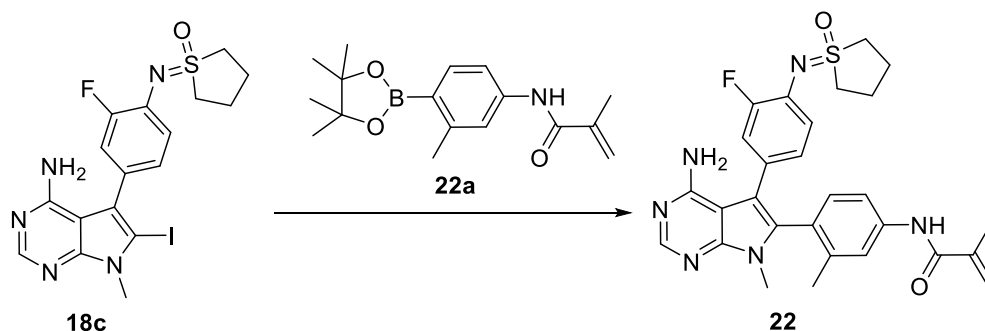
10 Compound **18c** (100 mg, 0.20 mmol) and compound **21a** (71 mg, 0.24 mmol) were dissolved in *N,N*-dimethylacetamide (4 mL) and water (1 mL), chlorine [(*n*-butyl di (1-adamantanyl) phosphine) -2- (2-aminobiphenyl)] palladium (II) (13.8 mg, 0.02 mmol) and K_3PO_4 (87.4 mg, 0.4 mmol) were added, after replaced with nitrogen gas three times, heated up to 80 °C and reacted for 2 h. Then cooled down to room temperature, diluted with water (20 mL), extracted with dichloromethane (20 mL $\times$ 3), and the organic phases were combined, dried with anhydrous sodium sulfate, concentrated, and the crude product were separated by high-performance liquid chromatography (preparation column: YMCC18, mobile phase A: 0.05% ammonia solution in H_2O , mobile phase B: acetonitrile, 30%~60% acetonitrile, 40mL/min) to obtain compound **21** (23.6 mg), white solid.

20 MS (ESI) m/z 523 $[M + H]^+$.

^1H NMR (400 MHz, DMSO- d_6) δ 10.40 (s, 1H), 8.19 (s, 1H), 7.77 (d, $J = 8.0$ Hz, 2H), 7.33 (d, $J = 8.1$ Hz, 2H), 7.26 – 7.16 (m, 1H), 7.05 (t, $J = 8.6$ Hz, 1H), 6.93 (d, $J = 8.5$ Hz, 1H), 5.93 (brs, 2H), 5.80 (s, 0.5H), 5.68 (s, 0.5H), 5.46 (d, $J = 14.6$ Hz, 1H), 3.60 (s, 3H), 3.29-3.12 (m, 4H), 2.27-2.08 (m, 4H).

25

Example 22 *N*- (4- (4-amino-5- (3-fluoro-4- ((1-oxotetrahydro-1 λ^6 -thiophene-1-ylidene) amino) phenyl) -7-methyl-7*H*-pyrrolo [2,3-*d*] pyrimidin-6-yl) -3-methylphenyl) methacrylamide

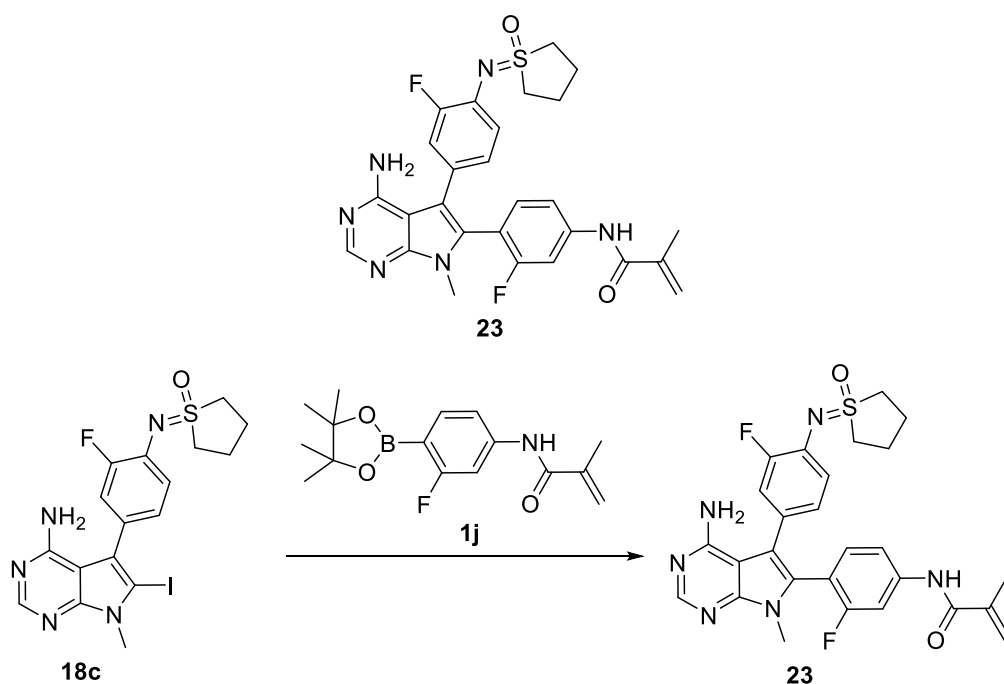


Compound **18c** (100 mg, 0.20 mmol) and compound **22a** (74 mg, 0.24 mmol) were dissolved in *N,N*-dimethylacetamide (4 mL) and water (1 mL), chlorine [(*n*-butyl di (1-adamantanyl) phosphine) -2- (2-aminobiphenyl)] palladium (II) (13.8 mg, 0.02 mmol) and K_3PO_4 (87.4 mg, 0.4 mmol) were added, after replaced with nitrogen three times, heated up to 80 °C to react for 2 h. Then cooled down to room temperature, diluted with water (20 mL), extracted with dichloromethane (20 mL $\times$ 3), and the organic phases were combined, dried with anhydrous sodium sulfate, concentrated, and the crude product was separated by high-performance liquid chromatography (preparation column: YMCC18, mobile phase A: 0.05% ammonia solution in H_2O , mobile phase B: acetonitrile, 30%~60% acetonitrile, 40mL/min) to obtain compound **22** (30.9 mg), white solid.

MS (ESI) m/z 533 $[M + H]^+$.

^1H NMR (400 MHz, $DMSO-d_6$) δ 9.83 (s, 1H), 8.19 (s, 1H), 7.67 – 7.58 (m, 2H), 7.27 (m, 2H), 7.01 (m, 1H), 6.87 (m, 1H), 5.99 (brs, 2H), 5.82 (s, 1H), 5.53 (s, 1H), 3.41 (s, 3H), 3.28 (m, 4H), 2.27 – 2.08 (m, 4H), 1.96 (s, 3H), 1.93 (s, 3H).

Example 23 *N*- (4- (4-amino-5- (3-fluoro-4- ((1-oxotetrahydro-1 λ^6 -thiophene-1-ylidene) amino) phenyl) -7-methyl-7*H*-pyrrolo [2,3-*d*] pyrimidin-6-yl) -3-fluorophenyl) methacrylamide



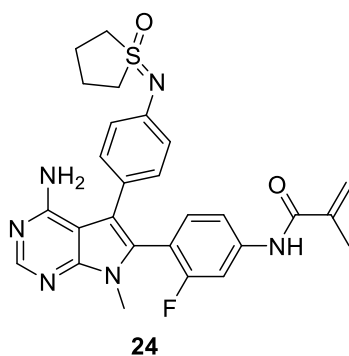
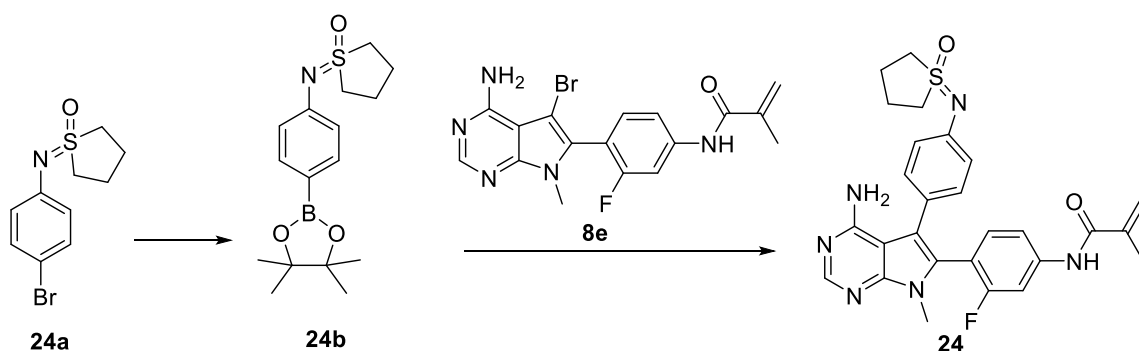
Compound **18c** (100 mg, 0.20 mmol) and compound **1j** (70 mg, 0.23 mmol) were dissolved in N, N-dimethylacetamide (4 mL) and water (1 mL), chlorine [(n-butyl di (1-adamantanyl) phosphine) -2- (2-aminobiphenyl)] palladium (II) (13.8 mg, 0.02 mmol), K₃PO₄ (87.4 mg, 0.4 mmol) were added, after replaced with nitrogen three times, heated up to 80 °C to react for 2 h. Then cooled to room temperature, diluted with water (20 mL), extracted with dichloromethane (20 mL × 3), and the organic phases were combined, dried with anhydrous sodium sulfate, concentrated, and the crude product was separated by high-performance liquid chromatography (preparation column: YMCC18, mobile phase A: 0.05% ammonia solution in H₂O, mobile phase B: acetonitrile, 30%~60% acetonitrile, 40mL/min) to obtain compound **23** (17.5 mg), white solid.

MS (ESI) *m/z* 537 [M + H]⁺.

¹H NMR (400 MHz, DMSO-*d*₆) δ 10.12 (s, 1H), 8.21 (s, 1H), 7.78 (d, *J* = 12.4 Hz, 1H), 7.52 (d, *J* = 8.0 Hz, 1H), 7.31 (t, *J* = 8.0 Hz, 1H), 7.05 (t, *J* = 8.4 Hz, 1H), 6.92 (d, *J* = 10.7 Hz, 2H), 6.04 (brs, 2H), 5.84 (s, 1H), 5.59 (s, 1H), 3.54 (s, 3H), 3.31 (m, 4H), 2.18 (dd, *J* = 33.7, 6.6 Hz, 4H), 1.97 (s, 3H).

Example 24 *N*-(4-(4-amino-7-methyl-5-(4-(1-oxotetrahydro-1 λ ⁶-thiophene-1-ylidene) amino) phenyl) -7*H*-pyrrolo [2,3-*d*] pyrimidin-6-yl) -3-fluorophenyl) methacrylamide

20



Step 1 1- (4- (4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) phenyl) imino) tetrahydro-1H-1 λ⁶-thiophene 1-oxide 24b

To a 100 mL round bottom flask, compound **24h** (1.02 g, 3.10 mmol), bis(pinacolato)diboron (0.973 g, 3.83 mmol), Pd(dppf)Cl₂ (0.461 mg, 0.63 mmol), potassium acetate (0.943g, 9.61 mmol), 1,4-dioxane (20 mL) were added sequentially, then heated up to 100 °C to react for 4 h, after TLC monitored the completion of the reaction, it was cooled down to room temperature, filtered through diatomaceous earth, extracted with ethyl acetate (50 mL × 3), and the organic phases were combined, washed with saturated saline (50 mL), and concentrated under reduced pressure to obtain a crude product. The crude product was purified by column chromatography (PE/EtOAc=1/1) to obtain compound **24b** (0.80 g), yellow solid.

MS (ESI) *m/z* 322.2 [M + H]⁺.

¹H NMR (400 MHz, CDCl₃) δ 7.62 (d, *J* = 8.3 Hz, 2H), 6.98 (d, *J* = 8.3 Hz, 2H), 3.37 – 3.30 (m, 1H), 3.15 – 3.08 (m, 1H), 2.20 (dd, *J* = 29.3, 6.9 Hz, 2H), 1.26 (s, 6H).

Step 2 N- (4- (4-amino-7-methyl-5- (4- (1-oxotetrahydro-1 λ⁶-thiophene-1-ylidene) amino) phenyl) -7H-pyrrolo [2,3-*d*] pyrimidin-6-yl) -3-fluorophenyl) methacrylamide 24

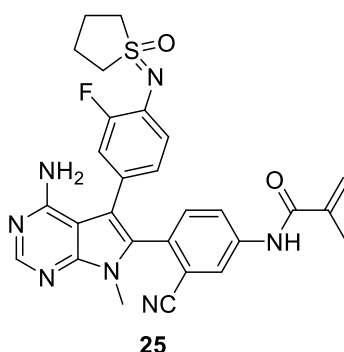
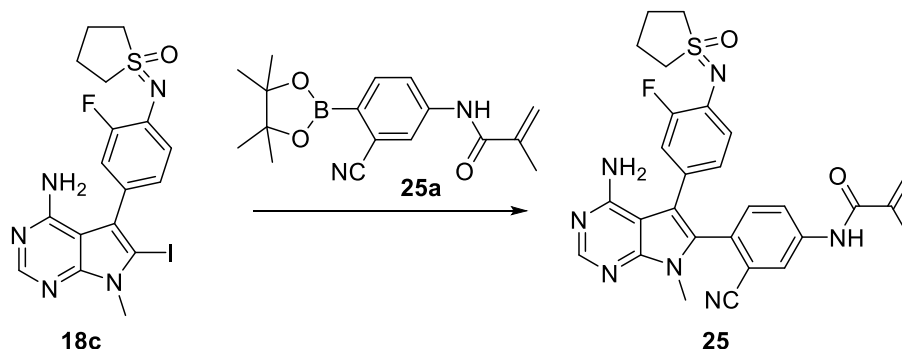
To a 25 mL round bottom flask, compound **4b** (45 mg, 0.14 mmol), compound **8e** (50 mg, 0.12 mmol), and Pd(dppf)Cl₂ (20 mg, 0.03 mmol), potassium phosphate (80 mg, 0.38 mmol), 1,4-dioxane (5 mL), and water (1 mL) were added in sequence, then heated up to 80 °C to react for 0.5 h, after TLC monitored the completion of the reaction, it was cooled down to room temperature, filtered through diatomaceous earth, extracted with ethyl acetate (20 mL × 3), and the organic phases were combined, washed with saturated saline (20 mL), and concentrated under reduced pressure to obtain a crude product. The crude product was purified by column chromatography (DCM/MeOH=6/1) to obtain compound **24** (22 mg), white solid.

MS (ESI) *m/z* 519.41 [M + H]⁺.

5

^1H NMR (400 MHz, CDCl_3) δ 8.28 (s, 1H), 7.65 – 7.61 (m, 1H), 7.48 (s, 1H), 7.05 (d, J = 7.7 Hz, 2H), 7.00 (t, J = 4.1 Hz, 2H), 6.91 (d, J = 8.5 Hz, 2H), 5.73 (s, 1H), 5.45 (d, J = 1.3 Hz, 1H), 4.98 (s, 2H), 3.59 (d, J = 0.9 Hz, 3H), 3.36 (dd, J = 12.6, 6.0 Hz, 2H), 3.13 (dd, J = 12.8, 6.6 Hz, 2H), 2.29 – 2.19 (m, 3H), 1.99 (d, J = 10.1 Hz, 3H).

Example 25 *N*-(4-(4-amino-5-(3-fluoro-4-((1-oxotetrahydro-1 λ^6 -thiophene-1-ylidene)amino) phenyl)-7-methyl-7H-pyrrolo [2,3-*d*] pyrimidin-6-yl)-3-cyanophenyl) methacrylamide



10

To a 25 mL round bottom flask, compound **18c** (80 mg, 0.16 mmol), compound **25a** (57 mg, 0.18 mmol), Pd(dppf)Cl_2 (12 mg, 0.016 mmol), potassium phosphate (102 mg, 0.48 mmol), 1,4-dioxane (10 mL), and water (1 mL) were added in sequence, then heated up to 80 °C to react for 1 h. After TLC monitored the completion of the reaction, it was cooled down to room temperature, filtered through diatomaceous earth, extracted with ethyl acetate (30 mL $\times$ 3), and the organic phases were combined, washed with saturated saline (30 mL), and concentrated under reduced pressure to obtain a crude product. The crude product was purified by column chromatography (DCM/MeOH=6/1) to obtain compound **25** (4 mg), white solid.

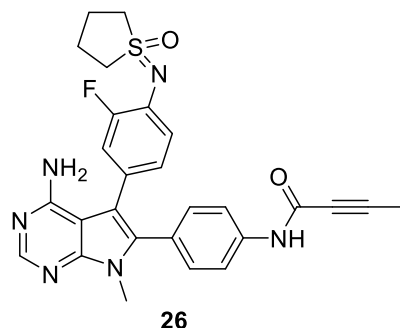
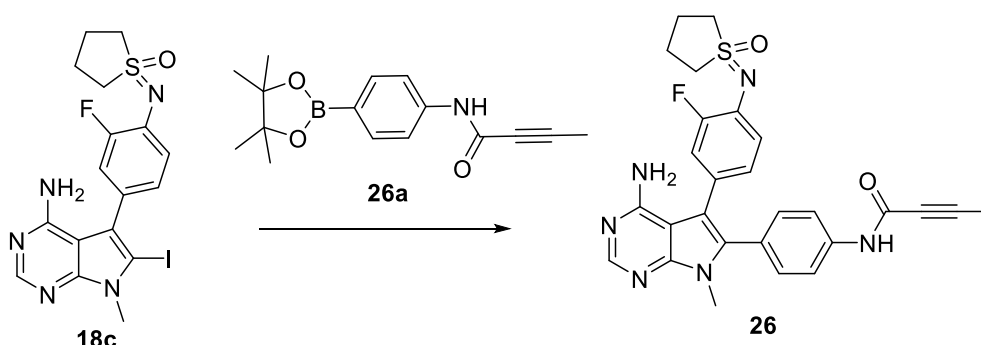
15

MS (ESI) m/z 544.73 $[\text{M} + \text{H}]^+$

20

^1H NMR (400 MHz, CDCl_3) δ 8.28 (s, 1H), 7.65 – 7.61 (m, 1H), 7.48 (s, 1H), 7.05 (d, J = 7.7 Hz, 2H), 7.00 (t, J = 4.1 Hz, 2H), 6.91 (d, J = 8.5 Hz, 2H), 5.73 (s, 1H), 5.45 (d, J = 1.3 Hz, 1H), 4.98 (s, 2H), 3.59 (d, J = 0.9 Hz, 3H), 3.36 (dd, J = 12.6, 6.0 Hz, 2H), 3.13 (dd, J = 12.8, 6.6 Hz, 2H), 2.29 – 2.19 (m, 3H), 1.99 (d, J = 10.1 Hz, 3H).

Example 26 *N*- (4- (4-amino-5- (3-fluoro-4- ((1-oxotetrahydro-1 λ^6 -thiophene-1-ylidene) amino) phenyl) -7-methyl-7*H*-pyrrolo [2,3-*d*] pyrimidin-6-yl) -3-cyanophenyl) methacrylamide

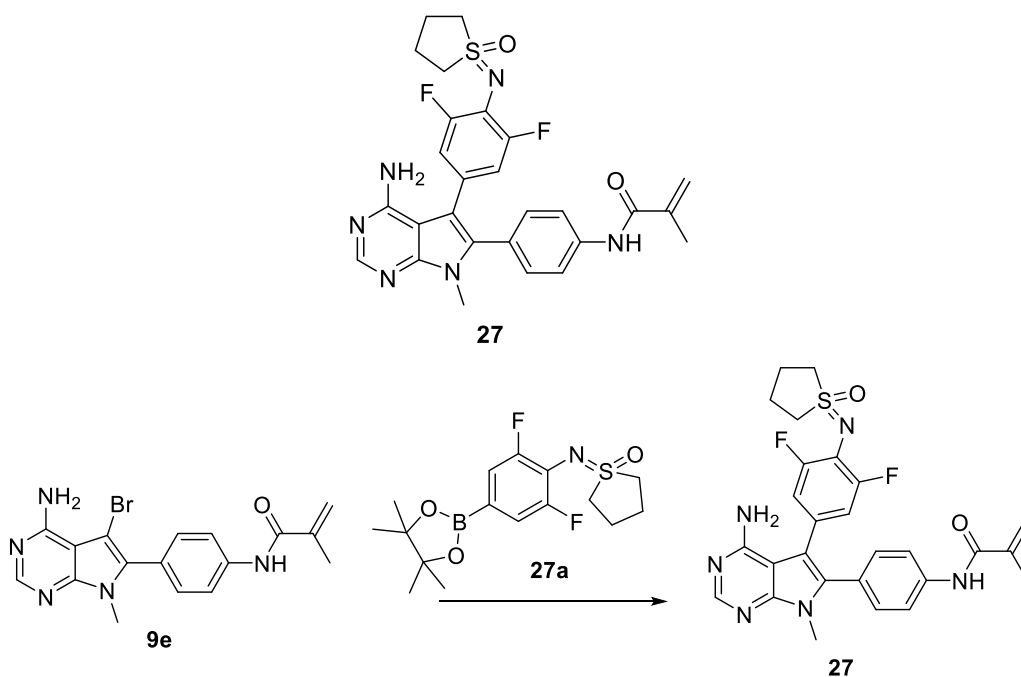


To a 25 mL round bottom flask, compound **18c** (120 mg, 0.25 mmol), compound **26a** (80 mg, 0.28 mmol), tetrakis (triphenylphosphine) palladium (29 mg, 0.025 mmol), anhydrous potassium phosphate (159 mg, 0.75 mmol), 1,4-dioxane (10 mL), and water (1 mL) were added in sequence, then heated up to 90 °C to react for 1 h, after the reaction was completed, it was cooled down to room temperature, filtered through diatomaceous earth, extracted with ethyl acetate (30 mL $\times$ 3), the organic phases were combined, washed with saturated saline (30 mL), and concentrated under reduced pressure to obtain a crude product. The crude product was purified by column chromatography (DCM/MeOH=6/1) to obtain compound **26** (13.8 mg), white solid.

MS (ESI) m/z 517.97 $[M + H]^+$

^1H NMR (400 MHz, CDCl_3) δ 8.28 (s, 1H), 7.43 (s, 2H), 7.34 (s, 1H), 7.14 (d, $J = 8.5$ Hz, 2H), 7.04 (d, $J = 7.4$ Hz, 1H), 6.84 (dd, $J = 8.7, 6.8$ Hz, 2H), 4.95 (s, 2H), 3.62 (s, 1H), 3.36 (dd, $J = 12.9, 6.8$ Hz, 2H), 3.21 – 3.14 (m, 2H), 2.25 (d, $J = 7.6$ Hz, 4H), 1.96 (d, $J = 3.9$ Hz, 3H).

Example 27 *N*- (4-(4-amino-5- (3,5-difluoro-4- ((1-oxotetrahydro-1 λ^6 -thiophene-1-ylidene) amino) phenyl) -7-methyl-7*H*-pyrrolo [2,3-*d*] pyrimidin-6-yl) phenyl) methacrylamide

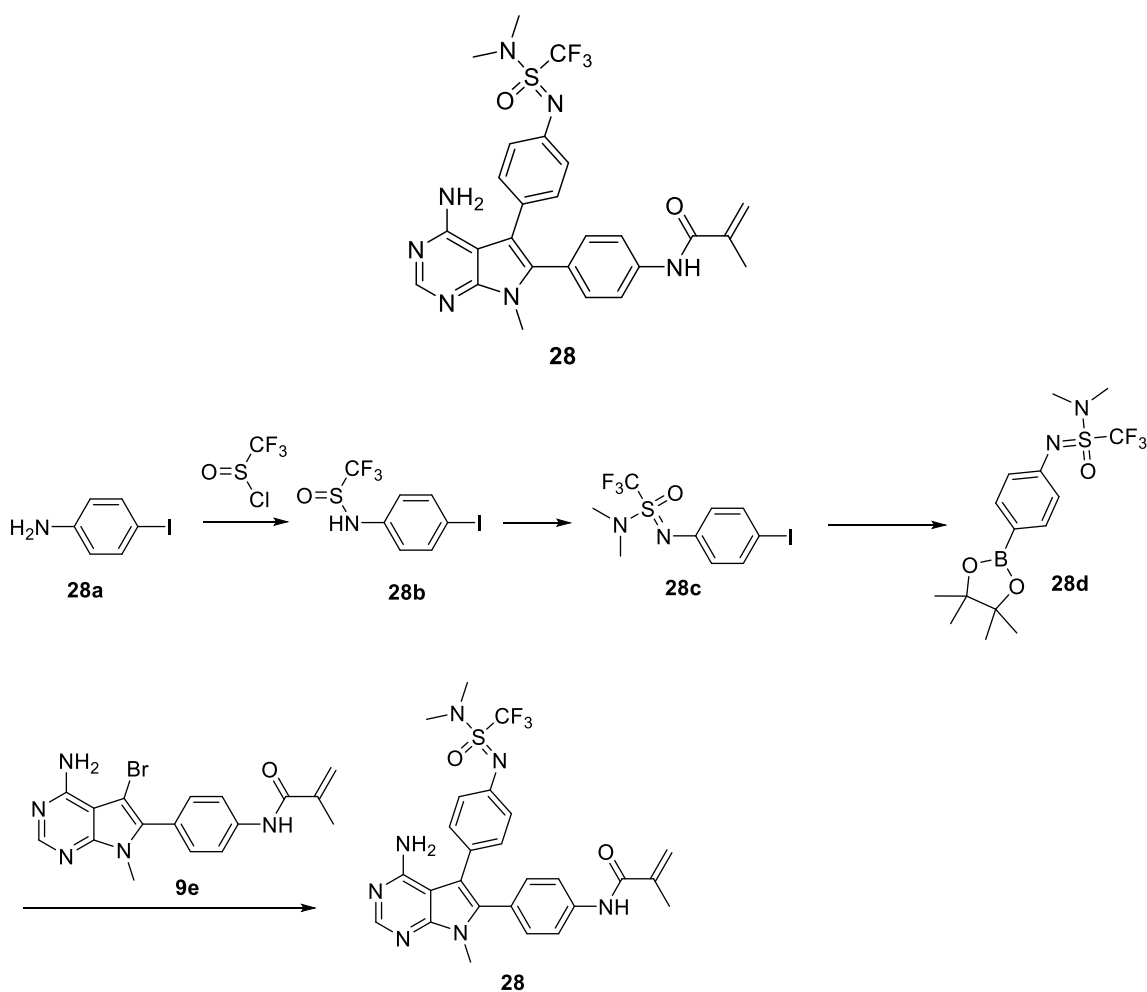


To a 25 mL round bottom flask, compound **9e** (78 mg, 0.20 mmol), compound **27a** (80 mg, 0.22 mmol), tetrakis (triphenylphosphine) palladium (25 mg, 0.02 mmol), anhydrous potassium phosphate (127 mg, 0.60 mmol), 1,4-dioxane (10 mL), and water (1 mL) were added in sequence, then heated up to 90 °C to react for 1 h. After TLC monitored the completion of the reaction, it was cooled down to room temperature, filtered through diatomaceous earth, extracted with ethyl acetate (30 mL × 3), and the organic phases were combined, washed with saturated saline (30 mL), and concentrated under reduced pressure to obtain a crude product. The crude product was purified by column chromatography (DCM/MeOH=6/1) to obtain compound **27** (18 mg), white solid.

MS (ESI) m/z 537.63 $[M + H]^+$.

^1H NMR (400 MHz, CDCl_3) δ 8.38 (s, 1H), 7.62 (d, $J = 8.5$ Hz, 3H), 7.24 (d, $J = 8.5$ Hz, 2H), 6.79 (d, $J = 8.7$ Hz, 2H), 5.84 (s, 1H), 5.53 (s, 1H), 5.21 (s, 2H), 3.72 (s, 3H), 3.52 – 3.44 (m, 2H), 3.31 (dd, $J = 12.8, 7.1$ Hz, 2H), 2.35 (d, $J = 2.1$ Hz, 4H), 2.11 (s, 3H).

Example 28 *N*-(4-(4-amino-5-(4-((dimethylamino)oxo)(trifluoromethyl)- λ^6 -sulfanylidene)amino)phenyl)-7-methyl-7H-pyrrolo [2,3-*d*] pyrimidin-6-yl) phenyl) methacrylamide



Step 1 1,1,1-trifluoro-*N*-(4-iodophenyl) methylthioamide

Compound **28a** (1.0 g, 4.6 mmol) was dissolved in DCM (10 mL), triethylamine (0.51 g, 5.0 mmol) was added, and it was cooled down to 0 °C, trifluoromethanesulfonyl chloride (0.73g, 4.8 mmol) was added dropwise, and warmed up to room temperature naturally to react for 1 h. The reaction solution was poured into water, extracted with ethyl acetate three times, dried with anhydrous sodium sulfate, and concentrated to obtain a crude product. The crude product was purified by column chromatography (PE/EtOAc=0-20%) to obtain compound **8b** (1.25 g), yellow oily liquid.

MS (ESI) m/z 335 $[M + H]^+$.

^1H NMR (400 MHz, CDCl_3) δ 7.69 (d, $J = 8.7$ Hz, 2H), 6.97 – 6.81 (m, 2H), 6.46 (s, 1H).

Step 2 1,1,1-trifluoro-*N'*-(4-iodophenyl) - *N*, *N*-dimethylmethanesulfonamide **28c**

Compound **28a** (1.4 g, 4.2 mmol) and *N*-chlorosuccinimide (0.62 g, 4.6 mmol) were dissolved in acetonitrile (30 mL), a solution of tetrabutylammonium fluoride in THF (4.6 mL, 4.6 mmol, 1M) was added at 0 °C to react at room temperature for 30 min, and the reaction solution was concentrated, then acetonitrile (20 mL) and a solution of dimethylamine in THF (8.35 mL, 16.7 mmol, 2M) were added, and reacted at room temperature for 2 h. The reaction solution was concentrated and dried, and the obtained crude product was purified by column chromatography (PE/EtOAc=0-20%) to obtain compound **28c** (1.4 g), reddish brown solid.

MS (ESI) m/z 379 $[M + H]^+$.

^1H NMR (400 MHz, CDCl_3) δ 7.57 (d, $J = 8.6$ Hz, 2H), 6.87 (d, $J = 8.6$ Hz, 2H), 3.08 (s, 6H).

Step 3 1,1,1-trifluoro-N,N-dimethyl-N'-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) phenyl) methanesulfonamide 28d

28c (1.0 g, 2.6 mmol), bis(pinacolato)diboron (1.0 g, 4.0 mmol), $\text{Pd}(\text{dppf})\text{Cl}_2$ (193 mg, 0.26 mmol), and potassium acetate (778 mg, 7.9 mmol) were placed in a bottle, 1,4-dioxane (15 mL) was added, after replaced with N_2 three times, the reaction was carried out at 100 °C for 18 h. The reaction solution was filtered and concentrated, and the obtained crude product was purified by column chromatography (PE/EtOAc=0-20%) to obtain compound **28d** (0.65 g), white solid.

MS (ESI) m/z 379 $[M + H]^+$.

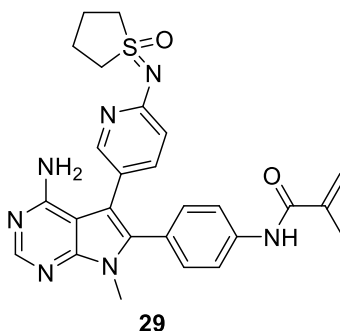
Step 4 N- (4- (4-amino-5- (4- ((dimethylamino) (oxo) (trifluoromethyl) - λ^6 -sulfanylidene) amino) phenyl) -7-methyl-7H-pyrrolo [2,3-d] pyrimidin-6-yl) phenyl) methacrylamide 28

To a 25 mL round bottom flask, compound **9e** (93 mg, 0.24 mmol), compound **28d** (100 mg, 0.26 mmol), tetrakis (triphenylphosphine) palladium (30 mg, 0.024 mmol), anhydrous potassium phosphate (120 mg, 0.54 mmol), 1,4-dioxane (10 mL), and water (1 mL) were added in sequence, and heated up to 90 °C to react for 1 h. After TLC monitored the completion of the reaction, it was cooled down to room temperature, filtered through diatomaceous earth, extracted with ethyl acetate (30 mL $\times$ 3), and the organic phases were combined, washed with saturated saline (30 mL), and concentrated under reduced pressure to obtain a crude product. The crude product was purified by column chromatography (DCM/MeOH=6/1) to obtain compound **28** (12.5 mg), white solid.

MS (ESI) m/z 558.53 $[M + H]^+$.

^1H NMR (400 MHz, CDCl_3) δ 8.37 (s, 1H), 7.63 – 7.54 (m, 3H), 7.24 (d, $J = 8.5$ Hz, 2H), 7.16 (d, $J = 8.3$ Hz, 2H), 7.05 (d, $J = 8.3$ Hz, 2H), 5.83 (s, 1H), 5.52 (s, 1H), 5.19 (s, 2H), 3.74 (s, 3H), 3.11 (s, 6H), 2.10 (s, 3H).

Example 29 N- (4- (4-amino-7-methyl-5- (6- (1-oxotetrahydro-1 λ^6 -thiophene-1-ylidene) amino) pyridin-3-yl) -7H-pyrrolo [2,3-d] pyrimidin-6-yl) phenyl) methacrylamide





MS (ESI) m/z 343 $[M + H]^+$.

Step 2 1-(5-(4-amino-6-iodo-7-methyl-7*H*-pyrrolo [2,3-*d*] pyrimidin-5-yl) pyridin-2-yl) imino) tetrahydro-1*H*-1 λ⁶-thiophene-1-oxide 29c

MS (ESI) m/z 471 $[M + H]^+$.

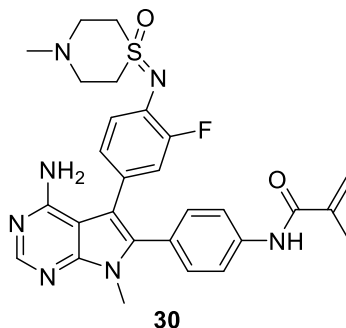
Step 3 N- (4- (4-amino-7-methyl-5- (6- (1-oxotetrahydro-1 λ^6 -thiophene-1- ylidene) amino) pyridine-3-yl) -7H-pyrrolo [2,3-*d*] pyrimidin-6-yl) phenyl) methacrylamide 29

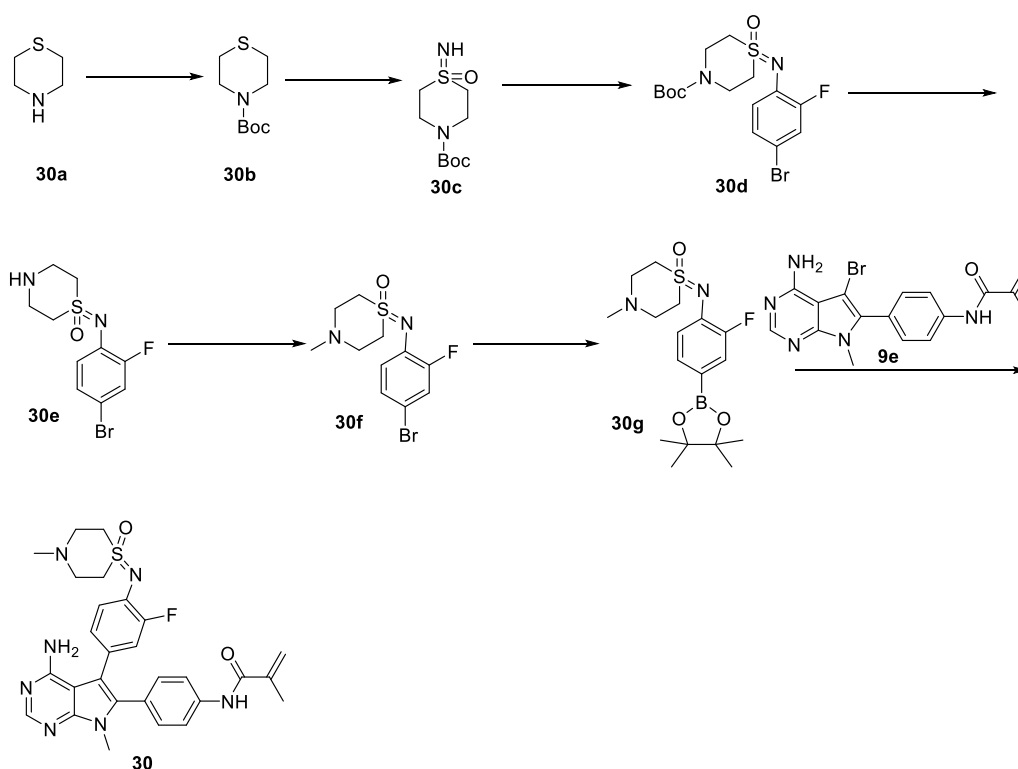
To a 25 mL round bottom flask, compound **29c** (20 mg, 0.05 mmol), compound **4a** (16 mg, 0.05 mmol), tetrakis (triphenylphosphine) palladium (6 mg, 0.005 mmol), anhydrous potassium phosphate (32 mg, 0.15 mmol), 1,4-dioxane (2 mL), and distilled water (0.5 mL) were added in sequence, and heated up to 90 °C to react for 1 h. After TLC monitored the completion of the reaction, it was cooled down to room temperature, filtered through diatomaceous earth, extracted with ethyl acetate (20 mL $\times$ 3), the organic phases were combined, washed with saturated saline (20 mL), and concentrated under reduced pressure to obtain a crude product. The crude product was purified by column chromatography (DCM/MeOH=6/1) to obtain compound **29** (7 mg), white solid.

MS (ESI) m/z 587.10 $[M + H]^+$.

^1H NMR (400 MHz, CDCl_3) δ 8.37 (s, 1H), 8.14 (d, 1.8 Hz, 1H), 7.68 – 7.53 (m, 3H), 7.41 (dd, J = 8.4, 2.4 Hz, 1H), 7.26 (d, J = 8.6 Hz, 2H), 6.78 (d, J = 8.1 Hz, 1H), 5.83 (s, 1H), 5.52 (s, 1H), 5.33 (s, 2H), 3.74 (s, 3H), 3.65 (dd, J = 13.5, 6.8 Hz, 2H), 3.40 (dd, J = 13.2, 6.7 Hz, 2H), 2.43 – 2.25 (m, 4H), 2.10 (s, 3H).

Example 30 N- (4- (4-amino-5- (3-fluoro-4- ((4-methyl-1-oxo-1 λ^6 -thiomorpholin-1-ylidene) amino) phenyl) -7-methyl-7H-pyrrolo [2,3-*d*] pyrimidin-6-yl) phenyl) methacrylamide





Step 1 thiomorpholine-4-carboxylic acid tert-butyl ester **30b**

To a 250 mL round bottom flask, compound **30a** (3 g, 29.07 mmol), Boc anhydride (6 g, 29.07 mmol), DMAP (350 mg, 2.91 mmol), triethylamine (7 mL, 58.14 mmol), and anhydrous dichloromethane (30 mL) were added in sequence, and reacted at room temperature for 5 h. After TLC monitored the completion of the reaction, it was extracted with dichloromethane (50 mL × 3), and the organic phases were combined, washed with saturated saline solution (50 mL), and concentrated under reduced pressure to obtain a crude product. The crude product was purified by column chromatography (PE/EA=8/1) to obtain compound **30b** (3.5 mg), white solid.

Step 2 1-imino-1λ⁶-thiomorpholine-4-carboxylic acid tert-butyl ester 1-oxide **30c**

To a 100 mL round bottom flask, compound **30b** (1.00 g, 4.92 mmol), ammonium carbamate (577 mg, 7.38 mmol), iodobenzene acetate (3.33 g, 10.3 mmol), and methanol (40 mL) were added in sequence, and reacted at room temperature for 1 h, after TLC monitored the completion of the reaction, it was concentrated under reduced pressure to obtain a crude product. The crude product was purified by column chromatography (PE/EA=1/2) to obtain compound **30c** (930 mg), white solid.

MS (ESI) m/z 235 $[M + H]^+$.

Step 3 1- (4-bromo-2-fluorophenyl) imino) -1 λ⁶-thiomorpholine-4-carboxylic acid tert-butyl ester 1-oxide **30d**

To a 100 mL round bottom flask, compound **30c** (900 mg, 3.84 mmol), 4-bromo-2-fluoro-1-iodobenzene (930 mg, 3.2 mmol), Pd₂(dba)₃ (74 mg, 0.08 mmol), Xantphos (140 mg, 0.24 mmol), and cesium carbonate (1.5 g, 4.60 mmol) were added in sequence, and reacted at 90 °C for 5 h, after TLC monitored the completion of the reaction, it was cooled down

to room temperature, filtered through diatomaceous earth, extracted with ethyl acetate (30 mL × 3), and the organic phases were combined, washed with saturated saline solution (30 mL), and concentrated under reduced pressure to obtain a crude product. The crude product was purified by column chromatography (PE/EA=1/1) to obtain compound **30d** (800 mg), light yellow solid.

5 MS (ESI) m/z 407 $[M + H]^+$.

Step 4 1- ((4-bromo-2-fluorophenyl) imino) -1 λ^6 -thiomorpholine 1-oxide 30e

To a 100 mL round bottom flask, compound **30d** (400 mg, 1.30 mmol), trifluoroacetic acid (2 mL), and anhydrous dichloromethane (8 mL) were added in sequence, and reacted at room temperature for 1 h, after TLC monitored the completion of the reaction, it was extracted with dichloromethane (30 mL × 3), and the organic phases were combined, washed with saturated saline solution (30 mL), concentrated under reduced pressure to obtain a crude product, dried to obtain compound **30e** (350 mg), light yellow solid, which was directly used in the next step.

15 MS (ESI) m/z 307 $[M + H]^+$.

Step 5 1- ((4-bromo-2-fluorophenyl) imino) -4-methyl-1 λ^6 -thiomorpholine 1-oxide 30f

To a 100 mL round bottom flask, compound **30e** (350 mg, 1.15 mmol), polyformaldehyde (71 mg, 2.30 mmol), sodium cyanoborohydride (216 mg, 3.45 mmol) and methanol (10 mL) were added in sequence. After 6 h of reaction at room temperature, the reaction was quenched with sodium bicarbonate and extracted with ethyl acetate (30 mL × 3), and the organic phases were combined and washed with saturated saline solution (30 mL). The crude product was concentrated under reduced pressure and purified by column chromatography (PE/EA=1/1) to obtain compound **30f** (170 mg), white solid.

25 MS (ESI) m/z 321 $[M + H]^+$.

^1H NMR (400 MHz, CDCl_3) δ 7.25 – 7.21 (m, 1H), 7.17 – 7.11 (m, 1H), 3.31 (tdd, $J = 13.3$, 9.2, 4.8 Hz, 1H), 3.02 – 2.92 (m, 1H), 2.44 (s, 3H).

Step 6 1- ((2-Fluoro-4- (4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) phenyl) imino) -4-methyl-1 λ^6 -thiomorpholine 1-oxide 30g

To a 100 mL round bottom flask, compound **30f** (170 mg, 0.53 mmol), bis(pinacolato)diboron (162 mg, 0.64 mmol), $\text{Pd}(\text{dppf})\text{Cl}_2$ (77 mg, 0.11 mmol), potassium acetate (157 mg, 1.59 mmol) and 1,4-dioxane (10 mL) were added in sequence, and heated up to 90 °C to react for 3 h. After the reaction was completed, it was cooled down to room temperature, filtered through diatomaceous earth, extracted with ethyl acetate (30 mL × 3), and the organic phases were combined, washed with saturated saline (30 mL), and concentrated under reduced pressure to obtain a crude product. The crude product was purified by column chromatography (PE/EA=1/1) to obtain compound **30g** (120 mg), yellow oil.

35 MS (ESI) m/z 369 $[M + H]^+$.

Step 7 N- (4- (4-amino-5- (3-fluoro-4- ((4-methyl-1-oxo-1 λ^6 -thiomorpholine-1-ylidene) amino) phenyl) -7-methyl-7H-pyrrolo [2,3-d] pyrimidin-6-yl) phenyl) methacrylamide 30

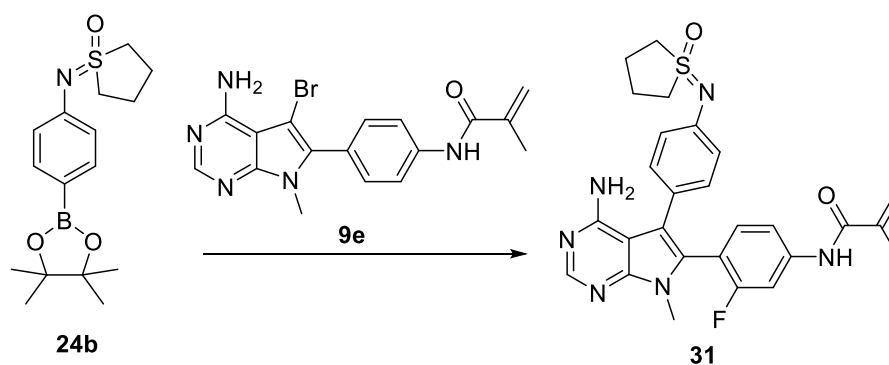
To a 25 mL round bottom flask, compound **30g** (126 mg, 0.34 mmol), compound **9e** (120 mg, 0.31 mmol), tetrakis (triphenylphosphine) palladium (36 mg, 0.03 mmol), anhydrous potassium

phosphate (477 mg, 2.25 mmol), 1,4-dioxane (10 mL), and water (1 mL) were added in sequence, and heated up to 90 °C to react for 1 h. After TLC monitored the completion of the reaction, it was cooled down to room temperature, filtered through diatomaceous earth, extracted with ethyl acetate (20 mL × 3), and the organic phases were combined, washed with saturated saline (20 mL), and concentrated under reduced pressure to obtain a crude product. The crude product was purified by column chromatography (DCM/MeOH=6/1) to obtain compound **30** (38 mg), white solid.

MS (ESI) m/z 548.20 $[M + H]^+$.

^1H NMR (400 MHz, CDCl_3) δ 8.37 (s, 1H), 7.62 – 7.55 (m, 3H), 7.23 (dd, $J = 14.9, 8.4$ Hz, 3H), 6.94 (dd, $J = 8.3, 4.6$ Hz, 2H), 5.83 (s, 1H), 5.52 (s, 1H), 5.20 (s, 2H), 5.20 (s, 4H), 3.73 (s, 3H), 2.45 (s, 4H), 2.10 (s, 3H).

Example 31 N- (4- (4-amino-7-methyl-5- (4- (1-oxotetrahydro-1 λ^6 -thiophene-1-ylidene) amino) phenyl) -7H-pyrrolo [2,3-*d*] pyrimidin-6-yl) phenyl) methacrylamide

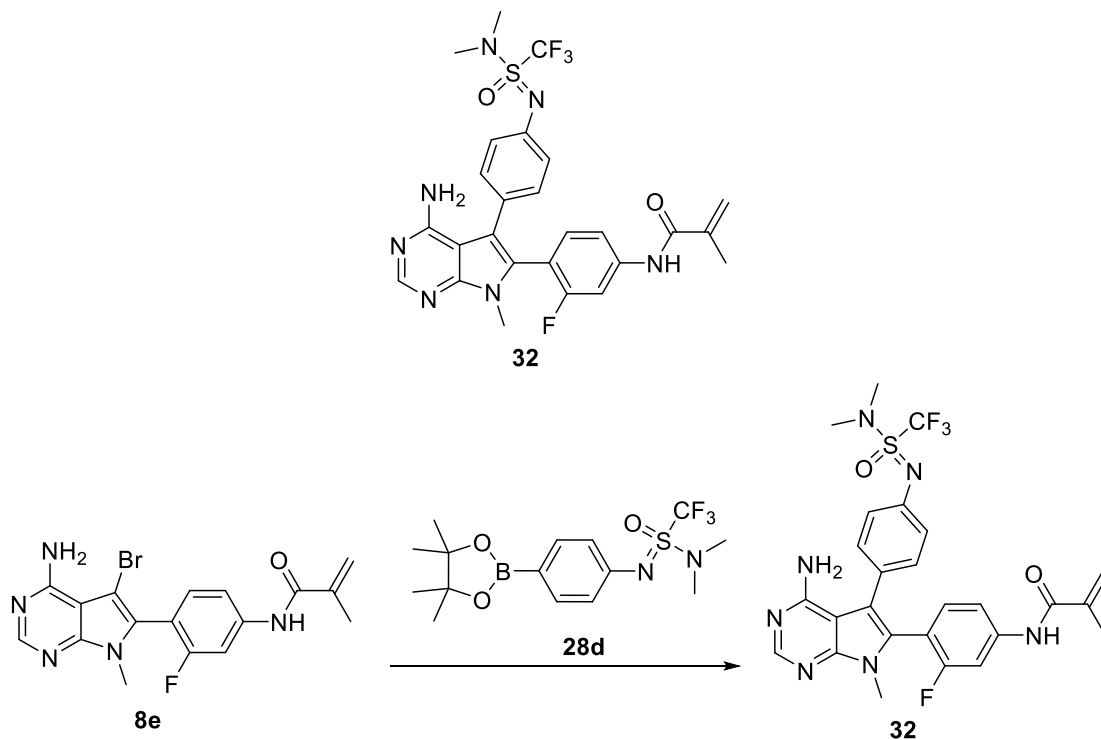


To a 25 mL round bottom flask, compound **9e** (150 mg, 0.39 mmol), compound **4b** (137 mg, 0.43 mmol), tetrakis (triphenylphosphine) palladium (50 mg, 0.039 mmol), anhydrous potassium phosphate (200 mg, 0.87 mmol), 1,4-dioxane (10 mL), and water (1 mL) were added in sequence, and heated up to 90 °C to react for 1 h. After TLC monitored the completion of the reaction, it was cooled down to room temperature, filtered through diatomaceous earth, extracted with ethyl acetate (30 mL × 3), and the organic phases were combined, washed with saturated saline (30 mL), and concentrated under reduced pressure to obtain a crude product. The crude product was purified by column chromatography (DCM/MeOH=6/1) to obtain compound **31** (48.3 mg), white solid.

MS (ESI) m/z 501.66 $[M + H]^+$.

^1H NMR (400 MHz, CDCl_3) δ 8.41 – 8.34 (m, 1H), 7.61 – 7.55 (m, 3H), 7.25 (d, $J = 8.6$ Hz, 2H), 7.14 (d, $J = 8.3$ Hz, 2H), 7.01 (d, $J = 8.3$ Hz, 2H), 5.82 (s, 1H), 5.51 (s, 1H), 5.12 (s, 2H), 3.76 – 3.71 (m, 3H), 3.46 (dd, $J = 12.5, 6.3$ Hz, 2H), 3.25 – 3.19 (m, 2H), 2.39 – 2.27 (m, 4H), 2.08 (d, $J = 10.1$ Hz, 3H).

Example 32 *N*- (4- (4-amino-5- (4- ((dimethylamino) (oxo) (trifluoromethyl) - λ^6 -sulfanylidene)amino)phenyl)-7-methyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-6-yl)-3-fluorophenyl) methacrylamide

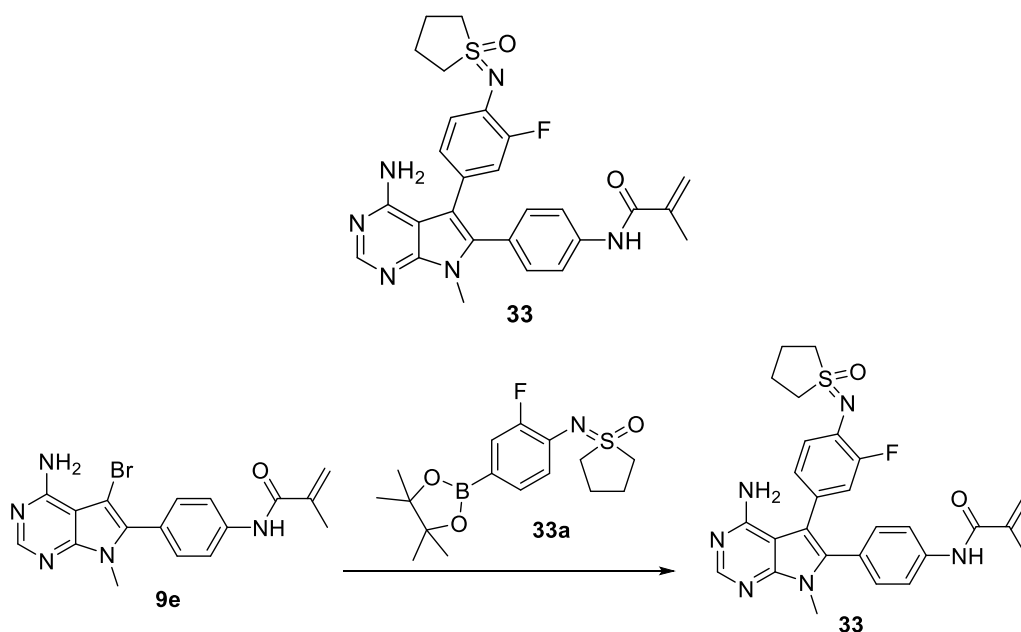


To a 25 mL round bottom flask, compound **8e** (100 mg, 0.25 mmol), compound **28d** (104 mg, 0.275 mmol), tetrakis (triphenylphosphine) palladium (29 mg, 0.025 mmol), anhydrous potassium phosphate (118 mg, 0.56 mmol), 1,4-dioxane (10 mL), and water (1 mL) were added in sequence, and heated up to 90 °C to react for 1 h. After TLC monitored the completion of the reaction, it was cooled down to room temperature, filtered through diatomaceous earth, extracted with ethyl acetate (30 mL $\times$ 3), the organic phases were combined, washed with saturated saline (30 mL), and concentrated under reduced pressure to obtain a crude product. The crude product was purified by column chromatography (DCM/MeOH=6/1) to obtain compound **32** (6 mg), white solid.

MS (ESI) m/z 508.76 $[M + H]^+$.

^1H NMR (400 MHz, CDCl_3) δ 8.40 (s, 1H), 7.79 (dd, $J = 25.0, 9.0$ Hz, 2H), 7.19 (s, 2H), 7.07 (s, 4H), 5.84 (s, 1H), 5.56 (s, 1H), 5.15 (s, 2H), 3.70 (s, 3H), 3.12 (s, 7H), 2.11 (s, 4H).

Example 33 *N*- (4- (4-amino-5- (3-fluoro-4- ((1-oxotetrahydro-1 λ^6 -thiophene-1-ylidene) amino) phenyl) -7-methyl-7*H*-pyrrolo [2,3-*d*] pyrimidin-6-yl) phenyl) methacrylamide

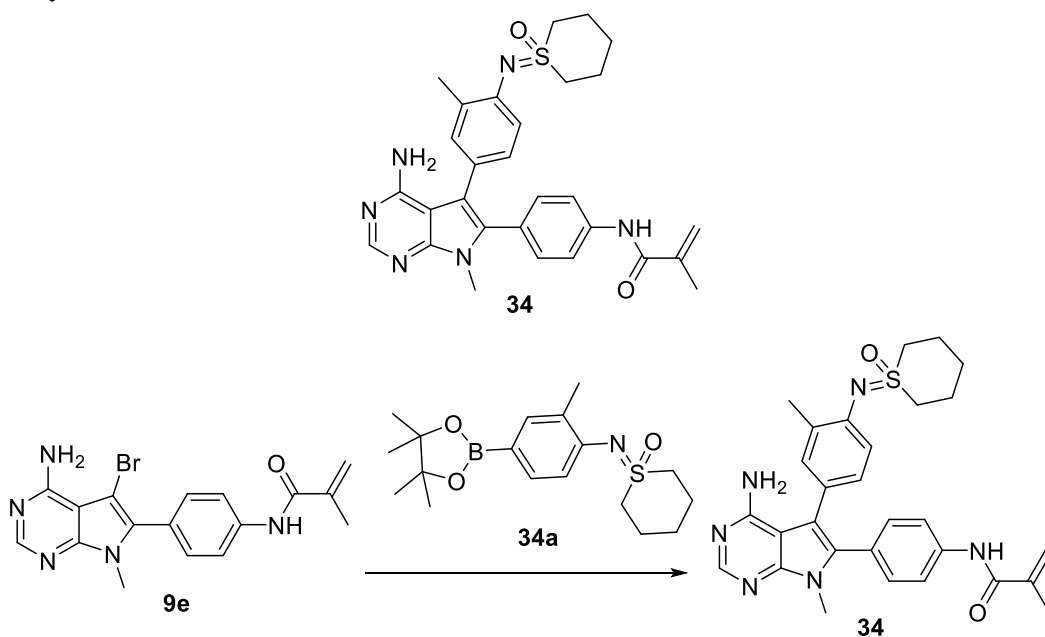


Compound **33** was synthesized with reference to Example **32**.

MS (ESI) m/z 519.70 $[M + H]^+$.

- 5 ^1H NMR (400 MHz, CDCl_3) δ 8.28 (s, 1H), 7.51 (s, 1H), 7.49 (d, $J = 3.2$ Hz, 2H), 7.16 (s, 1H), 7.14 (s, 1H), 7.04 (s, 1H), 6.87 – 6.82 (m, 2H), 5.74 (s, 1H), 5.43 (d, $J = 1.0$ Hz, 1H), 5.08 (s, 2H), 3.63 (s, 3H), 3.41 – 3.34 (m, 2H), 3.17 (dd, $J = 13.0, 6.9$ Hz, 2H), 2.25 (d, $J = 7.5$ Hz, 4H), 2.01 (s, 3H).

- 10 **Example 34** *N*- (4- (4-amino-7-methyl-5- (3-methyl-4- ((1-oxotetrahydro-2*H*-1 λ^6 -thiopyran-1-ylidene) amino) phenyl) -7*H*-pyrrolo [2,3-*d*] pyrimidin-6-yl) phenyl) methacrylamide



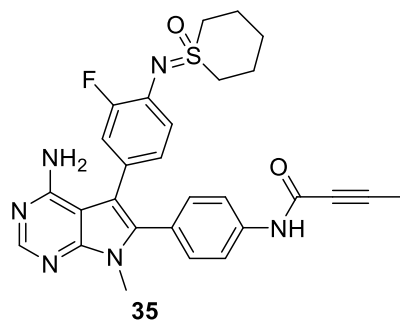
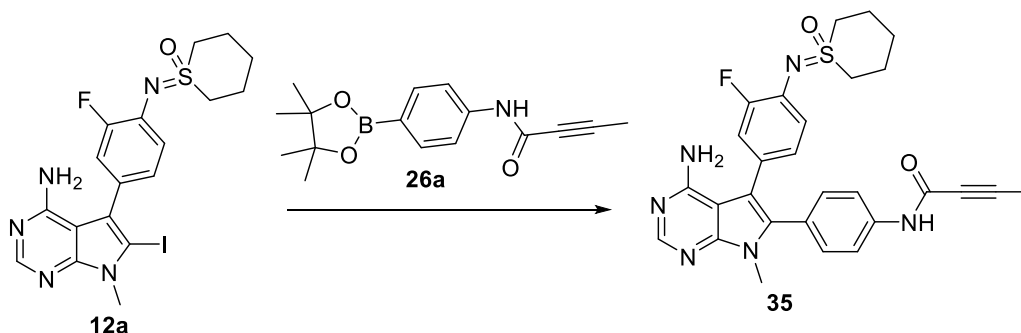
- 15 Compound **34** was synthesized with reference to Example **32**.

MS (ESI) m/z 529.08 $[M + H]^+$.

¹H NMR (400 MHz, CDCl₃) δ 8.35 (s, 1H), 7.57 (d, *J* = 8.6 Hz, 3H), 7.26 (d, *J* = 8.5 Hz, 2H), 7.14 (d, *J* = 8.1 Hz, 1H), 7.07 (s, 1H), 6.91 (d, *J* = 8.0 Hz, 1H), 5.83 (s, 1H), 5.52 (s, 1H), 5.37 (s, 2H), 3.73 (s, 3H), 3.41 (d, *J* = 13.1 Hz, 2H), 3.13 (dd, *J* = 17.1, 10.5 Hz, 2H), 2.27 (d, *J* = 7.5 Hz, 3H), 2.11 (d, *J* = 5.5 Hz, 7H), 1.79 (d, *J* = 5.2 Hz, 3H).

5

Example 35 *N*- (4- (4-amino-5- (3-fluoro-4- ((1-oxotetrahydro-2H-1 λ⁶-thiopyran-1-ylidene) amino) phenyl) -7-methyl-7H-pyrrolo [2,3-*d*] pyrimidin-6-yl) phenyl) but-2-ynamide



10

Compound **12a** (0.10 g, 0.20 mmol) was dissolved in 1,4-dioxane (6 mL) and H₂O (2 mL), compound **26a** (68.0 mg, 0.24 mmol), potassium phosphate (0.13 g, 0.60 mmol), and tetrakis (triphenylphosphine) palladium (23.0 mg, 0.02 mmol) were added, and reacted at 90 °C for 14 h under N₂ protection. After the reaction was completed, it was extracted with ethyl acetate (50 mL × 3), and the organic phases were combined and concentrated under reduced pressure to obtain a crude product. The crude product was purified by preparative TLC plate (EA/THF=3/1) to obtain compound **35** (10.5 mg), white solid.

15

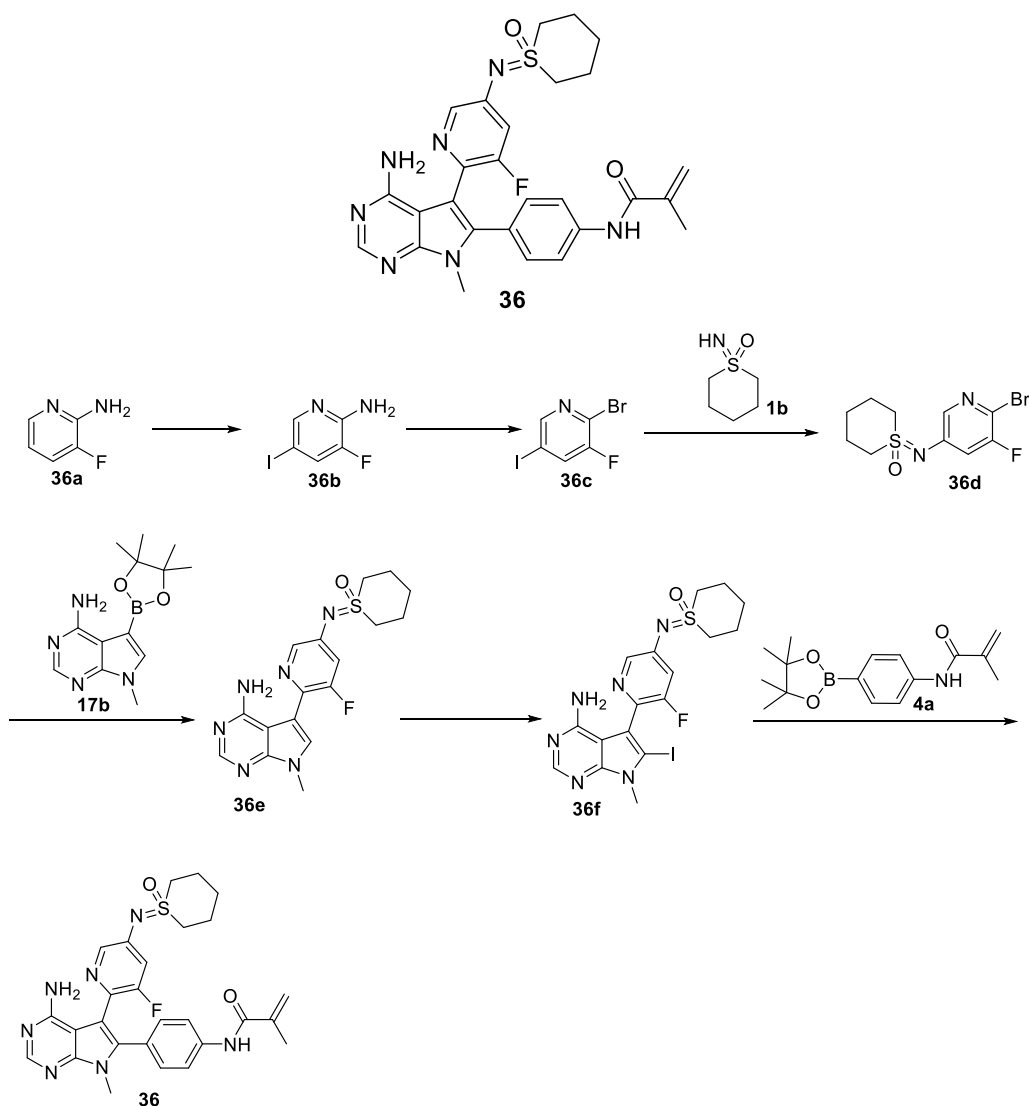
MS (ESI) *m/z* 531.20 [M + H]⁺.

¹H NMR (400 MHz, CDCl₃) δ 8.37 (s, 1H), 7.57 – 7.43 (m, 3H), 7.26 – 7.20 (m, 2H), 6.92 (dd, *J* = 12.6, 5.0 Hz, 2H), 5.23 (s, 2H), 3.72 (s, 3H), 3.36 (d, *J* = 14.3 Hz, 2H), 3.23 – 3.12 (m, 2H), 2.26 – 2.09 (m, 4H), 2.01 (s, 3H), 1.73 (m, 2H).

20

Example 36 *N*- (4- (4-amino-5- (3-fluoro-5- ((1-oxotetrahydro-2H-1 λ⁶-thiopyran-1-ylidene) amino) pyridin-2-yl) -7-methyl-7H-pyrrole [2,3-*d*] pyrimidin-6-yl) phenyl) methacrylamide

25



Step 1 3-fluoro-5-iodo-pyridine-2-amine

Compound **36a** (3.00 g, 26.8 mmol) was dissolved in DMF (20 mL), N-iodosuccinimide (6.63 g, 29.5 mmol) was added at room temperature, and the reaction was carried out at room temperature for 14 h. After the reaction was completed, it was extracted with ethyl acetate (50 mL $\times$ 3), and the organic phases were combined and concentrated under reduced pressure to obtain a crude product. The crude product was purified by column chromatography (PE/EtOAc=1/1) to obtain compound **36b** (4.5 g), white solid.

MS (ESI) m/z 239.10 $[M + H]^+$.

Step 2 3-fluoro-5-iodo-pyridine-2-amine 36c

Compound **6b** (2.00 g, 8.40 mmol) was dissolved in acetonitrile (20 mL), copper bromide (2.25 g, 10.1 mmol) was added at room temperature, and isoamyl nitrite (1.47 g, 12.6 mmol) was added slowly at 50 °C to react at that temperature for 3 h. After the reaction was completed, it was extracted with ethyl acetate (50 mL $\times$ 3), and the organic phases were combined and concentrated under reduced pressure to obtain a crude product. The crude product was purified by column chromatography (PE/EtOAc=5/1) to obtain compound **36c** (1.5 g), white solid.

MS (ESI) m/z 302.20 $[M + H]^+$.

Step 3 1-((6-bromo-5-fluoropyridin-3-yl) imino) hexahydro-1 λ^6 -thiopyran-1-oxide 36d

Compound **36c** (0.50 g, 1.66 mmol) was dissolved in 1,4-dioxane (10 mL), compound **1b** (0.22 g, 1.66 mmol), Cs₂CO₃ (1.62 g, 4.98 mmol), Xantphos (0.19 g, 0.332 mmol), and Pd₂(dba)₃ (0.15 g, 0.166 mmol) were added at room temperature, and it was protected with N₂ and reacted at 100 °C for 14 h. After TLC monitored the completion of the reaction, it was extracted with ethyl acetate (50 mL $\times$ 3), and the organic phases were combined and concentrated under reduced pressure to obtain a crude product. The crude product was purified by column chromatography (PE/EtOAc=1/1) to obtain compound **36d** (0.25 g), white solid.

MS (ESI) m/z 307.20 $[M + H]^+$.

Step 4 1-(6-(4-amino-7-methyl-7H-pyrrolo[2,3-*d*]pyrimidin-5-yl)-5-fluoropyridine -3-yl) imino) hexahydro-1 λ^6 -thiopyran-1-oxide 36e

Compound **17b** (0.20 g, 0.73 mmol) was dissolved in 1,4-dioxane (6 mL) and H₂O (2 mL), compound **36d** (0.25 g, 0.80 mmol), potassium phosphate (0.46 g, 2.20 mmol), and tetrakis (triphenylphosphine) palladium (84.0 mg, 0.073 mmol) were added, and it was protected with N₂ and reacted at 90 °C for 14 h. After the reaction was completed, it was extracted with ethyl acetate (50 mL $\times$ 3), and the organic phases were combined and concentrated under reduced pressure to obtain a crude product. The crude product was purified by column chromatography (DCM/MeOH=10/1) to obtain compound **36e** (180 mg), white solid.

MS (ESI) m/z 375.10 $[M + H]^+$.

Step 5 1-(6-(4-amino-6-iodo-7-methyl-7H-pyrrolo[2,3-*d*]pyrimidin-5-yl)-5-fluoropyridine -3-yl) imino) hexahydro-1 λ^6 -thiopyran-1-oxide 36f

Compound **36e** (0.15 g, 0.40 mmol) was dissolved in dichloromethane (10 mL), and it was cooled down to 0 °C, and at this temperature, trifluoroacetic acid (0.14 g, 1.2 mmol) and N-iodobutyrimide (110 mg, 0.48 mmol) were added to react at 0 °C for 1 h. After the reaction was completed, it was extracted with ethyl acetate (50 mL $\times$ 3), and the organic phases were combined and concentrated under reduced pressure to obtain crude product compound **36f** (180 mg), white solid.

MS (ESI) m/z 501.11 $[M + H]^+$.

Step 6 N- (4- (4-amino-5- (3-fluoro-5- ((1-oxotetrahydro-2H-1 λ^6 -thiopyran-1-ylidene) amino) pyridine-2-yl) -7-methyl-7H-pyrrole [2,3-*d*] pyrimidin-6-yl) phenyl) methacrylamide 36

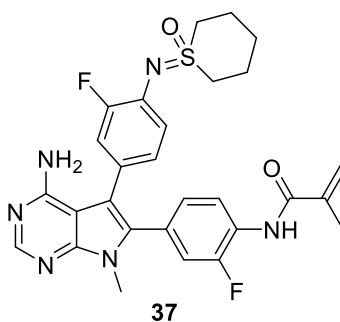
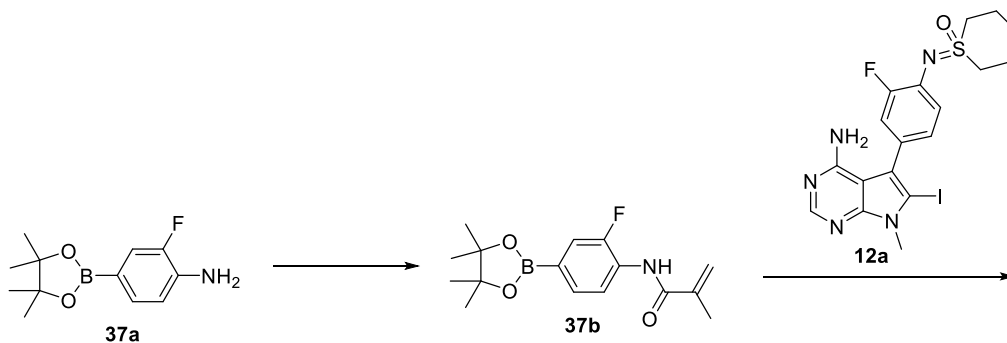
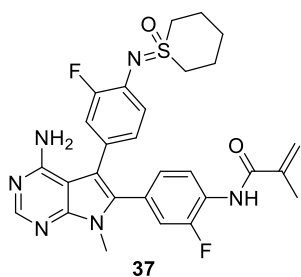
Compound **36f** (0.18 g, 0.36 mmol) was dissolved in dioxane (6 mL) and H₂O (2 mL), compound **4a** (124 mg, 0.43 mmol), potassium phosphate (0.23 g, 1.10 mmol), and tetrakis (triphenylphosphine) palladium (41.0 mg, 0.036 mmol) were added, and reacted at 90 °C for 14 h under N₂ protection. After the reaction was completed, it was extracted with ethyl acetate (50 mL $\times$ 3), and the organic phases were combined and concentrated under reduced pressure to obtain a crude product. The crude product was purified by preparative TLC plate (EtOAc/THF=3/1) to obtain compound **36** (78.3 mg), white solid.

MS (ESI) m/z 534.21 $[M + H]^+$.

^1H NMR (400 MHz, CDCl_3) δ 8.38 (s, 1H), 8.33 – 8.29 (m, 1H), 7.70 – 7.55 (m, 4H), 7.30 (s, 1H), 7.00 (dt, $J = 11.5, 4.0$ Hz, 1H), 6.30 (s, 2H), 5.84 (s, 1H), 5.52 (d, $J = 1.1$ Hz, 1H), 3.74 (d, $J = 3.4$ Hz, 4H), 3.40 – 3.33 (m, 3H), 3.24 – 3.16 (m, 3H), 2.19 – 2.09 (m, 9H), 1.83 – 1.76 (m, 3H).

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Example 37 *N*-(4-(4-amino-5-(3-fluoro-4-((1-oxotetrahydro-2H-1 λ^6 -thiopyran-1-ylidene) amino) phenyl)-7-methyl-7H-pyrrolo [2,3-*d*] pyrimidin-6-yl)-2-fluorophenyl) methacrylamide



10

Step 1 *N*-(2-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) phenyl) methacrylamide **37b**

Compound **37a** (1.00 g, 4.22 mmol) was dissolved in dichloromethane (20 mL), triethylamine (0.85 g, 8.44 mmol) was added at room temperature, cooled down to 0 °C, methacryloyl chloride (0.46 g, 4.33 mmol) was added to react at room temperature for 1 h. After the reaction was completed, it was extracted with ethyl acetate (50 mL $\times$ 3), and the organic phases were combined and concentrated under reduced pressure to obtain a crude product. The

15

crude product was purified by column chromatography (PE/EtOAc=5/1) to obtain compound **37b** (0.95 g), colorless oily liquid.

MS (ESI) m/z 306.20 $[M + H]^+$.

^1H NMR (400 MHz, $CDCl_3$) δ 8.62 – 8.23 (m, 1H), 8.04 – 7.75 (m, 1H), 7.52 (ddd, $J = 25.4$, 13.8, 11.0 Hz, 2H), 6.02 – 5.58 (m, 1H), 5.59 (s, 1H), 2.07 (s, 3H), 1.33 (s, 12H).

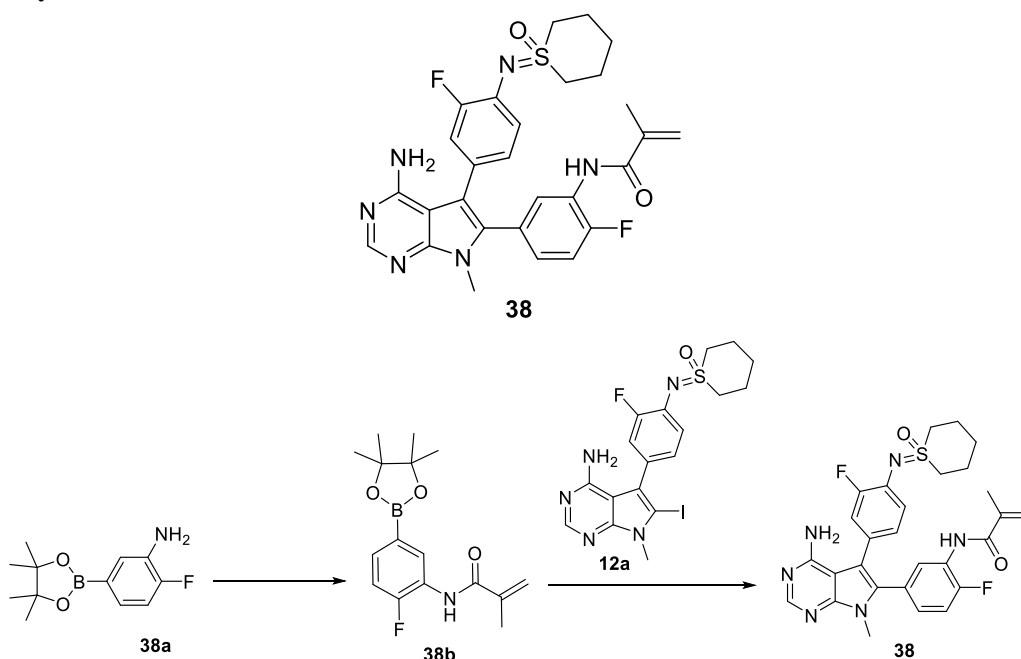
Step 2 *N*-(4-(4-amino-5-(3-fluoro-4-((1-oxotetrahydro-2H-1 λ^6 -thiopyran-1-ylidene) amino) phenyl)-7-methyl-7H-pyrrolo [2,3-*d*] pyrimidin-6-yl)-2-fluorophenyl) methacrylamide **37**

Compound **12a** (0.10 g, 0.20 mmol) was dissolved in 1,4-dioxane (6 mL) and H_2O (2 mL), compound **37b** (73.0 mg, 0.24 mmol), potassium phosphate (0.13 g, 0.60 mmol), and tetrakis (triphenylphosphine) palladium (23.0 mg, 0.02 mmol) were added, and reacted at 90 °C for 14 h under N_2 protection. After the reaction was completed, it was extracted with ethyl acetate (50 mL $\times$ 3), and the organic phases were combined and concentrated under reduced pressure to obtain a crude product. The crude product was purified by preparative TLC plate (EtOAc/THF=3/1) to obtain compound **37** (36.3 mg)

MS (ESI) m/z 551.10 $[M + H]^+$.

^1H NMR (400 MHz, $CDCl_3$) δ 8.46 (t, $J = 8.4$ Hz, 1H), 8.38 (s, 1H), 7.82 (s, 1H), 7.25 (t, $J = 8.5$ Hz, 1H), 7.11 (d, $J = 8.9$ Hz, 1H), 6.99 (dd, $J = 11.6$, 1.9 Hz, 1H), 6.94 (dd, $J = 7.1$, 5.0 Hz, 2H), 5.89 (s, 1H), 5.56 (d, $J = 1.3$ Hz, 1H), 5.27 (s, 2H), 3.77 (d, $J = 20.7$ Hz, 3H), 3.37 (d, $J = 14.5$ Hz, 2H), 3.19 (ddd, $J = 13.3$, 8.9, 4.2 Hz, 2H), 2.23 – 2.07 (m, 6H), 1.84 – 1.73 (m, 3H).

Example 38 *N*-(5-(4-amino-5-(3-fluoro-4-((1-oxotetrahydro-2H-1 λ^6 -thiopyran-1-ylidene) amino) phenyl)-7-methyl-7H-pyrrolo [2,3-*d*] pyrimidin-6-yl)-2-fluorophenyl) methacrylamide **KTH021115**



Step 1 *N*-(2-fluoro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) phenyl) methacrylamide

Compound **38a** (1.00 g, 4.22 mmol) was dissolved in dichloromethane (20 mL), triethylamine (0.85 g, 8.44 mmol) was added at room temperature, cooled down to 0 °C, methacryloyl chloride (0.46 g, 4.33 mmol) was added to react at room temperature for 1 h. After the reaction was completed, it was extracted with ethyl acetate (50 mL × 3), and the organic phases were combined and concentrated under reduced pressure to obtain a crude product. The crude product was purified by column chromatography (PE/EtOAc=5/1) to obtain compound **38b** (1.1 g), colorless oily liquid.

MS (ESI) m/z 306.20 $[M + H]^+$.

^1H NMR (400 MHz, $CDCl_3$) δ 8.74 (dd, $J = 8.5, 1.3$ Hz, 1H), 7.72 (s, 1H), 7.61 – 7.49 (m, 1H), 7.16 – 7.06 (m, 1H), 5.84 (d, $J = 19.4$ Hz, 1H), 5.57 – 5.47 (m, 1H), 2.10 (s, 3H), 1.34 (s, 14H).

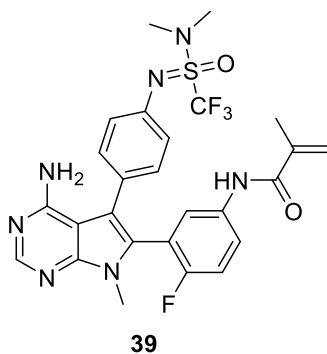
Step 2 N- (5- (4-amino-5- (3-fluoro-4- ((1-oxotetrahydro-2H-1 λ^6 -thiopyran-1- ylidene) amino) phenyl) -7-methyl-7H-pyrrolo [2,3-*d*] pyrimidin-6-yl) -2-fluorophenyl) methacrylamide **38**

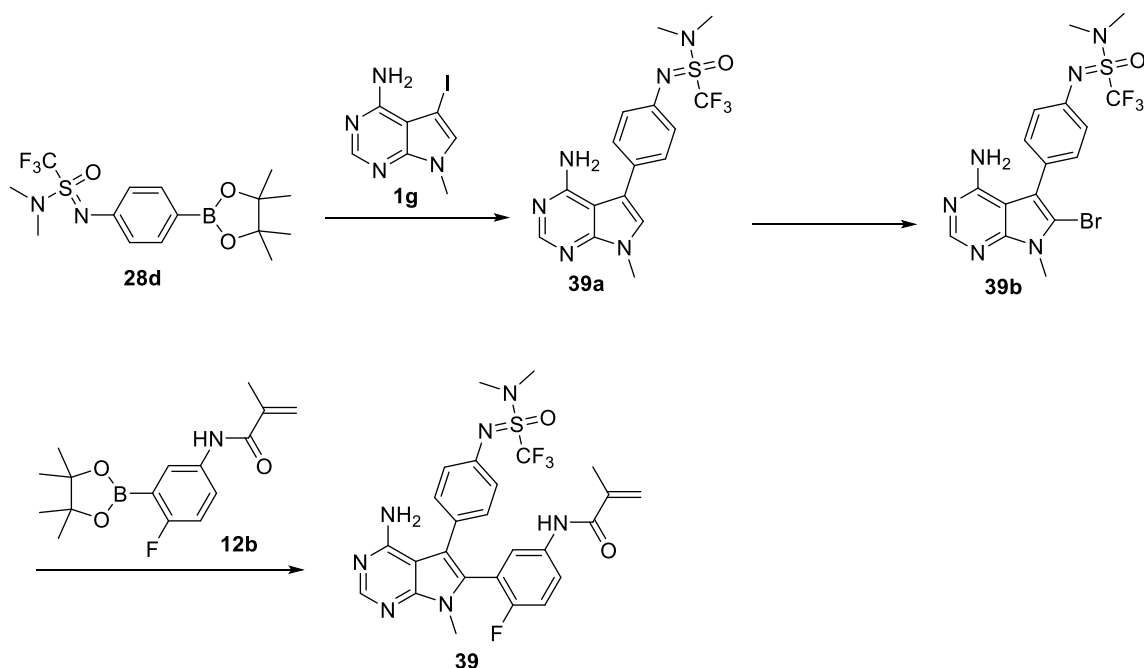
Compound **12a** (0.10 g, 0.20 mmol) was dissolved in 1,4-dioxane (6 mL) and H_2O (2 mL), compound **38b** (73.0 mg, 0.24 mmol), potassium phosphate (0.13 g, 0.60 mmol), and tetrakis (triphenylphosphine) palladium (23.0 mg, 0.02 mmol) were added, and reacted at 90 °C for 14 h under N_2 protection. After the reaction was completed, it was extracted with ethyl acetate (50 mL × 3), and the organic phases were combined and concentrated under reduced pressure to obtain a crude product. The crude product was purified by preparative TLC plate (EA/THF=3/1) to obtain compound **38** (37.3 mg).

MS (ESI) m/z 551.10 $[M + H]^+$.

^1H NMR (400 MHz, $CDCl_3$) δ 8.45 (dd, $J = 7.5, 2.1$ Hz, 1H), 8.37 (d, $J = 5.4$ Hz, 1H), 7.80 (s, 1H), 7.23 (t, $J = 8.6$ Hz, 1H), 7.07 (dd, $J = 10.7, 8.5$ Hz, 1H), 6.98 – 6.92 (m, 2H), 6.91 – 6.86 (m, 1H), 5.88 (s, 1H), 5.56 (t, $J = 4.8$ Hz, 1H), 5.14 (s, 2H), 3.76 (s, 3H), 3.41 – 3.31 (m, 2H), 3.17 (ddd, $J = 13.5, 9.0, 4.3$ Hz, 2H), 2.20 – 2.06 (m, 7H), 1.77 (d, $J = 15.1$ Hz, 2H).

Example 39 N- (3- (4-amino-5- (4- ((dimethylamino) (oxo) (trifluoromethyl) - λ^6 -sulfanylidene) amino) phenyl) -7-methyl-7H-pyrrolo [2,3-*d*] pyrimidin-6-yl) -4- fluorophenyl) methacrylamide





Step 1 N'-(4-(4-amino-7-methyl-7H-pyrrole [2,3-d] pyrimidin-5-yl) phenyl) -1,1,1-trifluoro-N,N-dimethylmethane sulfonamide 39a

Compound **28** (500 mg, 1.3 mmol), compound **1g** (302 mg, 1.1 mmol), Pd(dppf)Cl₂ (81 mg, 0.11 mmol), and potassium phosphate (584 mg, 2.8 mmol) were placed in a bottle, and 1,4-dioxane/H₂O (10 mL/1 mL) was added. After replaced with N₂ three times, the reaction was carried out at 85 °C for 16 h. The reaction solution was filtered and concentrated, and the obtained crude product was subjected to column chromatography (DCM/MeOH=0-10%) to obtain compound **39a** (200 mg), brown solid.

MS (ESI) *m/z* 399 [M + H]⁺.

Step 2 N'-(4-(4-amino-6-bromo-7-methyl-7H-pyrrole[2,3-d]pyrimidin-5-yl) phenyl) -1,1,1-trifluoro-N,N-dimethylmethane sulfonamide 39b

Compound **39a** (100mg, 0.25 mmol) was dissolved in DMF (3 mL), after it was cooled down to 0 °C, N-bromosuccinimide (49 mg, 0.28 mmol) was added to react at 0 °C for 1 h. The reaction solution was diluted with DCM, washed with water three times, and the organic phase was dried over anhydrous sodium sulfate and concentrated, the obtained crude product was purified by column chromatography (DCM/MeOH=0-10%) to obtain compound **39b** (100mg), red solid.

MS (ESI) *m/z* 476 [M + H]⁺.

Step 3 N-(3-(4-amino-5-(4-((dimethylamino) (oxo) (trifluoromethyl) - λ⁶-sulfanylidene) amino) phenyl) -7-methyl-7H-pyrrole [2,3-d] pyrimidin-6-yl) -4- fluorophenyl) methacrylamide 39

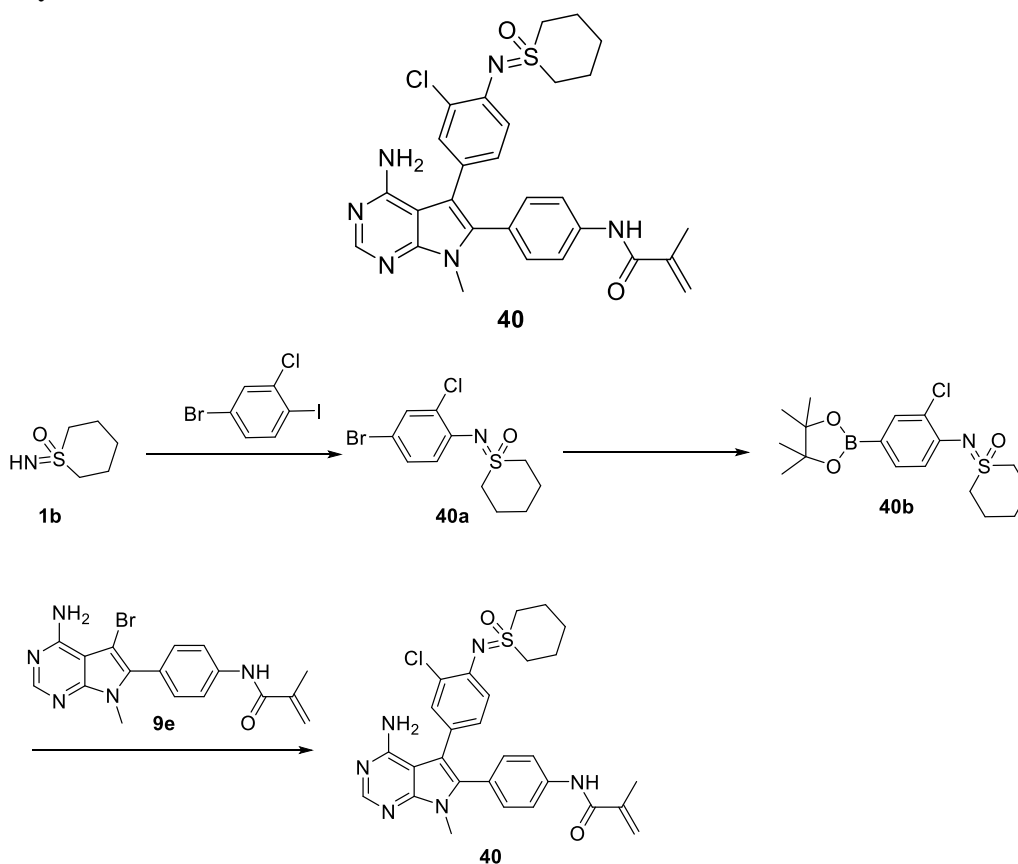
Compound **39b** (100 mg, 0.21 mmol), compound **12b** (83 mg, 0.27 mmol), Pd(PPh₃)₄ (49 mg, 0.042 mmol), and potassium phosphate (133 mg, 0.63 mmol) were placed in a bottle, and 1,4-dioxane/H₂O (4 mL/0.8 mL) was added. After replaced with N₂ three times, the reaction was carried out at 100 °C for 16 h. The reaction solution was filtered and concentrated, and the

obtained crude product was separated by column chromatography (DCM/MeOH=10/1) to obtain compound **39** (28 mg), light yellow solid.

MS (ESI) m/z 576 $[M + H]^+$.

^1H NMR (400 MHz, DMSO- d_6) δ 9.93 (s, 1H), 8.27 (s, 1H), 7.87 – 7.80 (m, 1H), 7.71 (dd, J = 6.6, 2.6 Hz, 1H), 7.32 (t, J = 9.2 Hz, 1H), 7.21 (d, J = 8.3 Hz, 2H), 7.05 (d, J = 8.4 Hz, 2H), 5.82 (s, 1H), 5.57 (s, 1H), 3.60 (s, 3H), 3.08 (s, 6H), 1.98 (s, 3H), 1.30 (s, 2H).

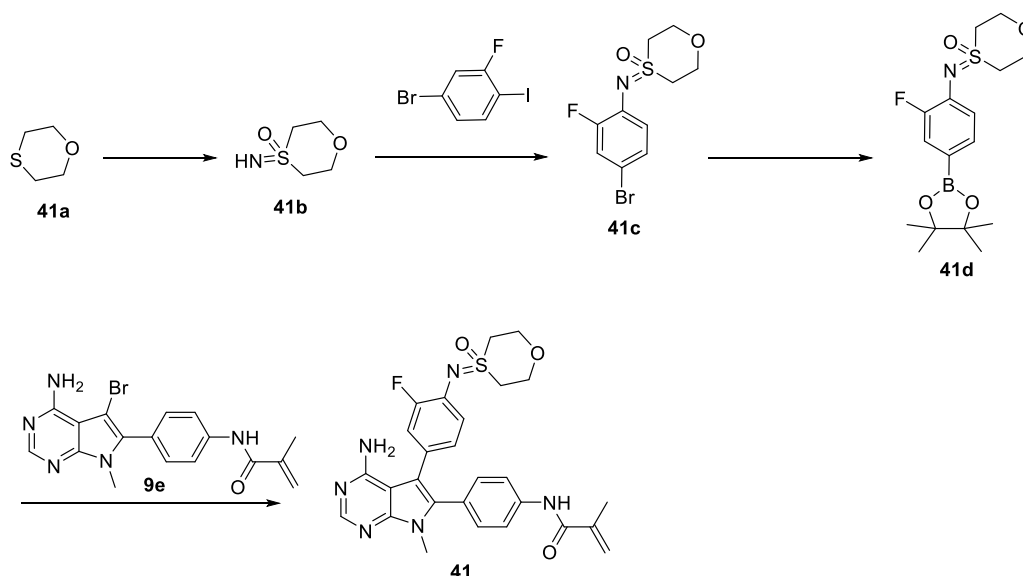
Example 40 *N*-(4-(4-amino-5-(3-chloro-4-((1-oxotetrahydro-2H-1 λ^6 - thiopyran -1-ylidene) amino) phenyl) -7-methyl-7H-pyrrolo [2,3-*d*] pyrimidin-6-yl) phenyl) methacrylamide



Step 1 1- ((4-bromo-2-chlorophenyl) imino) hexahydro-1 λ^6 - thiopyran-1-oxide

Compound **1b** (0.25 g, 1.9 mmol), cesium carbonate (0.72 g, 2.2 mmol), 4-bromo-2-chloro-1-iodobenzene (0.5 g, 1.58 mmol), $Pd_2(dba)_3$ (36 mg, 0.0395 mmol), and Xantphos (68 mg, 0.12 mmol) were added to 1,4-dioxane (8 mL), after replaced with N_2 three times, the reaction solution was heated up to 100 °C for 5 h. The reaction solution was filtered through diatomaceous earth, and the filter cake was washed with ethyl acetate (30 mL) and saturated saline solution (50 mL). The organic phase was dried over anhydrous sodium sulfate and concentrated under reduced pressure to obtain a crude product. The crude product was purified by column chromatography (PE/EtOAc=4/1 to 3/2) to obtain compound **40a** (0.43 g), light yellow solid.

MS (ESI) m/z 321.90 $[M + H]^+$.



Step 1 4-imino-1,4 λ⁶ - oxythiazole 4-oxide 41b

1,4-thiazole **41a** (2.0 g, 19.2 mmol) and ammonium carbamate (2.24 g, 28.8 mmol) were added into a flask in sequence, then methanol (40 mL) and iodobenzene diethyl ester (13.9 g, 43.2 mmol) were added. The reaction solution was stirred open at room temperature for 30 min, and then concentrated under reduced pressure to remove the solvent to obtain a crude product. The crude product was purified by column chromatography (MeOH/DCM =1/20) to obtain compound **41b** (1.9 g), white solid.

MS (ESI) m/z 136.04 $[M + H]^+$.

Step 2 4- ((4-bromo-2-fluorophenyl) imino) -1,4-λ⁶ - thiohexane-4-oxide 41c

Compound **41b** (700 mg, 5.17 mmol), cesium carbonate (1.9 g, 6.03 mmol), 4-bromo-2-fluoro-1-iodobenzene (1.28 g, 4.31 mmol), Pd₂(dba)₃ (99 mg, 0.108 mmol), and Xantphos (190 mg, 0.32 mmol) were added to 1,4-dioxane (15 mL), after replaced with N₂ three times, the reaction solution was heated up to 100 °C for 16 h. The reaction solution was filtered through diatomaceous earth, and the filter cake was washed with ethyl acetate (100 mL) and saturated saline solution (50 mL). The organic phase was dried over anhydrous sodium sulfate and concentrated under reduced pressure to obtain a crude product. The crude product was purified by column chromatography (PE/EtOAc=10/1 to 3/1) to obtain compound **41c** (1.1 g), light yellow solid.

MS (ESI) m/z 307.97 $[M + H]^+$.

Step 3 4- ((2-fluoro-4- (4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) phenyl) imino) -1,4-λ⁶-thiooxane-4-oxide 41d

Compound **41c** (300 mg, 0.97 mmol), bis(pinacolato)diboron (300 mg, 1.17 mmol), Pd(dppf)Cl₂ (140 mg, 0.194 mmol), potassium acetate (300 mg, 2.91 mmol), and 1,4-dioxane (6 mL) were added into a sealed tube, after replaced with N₂ three times, sealed, and the reaction solution was heated up to 100 °C and stirred for 16 h. Then water (10 mL) was added and extract with DCM (20 mL × 3). The organic phase was washed with saturated saline solution (20 mL), dried over anhydrous sodium sulfate, and concentrated under reduced pressure to obtain a crude

product. The crude product was purified by column chromatography (PE/EtOAc=5/1) to obtain compound **41d** (240 mg), yellow oily liquid.

MS (ESI) m/z 356 $[M + H]^+$.

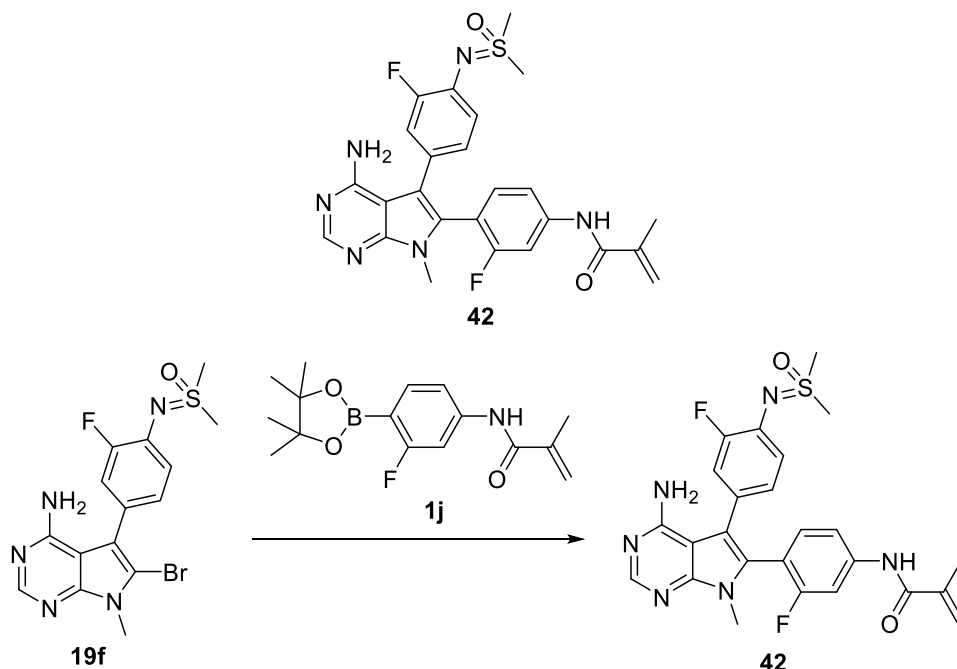
Step 4 *N*- (4- (4-amino-5- (3-fluoro-4- (4-oxo-1,4 λ^6 - thiohexane-4-ylidene) amino) phenyl) -7-methyl-7*H*-pyrrolo [2,3-*d*] pyrimidin-6-yl) phenyl) methacrylamide **41**

Compound **41d** (165 mg, 0.47 mmol), compound **9e** (130 mg, 0.36 mmol), Pd(PPh₃)₄ (83 mg, 0.072 mmol), and K₃PO₄ (230 mg, 1.08 mmol) were added into a sealed tube, after replaced with N₂ three times, 1,4-dioxane (5 mL) and H₂O (0.5 mL) were added, sealed, and the reaction solution was heated up to 100 °C and stirred for 16 h. Then dichloromethane (20 mL) and saturated saline solution (10 mL) were added to extract, the organic phase was dried over anhydrous sodium sulfate, and concentrated under reduced pressure to obtain a crude product. The crude product was purified by column chromatography (MeOH/DCM=1/30) to obtain compound **41** (90 mg), white solid.

MS (ESI) m/z 535.08 $[M + H]^+$.

¹H NMR (400 MHz, CDCl₃) δ 8.35 (s, 1H), 7.61 – 7.48 (m, 3H), 7.26 – 7.15 (m, 3H), 6.96 – 6.86 (m, 2H), 5.81 (s, 1H), 5.54 – 5.45 (s, 1H), 4.24 – 4.12 (m, 4H), 3.69 (s, 3H), 3.43 – 3.23 (m, 4H), 2.22 (s, 3H), 2.02 – 1.99 (m, 2H).

Example 42 *N*- (4- (4-amino-5- (4- (dimethyl (oxo) - λ^6 - sulfanylidene) amino) -3-fluorophenyl) -7-methyl-7*H*-pyrrolo [2,3-*d*] pyrimidin-6-yl) -3-fluorophenyl) methacrylamide



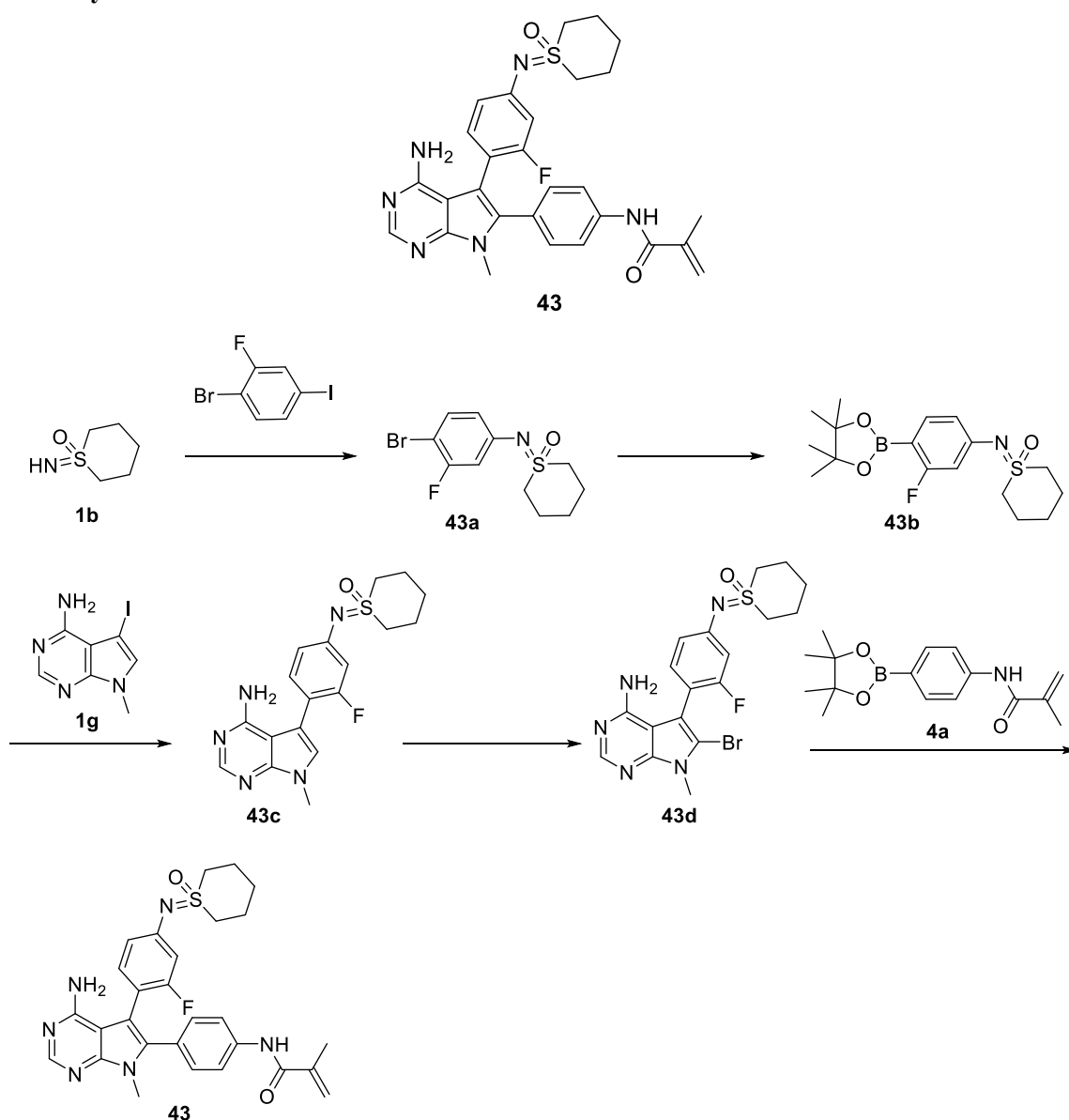
Compound **19f** (100 mg, 0.24 mmol), compound **1j** (89 mg, 0.29 mmol), Pd(PPh₃)₄ (56 mg, 0.049 mmol), and K₃PO₄ (156 mg, 0.73 mmol) were added into a sealed tube, after replaced with N₂ three times, 1,4-dioxane (5 mL) and H₂O (0.5 mL) were added, sealed, and the reaction solution was heated up to 100 °C and stirred for 16 h. Then dichloromethane (20 mL) and

saturated saline solution (10 mL) were added to extract, the organic phase was dried over anhydrous sodium sulfate, and concentrated under reduced pressure to obtain a crude product. The crude product was purified by column chromatography (MeOH/DCM=1/30) to obtain compound **42** (40 mg), white solid.

5 MS (ESI) m/z 511.75 $[M + H]^+$.

^1H NMR (400 MHz, MeOD- d_4) δ 8.22 (s, 1H), 7.76 (dd, $J = 12.1, 2.1$ Hz, 1H), 7.41 (dd, $J = 8.4, 2.1$ Hz, 1H), 7.21 (td, $J = 8.5, 4.7$ Hz, 2H), 6.98 (d, $J = 11.1$ Hz, 2H), 5.84 (s, 1H), 5.57 (d, $J = 1.6$ Hz, 1H), 4.60 (s, 1H), 3.64 (d, $J = 0.9$ Hz, 3H), 3.26 (s, 6H), 2.05 (s, 3H).

10 **Example 43** *N*- (4- (4-amino-5-(2-fluoro-4- ((1-oxotetrahydro-2*H*-1 λ^6 - thiopyran-1-ylidene) amino) phenyl) -7-methyl-7*H*-pyrrolo [2,3-*d*] pyrimidin-6-yl) phenyl) methacrylamide



15 **Step 1** 1- ((4-bromo-3-fluorophenyl) imino) hexahydro-1 λ^6 - thiopyran-1-oxide **43a**

Compound **1b** (270 mg, 2.02 mmol), carbofuran (820 mg, 2.52 mmol), 1-bromo-2-fluoro-4-iodobenzene (500 mg, 1.68 mmol), Pd₂(dba)₃ (39 mg, 0.042 mmol), and Xantphos (73 mg, 0.126 mmol) were added to 1,4-dioxane (10 mL), after replaced with N₂ three times, the reaction solution was heated up to 100 °C for 13 h. The reaction solution was filtered through diatomaceous earth, the filter cake was washed with ethyl acetate (50 mL), and saturated saline solution (50 mL) was used for washing. The organic phase was dried over anhydrous sodium sulfate and concentrated under reduced pressure to obtain a crude product. The crude product was purified by column chromatography (PE/EtOAc=4/1 to 1/1) to obtain compound **43a** (560 mg).

MS (ESI) *m/z* 306.2 [M + H]⁺.

Step 2 1- ((3-Fluoro-4- (4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) phenyl) imino) hexahydro-1 λ⁶ - thiophene 1-oxide 43b

Compound **43a** (0.56g, 1.73 mmol), bis(pinacolato)diboron (**0.53 g, 2.1 mmol**), Pd(dppf)Cl₂ (0.25 mg, 0.34 mmol), and potassium acetate (0.51 mg, 5.2 mmol) were placed in a bottle, 1,4-dioxane (5mL) was added, after replaced with N₂ three times, the reaction was carried out at 100 °C for 18 h. The reaction solution was filtered and concentrated, and the obtained crude product was purified by column chromatography (PE/EtOAc=0-20%) to obtain compound **43b** (427 mg), yellow oily liquid.

Step 3 1- (4- (4-amino-7-methyl-7H-pyrrolo [2,3-*d*] pyrimidin-5-yl) -3- fluorophenyl) imino) hexahydro-1 λ⁶ - thiopyran-1-oxide 43c

Compound **43b** (100 mg, 0.28 mmol), compound **1g** (65 mg, 0.24 mmol), Pd(PPh₃)₄ (54 mg, 0.056 mmol), and K₃PO₄ (150 mg, 0.84 mmol) were added into a sealed tube, after replaced with argon gas three times, 1,4-dioxane (4 mL) and H₂O (0.5 mL) were added, sealed, and the reaction solution was heated up to 100 °C and stirred for 16 h. Dichloromethane (20 mL) and saturated saline solution (10 mL) were added to extract, the organic phase was dried over anhydrous sodium sulfate, and concentrated under reduced pressure to obtain a crude product. The crude product was purified by column chromatography (MeOH/DCM=1/30) to obtain compound **43c** (80 mg), yellow solid.

MS (ESI) *m/z* 373.4 [M + H]⁺.

Step 4 (4- (4-amino-6-bromo-7-methyl-7H-pyrrolo [2,3-*d*] pyrimidin-5-yl) -2- fluorophenyl) imino) dimethyl - λ⁶ - sulfonylone 43d

Compound **43c** (55 mg, 0.15 mmol) was dissolved in DMF (3 mL), and a solution of N-bromosuccinimide (29 mg, 0.16 mmol) in DMF (0.5 mL) was added dropwise at 0 °C, the reaction solution was stirred at 0 °C for 1 h. Then DCM (30 mL) was added, and washed with saturated saline solution (10 mL × 3), and the organic phase was dried over anhydrous sodium sulfate, and concentrated under reduced pressure to obtain a crude product. The crude product was purified by column chromatography (MeOH/DCM=1/50) to obtain compound **43d** (54 mg), yellow solid.

MS (ESI) *m/z* 412.3 [M + H]⁺.

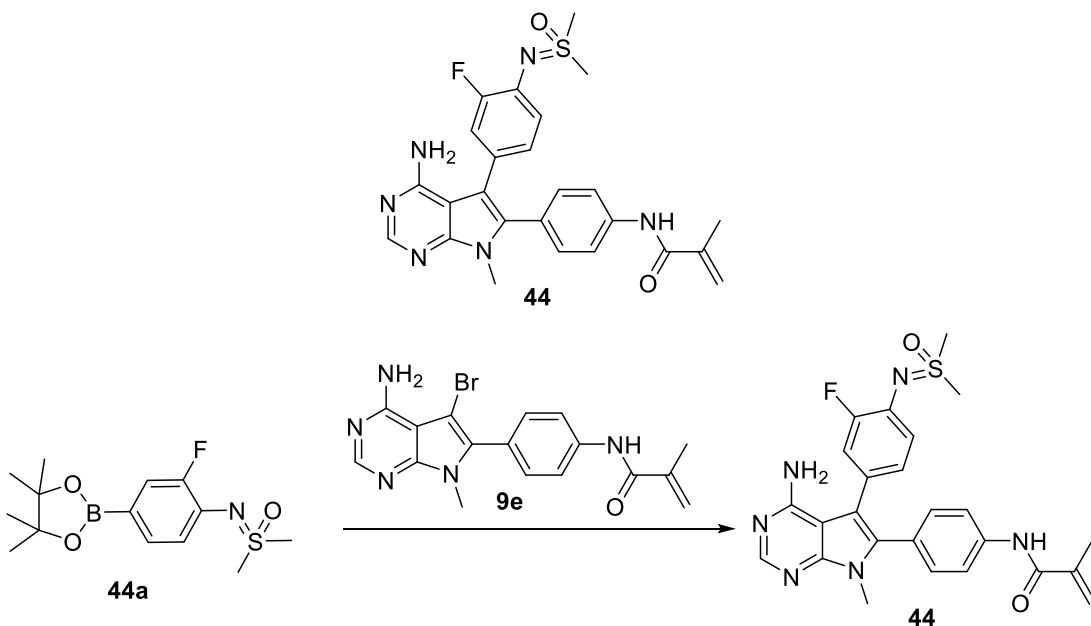
Step 5 *N*- (4- (4-amino-5- (2-fluoro-4- (1-oxotetrahydro-2*H*-1λ⁶ - thiopyran-1- ylidene) amino) phenyl) -7-methyl-7*H*-pyrrolo [2,3-*d*] pyrimidin-6-yl) phenyl) methacrylamide **43**

Compound **43d** (57 mg, 0.15 mmol), compound **4a** (50 mg, 0.18 mmol), Pd(PPh₃)₄ (30 mg, 0.03 mmol), and K₃PO₄ (100 mg, 0.45 mmol) were added into a sealed tube, after replaced with argon gas three times, 1,4-dioxane (3 mL) and H₂O (0.4 mL) were added, sealed, and the reaction solution was heated up to 100 °C and stirred for 16 h. Then dichloromethane (20 mL) and saturated saline solution (10 mL) were added to extract, the organic phase was dried over anhydrous sodium sulfate, and concentrated under reduced pressure to obtain a crude product. The crude product was purified by column chromatography (MeOH/DCM=1/30) to obtain compound **43** (12 mg), white solid.

MS (ESI) *m/z* 533.54 [M + H]⁺.

¹H NMR (400 MHz, MeOD-*d*₄) δ 8.18 (s, 1H), 7.70 – 7.62 (m, 2H), 7.32 – 7.26 (m, 2H), 7.21 (t, *J* = 8.6 Hz, 1H), 7.00 – 6.91 (m, 2H), 5.81 (s, 1H), 5.53 (d, *J* = 1.8 Hz, 1H), 4.58 (s, 1H), 3.68 (s, 3H), 3.43 – 3.34 (m, 2H), 3.30 – 3.19 (m, 2H), 2.13 – 1.99 (m, 5H), 1.82 – 1.52 (m, 4H).

Example 44 *N*- (4- (4-amino-5- (4- (dimethyl (oxo) - λ⁶ -sulfanylidene) amino) -3-fluorophenyl) -7-methyl-7*H*-pyrrolo [2,3-*d*] pyrimidin-6-yl) phenyl) methacrylamide

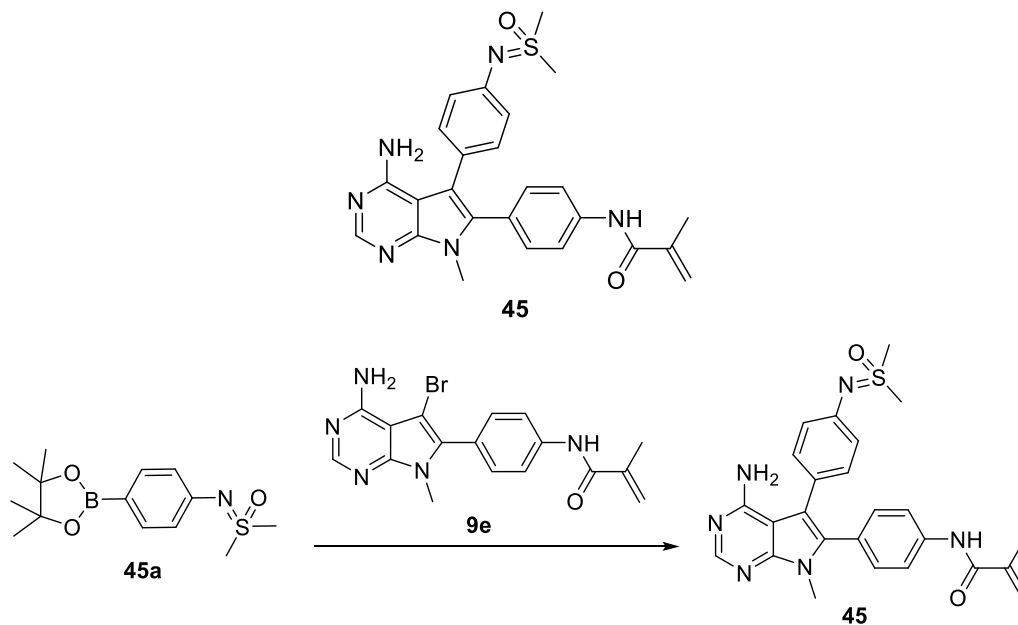


Compound **9e** (210 mg, 0.53 mmol), compound **44a** (200 mg, 0.64 mmol), Pd(PPh₃)₄ (120 mg, 0.11 mmol), and K₃PO₄ (340 mg, 1.59 mmol) were added into a sealed tube, after replaced with argon gas three times, 1,4-dioxane (5 mL) and H₂O (0.5 mL) were added, sealed, and the reaction solution was heated up to 100 °C and stirred for 16 h. Dichloromethane (20 mL) and saturated saline solution (10 mL) were added to extract, the organic phase was dried over anhydrous sodium sulfate, and concentrated under reduced pressure to obtain a crude product. The crude product was purified by column chromatography (MeOH/DCM=1/30) to obtain compound **44** (100 mg), white solid.

MS (ESI) *m/z* 493.26 [M + H]⁺.

¹H NMR (400 MHz, MeOD-d₄) δ 8.17 (s, 1H), 7.71 – 7.60 (m, 2H), 7.28 (d, *J* = 8.6 Hz, 2H), 7.19 (t, *J* = 8.4 Hz, 1H), 7.03 – 6.89 (m, 2H), 5.80 (s, 1H), 5.52 (s, 1H), 4.57 (s, 1H), 3.67 (s, 3H), 3.24 (s, 6H), 2.02 (s, 3H).

5 **Example 45** *N*- (4- (4-amino-5- (4- (dimethyl (oxo) - λ⁶ - sulfanylidene) amino) phenyl) -7-methyl-7*H*-pyrrolo [2,3-*d*] pyrimidin-6-yl) phenyl) methacrylamide

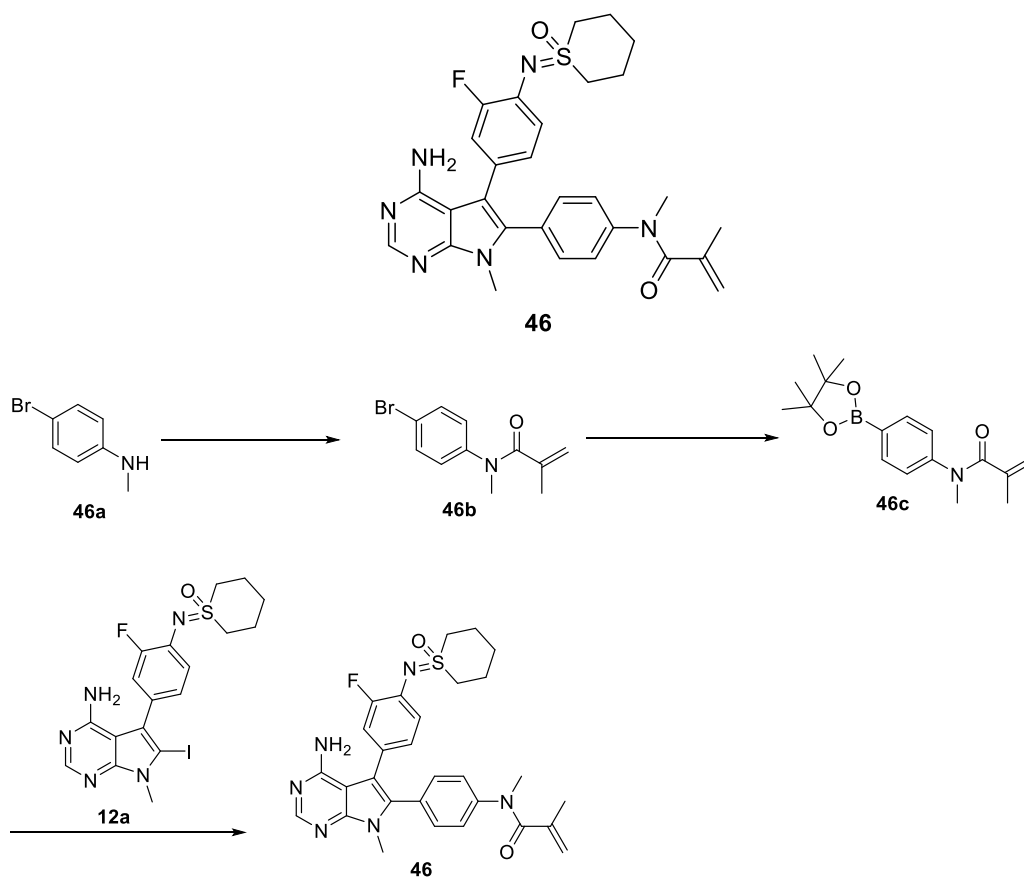


Compound **9e** (120 mg, 0.31 mmol), compound **45a** (110 mg, 0.37 mmol), Pd(PPh₃)₄ (72 mg, 0.062 mmol), and K₃PO₄ (198 mg, 0.93 mmol) were added into a sealed tube, after replaced with argon gas three times, 1,4-dioxane (5 mL) and H₂O (0.5 mL) were added, seal, and the reaction solution was heated up to 100 °C and stirred for 16 h. Dichloromethane (20 mL) and saturated saline solution (10 mL) were added to extract, the organic phase was dried over anhydrous sodium sulfate, and concentrated under reduced pressure to obtain a crude product. The crude product was purified by column chromatography (MeOH/DCM = 1/30) to obtain compound **45** (80 mg), white solid.

MS (ESI) *m/z* 475.61 [M + H]⁺.

¹H NMR (400 MHz, MeOD-d₄) δ 8.17 (s, 1H), 7.68 – 7.60 (m, 2H), 7.31 – 7.23 (*m*, 2H), 7.19 – 7.10 (m, 2H), 7.07 – 6.99 (m, 2H), 5.80 (s, 1H), 5.57 – 5.49 (m, 1H), 4.56 (s, 1H), 3.68 (s, 3H), 3.22 (s, 6H), 2.02 (t, *J* = 1.2 Hz, 3H).

Example 46 *N*- (4- (4-amino-5- (3-fluoro-4- ((1-oxotetrahydro 2*H*-1λ⁶ - thiopyran -1-ylidene) amino) phenyl) -7-methyl-7*H*-pyrrolo [2,3-*d*] pyrimidin-6-yl) phenyl) - *N*-methylmethacrylamide



Step 1 *N*-(4-bromophenyl)-*N*-methylmethacrylamide **46b**

Compound **46a** (500 mg, 2.69 mmol) and triethylamine (0.75 mL, 5.38 mmol) were dissolved in DCM (50 mL) at 0 °C, 2-methylacryloyl chloride (290 mg, 2.82 mmol) was added dropwise to the reaction solution, and the reaction was stirred for 1 h. The reaction solution was then diluted with water (100 mL) and extracted with DCM (100 mL) three times. The organic phase was washed with saturated saline solution, dried over anhydrous Na₂SO₄, and concentrated under reduced pressure, the obtained crude product was purified by silica gel column chromatography (EA/PE=1/4) to obtain compound **46b** (400 mg), yellow solid.

MS (ESI) *m/z* 254.1 [M + H]⁺.

Step 2 *N*-methyl-*N*-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl) methacrylamide **46c**

Compound **46b** (300 mg, 1.18 mmol), bis(pinacolato)diboron (360 mg, 1.42 mmol), Pd(dppf)Cl₂ (172 mg, 0.236 mmol), and potassium acetate (347 mg, 3.54 mmol) were placed in a bottle, and dioxane (8 mL) was added, after replaced with N₂ three times, the reaction was carried out at 100 °C for 18 h. The reaction solution was filtered and concentrated, and the obtained crude product was purified by column chromatography (PE/EtOAc=0-20%) to obtain compound **46c** (260 mg), yellow oily liquid.

MS (ESI) *m/z* 302 [M + H]⁺.

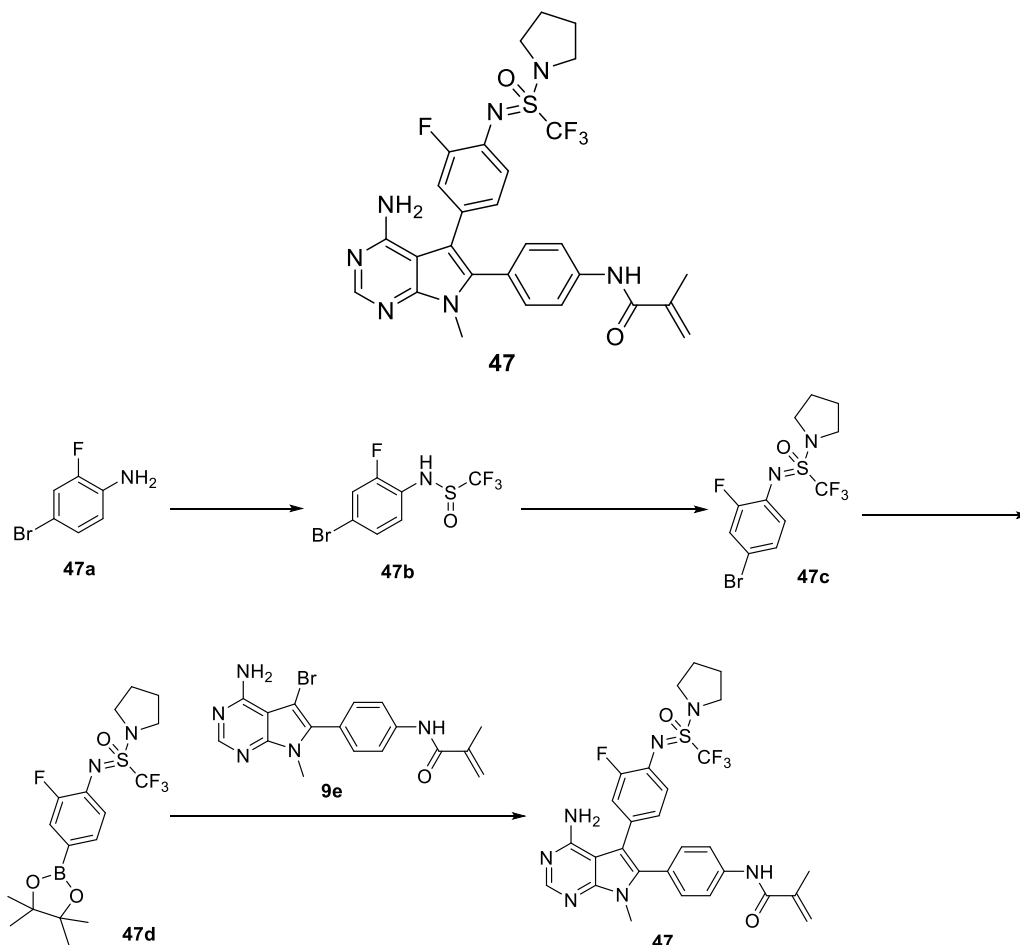
Step 3 N- (4- (4-amino-5- (3-fluoro-4- ((1-oxotetrahydro2H-1 λ^6 - thiopyran-1- ylidene) amino) phenyl) -7-methyl-7H-pyrrolo [2,3-*d*] pyrimidin-6-yl) phenyl) - N-methylmethacrylamide **46**

Compound **12a** (110 mg, 0.22 mmol), compound **46c** (80 mg, 0.27 mmol), Pd(PPh₃)₄ (51 mg, 0.044 mmol), and K₃PO₄ (140 mg, 0.66 mmol) were added into a sealed tube, after replaced with argon gas three times, 1,4-dioxane (5 mL) and H₂O (0.5 mL) were added, sealed, and the reaction solution was heated up to 100 °C and stirred for 16 h. Dichloromethane (20 mL) and saturated saline solution (10 mL) were added to extract, the organic phase was dried over anhydrous sodium sulfate, and concentrated under reduced pressure to obtain a crude product. The crude product was purified by column chromatography (MeOH/DCM=1/30) to obtain compound **46** (75 mg), white solid.

MS (ESI) *m/z* 547.56 [M + H]⁺.

¹H NMR (400 MHz, CDCl₃) δ 8.36 (s, 1H), 7.22 (dd, *J* = 8.5, 2.6 Hz, 3H), 7.13 (*d*, *J* = 8.4 Hz, 2H), 6.92 (dd, *J* = 8.1, 2.1 Hz, 1H), 6.82 (dd, *J* = 11.5, 2.0 Hz, 1H), 5.08 (*d*, *J* = 10.0 Hz, 3H), 5.01 (s, 1H), 3.71 (s, 3H), 3.38 (*s*, 5H), 3.15 (ddd, *J* = 13.6, 8.7, 4.2 Hz, 2H), 2.12 (td, *J* = 9.3, 8.5, 5.1 Hz, 4H), 1.76 (s, 3H), 1.25 (s, 2H).

Example 47 N- (4- (4-amino-5- (3-fluoro-4-((oxo (pyrrolidine-1-yl) (trifluoromethyl) - λ^6 -sulfanylidene) amino) phenyl) -7-methyl-7H-pyrrolo [2,3-*d*] pyrimidin-6-yl) phenyl) methacrylamide



Step 1 N- (4-bromo-2-fluorophenyl) -1,1,1-trifluoromethanesulfonamide 47b

Trifluoromethanesulfonyl chloride (2.4 g, 15.79 mmol) was dissolved in dichloromethane (30 mL), cooled down to 0 °C, a solution of compound **47a** (3.0 g, 15.79 mmol) in dichloromethane (10 mL) was added dropwise, then DIPEA (2.04 g, 15.79 mmol) was added, and heated up to room temperature to react for 2 h. The reaction solution was poured into water and extracted with DCM three times, dried over anhydrous sodium sulfate, and concentrated to obtain a crude product. The crude product was purified by column chromatography (PE/EtOAc=0-3%) to obtain compound **47b** (2.8 g), white solid.

MS (ESI) m/z 306.56 $[M + H]^+$.

Step 2 1- (N- (4-bromo-2-fluorophenyl) - S - (trifluoromethyl) sulfonylimino) pyrrolidine 47c

Compound **47b** (300 mg, 0.99 mmol) and N-chlorosuccinimide (145 mg, 1.1 mmol) were dissolved in acetonitrile (8 mL), tetrabutylammonium fluoride (1.1 mL, 1.1 mmol, 1M) was added at 0 °C, and the reaction was carried out at room temperature for 30 min, the reaction solution was concentrated, and then acetonitrile (8 mL) and tetrahydropyridine (280 mg, 4.0 mmol) were added, and reacted at room temperature for 2 h. The reaction solution was concentrated and dried, and the crude product was purified by column chromatography (PE/EtOAc=0-20%) to obtain compound **47c** (124 mg), yellow oily liquid

MS (ESI) m/z 374.2 $[M + H]^+$.

Step 3 1- (N- (2-fluoro-4- (4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) phenyl) - S - (trifluoromethyl) sulfonylimide) pyrrolidine 47d

Compound **47c** (124 mg, 0.33 mmol), bis(pinacolato)diboron (100 mg, 0.4 mmol), Pd(dppf)Cl₂ (48 mg, 0.066 mmol), and potassium acetate (98 mg, 0.99 mmol) were placed in a bottle, 1,4-dioxane (3 mL) was added, after replaced with N₂ three times, the reaction was carried out at 100 °C for 18 h. The reaction solution was filtered and concentrated, and the crude product was purified by column chromatography (PE/EtOAc =0-20%) to obtain compound **47d** (70 mg).

MS (ESI) m/z 423 $[M + H]^+$.

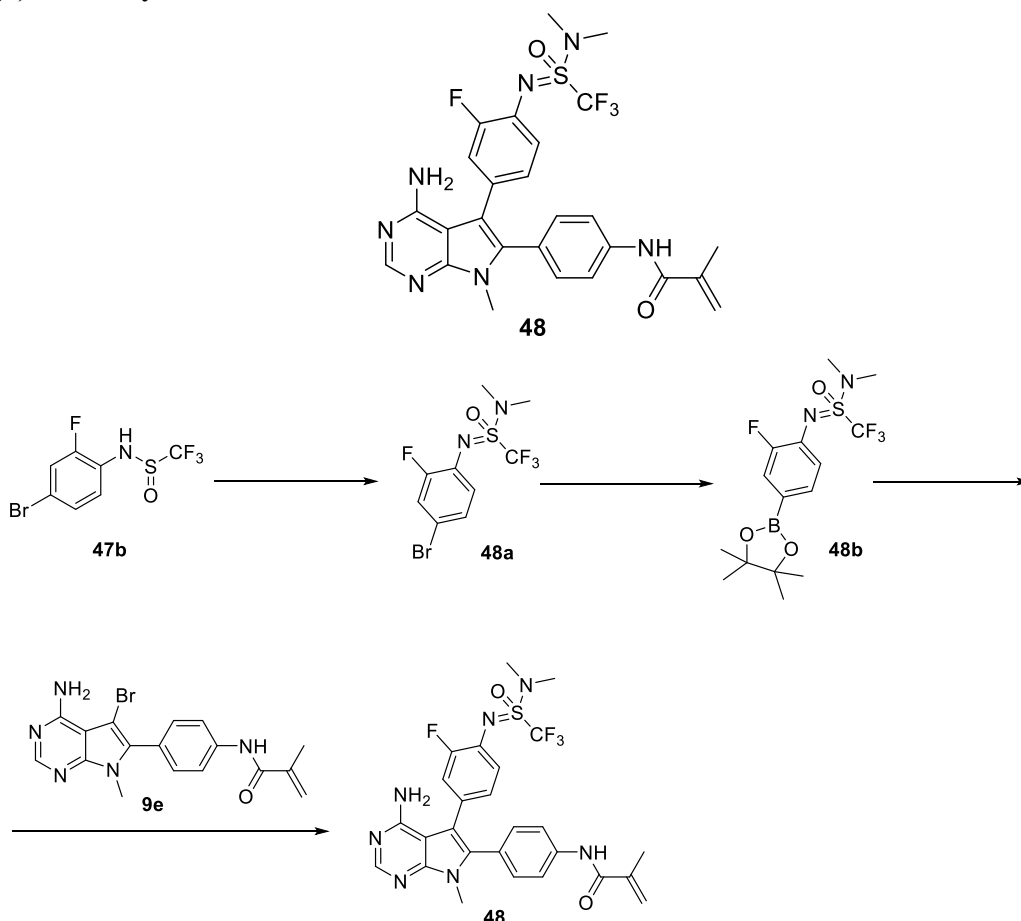
Step 4 N- (4- (4-amino-5- (3-fluoro-4- ((oxo (pyrrolidine-1-yl) (trifluoromethyl) - λ^6 - sulfanylidene) amino) phenyl) -7-methyl-7H-pyrrolo [2,3-*d*] pyrimidin-6-yl) phenyl) methacrylamide 47

Compound **9e** (25 mg, 0.065 mmol), compound **47d** (30 mg, 0.07 mmol), Pd(PPh₃)₄ (15 mg, 0.013 mmol), and K₃PO₄ (42 mg, 0.2 mmol) were added into a sealed tube, after replaced with argon gas three times, 1,4-dioxane (5 mL) and H₂O (0.5 mL) were added, sealed, and the reaction solution was heated up to 100 °C and stirred for 16 h. Dichloromethane (20 mL) and saturated saline solution (10 mL) were added to extract, the organic phase was dried over anhydrous sodium sulfate, and concentrated under reduced pressure to obtain a crude product. The crude product was purified by column chromatography (MeOH/DCM=1/30) to obtain compound **47** (10 mg), white solid.

MS (ESI) m/z 602.3 $[M + H]^+$.

^1H NMR (400 MHz, MeOD- d_4) δ 8.19 (s, 1H), 7.71 – 7.59 (m, 2H), 7.31 – 7.21 (m, 2H), 7.15 (t, J = 8.4 Hz, 1H), 7.03 – 6.94 (m, 2H), 5.81 (s, 1H), 5.52 (d, J = 1.8 Hz, 1H), 3.68 (s, 3H), 3.55 (d, J = 7.5 Hz, 2H), 3.43 (d, J = 8.6 Hz, 2H), 2.05 – 1.91 (m, 6H), 1.31 (d, J = 17.8 Hz, 2H).

5 **Example 48** *N*-(4-(4-amino-5-(4-(((dimethylamino) (oxo) (trifluoromethyl) - λ^6 - sulfanylidene) amino) -3-fluorophenyl) -7-methyl-7H-pyrrolo [2,3 - d] pyrimidin-6-yl) phenyl) methacrylamide



10 **Step 1** *N'*-(4-bromo-2-fluorophenyl)-1,1,1-trifluoro-*N,N*- dimethylmethanesulfonimide **48a**

Compound **47b** (500 mg, 1.6 mmol) and *N*-chlorosuccinimide (235 mg, 1.76 mmol) were dissolved in acetonitrile (8 mL), tetrabutylammonium fluoride (1.76 mL, 1.76 mmol, 1M) was added at 0 °C, and the reaction was carried out at room temperature for 30 min, the reaction solution was concentrated, and then acetonitrile (8 mL) and dimethylamine (3.5 mL, 7.0 mmol, 2M in THF) were added, and reacted at room temperature for 2 h. The reaction solution was concentrated and dried, and the crude product was purified by Flash (PE/EtOAc=0-20%) to obtain compound **48a** (400 mg), yellow oily liquid

MS (ESI) m/z 349.2 $[\text{M} + \text{H}]^+$.

20 **Step 2** 1,1,1-trifluoro-*N'*-(2-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) phenyl)- *N,N*-dimethylsulfonamide **48b**

Compound **48a** (100 mg, 0.29 mmol), bis(pinacolato)diboron (87 mg, 0.34 mmol), Pd(dppf)Cl₂ (42 mg, 0.058 mmol), and potassium acetate (85 mg, 0.87 mmol) were placed in a bottle, 1,4-dioxane (5 mL) was added, after replaced with N₂ three times, the reaction was carried out at 100 °C for 18 h. The reaction solution was filtered and concentrated, and the crude product was purified by column chromatography (PE/EtOAc=0-20%) to obtain compound **48b** (90 mg), yellow oily liquid.

MS (ESI) m/z 397 [M + H]⁺.

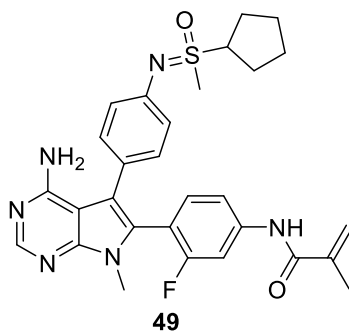
Step 3 N- (4- (4-amino-5- (4- ((dimethylamino) (oxo) (trifluoromethyl) - λ⁶ - sulfanylidene) amino) -3-fluorophenyl) -7-methyl-7H-pyrrolo [2,3 - d] pyrimidin-6-yl) phenyl) methacrylamide 48

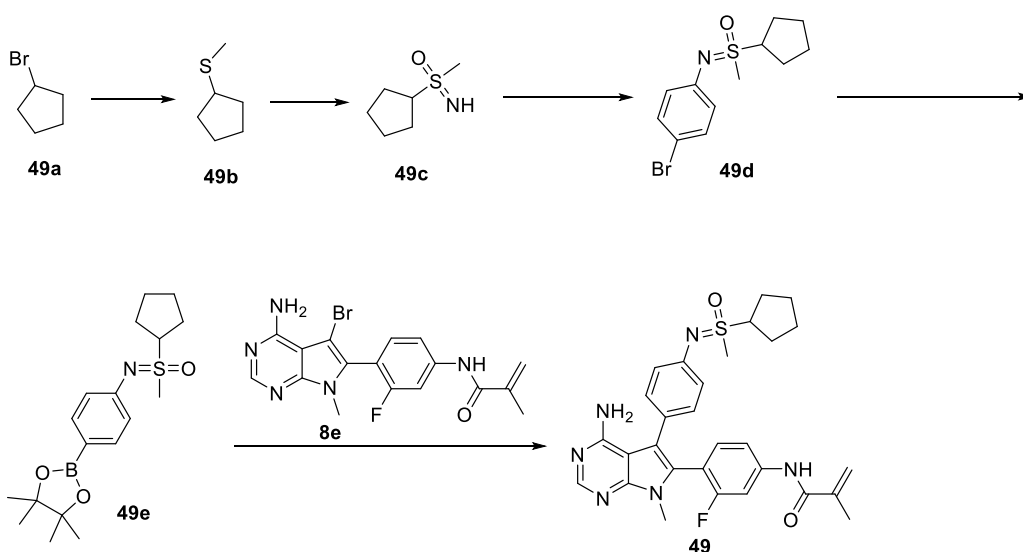
Compound **9e** (65 mg, 0.17 mmol), compound **48b** (80 mg, 0.20 mmol), Pd(PPh₃)₄ (38 mg, 0.034 mmol), and K₃PO₄ (110 mg, 0.51 mmol) were added into a sealed tube, after replaced with argon gas three times, 1,4-dioxane (5 mL) and H₂O (0.5 mL) were added, sealed, and the reaction solution was heated up to 100 °C and stirred for 16 h. Dichloromethane (20 mL) and saturated saline solution (10 mL) were added to extract, and the organic phase was dried over anhydrous sodium sulfate, and concentrated under reduced pressure to obtain a crude product. The crude product was purified by column chromatography (MeOH/DCM=1/30) to obtain compound **48** (30 mg), white solid.

MS (ESI) m/z 576.54 [M + H]⁺.

¹H NMR (400 MHz, MeOD-d₄) δ 8.09 (s, 1H), 7.60 – 7.55 (m, 2H), 7.18 (d, J = 8.7 Hz, 2H), 7.05 (t, J = 8.4 Hz, 1H), 6.95 – 6.83 (m, 2H), 5.71 (s, 1H), 5.42 (d, J = 1.8 Hz, 1H), 4.45 (s, 1H), 3.58 (s, 2H), 2.97 (s, 5H), 1.93 (d, J = 1.3 Hz, 2H), 1.19 (s, 3H).

Example 49 N- (4- (4-amino-5- (4- (cyclopentyl (methyl) (oxo) - λ⁶-sulfanylidene) amino) phenyl) -7-methyl-7H-pyrrole [2,3-d] pyrimidin-6-yl) -3-fluorophenyl) methacrylamide





Step 1 cyclopentyl-1-thioethane 49b

Compound **49a** (1.4 g, 9.4 mmol) was dissolved in ethanol (20 mL), sodium methylthionate aqueous solution (4.9g, 14.0mmol) was added at room temperature sequentially to react at room temperature for 16 h. The reaction solution was cooled down to room temperature and extracted with ethyl acetate (50 mL). The organic phase was concentrated under reduced pressure to obtain crude product **49b**, which was directly used in the next step.

Step 2 cyclopentylmethylsulfoximine 49c

Compound **49b** (0.9 g, 9.4 mmol) was dissolved in 20 mL of ethanol, ammonium formate (1.46 g, 15.0 mmol) and iodobenzene diethyl ester (7.5 g, 24 mmol) were added in an ice bath sequentially, the reaction was carried out at room temperature for 3 h, after TLC monitored the completion of the reaction, it was cooled down to room temperature, and the crude product was purified by column chromatography (DCM/MeOH=10/1) to obtain compound **49c** (100 mg), brown oily substance.

MS (ESI) m/z 148 $[M + H]^+$.

^1H NMR (400 MHz, CDCl_3) δ 3.52 (t, $J=8.13$ Hz, 1 H), 2.85 - 2.99 (m, 3 H), 1.94 - 2.15 (m, 4 H), 1.73 - 1.87 (m, 2 H), 1.59 - 1.73 (m, 2 H).

Step 3 4-bromophenyl-cyclopentylmethylsulfoximine 49d

To a 50 mL three necked bottle, 4-bromoiodobenzene (210 mg, 0.75 mmol) was dissolved in degassed 1,4-dioxane (3 mL), and then compound **49c** (100 mg, 0.68 mmol), $\text{Pd}_2(\text{dba})_3$ (60 mg, 0.06 mmol), Xantphos (68 mg, 0.12 mmol), and cesium carbonate (442 mg, 1.36 mmol) were added, the reaction was heated up to 90 °C and stirred for 4 h. After the reaction was completed, it was cooled down to room temperature, ethyl acetate (20 mL) and saturated sodium bicarbonate solution (10 mL) were added and extracted with ethyl acetate (20 mL $\times$ 3), and the organic phases were combined, washed with saturated saline solution (50 mL), and concentrated under reduced pressure to obtain a crude product, and the crude product was purified by column chromatography (PE/EtOAc=3/1) to obtain compound **49d** (150 mg).

MS (ESI) m/z 302 $[M + H]^+$.

Step 4 cyclopentyl (methyl) (4- (4,4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) phenyl) imino) - λ^6 -sulfone 49e

In a 50 mL three necked bottle, compound **49d** (150 mg, 0.5 mmol) was dissolved in degassed 1,4-dioxane (5 mL), and then bis(pinacolato)diboron (152 mg, 0.6 mmol), KOAc (150 mg, 1.5 mmol), and Pd(dppf)Cl₂ (50 mg, 0.05 mmol) were added, the reaction was heated up to 90 °C and stirred for 3 h, after the reaction was completed, it was cooled down to room temperature, ethyl acetate (20 mL) and saturated sodium chloride solution (10 mL) were added and extracted with ethyl acetate (20 mL $\times$ 3), and the organic phases were combined, washed with saturated saline solution (50 mL), and concentrated under reduced pressure to obtain a crude product, and the crude product was purified by column chromatography (PE/EtOAc=2/1) to obtain compound **49e** (50 mg).

MS (ESI) m/z 350 [M + H]⁺.

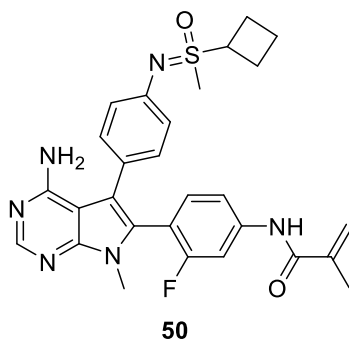
Step 5 N- (4- (4-amino-5- (4- (cyclopentyl (methyl) (oxo) - λ^6 -sulfanylidene) amino) phenyl) -7-methyl-7H-pyrrole [2,3-*d*] pyrimidin-6-yl) -3-fluorophenyl) methacrylamide 49

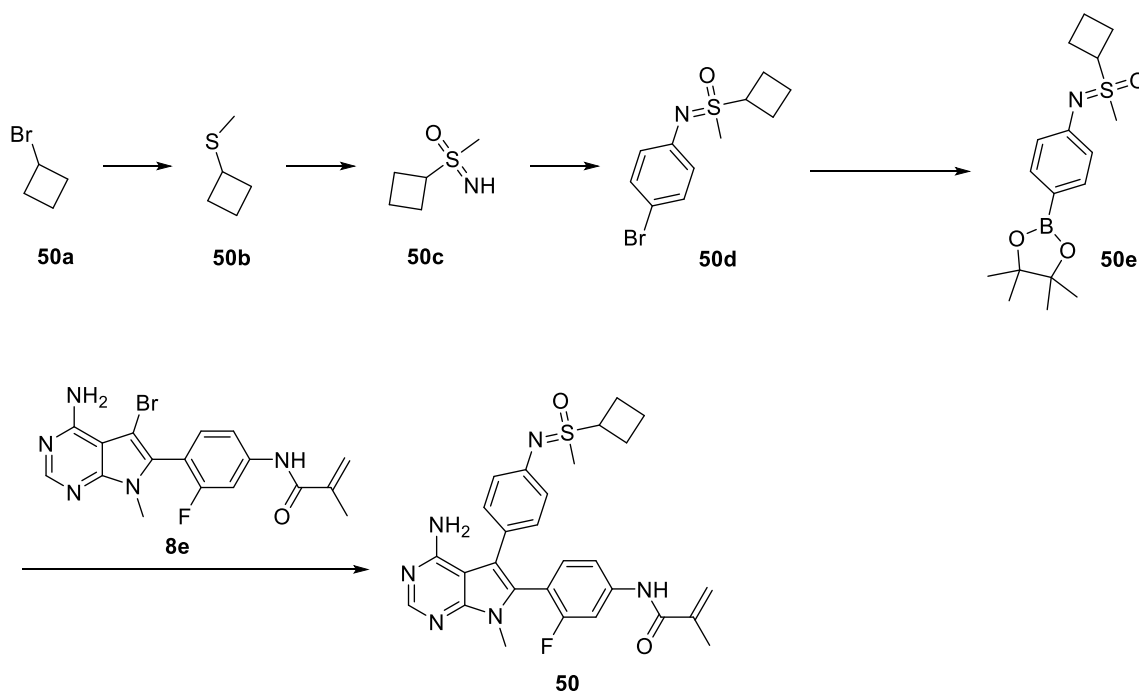
In a 50 mL three necked bottle, compound **49e** (50 mg, 0.14 mmol) was dissolved in degassed DMF (2 mL) and water (0.2 mL), and then, compound **8e** (111 mg, 0.27 mmol), K₃PO₄ (176 mg, 0.83 mmol), and Pd(dppf)Cl₂ (30 mg, 0.03 mmol) were added, the reaction was heated up to 90 °C and stirred for 3 h, after the reaction was completed, it was cooled down to room temperature, ethyl acetate (20 mL) and saturated sodium chloride solution (10 mL) were added and extracted with ethyl acetate (20 mL $\times$ 3), and the organic phases were combined, washed with saturated saline solution (50 mL), and concentrated under reduced pressure to obtain a crude product, and the crude product was purified by column chromatography (DCM/MeOH=10/1) to obtain compound **49** (7.7 mg), white solid.

MS (ESI) m/z 533 [M + H]⁺.

¹H NMR (400 MHz, CDCl₃) δ 8.32 (s, 1 H), 7.66 - 7.76 (m, 2 H), 7.59 (s, 1 H), 6.97 - 7.13 (m, 5 H), 5.81 (s, 1H), 5.53 (s, 1 H), 5.31 (s, 2 H), 3.64 - 3.69 (m, 3 H), 2.99 (s, 3 H), 2.18 - 2.28 (m, 3 H), 2.14 (br. s., 3 H), 2.06 - 2.12 (m, 3 H), 2.01 (br. s., 3 H).

Example 50 N-(4- (4-amino-5- (4- ((cyclobutyl (methyl) (oxo) - λ^6 -sulfanylidene) amino) phenyl) -7-methyl-7H-pyrrole [2,3-*d*] pyrimidin-6-yl) -3-fluorophenyl) methacrylamide





Step 1 cyclobutyl methyl sulfide **50b**

Compound **50a** (1.26 g, 9.4 mmol) was dissolved in ethanol (20 mL), sodium methylthionate aqueous solution (4.9 g, 14.0 mmol) was added at room temperature sequentially, and then the reaction was carried out at room temperature for 16 h. The reaction solution was cooled down to room temperature and extracted with 50 mL of ethyl acetate. The extracted mixture was concentrated under reduced pressure to obtain crude product **50b**, which was directly used in the next step.

Step 2 cyclobutylmethylsulfonimide **50c**

Compound **50b** (0.9 g, 9.4 mmol) was dissolved in 20 mL of ethanol, ammonium formate (1.46 g, 15.0 mmol) was added sequentially, in ice bath, iodobenzene diacetate (7.5 g, 24 mmol) was added, and the reaction was carried out at room temperature for 3 h, after TLC monitored the completion of the reaction, it was cooled down to room temperature, concentrated under reduced pressure, and the crude product was purified by column chromatography (DCM/MeOH=10/1) to obtain compound **50c** (75 mg), brown oily substance.

MS (ESI) m/z 134 $[M + H]^+$.

^1H NMR (400 MHz, CDCl_3) δ 3.90 (t, $J=8.33$ Hz, 1 H), 2.86 (s, 3 H), 2.45 - 2.63 (m, 2 H), 2.32 (dtd, $J=12.22, 8.23, 8.23, 4.23$ Hz, 2 H), 1.95 - 2.13 (m, 3 H).

Step 3 4-bromophenyl-cyclobutylmethylsulfonimide **50d**

To a 50 mL three necked bottle, 4-bromiodobenzene (100 mg, 0.33 mmol) was dissolved in degassed 1,4-dioxane (3 mL), and then compound **50c** (40 mg, 0.3 mmol), $\text{Pd}_2(\text{dba})_3$ (30 mg, 0.03 mmol), Xantphos (34 mg, 0.06 mmol), cesium carbonate (295mg, 0.9mmol) were added, heated up to 90 °C and stirred for 4 h. After the reaction was completed, it was cooled down to room temperature, ethyl acetate (20 mL) and saturated sodium bicarbonate solution (10 mL) were added and extracted with ethyl acetate (20 mL $\times$ 3), and the organic phases were combined, washed with

saturated saline solution (50 mL), and concentrated under reduced pressure to obtain a crude product, and the crude product was purified by column chromatography (PE/EtOAc=3/1) to obtain compound **50d** (75 mg).

MS (ESI) m/z 288 $[M + H]^+$.

5

Step 4 cyclobutyl (methyl) (4- (4,4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) phenyl) imino) - λ^6 -thianone 50e

To a 50 mL three necked bottle, compound **50d** (75 mg, 0.26 mmol) was dissolved in degassed 1,4-dioxane (5 mL), and then bis(pinacolato)diboron ester (75 mg, 0.3 mmol), KOAc (75 mg, 0.6 mmol), and Pd(dppf)Cl₂ (22 mg, 0.03 mmol) were added, the reaction was heated up to 90 °C and stirred for 3 h, after the reaction was completed, it was cooled down to room temperature, ethyl acetate (20 mL) and saturated sodium chloride solution (10 mL) were added and extracted with ethyl acetate (20 mL $\times$ 3), and the organic phases were combined, washed with saturated saline solution (50 mL), and concentrated under reduced pressure to obtain a crude product, and the crude product was purified by column chromatography (PE/EtOAc=2/1) to obtain compound **50e** (93 mg).

15

MS (ESI) m/z 335 $[M + H]^+$.

Step 5 N- (4- (4-amino-5- (4- ((cyclobutyl (methyl) (oxo) - λ^6 -sulfanylidene) amino) phenyl) -7-methyl-7H-pyrrole [2,3-*d*] pyrimidin-6-yl) -3-fluorophenyl) methacrylamide 50

In a 50 mL three necked bottle, compound **50e** (93 mg, 0.27 mmol) was dissolved in degassed DMF (3 mL) and water (0.3 mL), and then compound **8e** (111 mg, 0.27 mmol), K₃PO₄ (176 mg, 0.83 mmol), and Pd(dppf)Cl₂ (30 mg, 0.03 mmol) were added, the reaction was heated up to 90 °C and stirred for 3 h, after the reaction was completed, it was cooled down to room temperature, ethyl acetate (20 mL) and saturated sodium chloride solution (10 mL) were added and extracted with ethyl acetate (20 mL $\times$ 3), and the organic phases were combined, washed with saturated saline solution (50 mL), and concentrated under reduced pressure to obtain a crude product, and the crude product was purified by column chromatography (DCM/MeOH=10/1) to obtain compound **50** (4.5 mg), white solid.

25

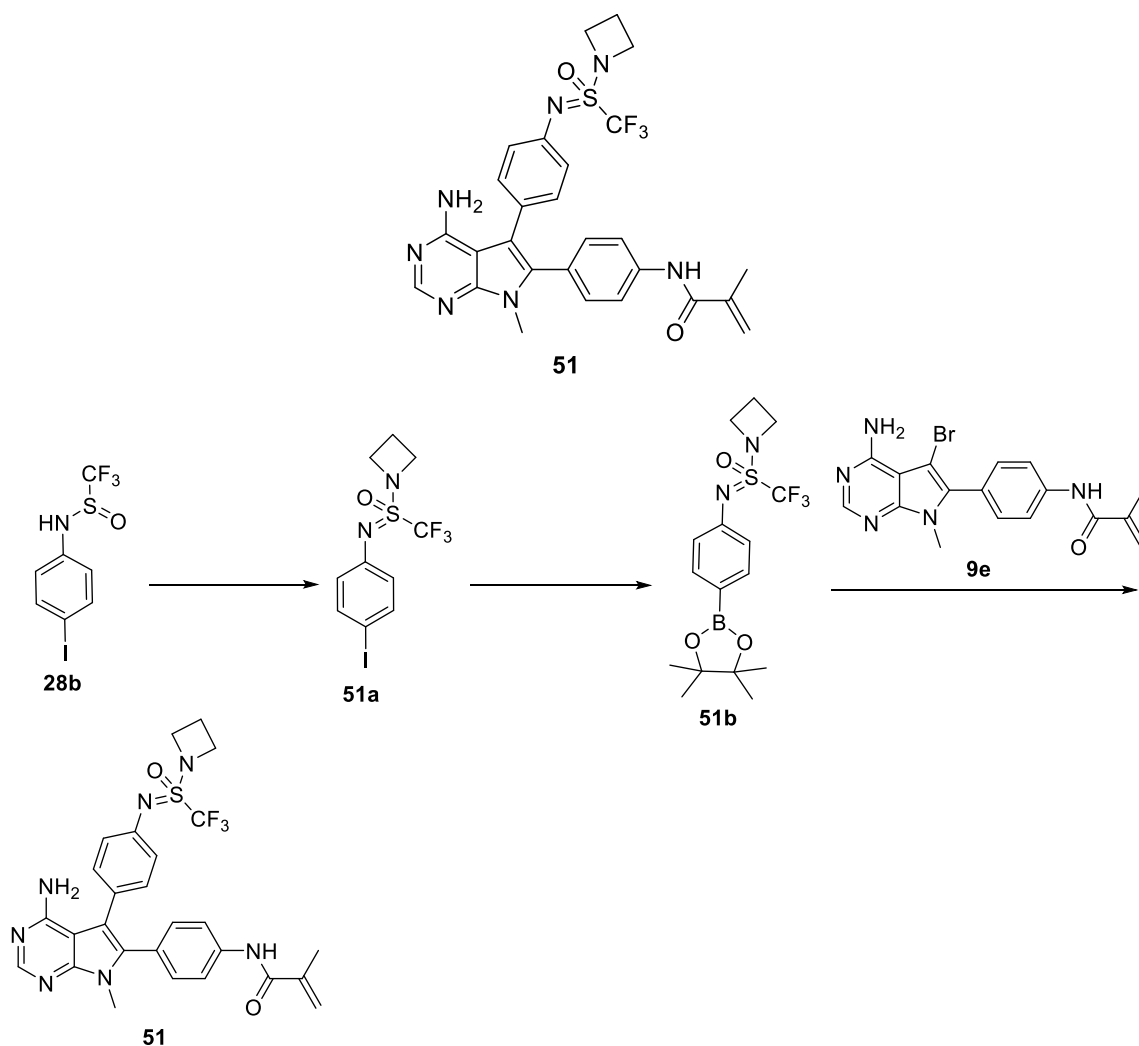
MS (ESI) m/z 533 $[M + H]^+$.

30

¹H NMR (400 MHz, CDCl₃) δ 8.38 (s, 1 H), 7.72 (d, J =12.09 Hz, 1 H), 7.59 (s, 1 H), 6.98 - 7.20 (m, 5 H), 5.83 (s, 1 H), 5.54 (s, 1 H), 5.06 (br. s., 2 H), 4.00 (s, 1 H), 3.68 (s, 3 H), 2.94 (s, 3 H), 2.68 (br. s., 2 H), 2.35 (d, J =8.60 Hz, 2 H), 1.96 - 2.15 (m, 5 H).

Example 51 N- (4- (4-amino-5- (4- ((azetidin-1-yl (oxo) (trifluoromethyl) - λ^6 -sulfanylidene) amino) phenyl) -7-methyl-7H-pyrrole [2,3-*d*] pyrimidin-6-yl) phenyl) methacrylamide

35



Step 1 1- (*N*- (4-iodobenzene) - S - (trifluoromethyl) sulfonylimide) azetidine **51a**

Compound **28b** (500 mg, 1.49 mmol) and N-chlorosuccinimide (292 mg, 1.64 mmol) were dissolved in dry acetonitrile (8 mL), a solution of tetrabutylammonium fluoride in tetrahydrofuran (1.64 mL, 1.64 mmol, 1M) was added at 0 °C, the reaction was carried out at room temperature for 30 min, the reaction solution was concentrated, and then dry acetonitrile (8 mL) and heterocyclic cyclohexane (340 mg, 6.0 mmol) were added, and reacted at room temperature for 2 h. The reaction solution was concentrated and dried, and the obtained crude product was purified by Flash (PE/EtOAc=0-20%) to obtain compound **51a** (230 mg), yellow oily liquid.

MS (ESI) m/z 390 $[M + H]^+$.

Step 2 1- (*N*- (4- (4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) phenyl) - S - (trifluoromethyl) sulfonylimide) azetidine **51b**

Compound **51a** (230 mg, 0.59 mmol), bis(pinacolato)diboron (180 mg, 0.71 mmol), Pd(dppf)Cl₂ (87 mg, 0.12 mmol), and potassium acetate (154 mg, 1.77 mmol) were placed in a bottle, 1,4-dioxane (6 mL) was added, after replaced with N₂ three times, the reaction was carried out at 100 °C for 18 h. The reaction solution was filtered and concentrated, and the crude product

was purified by column chromatography (PE/EtOAc=0-20%) to obtain compound **51b** (180 mg), yellow solid.

MS (ESI) m/z 391 $[M + H]^+$.

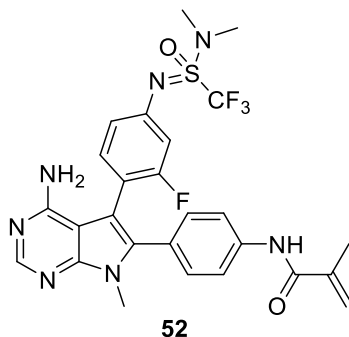
5 **Step 3 N- (4- (4-amino-5- (4- ((azetidine-1-yl- (oxo) (trifluoromethyl) - λ^6 - sulfanylidene) amino) phenyl) -7-methyl-7H-pyrrolo [2,3-d] pyrimidin-6-yl) phenyl) methacrylamide **51****

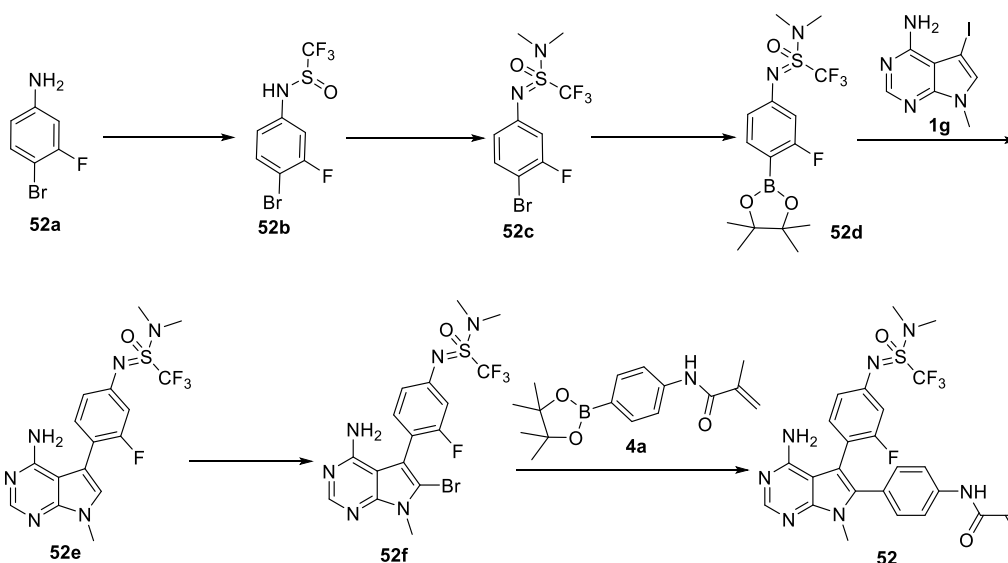
Compound **9e** (42 mg, 0.11 mmol), compound **51b** (50 mg, 0.13 mmol), Pd(PPh₃)₄ (25 mg, 0.021 mmol), and K₃PO₄ (68 mg, 0.32 mmol) were added into a sealed tube, and it was replaced with argon gas three times, 1,4-dioxane (5 mL) and H₂O (0.5 mL) were added, sealed, and the reaction solution was heated up to 100 °C and stirred for 16 h. Dichloromethane (20 mL) and saturated saline solution (10 mL) were added to extract, and the organic phase was dried over anhydrous sodium sulfate, and concentrated under reduced pressure to obtain a crude product. The crude product was purified by column chromatography (MeOH/DCM=1/30) to obtain compound **51** (11 mg), white solid.

15 MS (ESI) m/z 570.05 $[M + H]^+$.

¹H NMR (400 MHz, MeOD-d₄) δ 8.19 (s, 1H), 7.72 – 7.59 (m, 2H), 7.39 (d, J = 8.5 Hz, 2H), 7.33 (d, J = 8.5 Hz, 2H), 7.30 – 7.21 (m, 2H), 5.80 (s, 1H), 5.52 (d, J = 1.8 Hz, 1H), 4.58 (s, 1H), 4.28 – 4.19 (m, 1H), 3.86 – 3.72 (m, 2H), 3.68 (s, 4H), 2.30 – 2.18 (m, 1H), 2.07 – 1.93 (m, 4H).

20 **Example 52 N- (4- (4-amino-5- (4- (((dimethylamino) (oxo) (trifluoromethyl) - λ^6 - sulfanylidene) amino) -2-fluorophenyl) -7-methyl-7H-pyrrolo [2,3-d] pyrimidin-6-yl) phenyl) methacrylamide**





Step 1 *N*-(4-bromo-3-fluorophenyl)-1,1,1-trifluoromethylsulfonimide **52b**

Trifluoromethanesulfonyl chloride (2.41g, 15.79 mmol) was dissolved in dichloromethane (15 mL), cooled down to 0 °C, a solution of compound **52a** (3.0 g, 15.79 mmol) in dichloromethane (10 mL) was added dropwise, and *N,N*-diisopropylethylamine (2.04 g, 15.79 mmol) was added, then heated up to room temperature and reacted for 2 h. The reaction solution was poured into water and extracted with dichloromethane three times, dried over anhydrous sodium sulfate, and concentrated to obtain a crude product, and the crude product was purified by column chromatography (PE/EtOAc=0-3%) to obtain compound **52b** (2.6 g), brown solid.

MS (ESI) m/z 306.56 $[M + H]^+$.

Step 2 *N'*-(4-bromo-3-fluorophenyl)-1,1,1-trifluoro-*N,N*-dimethylmethanesulfonimide **52c**

Compound **52b** (600 mg, 1.98 mmol) and *N*-chlorosuccinimide (318 mg, 2.18 mmol) were dissolved in dry acetonitrile (10 mL), at 0 °C, a solution of tetrabutylammonium fluoride in tetrahydrofuran (2.2 mL, 2.2 mmol, 1M) was added, and the reaction was carried out at room temperature for 30 min. The reaction solution was concentrated, and then dry acetonitrile (10 mL) and dimethylamine tetrahydrofuran solution (4.0 mL, 8.0 mmol, 2M in THF) were added, and reacted at room temperature for 2 h. The reaction solution was concentrated, dried, and purified by column chromatography (PE/EtOAc=0-20%) to obtain compound **52c** (480 mg), yellow oily liquid

MS (ESI) m/z 349.2 $[M + H]^+$.

Step 3 1,1,1-trifluoro-*N'*-(3-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-*N,N*-dimethylsulfonimide **52d**

Compound **52c** (300 mg, 0.87 mmol), bis(pinacolato)diboron (261 mg, 1.02 mmol), Pd(dppf)Cl₂ (126 mg, 0.174 mmol), and potassium acetate (255 mg, 2.61 mmol) were placed into a bottle, 1,4-dioxane (mL) was added, after replaced with N₂ three times, the reaction was carried out at 100 °C for 18 h. The reaction solution was filtered and concentrated, and the crude product

was purified by column chromatography (PE/EtOAc=0-20%) to obtain compound **52d** (280 mg), yellow oily liquid.

MS (ESI) m/z 397 $[M + H]^+$.

5 **Step 4 N'-(4-(4-amino-7-methyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)-3- fluorophenyl) -1,1,1-trifluoro-N, N-dimethylmethanesulfonimide 52e**

Compound **1g** (115 mg, 0.42 mmol), compound **52d** (200mg, 0.5 mmol), Pd(PPh₃)₄ (97 mg, 0.084 mmol), and K₃PO₄ (267mg, 1.26 mmol) were added into a sealed tube, after replaced with N₂ three times, 1,4-dioxane (4 mL) and H₂O (0.5 mL) were added, sealed, and the reaction
10 solution was heated up to 100 °C and stirred for 16 h. Dichloromethane (20 mL) and saturated saline solution (10 mL) were added to extract, and the organic phase was dried over anhydrous sodium sulfate, and concentrated under reduced pressure to obtain a crude product. The crude product was purified by column chromatography (MeOH/DCM=1/30) to obtain compound **52e** (85 mg), yellow solid.

15 MS (ESI) m/z 417 $[M + H]^+$.

Step 5 N'-(4-(4-amino-6-bromo-7-methyl-7H-pyrrolo [2,3-d] pyrimidin-5-yl)-3- fluorophenyl) -1,1,1-trifluoro-N, N-dimethylmethanesulfonimide 52f

Compound **52e** (85 mg, 0.21 mmol) was dissolved in DMF (3 mL), and a solution of
20 N-bromosuccinimide (41 mg, 0.23 mmol) in DMF (0.5 mL) was added dropwise at 0 °C, and the reaction solution was stirred at 0 °C for 1 h. Then DCM (20 mL) was added, and washed with saturated saline solution (10 mL × 3), and the organic phase was dried over anhydrous sodium sulfate, and concentrated under reduced pressure to obtain a crude product. The crude product was purified by column chromatography (MeOH/DCM=1/40) to obtain compound **52f** (51 mg),
25 yellow solid.

MS (ESI) m/z 495 $[M + H]^+$.

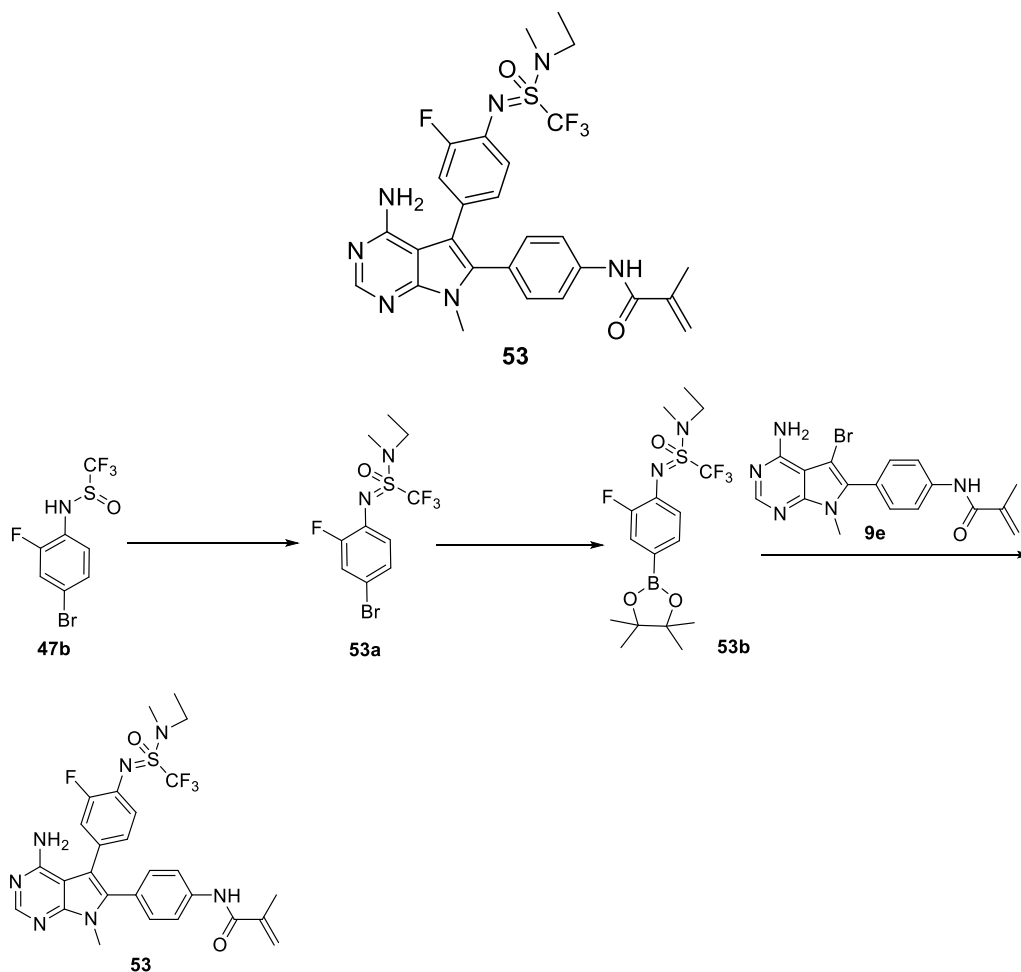
30 **Step 6 N- (4- (4-amino-5- (4- (((dimethylamino) (oxo) (trifluoromethyl) - λ⁶ - sulfanylidene) amino) -2-fluorophenyl) -7-methyl-7H-pyrrolo [2,3-d] pyrimidin-6-yl) phenyl) methacrylamide 52**

Compound **52f** (51mg, 0.103 mmol), compound **4a** (61.2 mg, 0.124 mmol), Pd(PPh₃)₄ (23 mg, 0.021 mmol), and K₃PO₄ (66 mg, 0.31 mmol) was added into a sealed tube, after replaced with N₂ three times, 1,4-dioxane (5 mL) and H₂O (0.5 mL) were added, sealed, and the reaction
35 solution was heated up to 100 °C and stirred for 16 h. Dichloromethane (30 mL) and saturated saline solution (20 mL) were added to extract, and the organic phase was dried over anhydrous sodium sulfate, and concentrated under reduced pressure to obtain a crude product. The crude product was purified by column chromatography (MeOH/DCM=1/30) to obtain compound **52** (18 mg), white solid.

MS (ESI) m/z 576.44 $[M + H]^+$.

40 ¹H NMR (400 MHz, MeOD-d₄) δ 8.18 (s, 1H), 7.64 (d, J = 8.2 Hz, 2H), 7.28 – 7.19 (m , 3H), 6.87 – 6.79 (m , 2H), 5.80 (s, 1H), 5.52 (s, 1H), 4.58 (s, 2H), 3.71 (s, 3H), 3.08 (s, 5H), 2.02 (s, 3H).

Example 53 *N*-(4-(4-amino-5-(4-(((ethyl (methyl) amino) (oxo) (trifluoromethyl) -λ⁶ -sulfanylidene) amino) -3-fluorophenyl) -7-methyl-7*H*-pyrrolo [2,3-*d*] pyrimidin-6-yl) phenyl) methacrylamide



5

Step 1 *N'*-(4-bromo-2-fluorophenyl)-*N*-ethyl-1,1,1-trifluoro-*N*-methylsulfonylimide **53a**

Compound **47b** (500 mg, 1.49 mmol) and *N*-chlorosuccinimide (292 mg, 1.64 mmol) were added in acetonitrile (8 mL), a solution of tetrabutylammonium fluoride in THF (1.64 mL, 1.64 mmol, 1M) was added at 0 °C, and the reaction was carried out at room temperature for 30 min. The reaction solution was concentrated, and then acetonitrile (8 mL) and *N*-methylethylamine (360 mg, 6.0 mmol) were added, and reacted at room temperature for 2 h. The reaction solution was concentrated and dried, and the obtained crude product was purified by column chromatography (PE/EtOAc=0-20%) to obtain compound **53a** (420 mg).

MS (ESI) *m/z* 363.2 [M + H]⁺

15

Step 2 *N*-ethyl-1,1,1-trifluoro-*N'*-(2-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) phenyl) - *N*-methylmethane sulfonamide **53b**

Compound **53a** (420 mg, 1.16 mmol), bis(pinacolato)diboron (352 mg, 1.39 mmol), Pd(dppf)Cl₂ (170 mg, 0.23 mmol), and potassium acetate (340 mg, 3.48 mmol) were placed in a bottle, and 1,4-dioxane (8 mL) was added, after replaced with N₂ three times. The reaction was carried out at 100 °C for 18 h. The reaction solution was filtered and concentrated, and the crude

20

product was purified by column chromatography (PE/EtOAc=0-20%) to obtain compound **53b** (360 mg).

MS (ESI) m/z 411 $[M + H]^+$

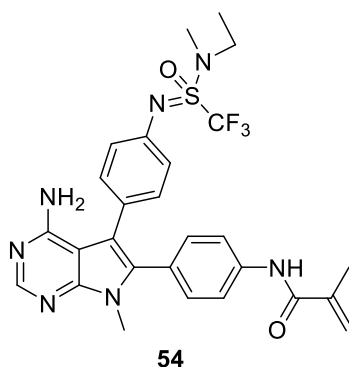
5 **Step 3** *N*- (4- (4-amino-5- (4- (((ethyl (methyl) amino) (oxo) (trifluoromethyl) - λ^6 - sulfanylidene) amino) -3-fluorophenyl) -7-methyl-7*H*-pyrrolo [2,3-*d*] pyrimidin-6-yl) phenyl) methacrylamide **53**

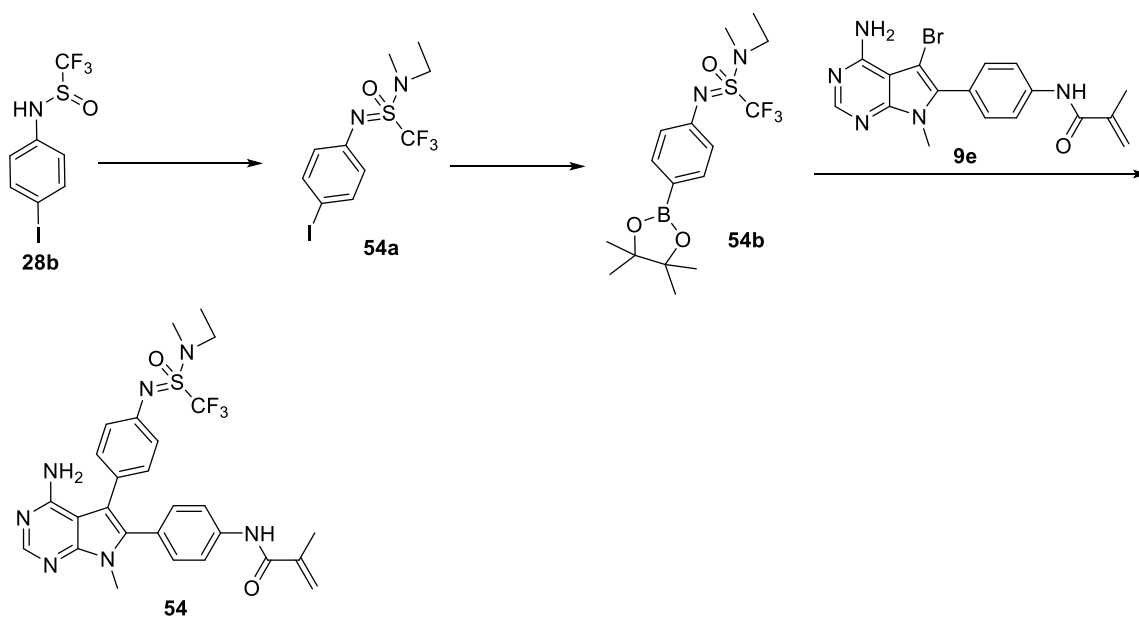
Compound **9e** (117 mg, 0.305 mmol), compound **53b** (150 mg, 0.366 mmol), Pd(PPh₃)₄ (70 mg, 0.061 mmol), and K₃PO₄ (200 mg, 0.915 mmol) were added into a sealed tube, after replaced with N₂ three times, 1,4-dioxane (5 mL) and H₂O (0.5 mL) were added, sealed, and the reaction solution was heated up to 100 °C and stirred for 16 h. Dichloromethane (30 mL) and saturated saline solution (20 mL) were added to extract, and the organic phase was dried over anhydrous sodium sulfate, and concentrated under reduced pressure to obtain a crude product. The crude product was purified by column chromatography (MeOH/DCM=1/30) to obtain compound **53** (80 mg), white solid.

MS (ESI) m/z 589.90 $[M + H]^+$.

¹H NMR (400 MHz, MeOD-*d*₄) δ 8.32 (s, 1H), 7.78 – 7.52 (m, 2H), 7.26 (dd, J = 8.4, 3.5 Hz, 2H), 7.21 – 7.10 (m, 1H), 7.05 – 6.90 (m, 2H), 5.81 (s, 1H), 5.52 (s, 1H), 4.65 (s, 3H), 4.56 (s, 1H), 3.68 (d, J = 3.3 Hz, 3H), 3.47 (p, J = 7.3 Hz, 2H), 3.03 (s, 3H), 1.11 (td, J = 7.1, 1.9 Hz, 3H).

20 **Example 54** *N*- (4- (4-amino-5- (4- (((ethyl (methyl) amino) (oxo) (trifluoromethyl) - λ^6 - sulfanylidene) amino) phenyl) -7-methyl-7*H*-pyrrolo [2,3-*d*] pyrimidin-6-yl) phenyl) methacrylamide





Step 1 *N*-ethyl-1,1,1-trifluoro-*N'*- (4-iodophenyl) - *N*-methylmethanesulfonyl imide **54a**

Compound **28b** (500 mg, 1.49 mmol) and *N*-chlorosuccinimide (292 mg, 1.64 mmol) were added in acetonitrile (8 mL), a solution of tetrabutylammonium fluoride in THF (1.64 mL, 1.64 mmol, 1M) was added at 0 °C, and the reaction was carried out at room temperature for 30 min. The reaction solution was concentrated, then acetonitrile (8 mL) and *N*-methylethylamine (360 mg, 5.96 mmol) were added, and reacted at room temperature for 2 h. The reaction solution was concentrated and dried, and the crude product was purified by column chromatography (PE/EtOAc=0-20%) to obtain compound **54a** (420 mg).

MS (ESI) m/z 391.97 $[M + H]^+$

Step 2 *N*-ethyl-1,1,1-trifluoro-*N*-methyl-*N'*- (4- (4,4,5,5-tetramethyl-1,3,2- dioxaborolan -2-yl) phenyl) methane sulfonamide **54b**

Compound **54a** (220 mg, 0.56 mmol), bis(pinacolato)diboron (171 mg, 0.67 mmol), Pd(dppf)Cl₂ (83 mg, 0.11 mmol), and potassium acetate (165 mg, 1.68 mmol) were placed in a bottle, and dioxane (6 mL) was added. After replaced with N₂ three times, the reaction was carried out at 100 °C for 18 h. The reaction solution was filtered and concentrated, and the crude product was purified by column chromatography (PE/EtOAc=0-20%) to obtain compound **54b** (180 mg).

MS (ESI) m/z 393 $[M + H]^+$

Step 3 *N*- (4- (4-amino-5- (4- (((ethyl (methyl) amino) (oxo) (trifluoromethyl) - λ⁶ - sulfanylidene) amino) phenyl) -7-methyl-7H-pyrrolo [2,3-*d*] pyrimidin-6-yl) phenyl) methacrylamide **54**

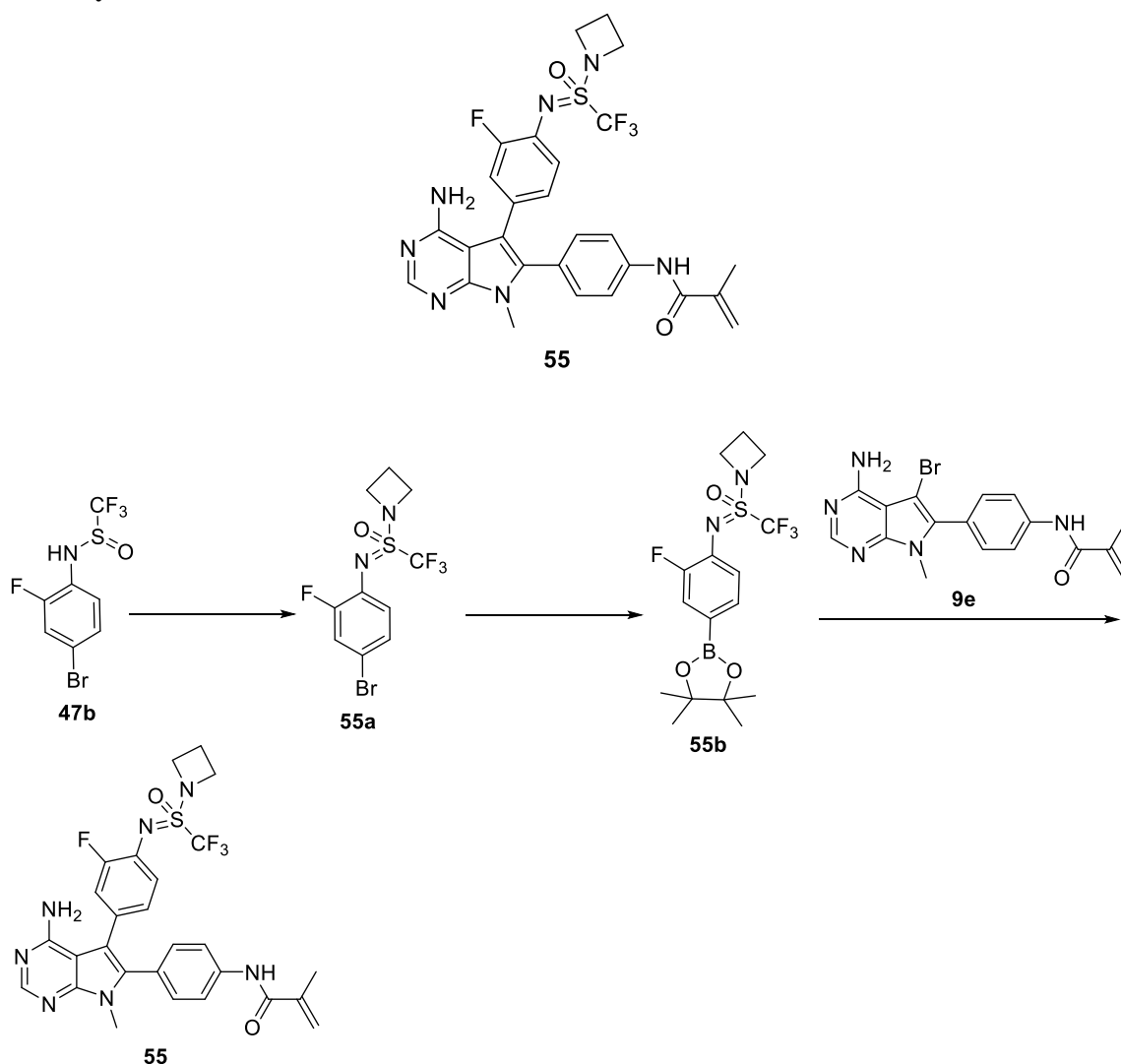
Compound **9e** (24.6 mg, 0.064 mmol), compound **54b** (30 mg, 0.077 mmol), Pd(PPh₃)₄ (14.7 mg, 0.013 mmol), and K₃PO₄ (41 mg, 0.192 mmol) were added into a sealed tube, after replaced with N₂ three times, 1,4-dioxane (3 mL) and H₂O (0.4 mL) were added, sealed, and the reaction solution was heated up to 100 °C and stirred for 16 h. Then dichloromethane (20 mL) and saturated saline solution (10 mL) were added to extracted, and the organic phase was dried over anhydrous sodium sulfate, and concentrated under reduced pressure to obtain a crude product. The

crude product was purified by column chromatography (MeOH/DCM=1/30) to obtain compound **54** (12 mg), white solid.

MS (ESI) m/z 572.68 $[M + H]^+$.

^1H NMR (400 MHz, MeOD- d_4) δ 8.18 (s, 1H), 7.68 – 7.60 (m, 2H), 7.30 – 7.22 (m, 2H), 7.22 – 7.14 (m, 2H), 7.08 – 7.00 (m, 2H), 5.80 (s, 1H), 5.52 (d, J = 1.9 Hz, 1H), 4.57 (s, 2H), 3.69 (s, 3H), 3.47– 3.41 (m, 2H), 3.01 (s, 3H), 2.02 (d, J = 1.2 Hz, 3H), 1.10 (t, J = 7.1 Hz, 3H).

Example 55 *N*-(4-(4-amino-5-(4-((azetidine 1-yl (oxo) (trifluoromethyl) - λ^6 - sulfanylidene) amino) -3-fluorophenyl) -7-methyl-7H-pyrrolo [2,3-*d*] pyrimidin-6-yl) phenyl) methacrylamide



Step 1 1-(*N*-(4-bromo-2-fluorophenyl) - S - (trifluoromethyl) sulfonylimino) azetidine **55a**

Compound **47b** (200 mg, 0.66 mmol) and N-chlorosuccinimide (106 mg, 0.73 mmol) were added in dry acetonitrile (6 mL), a solution of tetrabutylammonium fluoride in tetrahydrofuran (0.73 mL, 0.73 mmol, 1M) was added at 0 °C, and the reaction was carried out at room temperature for 30 min. The reaction solution was concentrated, then dry acetonitrile (8 mL) and

azetidine (128 mg, 2.6 mmol) were added, and reacted at room temperature for 2 h. The reaction solution was concentrated and dried, and the crude product was purified by column chromatography (PE/EtOAc=0-20%) to obtain compound **55a** (130 mg), yellow oily liquid.

MS (ESI) m/z 361.2 $[M + H]^+$.

5

Step 2 1- (N- (2-bromo-4- (4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) phenyl) - S - (trifluoromethyl) sulfonylimide) azetidine **55b**

Compound **55a** (130 mg, 0.36 mmol), bis(pinacolato)diboron (110 mg, 0.43 mmol), Pd(dppf)Cl₂ (53 mg, 0.072 mmol), and potassium acetate (110 mg, 1.1 mmol) were placed in a bottle, 1,4-dioxane (6 mL) was added, after replaced with N₂ three times, the reaction was carried out at 100 °C for 18 h. The reaction solution was filtered and concentrated, and the crude product was purified by column chromatography (PE/EtOAc=0-20%) to obtain compound **55b** (100 mg).

MS (ESI) m/z 408 $[M + H]^+$.

Step 3 N- (4- (4-amino-5- (4- ((azetidine 1-yl (oxo) (trifluoromethyl) -λ⁶ - sulfanylidene) amino) -3-fluorophenyl) -7-methyl-7H-pyrrolo [2,3-*d*] pyrimidin-6-yl) phenyl) methacrylamide **55**

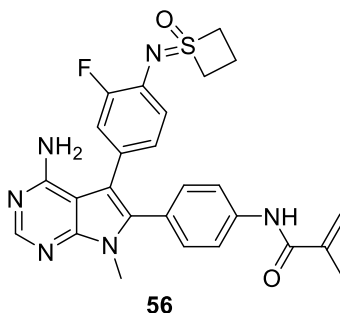
Compound **9e** (75 mg, 0.19 mmol), compound **55b** (94 mg, 0.23 mmol), Pd(dppf)Cl₂ (28 mg, 0.0384 mmol), and K₃PO₄ (120 mg, 0.58 mmol) were added into a sealed tube, after replaced with N₂ three times, 1,4-dioxane (3 mL) and H₂O (0.4 mL) were added, sealed, and the reaction solution was heated up to 100 °C and stirred for 16 h. Dichloromethane (20 mL) and saturated saline solution (10 mL) were added to extract, and the organic phase was dried over anhydrous sodium sulfate, and concentrated under reduced pressure to obtain a crude product. The crude product was purified by column chromatography (MeOH/DCM=1/30) to obtain compound **55** (20 mg), white solid.

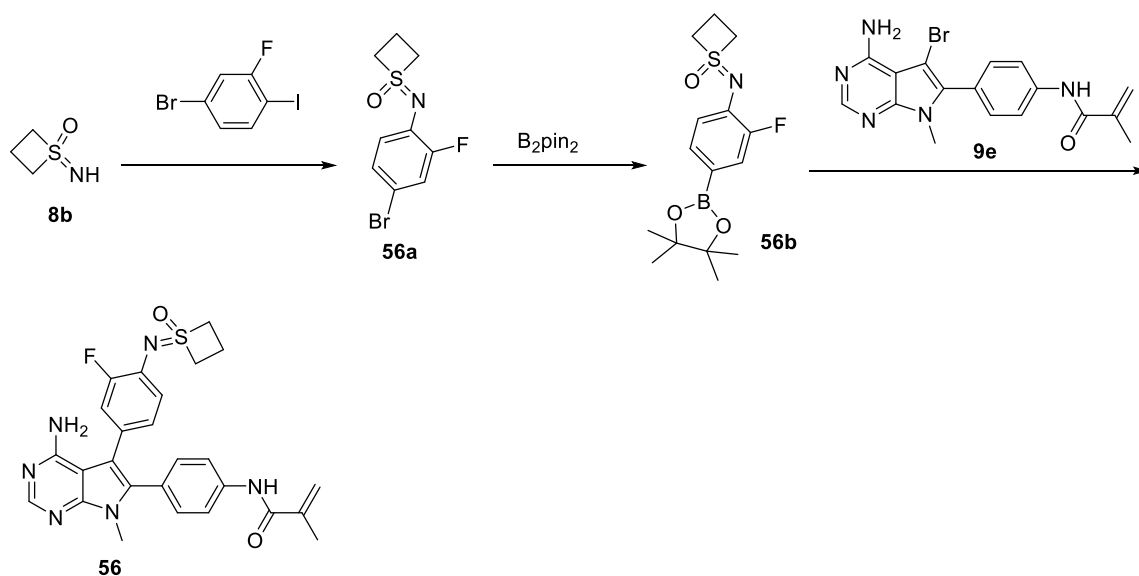
MS (ESI) m/z 588.64 $[M + H]^+$.

¹H NMR (400 MHz, MeOD-*d*₄) δ 8.19 (s, 1H), 7.67 (s, 2H), 7.28 (d, *J* = 7.9 Hz, 3H), 7.16 (s, 1H), 7.00 (s, 2H), 5.81 (s, 1H), 5.53 (s, 1H), 4.24 (s, 2H), 4.18 (s, 2H), 3.68 (s, 3H), 2.37 (s, 2H), 2.03 (s, 3H), 1.30 (s, 1H).

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Example 56 N- (4- (4-amino-5- (3-fluoro-4- (1-oxo-1 λ⁶-thiocyclobutan-1-ylidene) amino) phenyl) -7-methyl-7H-pyrrolo [2,3-*d*] pyrimidin-6-yl) - phenyl) methacrylamide





Step 1 1-((4-bromo-2-fluorophenyl) imino) -1 λ^6 -thietane-1-oxide **56a**

Compound **8b** (720 mg, 6.8 mmol), cesium carbonate (3.3 g, 10.2 mmol), 1-bromo-3-fluoro-4-iodobenzene (2.47 g, 8.2 mmol), $\text{Pd}_2(\text{dba})_3$ (187 mg, 0.2 mmol), and Xantphos (354 mg, 0.6 mmol) were added to 1,4-dioxane (15 mL), and the reaction solution was heated up to 100 °C for 16 h. The reaction solution was filtered through diatomaceous earth, and the filter cake was washed with ethyl acetate (100 mL) and saturated saline solution (50 mL). The organic phase was dried over anhydrous sodium sulfate and concentrated under reduced pressure to obtain a crude product. The crude product was purified by column chromatography (PE/EtOAc=4/1 to 3/2) to obtain compound **56a** (1.1 g), light yellow solid.

^1H NMR (400 MHz, CDCl_3) δ 7.20 (dd, $J = 10.0, 2.4$ Hz, 1H), 7.13 (dd, $J = 8.4, 2.4$ Hz, 1H), 6.96 (t, $J = 8.4$ Hz, 1H), 4.31-4.19 (m, 4H), 2.32 (p, $J = 8.4$ Hz, 2H).

Step 2 1-((2-fluoro-4- (4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) phenyl) imino) -1 λ^6 -thietane-1-oxide **56b**

Compound **56a** (556 mg, 2.0 mmol), bis(pinacolato)diboron (660 mg, 2.6 mmol), $\text{Pd}(\text{dppf})\text{Cl}_2$ (293 mg, 0.4 mmol), potassium acetate (588 mg, 6.0 mmol), and 1,4-dioxane (10 mL) were added into a sealed tube, after replaced with argon gas three times, sealed, and the reaction solution was heated up to 90 °C and stirred for 16 h. Water (10 mL) was added and extracted with DCM (20 mL $\times$ 3). The organic phase was washed with saturated saline solution (20 mL), dried over anhydrous sodium sulfate, and concentrated under reduced pressure to obtain a crude product. The crude product was purified by column chromatography (PE/EtOAc=3/2) to obtain compound **56b** (356 mg), white solid.

^1H NMR (400 MHz, CDCl_3) δ 7.60-7.34 (m, 2H), 7.06 (t, $J = 8.1$ Hz, 1H), 4.38-4.18 (m, 4H), 2.39-2.27 (m, 2H), 1.32 (s, 12H).

Step 3 N- (4- (4-amino-5- (3-fluoro-4- (1-oxo-1 λ^6 -thiocyclobutan-1-ylidene) amino) phenyl) -7-methyl-7H-pyrrolo [2,3-d] pyrimidin-6-yl) - phenyl) methacrylamide **56**

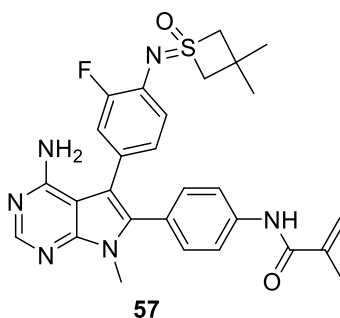
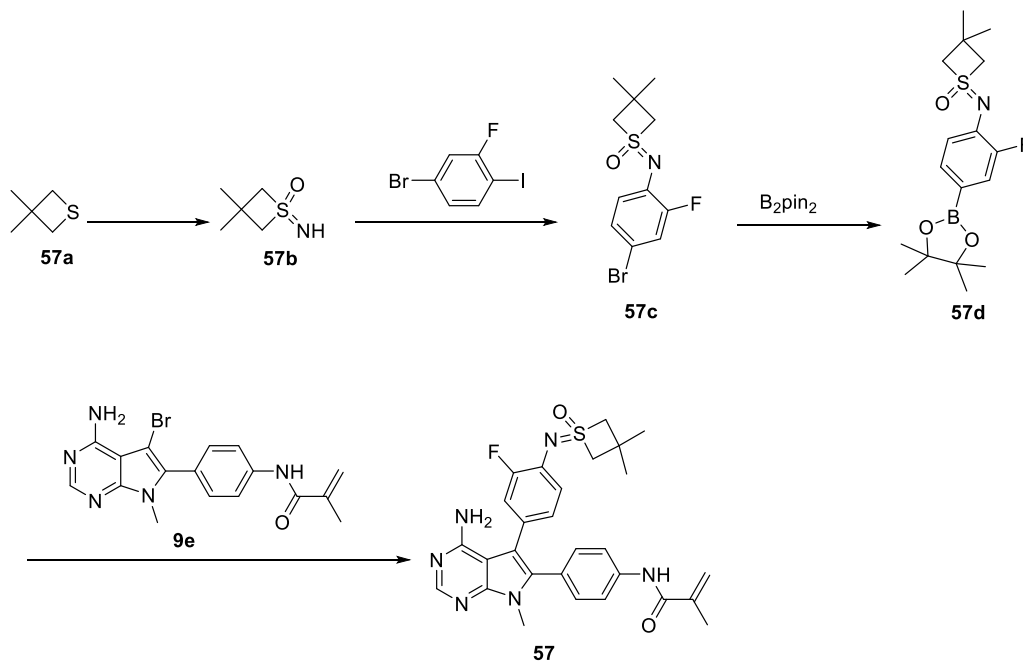
Compound **56b** (65 mg, 0.2 mmol), compound **9e** (64 mg, 0.17 mmol), $\text{Pd}(\text{PPh}_3)_4$ (23 mg, 0.02 mmol), and K_3PO_4 (106 mg, 0.5 mmol) were added into a sealed tube, after replaced with

argon gas three times, 1,4-dioxane (5 mL) and H₂O (0.5 mL) were added, sealed, and the reaction solution was heated up to 100 °C and stirred for 16 h. Dichloromethane (20 mL) and saturated saline solution (10 mL) were added to extract, and the organic phase was dried over anhydrous sodium sulfate, and concentrated under reduced pressure to obtain a crude product. The crude product was purified by column chromatography (MeOH/DCM=1/10) to obtain compound **56** (12 mg), white solid.

MS (ESI) m/z 505 [M + H]⁺.

¹H NMR (400 MHz, CDCl₃) δ 8.33 (s, 1H), 7.57 (d, J = 8.4 Hz, 3H), 7.21 (d, J = 8.4 Hz, 2H), 7.02 (dd, J = 9.2, 7.8 Hz, 1H), 6.97-6.86 (m, 2H), 5.80 (s, 1H), 5.49 (s, 1H), 5.18 (brs, 2H), 4.35-4.22 (m, 4H), 3.69 (s, 3H), 2.35 (q, J = 8.4 Hz, 2H), 2.07 (s, 3H).

Example 57 *N*-(4-(4-amino-5-(4-((3,3-dimethyl-1-oxo-1 λ^6 -thiocyclobutyl-1-ylidene)amino)-3-fluorophenyl)-7-methyl-7H-pyrrolo [2,3-*d*] pyrimidin-6-yl) phenyl) methacrylamide



Step 1 1-amino-3,3-dimethyl-1 λ^6 -thietane-1-oxide **57b**

3,3-dimethylthietane **57a** (1 g, 10 mmol) and ammonium carbamate (1.17 g, 15 mmol) were added into a flask in sequence, then MeOH (100 mL) and iodobenzene diethyl ester (6.44 g, 20 mmol) were added, the reaction solution was stirred open at room temperature for 30 min, and then it was concentrated under reduced pressure to remove the solvent to obtain a crude product.

The crude product was purified by column chromatography (MeOH/DCM=1/20) to obtain compound **57b** (1.1 g), colorless oil.

¹H NMR (400 MHz, CDCl₃) δ 3.86 (s, 4H), 2.07 (s, 2H), 1.49 (d, J = 7.3 Hz, 6H).

5 **Step 2 1-((4-bromo-2-fluorophenyl)imino)-3,3-dimethyl-1 λ ⁶-thietan-1- oxide 57c**

Compound **57b** (266 mg, 2 mmol), cesium carbonate (978 mg, 3 mmol), 1-bromo-3-fluoro-4-iodobenzene (722 mg, 2.4 mmol), Pd₂(dba)₃ (55 mg, 0.06 mmol), and Xantphos (104 mg, 0.18 mmol) were added to 1,4-dioxane (5 mL), and the reaction solution was heated up to 100 °C for 16 h. The reaction solution was filtered through diatomaceous earth, and the filter cake was washed with ethyl acetate (100 mL) and saturated saline solution (50 mL). The organic phase was dried over anhydrous sodium sulfate and concentrated under reduced pressure to obtain a crude product. The crude product was purified by column chromatography (PE/EtOAc=4/1 to 3/2) to obtain compound **57c** (0.2 g), light yellow solid.

15 ¹H NMR (400 MHz, CDCl₃) δ 7.20 (dd, J = 10.4, 2.4 Hz, 1H), 7.13 (dd, J = 8.4, 2.4 Hz, 1H), 6.97 (t, J = 8.4 Hz, 1H), 4.04 (d, J = 12.8 Hz, 2H), 3.99 (d, J = 12.8 Hz, 2H), 1.54 (s, 3H), 1.52 (s, 3H).

Step 3 1- ((2-fluoro-4- (4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) phenyl) imino) -3,3-dimethyl-1 λ ⁶-thietane-1-oxide 57d

20 Compound **57c** (200 mg, 0.65 mmol), bis(pinacolato)diboron (216 mg, 0.85 mmol), Pd(dppf)Cl₂ (95 mg, 0.13 mmol), potassium acetate (191 mg, 1.95 mmol), and 1,4-dioxane (4 mL) were added into a sealed tube, after replaced with argon gas three times, sealed, and the reaction solution was heated up to 90 °C and stirred for 16 h. Water (10 mL) was added and extracted with DCM (20 mL $\times$ 3). The organic phase was washed with saturated saline solution (20 mL), dried over anhydrous sodium sulfate, and concentrated under reduced pressure to obtain a crude product. The crude product was purified by column chromatography (PE/EtOAc=3/2) to obtain compound **57d** (190 mg), white solid.

25 ¹H NMR (400 MHz, CDCl₃) δ 7.61-7.34 (m, 2H), 7.06 (t, J = 8.1 Hz, 1H), 4.10-3.95 (m, 4H), 1.53 (s, 3H), 1.50 (s, 3H), 1.32 (s, 12H).

30

Step 4 N- (4- (4-amino-5- (4- (3,3-dimethyl-1-oxo-1 λ ⁶-thiocyclobutyl-1-ylidene) amino) -3-fluorophenyl) -7-methyl-7H-pyrrolo [2,3-*d*] pyrimidin-6-yl) phenyl) methacrylamide 57

35 Compound **57d** (190 mg, 0.53 mmol), compound **9e** (164 mg, 0.42 mmol), Pd(PPh₃)₄ (59 mg, 0.05 mmol), and K₃PO₄ (267 mg, 1.26 mmol) were added into a sealed tube, after replaced with argon gas three times, 1,4-dioxane (5 mL) and H₂O (0.5 mL) were added, sealed, and the reaction solution was heated up to 100 °C and stirred for 16 h. Dichloromethane (20 mL) and saturated saline solution (10 mL) were added to extract, and the organic phase was dried over anhydrous sodium sulfate, and concentrated under reduced pressure to obtain a crude product. The crude product was purified by column chromatography (MeOH/DCM=1/10) to obtain compound **57** (14 mg), white solid.

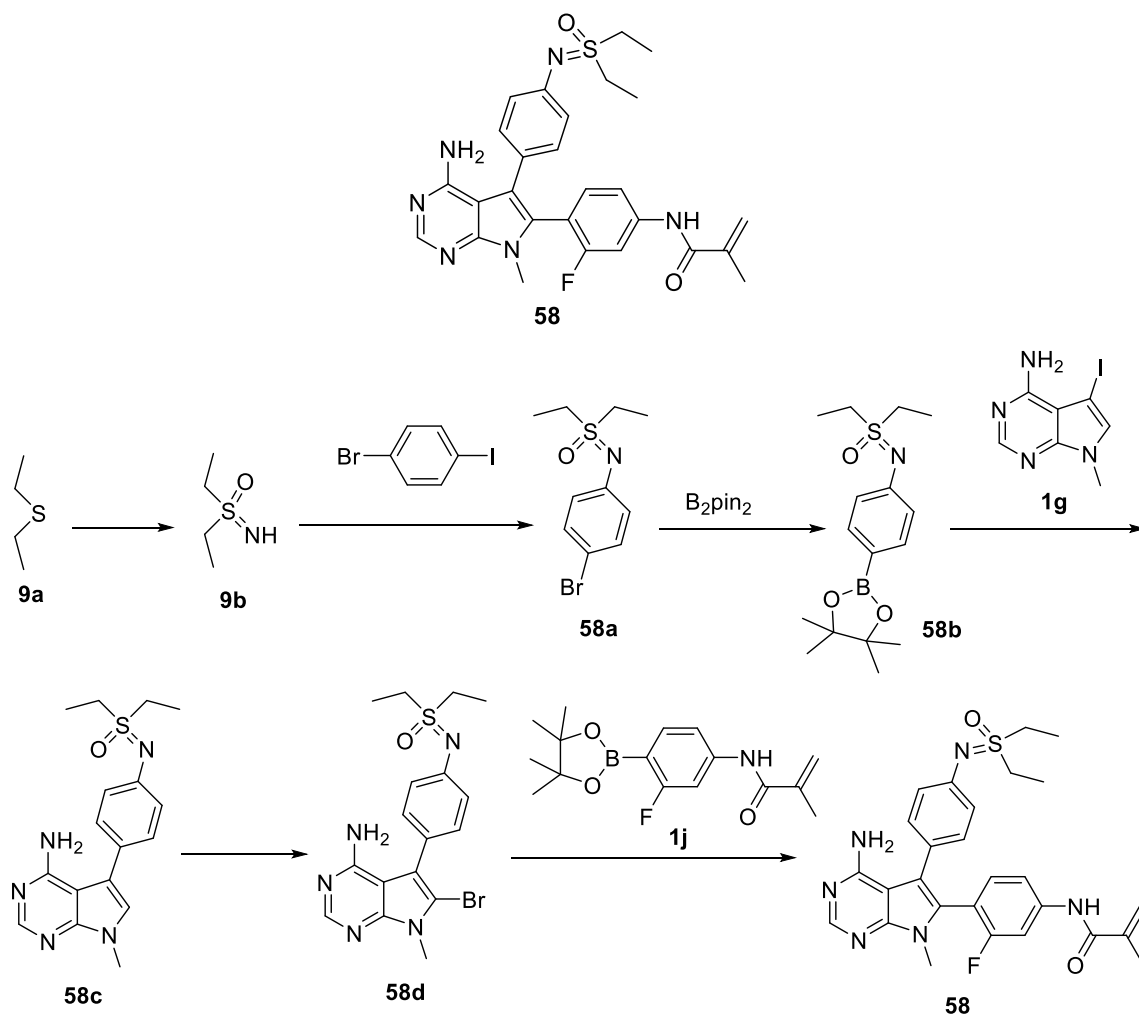
40

MS (ESI) m/z 533 [M + H]⁺.

¹H NMR (400 MHz, CDCl₃) δ 8.34 (s, 1H), 7.58 (d, J = 8.8 Hz, 2H), 7.56 (*m*, 1H), 7.22 (d, J = 8.8 Hz, 2H), 7.02 (t, J = 8.4 Hz, 1H), 6.92 (dd, J = 6.8, 2.0 Hz, 1H), 6.90 (dd, J = 12.0, 2.0 Hz,

1H), 5.80 (s, 1H), 5.49 (s, 1H), 5.25 (brs, 2H), 4.09 (d, $J = 12.0$ Hz, 2H), 4.01 (d, $J = 12.0$ Hz, 2H), 3.70 (s, 3H), 2.07 (s, 3H), 1.54 (s, 3H), 1.53 (s, 3H).

Example 58 *N*-(4-(4-amino-5-(4-(diethyl (oxo) - λ^6 -sulfanylidene) amino) phenyl)-7-methyl-7H-pyrrolo [2,3-*d*] pyrimidin-6-yl)-3-fluorophenyl) methacrylamide



Step 1 imine-1 λ^6 -diethylsulfoxide **9b**

Diethylthioether **9a** (4.5 g, 50 mmol) and ammonium carbamate (5.85 g, 75 mmol) were added into a flask in sequence, then MeOH (100 mL) and iodobenzene diethyl ester (32.2 g, 100 mmol) were added. The reaction solution was stirred open at room temperature for 30 min, and then it was concentrated under reduced pressure to remove the solvent to obtain a crude product. The crude product was purified by column chromatography (MeOH/DCM=1/20) to obtain compound **9b** (3.6 g), colorless oil.

^1H NMR (400 MHz, CDCl_3) δ 3.12-2.93 (q, $J = 7.5$ Hz, 4H), 2.66 (s, 1H), 1.38 (t, $J = 7.5$ Hz, 6H).

Step 2 ((4-bromo-phenyl) imino) -1 λ^6 -diethylsulfoxide **58a**

Compound **9b** (182 mg, 1.5 mmol), cesium carbonate (0.74 g, 2.25 mmol), 1-bromo-4-iodobenzene (0.5 g, 1.8 mmol), Pd₂(dba)₃ (46 mg, 0.05 mmol), and Xantphos (83 mg, 0.15 mmol) were added to 1,4-dioxane (5 mL), and the reaction solution was heated up to 100 °C for 16 h. The reaction solution was filtered through diatomaceous earth, the filter cake was washed with ethyl acetate (100 mL), and saturated saline solution (50 mL) was used for washing. The organic phase was dried over anhydrous sodium sulfate and concentrated under reduced pressure to obtain a crude product. The crude product was purified by column chromatography (PE/EtOAc=4/1 to 3/2) to obtain compound **58a** (0.38 g), brownish yellow oil.

¹H NMR (400 MHz, CDCl₃) δ 7.30-7.28 (m, 2H), 7.00-6.96 (m, 2H), 3.22-3.13 (m, 4H), 1.39 (t, *J* = 7.5 Hz, 6H).

Step 3 1- (4- (4,4,5,5-methyl-1,3,2-dioxaborolan-2-yl) - phenyl) imino) -1 λ⁶-diethylsulfoxide 58b

Compound **58a** (380 mg, 1.37 mmol), bis(pinacolato)diboron (420 mg, 1.65 mmol), Pd(dppf)Cl₂ (200 mg, 0.274 mmol), potassium acetate (403 mg, 4.11 mmol), and 1,4-dioxane (10 mL) were added into a sealed tube, after replaced with argon gas three times, sealed, and the reaction solution was heated up to 90 °C and stirred for 16 h. Water (10 mL) was added and extracted with DCM (20 mL × 3). The organic phase was washed with saturated saline solution (20 mL), dried over anhydrous sodium sulfate, and concentrated under reduced pressure to obtain a crude product. The crude product was purified by column chromatography (PE/EtOAc=3/2) to obtain compound **58b** (320 mg), white solid.

Step 4 (4- (4-amino-7-methyl-7H-pyrrolo [2,3-*d*] pyrimidin-6-yl) - phenyl) imino) -1 λ⁶-diethylsulfoxide 58c

Compound **58b** (265 mg, 0.82 mmol), compound **1g** (206 mg, 0.75 mmol), Pd(PPh₃)₄ (87 mg, 0.075 mmol), and K₃PO₄ (477 mg, 2.25 mmol) were added into a sealed tube, after replaced with argon gas three times, 1,4-dioxane (8 mL) and H₂O (0.8 mL) were added, sealed, and the reaction solution was heated up to 100 °C and stirred for 16 h. Dichloromethane (20 mL) and saturated saline solution (10 mL) were added to extract, the organic phase was dried over anhydrous sodium sulfate, and concentrated under reduced pressure to obtain a crude product. The crude product was purified by column chromatography (MeOH/DCM=1/10) to obtain compound **58c** (152 mg), light yellow solid.

¹H NMR (400 MHz, CDCl₃) δ 8.33 (s, 1H), 7.31 (d, *J* = 8.3 Hz, 2H), 7.18 (*d*, *J* = 8.3 Hz, 2H), 6.88 (s, 1H), 5.11 (s, 2H), 3.83 (s, 3H), 3.24 (qd, *J* = 7.5, 4.2 Hz, 4H), 1.44 (t, *J* = 7.5 Hz, 6H).

Step 5 (4- (4-amino-6-bromo-7-methyl-7H-pyrrolo [2,3-*d*] pyrimidin-5-yl) - phenyl) imino) -1 λ⁶-diethylsulfoxide 58d

Compound **58c** (70 mg, 0.2 mmol) was dissolved in anhydrous DMF (2 mL), a solution of N-bromosuccinimide (40 mg, 0.22 mmol) in DMF (2 mL) was added slowly dropwise at 0 °C, and the reaction was carried out for 1 h. After the reaction was completed, the reaction was quenched with added sodium thiosulfate aqueous solution, extracted with DCM/H₂O twice, and the organic layers were combined, and washed once with saturated salt water, and the organic phase was dried over anhydrous sodium sulfate, concentrated under reduced pressure, and

subjected to column chromatography (DCM/MeOH=20/1) to obtain compound **58d** (39 mg), light yellow solid.

¹H NMR (400 MHz, CDCl₃) δ 8.26 (s, 1H), 7.30 (d, *J* = 8.4 Hz, 2H), 7.20 (d, *J* = 8.4 Hz, 2H), 5.25 (s, 2H), 3.82 (s, 3H), 3.30-3.22 (m, 4H), 1.45 (t, *J* = 7.4 Hz, 6H).

5

Step 6 N- (4- (4-amino-5- (4- (diethyl (oxo) - λ⁶-sulfanylidene) amino) phenyl) -7-methyl-7H-pyrrolo [2,3-*d*] pyrimidin-6-yl) -3-fluorophenyl) methacrylamide **58**

Compound **58d** (40 mg, 0.1 mmol), compound **1j** (39 mg, 0.12 mmol), Pd(PPh₃)₄ (12 mg, 0.01 mmol), and K₃PO₄ (64 mg, 0.3 mmol) were added into a sealed tube, after replaced with argon gas three times, 1,4-dioxane (2 mL) and H₂O (0.2 mL) were added, sealed, and the reaction solution was heated up to 100 °C and stirred for 16 h. Dichloromethane (20 mL) and saturated saline solution (10 mL) were added to extract, and the organic phase was dried over anhydrous sodium sulfate, and concentrated under reduced pressure to obtain a crude product. The crude product was purified by column chromatography (MeOH/DCM=1/10) to obtain compound **58** (22 mg), white solid.

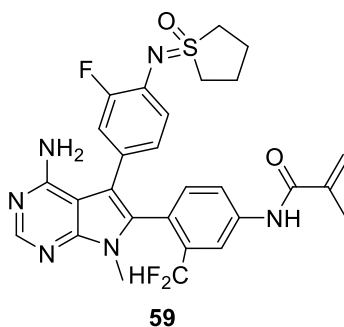
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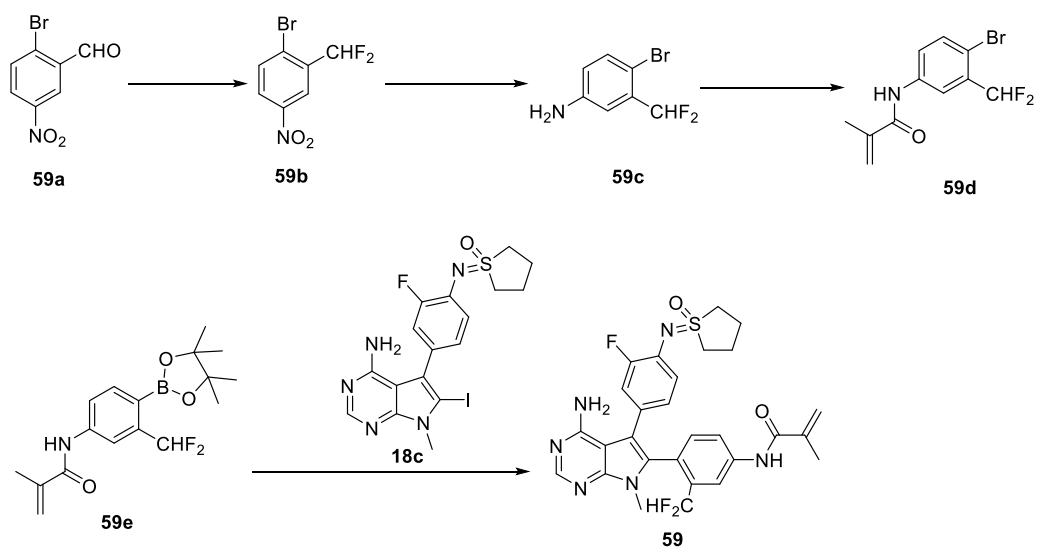
MS (ESI) *m/z* 521 [M + H]⁺.

¹H NMR (400 MHz, CDCl₃) δ 8.35 (s, 1H), 7.69 (dd, *J* = 11.6, 1.9 Hz, 1H), 7.61 (s, 1H), 7.10-7.00 (m, 6H), 5.80 (s, 1H), 5.51 (d, *J* = 1.5 Hz, 1H), 5.04 (s, 2H), 3.65 (s, 3H), 3.28-3.12 (m, 4H), 2.07 (s, 3H), 1.41 (t, *J* = 7.4 Hz, 6H).

20

Example 59 N- (4- (4-amino-5- (3-fluoro-4- ((1-oxotetrahydro-1 λ⁶-thiophene-1- ylidene) amino) phenyl) -7-methyl-7H-pyrrolo [2,3-*d*] pyrimidin-6-yl) -3- (difluoromethyl) phenyl) methacrylamide





Step 1 1-bromo-2-difluoromethyl-4-nitrobenzene **59b**

To a 100 mL round bottom flask, compound **59a** (2 g, 8.69 mmol), bis (2-methoxyethyl) aminotrifluoride (2.88 g, 13.02 mmol), anhydrous dichloromethane (20 mL) were added sequentially, and the reaction was carried out at room temperature for 4 h, after TLC monitored the completion of the reaction, the reaction was quenched with saturated ammonium chloride solution, extracted with dichloromethane (30 mL $\times$ 3), and the organic phases were combined, washed with saturated saline solution (30 mL), and concentrated under reduced pressure to obtain a crude product. The crude product was purified by column chromatography (PE/EA=100/0) to obtain compound **59b** (2.75 g), white solid.

Step 2 4-bromo-3-difluoromethylaniline **59c**

To a 100 mL round bottom flask, compound **59b** (2.7 g, 10.71 mmol), reduced iron powder (3.0 g, 53.57 mmol), ammonium chloride (2.8 g, 52.35 mmol), ethanol (20 mL), and water (10 mL) were added in sequence, and the reaction was carried out at 80 °C for 4 h, after TLC monitored the completion of the reaction, it was cooled down to room temperature, filtered through diatomaceous earth, extracted with dichloromethane (30 mL $\times$ 3), and the organic phases were combined, washed with saturated saline (30 mL), and concentrated under reduced pressure to obtain a crude product. The crude product was purified by column chromatography (PE/EA=3/1) to obtain compound **59c** (1.02 g), white solid.

Step 3 4-bromo-3-difluoromethylphenylmethacrylamide **59d**

To a 100 mL round bottom flask, compound **59c** (1.02 g, 4.59 mmol), methyl acryloyl chloride (0.458 g, 5.05 mmol), trifluoroacetic acid (0.929 g, 9.19 mmol), and dichloromethane (20 mL) were added in sequence, the reaction was carried out in an ice bath for 1 h, after TLC monitored the completion of the reaction, the reaction was quenched with saturated sodium bicarbonate solution, extracted with dichloromethane (30 mL $\times$ 3), and the organic phases were combined, washed with saturated saline solution (30 mL), and concentrated under reduced pressure to obtain a crude product. The crude product was purified by column chromatography (PE/EA=1/1) to obtain compound **59d** (1.01 g), white solid.

Step 4 *N*- (3- (difluoromethyl) -4- (4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) phenyl) methacrylamide **59e**

To a 100 mL round bottom flask, compound **59d** (1.01 g, 3.49 mmol), diborate pinacol ester (1.07 g, 4.19 mmol), Pd(dppf)Cl₂ (507 mg, 0.70 mmol), potassium acetate (157 mg, 1.59 mmol) and 1,4-dioxane (20 mL) were added sequentially, the reaction was heated up to 90 °C and reacted for 3 h. After TLC monitored the completion of the reaction, it was cooled down to room temperature, filtered through diatomaceous earth, extracted with ethyl acetate (30 mL × 3), and the organic phases were combined, washed with saturated saline (30 mL), and concentrated under reduced pressure to obtain a crude product. The crude product was purified by column chromatography (PE/EA=1/1) to obtain compound **59e** (120 mg), light yellow solid.

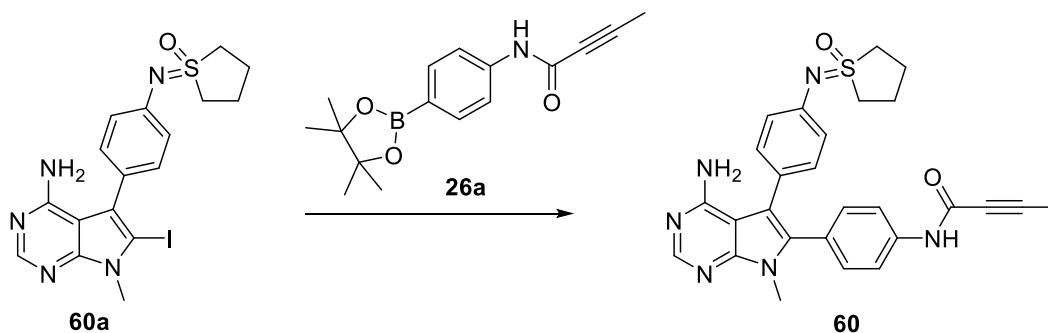
Step 5 *N*- (4- (4-amino-5- (3-fluoro-4- ((1-oxotetrahydro-1 λ^6 -thiophene-1-ylidene) amino) phenyl) -7-methyl-7*H*-pyrrolo [2,3-*d*] pyrimidin-6-yl) -3- (difluoromethyl) phenyl) methacrylamide **59**

To a 100 mL round bottom flask, compound **59e** (0.91 g, 0.18 mmol), compound **18c** (0.100 g, 0.21 mmol), and tetrakis (triphenylphosphine) palladium (20.8 mg, 0.018 mmol), anhydrous potassium phosphate (130 mg, 0.54 mmol), 1,4-dioxane (10 mL), and water (1 mL) were added in sequence, the reaction was heated up to 90 °C and reacted for 2 h. After TLC monitored the completion of the reaction, it was cooled down to room temperature, filtered through diatomaceous earth, extracted with ethyl acetate (30 mL × 3), and the organic phases were combined, washed with saturated saline (30 mL), and concentrated under reduced pressure to obtain a crude product. The crude product was purified by column chromatography (DCM/MeOH=6/1) to obtain compound **59** (44 mg), white solid.

MS (ESI) m/z 568.10 [M + H]⁺.

¹H NMR (400 MHz, CDCl₃) δ 8.41 (s, 1H), 7.99 (d, J = 8.0 Hz, 1H), 7.77 (d, J = 5.0 Hz, 2H), 7.37 (d, J = 8.3 Hz, 1H), 7.29 (s, 1H), 7.12 (t, J = 8.5 Hz, 1H), 6.90 (d, J = 8.0 Hz, 2H), 5.87 (s, 1H), 5.56 (s, 1H), 5.13 (s, 2H), 3.56 (s, 3H), 3.51 – 3.40 (m, 2H), 3.25 (s, 2H), 2.33 (d, J = 7.4 Hz, 4H), 2.12 (s, 3H).

Example 60 *N*- (4- (4-amino-7-methyl-5- (4- ((1-oxotetrahydro-1 λ^6 -thiophene-1-ylidene) amino) phenyl) -7*H*-pyrrolo [2,3-*d*] pyrimidin-6-yl) phenyl) but-2-ynamide

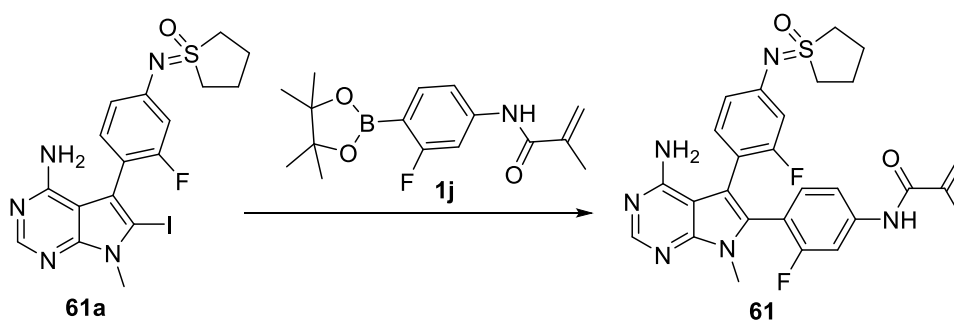


Compound **60** was synthesized with reference to Example **12**

MS (ESI) m/z 499.70 [M + H]⁺.

¹H NMR (400 MHz, CDCl₃) δ 8.37 (s, 1H), 7.63 – 7.50 (m, 4H), 7.40 (d, *J* = 27.0 Hz, 3H), 6.95 (s, 1H), 5.26 (s, 2H), 3.86 (s, 3H), 3.25 (d, *J* = 5.5 Hz, 2H), 3.13 (s, 2H), 2.05 (s, 3H), 2.03 (d, *J* = 21.8 Hz, 4H).

5 **Example 61** *N*- (4- (4-amino-5- (2-fluoro-4- ((1-oxotetrahydro-1 λ⁶-thiophene-1- ylidene) amino) phenyl) -7-methyl-7*H*-pyrrolo [2,3-*d*] pyrimidin-6-yl) -3-fluorophenyl) methacrylamide



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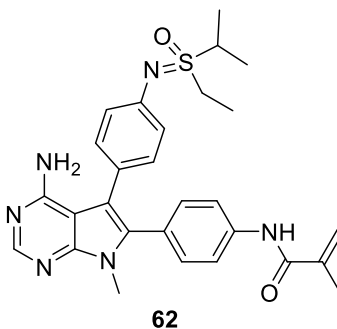
Compound **61** was synthesized with reference to Example **12**.

MS (ESI) *m/z* 537.57 [*M* + *H*]⁺.

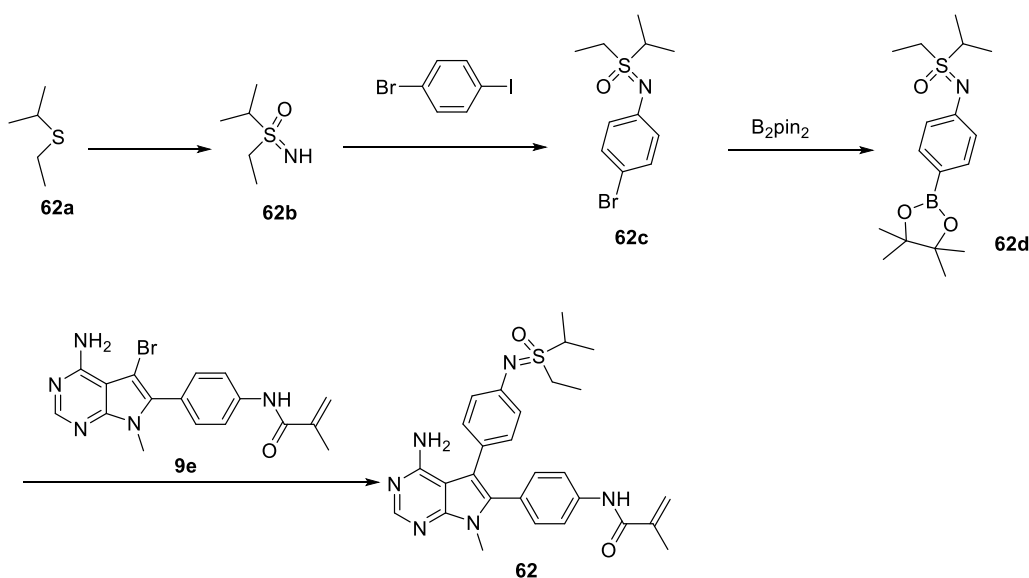
¹H NMR (400 MHz, CDCl₃) δ 8.36 (s, 1H), 7.81 – 7.66 (m, 2H), 7.30 (dd, *J* = 8.9, 4.2 Hz, 1H), 7.23 (d, *J* = 11.4 Hz, 1H), 7.15 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.04 (s, 1H), 5.84 (s, 1H), 5.53 (s, 1H), 5.18 (s, 2H), 3.86 (s, 3H), 3.33 (dd, *J* = 12.7, 6.5 Hz, 2H), 3.18 (dd, *J* = 12.9, 6.7 Hz, 2H), 2.38 – 2.13 (m, 4H), 2.10 (s, 3H).

15

Example 62 *N*- (4- (4-amino-5- (4- (ethyl (isopropyl) (oxo) -1 λ⁶-sulfanylidene) phenyl) -7-methyl-7*H*-pyrrolo [2,3-*d*] pyrimidin-6-yl) - phenyl) methacrylamide



20



Step 1 (imino) (isopropyl) -1 λ^6 -ethylsulfoxide

Ethyl isopropyl sulfide (3 g, 30 mmol) and ammonium carbamate (3.5 g, 45 mmol) were added to a flask sequentially, and then MeOH (100 mL) and iodobenzene diethyl ester (19.3 g, 60 mmol) were added. The reaction solution was stirred open at room temperature for 30 min, and then concentrated under reduced pressure to remove the solvent to obtain a crude product. The crude product was purified by column chromatography (MeOH/DCM=1/20) to obtain compound **62b** (4 g), light brown oil.

^1H NMR (400 MHz, CDCl_3) δ 3.18 (hept, $J = 6.8$ Hz, 1H), 3.03 (q, $J = 7.5$ Hz, 2H), 2.05 (s, 1H), 1.42-1.37 (m, 9H).

Step 2 ((4-bromophenyl) imino) (isopropyl) -1 λ^6 -ethylsulfoxide **62c**

Compound **62b** (675 mg, 5 mmol), cesium carbonate (2.45 g, 7.5 mmol), 1-bromo-4-iodobenzene (1.7 g, 6 mmol), $\text{Pd}_2(\text{dba})_3$ (137 mg, 0.15 mmol), and Xantphos (260 mg, 0.45 mmol) were added to 1,4-dioxane (10 mL), and the reaction solution was heated up to 100 °C for 16 h. The reaction solution was filtered through diatomaceous earth, the filter cake was washed with ethyl acetate (100 mL), and saturated saline solution (50 mL) was used for washing. The organic phase was dried over anhydrous sodium sulfate and concentrated under reduced pressure to obtain a crude product. The crude product was purified by column chromatography (PE/EtOAc=4/1 to 3/2) to obtain compound **62c** (1.3 g), brownish yellow oil.

^1H NMR (400 MHz, CDCl_3) δ 7.27 (d, $J = 8.7$ Hz, 2H), 6.98 (d, $J = 8.7$ Hz, 2H), 3.39 (hept, $J = 6.9$ Hz, 1H), 3.22-3.06 (m, 2H), 1.46 (d, $J = 6.8$ Hz, 3H), 1.41-1.35 (m, 6H).

Step 3 (isopropyl) ((4- (4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) phenyl) imino) -1 λ^6 -diethylsulfoxide **62d**

Compound **62c** (1.3 g, 4.5 mmol), bis(pinacolato)diboron (1.4 g, 5.4 mmol), $\text{Pd}(\text{dppf})\text{Cl}_2$ (656 mg, 0.9 mmol), potassium acetate (1.3 g, 13.5 mmol), and 1,4-dioxane (12 mL) were added into a sealed tube, after replaced with argon gas three times, sealed, and the reaction solution was heated up to 90 °C and stirred for 16 h. Water (10 mL) was added and extracted with DCM (20 mL $\times$ 3). The organic phase was washed with saturated saline solution (20 mL), dried over

anhydrous sodium sulfate, and concentrated under reduced pressure to obtain a crude product. The crude product was purified by column chromatography (PE/EtOAc=3/2) to obtain compound **62d** (1.4 g), light yellow solid.

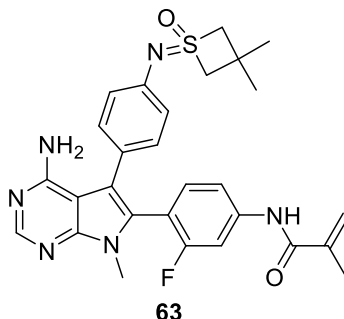
Step 4: *N*- (4- (4-amino-5- (4- (ethyl (isopropyl) (oxo) -1 λ^6 -sulfanylidene) phenyl) -7-methyl-7*H*-pyrrolo [2,3-*d*] pyrimidin-6-yl) - phenyl) methacrylamide **62**

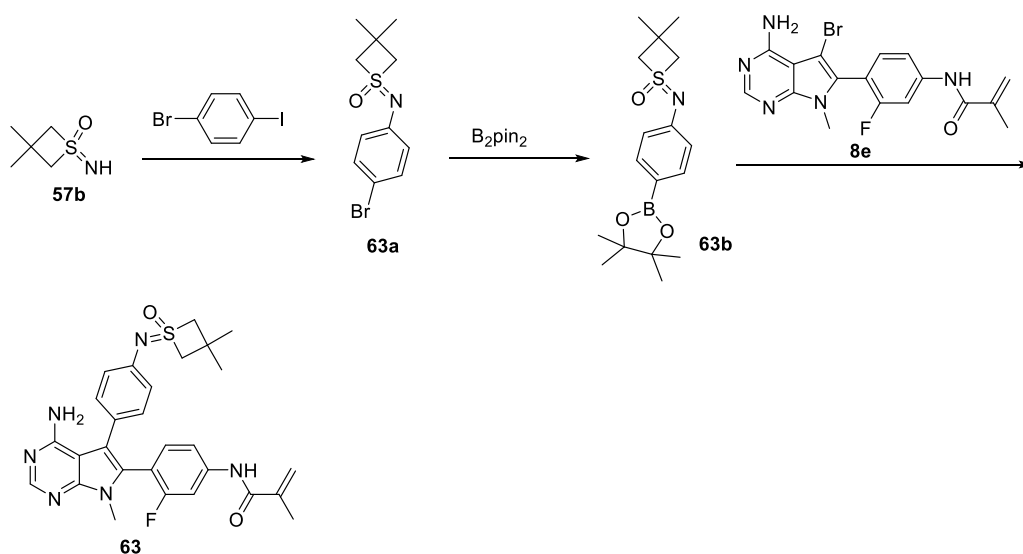
Compound **62d** (85 mg, 0.24 mmol), compound **9e** (77 mg, 0.2 mmol), Pd(PPh₃)₄ (23 mg, 0.02 mmol), and K₃PO₄ (127 mg, 0.6 mmol) were added into a sealed tube, after replaced with argon gas three times, 1,4-dioxane (2 mL) and H₂O (0.2 mL) were added, sealed, and the reaction solution was heated up to 100 °C and stirred for 16 h. Dichloromethane (20 mL) and saturated saline solution (10 mL) were added to extract, and the organic phase was dried over anhydrous sodium sulfate, and concentrated under reduced pressure to obtain a crude product. The crude product was purified by column chromatography (MeOH/DCM=1/10) to obtain compound **62** (33 mg), white solid.

MS (ESI) *m/z* 517 [M + H]⁺.

¹H NMR (400 MHz, CDCl₃) δ 8.34 (s, 1H), 7.53 (d, *J* = 8.4, 2H), 7.51 (s, 1H), 7.22 (d, *J* = 8.4, 2H), 7.09-7.03 (m, 4H), 5.79 (s, 1H), 5.48 (q, *J* = 1.6 Hz, 1H), 4.99 (s, 2H), 3.70 (s, 3H), 3.41 (hept, *J* = 6.9 Hz, 1H), 3.26-3.08 (m, 2H), 2.07 (s, 3H), 1.48 (d, *J* = 6.8 Hz, 3H), 1.43 (d, *J* = 7.0 Hz, 3H), 1.40 (t, *J* = 7.4 Hz, 3H).

Example 63 *N*- (4- (4-amino-5- (4- ((3,3-dimethyl-1-oxo-1 λ^6 - thiocyclobutyl-1- ylidene) amino) phenyl) -7-methyl-7*H*-pyrrolo [2,3-*d*] pyrimidin-6-yl) phenyl) methacrylamide





Step 1 1- ((4-bromo-phenyl) imino) -3,3-dimethyl-1 λ^6 -thietane-1-oxide 63a

Compound **57b** (760 mg, 5.7 mmol), cesium carbonate (2.78 g, 8.6 mmol), 1-bromo-4-iodobenzene (1.94 g, 6.9 mmol), $\text{Pd}_2(\text{dba})_3$ (155 mg, 0.17 mmol), and Xantphos (297 mg, 0.51 mmol) were added to 1,4-dioxane (15 mL), and the reaction solution was heated up to 100 °C for 16 h. The reaction solution was filtered through diatomaceous earth, the filter cake was washed with ethyl acetate (100 mL), and saturated saline solution (50 mL) was used for washing. The organic phase was dried over anhydrous sodium sulfate and concentrated under reduced pressure to obtain a crude product. The crude product was purified by column chromatography (PE/EtOAc=4/1 to 3/2) to obtain compound **63a** (1.2 g), light yellow solid.

Step 3 1- (4- (4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) phenyl) imino) -3,3-dimethyl-1 λ^6 -thietane-1-oxide 63b

Compound **63a** (611 mg, 2.1 mmol), bis(pinacolato)diboron ester (700 mg, 2.75 mmol), $\text{Pd}(\text{dppf})\text{Cl}_2$ (307 mg, 0.42 mmol), potassium acetate (617 mg, 6.3 mmol), and 1,4-dioxane (10 mL) were added into a sealed tube, after replaced with argon gas three times, sealed, and the reaction solution was heated up to 90 °C and stirred for 16 h. Water (10 mL) was added to extract with DCM (20 mL $\times$ 3). The organic phase was washed with saturated saline solution (20 mL), dried over anhydrous sodium sulfate, and concentrated under reduced pressure to obtain a crude product. The crude product was purified by column chromatography (PE/EtOAc=3/2) to obtain compound **63b** (590 mg), white solid.

^1H NMR (400 MHz, CDCl_3) δ 7.70 (d, J = 8.3 Hz, 2H), 7.00 (d, J = 8.3 Hz, 2H), 3.95 (d, J = 1.6 Hz, 4H), 1.53 (s, 3H), 1.48 (s, 3H), 1.33 (s, 12H).

Step 4 *N*- (4- (4-amino-5- (4- (3,3-dimethyl-1-oxo-1 λ^6 -thiocyclobutyl-ylidene) amino) phenyl) -7-methyl-7H-pyrrolo [2,3-*d*] pyrimidin-6-yl) phenyl) methacrylamide 63

Compound **63b** (144 mg, 0.43 mmol), compound **8e** (145 mg, 0.36 mmol), $\text{Pd}(\text{PPh}_3)_4$ (42 mg, 0.04 mmol), and K_3PO_4 (229 mg, 1.08 mmol) were added into a sealed tube, after replaced with argon three times, 1,4-dioxane (4 mL) and H_2O (0.4 mL) were added, sealed, and the reaction solution was heated up to 100 °C and stirred for 16 h. Dichloromethane (20 mL) and saturated

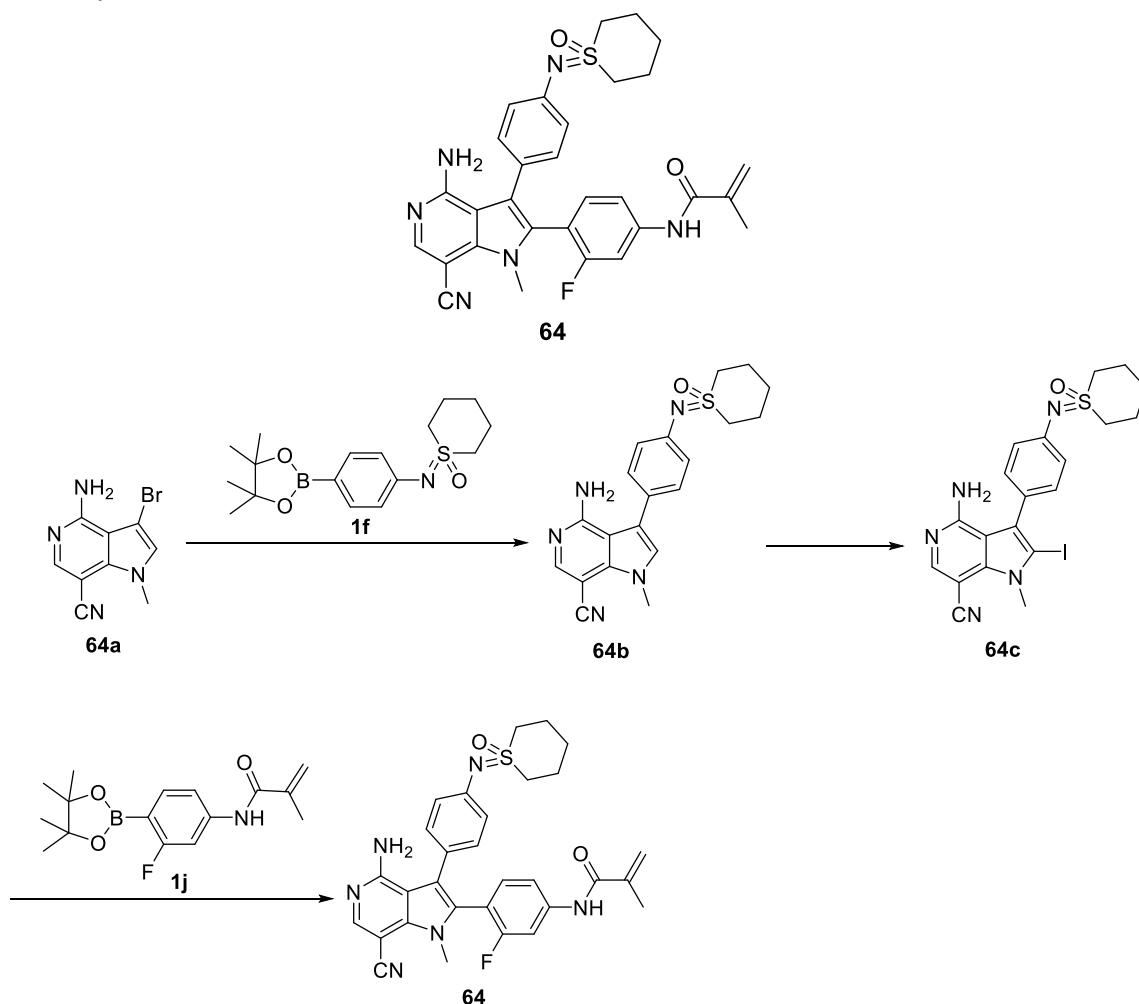
saline solution (10 mL) were added to extract, and the organic phase was dried over anhydrous sodium sulfate, and concentrated under reduced pressure to obtain a crude product. The crude product was purified by column chromatography (DCM/MeOH=10/1) to obtain compound **63** (90 mg), white solid.

5 MS (ESI) m/z 533 $[M + H]^+$.

^1H NMR (400 MHz, CDCl_3) δ 8.36 (s, 1H), 7.71 (dd, $J = 11.5, 1.9$ Hz, 1H), 7.58 (s, 1H), 7.15-7.03 (m, 4H), 6.94 (d, $J = 8.1$ Hz, 2H), 5.80 (s, 1H), 5.51 (d, $J = 1.7$ Hz, 1H), 5.02 (s, 2H), 4.00 (d, $J = 12.8$ Hz, 2H), 3.94 (d, $J = 12.8$ Hz, 2H), 3.65 (s, 3H), 2.07 (s, 3H), 1.54 (s, 3H), 1.52 (s, 3H).

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Example 64 *N*- (4- (4-amino-7-cyano-1-methyl-3- (4- ((1-oxotetrahydro-2*H*-1 λ^6 -thiopyran-1-ylidene) amino) phenyl) -1*H* pyrrolo [3,2-*c*] pyridine-2-yl) -3-fluorophenyl) methacrylamide



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Step 1 4-amino-1-methyl-3- (4- ((1-oxotetrahydro-2*H*-1 λ^6 -thiopyran-1-ylidene) amino) phenyl) -1*H*-pyrrolo [3,2-*c*] pyridine-7-nitrile **64b**

Compound **64a** (45 mg, 0.179 mmol), compound **1f** (73 mg, 0.215 mmol), $\text{Pd}(\text{DtBPF})\text{Cl}_2$ (12 mg, 0.018 mmol), and cesium fluoride (82 mg, 0.538 mmol) were placed in a 25 mL two necked flask, after replaced with argon gas three times, DMF/ H_2O (v/v=8/1, 2.7 mL) was added to react

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overnight at 90 °C. After the reaction was completed, the reaction solution was poured into water (20 mL) and extracted with ethyl acetate (50 mL × 3) three times. The organic phase was concentrated, and the crude product was purified by column chromatography (DCM/MeOH=30/1) to obtain compound **64b** (40 mg), white solid.

5 MS (ESI) m/z 380.1 $[M + H]^+$.

Step 2 4-amino-2-iodo-1-methyl-3- (4- ((1-oxotetrahydro-2H-1 λ^6 -thiopyran-1-ylidene) amino) phenyl) -1H-pyrrolo [3,2-c] pyridine-7-nitrile **64c**

10 Compound **64b** (40 mg, 0.105 mmol) was placed in a 25 mL reaction flask, dichloromethane (4.5 mL) and trifluoroacetic acid (25 μ L) were added in sequence. At 0 °C, N-iodosuccinimide (27 mg, 0.116 mmol) was added, and the reaction was carried out at maintained 0 °C for 1 h. After the reaction was completed, the reaction solution was concentrated, and the crude product was purified by column chromatography (DCM/MeOH=30/1) to obtain compound **64c** (42 mg), white solid.

15 MS (ESI) m/z 505.9 $[M + H]^+$.

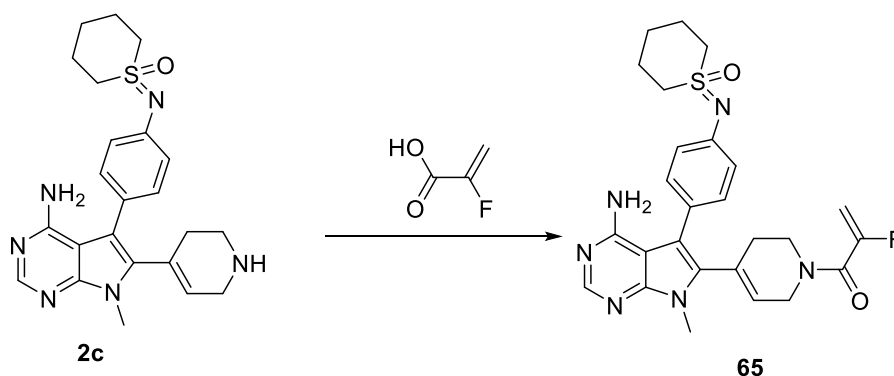
Step 3 N-(4-(4-amino-7-cyano-1-methyl-3-(4- ((1-oxotetrahydro-2H-1 λ^6 -thiopyran-1-ylidene) amino) phenyl) -1H pyrrolo [3,2-c] pyridine-2-yl) -3-fluorophenyl) methacrylamide **64**

20 Compound **64c** (40 mg, 0.083 mmol), compound **1j** (31 mg, 0.100 mmol), Pd(dppf)Cl₂ (7 mg, 0.008 mmol), and potassium phosphate (53 mg, 0.250 mmol) were placed in a 25 mL two necked flask, after replaced with argon gas three times, DMF/H₂O (v/v=8/1, 1.8 mL) was added to dissolve, and the reaction was carried out at 90 °C. After the reaction was completed, the reaction solution was poured into water (20 mL) and extracted with ethyl acetate (50 mL × 3) three times.
25 The organic phase was concentrated, and the crude product was purified by column chromatography (DCM/MeOH=20/1) to obtain compound **64** (13 mg), white solid.

MS (ESI) m/z 557.0 $[M + H]^+$.

¹H NMR (400 MHz, CDCl₃) δ 8.15 (s, 1H), 7.70 (d, J = 11.4 Hz, 1H), 7.63 (s, 1H), 7.39 (dd, J = 20.0, 8.1 Hz, 2H), 7.33 – 7.27 (m, 2H), 7.18 (d, J = 8.0 Hz, 1H), 6.89 (s, 1H), 5.83 (s, 1H),
30 5.51 (s, 1H), 5.31 (s, 2H), 4.06 (s, 3H), 3.24 (s, 2H), 3.05 (t, J = 11.1 Hz, 2H), 2.08 (s, 3H), 1.99 – 1.87 (m, 2H), 1.86 – 1.75 (m, 2H), 1.56 – 1.42 (m, 2H).

Example 65 1- (4- (4-amino-7-methyl-5- (4- ((1-oxotetrahydro-2H-1 λ^6 -thiopyran-1-ylidene) amino) phenyl) -7H-pyrrolo [2,3-d] pyrimidin-6-yl) -3,6-dihydropyridine-1 (2H) - yl) -2-fluoropropan-2-enyl-1-one
35

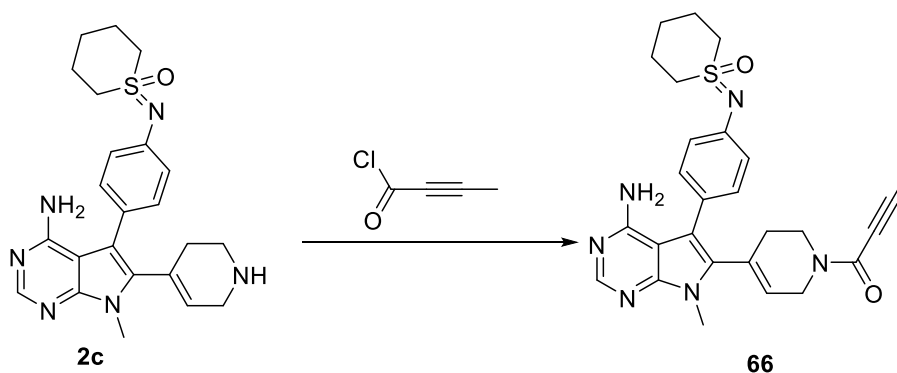


Compound **2c** (176 mg, 0.40 mmol), 2-fluoroacrylic acid (36.3 mg, 0.40 mmol), and DIPEA (517 mg, 4.0 mmol) were added into a round bottomed reaction flask, dry DMF (5 mL) was added to dissolve, then HATU (228 mg, 0.60 mmol) was added, and stirred at room temperature for 4 h. After the reaction was completed, it was extracted with EA/H₂O three times, and the organic layers were combined, washed with saturated saline solution, dried over anhydrous sodium sulfate, concentrated under reduced pressure, and purified by column chromatography (DCM/MeOH=30/1) to obtain compound **65** (136 mg), yellow solid.

MS (ESI) m/z 509.2 [M+H]⁺.

¹H NMR (400 MHz, MeOD-d₄) δ 8.35 (s, 1H), 7.46-7.33 (m, 4H), 6.05 (s, 1H), 5.36-5.11 (m, 2H), 4.25 (d, J = 33.9 Hz, 2H), 3.85 (s, 3H), 3.81-3.73 (m, 2H), 3.70 (t, J = 5.5 Hz, 2H), 3.67-3.57 (m, 2H), 2.30-2.19 (m, 2H), 2.18-2.07 (m, 4H), 1.90-1.79 (m, 1H), 1.78-1.68 (m, 1H).

Example 66 1- (4- (4-amino-7-methyl-5- (4- (1-oxotetrahydro-2H-1λ⁶-thiopyran-1-ylidene) amino) phenyl) -7H-pyrrolo [2,3-*d*] pyrimidin-6-yl) -3,6-dihydropyridine-1 (2H) - yl) but-2-ynyl-1-one



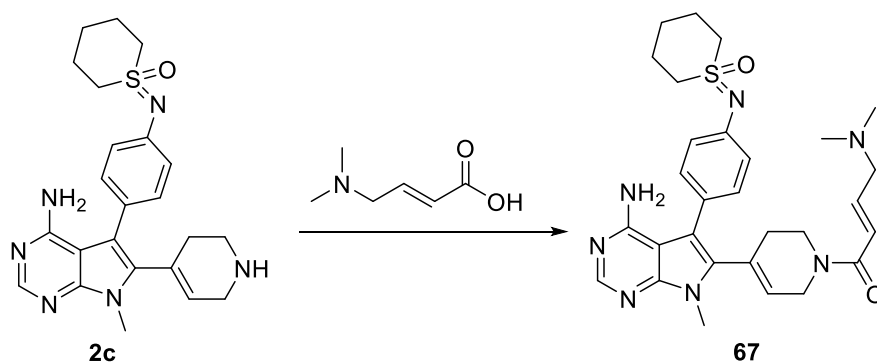
Compound **2c** (150 mg, 0.34 mmol) was dissolved in dry DCM (3 mL), and triethylamine (35 mg, 0.34 mmol) was added at 0 °C. But-2-ynyl chloride (34.9 mg, 0.34 mmol) was diluted with DCM (2 mL), and added slowly dropwise into the above reaction solution, and stirred at 0 °C for 1 h. After the reaction was completed, it was extracted with DCM/H₂O three times, and the organic layers were combined, washed with saturated saline solution, dried over anhydrous sodium sulfate, concentrated under reduced pressure, and purified by column chromatography (DCM/MeOH=30/1) to obtain compound **66** (73 mg), yellow solid

MS (ESI) m/z 503.2 [M+H]⁺.

¹H NMR (400 MHz, MeOD-d₄) δ 8.35 (s, 1H), 7.48-7.22 (m, 4H), 6.10-5.96 (m, 1H), 4.43 (q, *J* = 2.8 Hz, 1H), 4.18 (q, *J* = 2.8 Hz, 1H), 3.88 (t, *J* = 5.6 Hz, 1H), 3.84 (d, *J* = 1.2 Hz, 3H), 3.75-3.70 (m, 1H), 3.69-3.63 (m, 2H), 3.61-3.50 (m, 2H), 2.28-2.21 (m, 1H), 2.20-2.09 (m, 5H), 2.07 (s, 1H), 2.03 (s, 2H), 1.88-1.77 (m, 1H), 1.76-1.67 (m, 1H).

5

Example 67 (*E*)-1-(4-(4-amino-7-methyl-5- (4- ((1-oxotetrahydro-2*H*-1λ⁶- thiopyran -1-ylidene) amino) phenyl) -7*H*-pyrrolo [2,3-*d*] pyrimidin-6-yl) -3,6-dihydropyridine-1 (2*H*) -yl) -4- (dimethylamino) but-2-enyl-1-one



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Compound **2c** (176 mg, 0.4 mmol) and (*E*) -4- (dimethylamino) but-2-olefine acid (66 mg, 0.4 mmol) were dissolved in DMF (4 mL), triethylamine (404.8 mg, 4 mmol) and T3P (191 mg, 0.6 mmol) were added in sequence at 0 °C overnight. After the reaction was completed, it was extracted with ethyl acetate/H₂O three times, the organic layers were combined, washed with saturated saline solution, dried over anhydrous sodium sulfate, concentrated under reduced pressure, and perform column chromatography (DCM/MeOH=20/1) to obtain compound **67** (41 mg), yellow solid.

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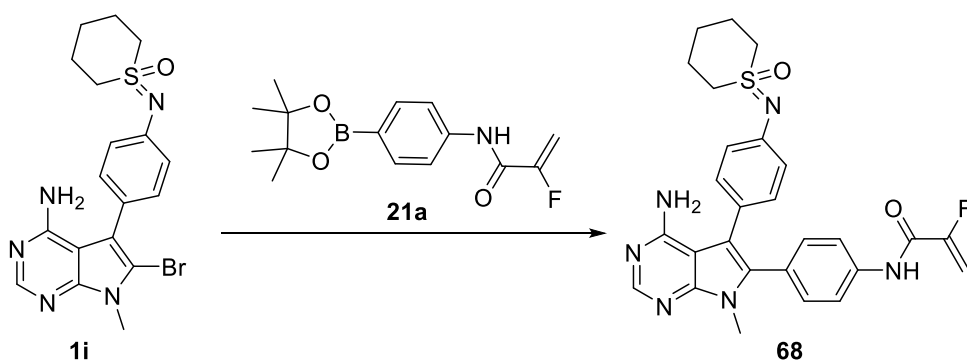
MS (ESI) *m/z* 548.3 [M+H]⁺.

¹H NMR (400 MHz, MeOD-d₄) δ 8.37 (s, 1H), 7.61-7.35 (m, 4H), 7.10-6.91 (m, 1H), 6.82-6.60 (m, 1H), 6.06 (s, 1H), 4.34 (d, *J* = 3.3 Hz, 1H), 4.25 (d, *J* = 3.3 Hz, 1H), 4.04-3.92 (m, 4H), 3.85 (s, 3H), 3.84-3.67 (m, 4H), 2.92 (d, *J* = 6.4 Hz, 6H), 2.32-2.12 (m, 6H), 1.94-1.72 (m, 2H).

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Example 68 *N*- (4- (4-amino-7-methyl-5- (4- ((1-oxotetrahydro-2*H*-1 λ⁶-thiopyran -1-ylidene) amino) phenyl) -7*H*-pyrrolo [2,3-*d*] pyrimidin-6-yl) phenyl) -2- fluoroacrylamide

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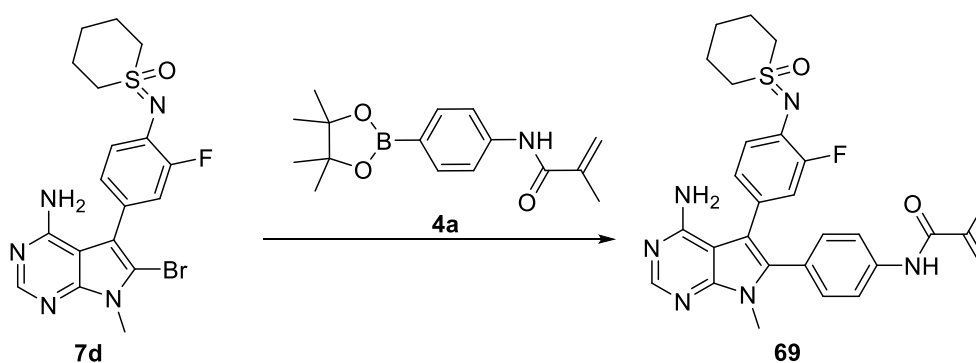


Compound **1i** (200 mg, 0.46 mmol) was dissolved in 1,4-dioxane (5 mL) and water (1 mL), compound **21a** (161.3 mg, 0.55 mmol), Pd(PPh₃)₄ (106.3 mg, 0.092 mmol), and K₃PO₄ (293 mg, 1.38 mmol) were added in sequence. After the air in the reaction bottle was replaced with nitrogen gas, the reaction was stirred overnight at 100 °C. After the reaction was completed, it was filtered with silica gel, and the filtrate was recovered, concentrated under reduced pressure, dissolved in ethyl acetate, washed with saturated saline solution, dried over anhydrous sodium sulfate, concentrated under reduced pressure and subjected to column chromatography (DCM/MeOH=30/1) to obtain compound **68** (118 mg), white solid.

MS (ESI) *m/z* 519.2 [M+H]⁺.

¹H NMR (400 MHz, MeOD-*d*₄) δ 8.36 (s, 1H), 7.74 (d, *J* = 8.7 Hz, 2H), 7.32 (d, *J* = 8.7 Hz, 2H), 7.15 (d, *J* = 8.5 Hz, 2H), 7.08 (d, *J* = 8.5 Hz, 2H), 5.73 (dd, *J* = 46.5, 3.4 Hz, 1H), 5.32 (dd, *J* = 15.1, 3.5 Hz, 1H), 3.78 (s, 3H), 3.43-3.34 (m, 2H), 3.29-3.19 (m, 2H), 2.09-1.98 (m, 4H), 1.79-1.61 (m, 2H).

Example 69 *N*- (4- (4-amino-5- (3-fluoro-4- ((1-oxotetrahydro-2*H*-1λ⁶-thiopyran-1-ylidene) amino) phenyl) -7-methyl-7*H*-pyrrolo [2,3-*d*] pyrimidin-6-yl) phenyl) methacrylamide

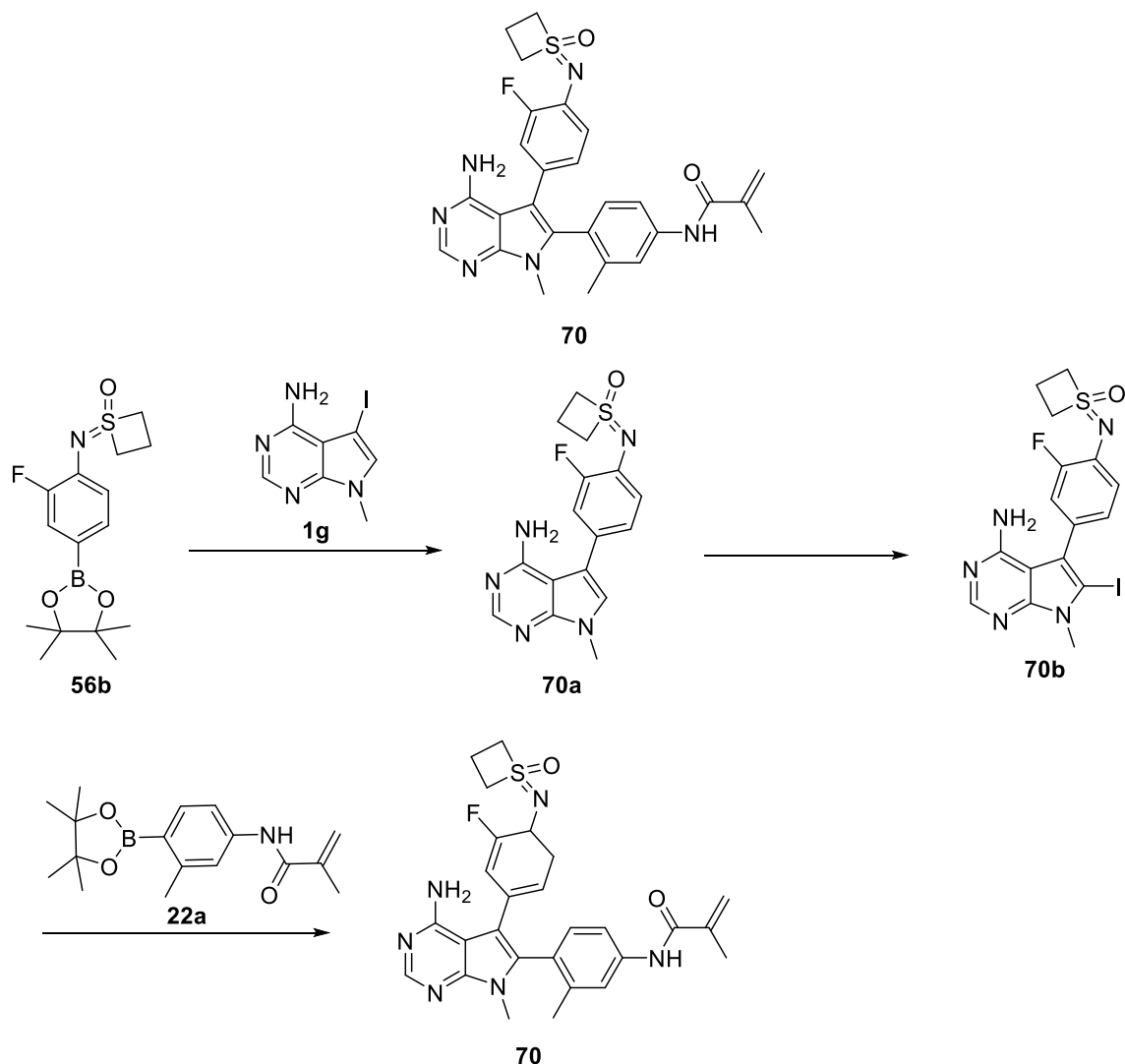


Compound **7d** (300 mg, 0.67 mmol) was dissolved in 1,4-dioxane (8 mL) and water (2 mL), and compound **4a** (229.2 mg, 0.8 mmol), Pd(PPh₃)₄ (154.8 mg, 0.13 mmol), and K₃PO₄ (426.7 mg, 2.01 mmol) were added in sequence. After the air in the reaction flask was replaced with nitrogen gas, the reaction was stirred overnight at 100 °C. After the reaction was completed, it was filtered with silica gel, and the filtrate was recovered, concentrated under reduced pressure, dissolved in ethyl acetate, washed with saturated saline solution, dried over anhydrous sodium sulfate, concentrated under reduced pressure and perform column chromatography (DCM/MeOH=30/1) to obtain compound **69** (116 mg), white solid.

MS (ESI) *m/z* 533.2 [M+H]⁺.

¹H NMR (400 MHz, DMSO-*d*₆) δ 9.90 (s, 1H), 8.17 (s, 1H), 7.71 (d, *J* = 8.7 Hz, 2H), 7.26 (d, *J* = 8.7 Hz, 2H), 7.10 (dd, *J* = 9.3, 8.3 Hz, 1H), 6.94-6.79 (m, 2H), 5.99 (s, 1H), 5.80 (s, 1H), 5.53 (s, 1H), 4.08-4.00 (m, 1H), 3.58 (s, 3H), 3.32 (s, 2H), 3.31-3.22 (m, 2H), 1.95 (s, 3H), 1.93-1.83 (m, 4H), 1.68-1.50 (m, 2H).

Example 70 *N*- (4- (4-amino-5- (5-fluoro-4- (1-oxo-1 λ^6 -thiocyclobutan-1-ylidene) amino) cyclohexyl-1,5-dienyl-1-yl) -7-methyl-7*H*-pyrrolo [2,3-*d*] pyrimidin-6-yl) -3- methylphenyl) methacrylamide



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Compound **70** was synthesized with reference to Example **29**.

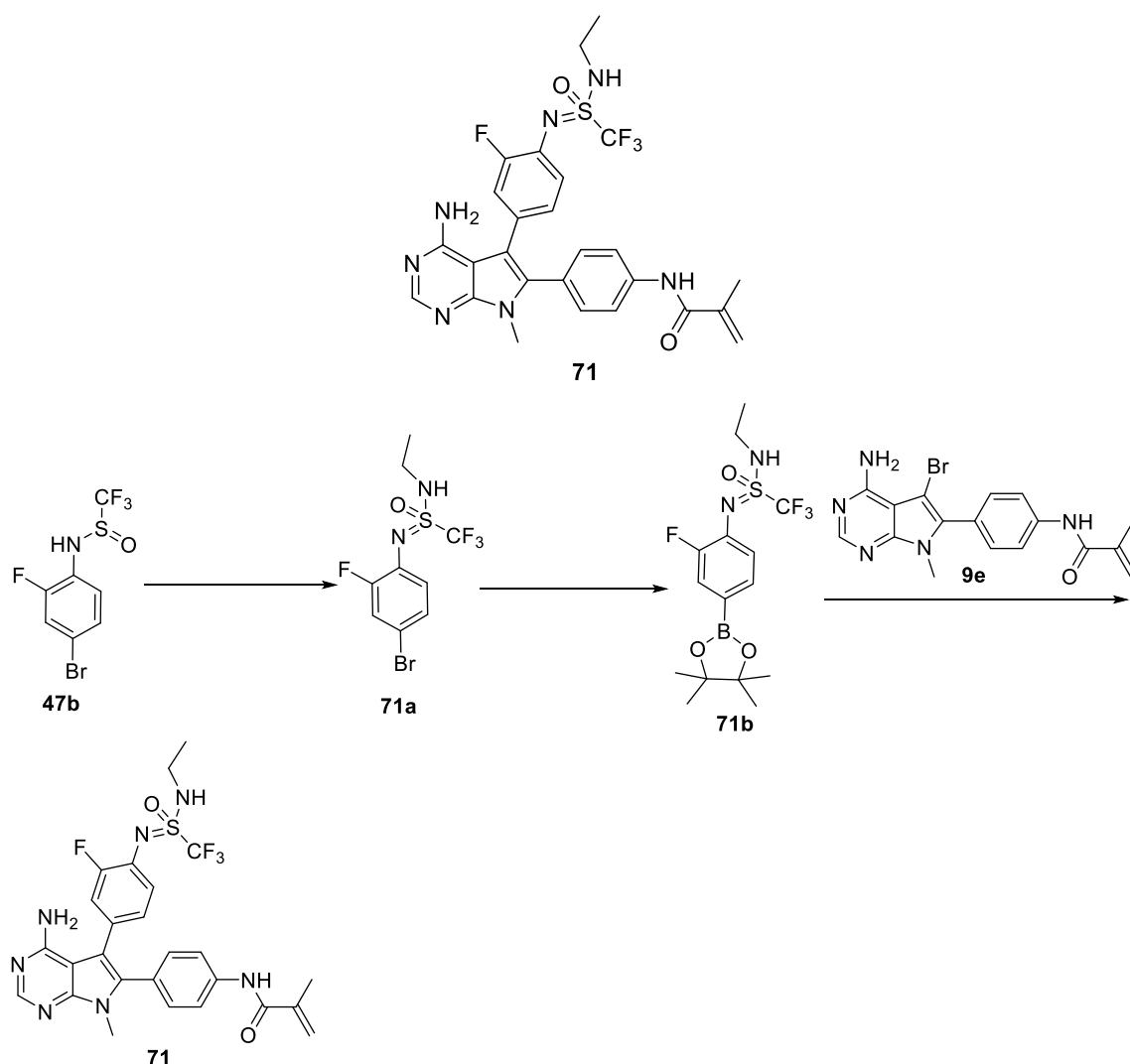
MS (ESI) m/z 519.47 $[M + H]^+$.

^1H NMR (400 MHz, CDCl_3) δ 8.30 (s, 1H), 7.43 (d, $J = 2.1$ Hz, 2H), 7.35 (dd, $J = 8.2, 2.0$ Hz, 1H), 7.10 (d, $J = 8.2$ Hz, 1H), 6.92 (t, $J = 8.6$ Hz, 1H), 6.81 (s, 2H), 5.73 (s, 1H), 5.42 (d, $J = 1.1$ Hz, 1H), 4.96 (s, 2H), 4.21 (d, $J = 8.5$ Hz, 4H), 3.45 (s, 1H), 2.26 (s, 2H), 2.01 (s, 3H), 1.94 (s, 1H).

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Example 71 *N*- (4- (4-amino-5- (4- (((ethylamino) (oxo) (trifluoromethyl) -1 λ^6 -sulfaneylidene) amino) -3-fluorophenyl) -7-methyl-7*H*-pyrrolo [2,3-*d*] pyrimidin-6-yl) phenyl) methacrylamide KTH021161

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Step 1 N-ethyl-1,1,1-trifluoro-*N'*-(4-iodophenyl) - *N*-methylmethanesulfonimide 71a

Compound **47b** (600 mg, 1.96 mmol) and *N*-chlorosuccinimide (292 mg, 2.16 mmol) were dissolved in acetonitrile (8 mL), tetrabutylammonium fluoride (2.16 mL, 2.16 mmol, 1M) was added at 0 °C, and the reaction was carried out at room temperature for 30 min. The reaction solution was concentrated, and then acetonitrile (8 mL) and ethylamine (360 mg, 8.0 mmol) were added, and reacted at room temperature for 2 h. The reaction solution was concentrated, and dried, and the crude product was purified by column chromatography (PE/EtOAc=0-20%) to obtain compound **71a** (422 mg).

MS (ESI) m/z 349 $[M + H]^+$

Step 2 N-ethyl-1,1,1-trifluoro-*N'*-(2-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) phenyl) methylsulfonfyl imine 71b

Compound **71a** (260 mg, 0.74 mmol), bis(pinacolato)diboron (227 mg, 0.89 mmol), Pd(dppf)Cl₂ (110 mg, 0.15 mmol), and potassium acetate (220 mg, 2.23 mmol) were placed in a bottle, 1,4-dioxane (6 mL) was added, after replaced N₂ three times, the reaction was carried out at 100 °C for 12 h. The reaction solution was filtered and concentrated, and the crude product was purified by column chromatography (PE/EtOAc=0-20%) to obtain compound **71b** (250 mg).

MS (ESI) m/z 396 $[M + H]^+$

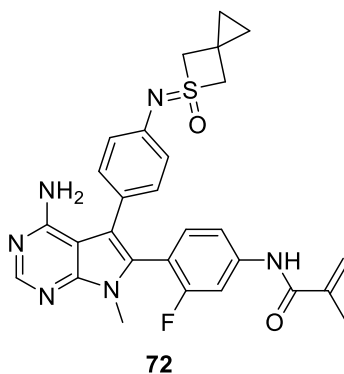
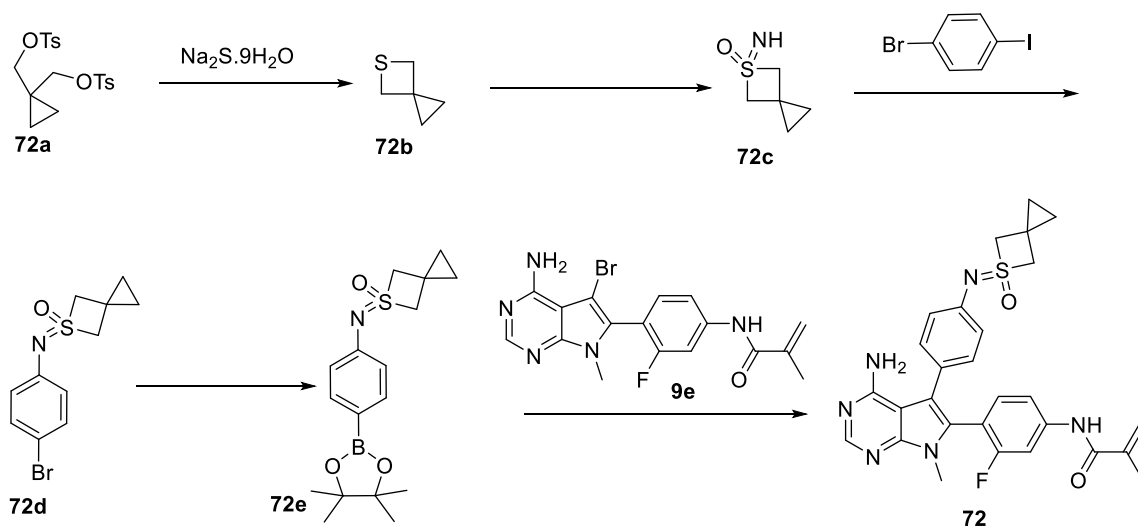
Step 3 *N*-(4-(4-amino-5-(4-(((ethylamino) (oxo) (trifluoromethyl) -1 λ^6 - sulfaneylidene) amino) -3-fluorophenyl) -7-methyl-7*H*-pyrrolo [2,3-*d*] pyrimidin-6-yl) phenyl) methacrylamide 71

Compound **9e** (100 mg, 0.26 mmol), compound **71b** (123 mg, 0.31 mmol), $\text{Pd(PPh}_3)_4$ (65 mg, 0.056 mmol), and K_3PO_4 (165 mg, 0.78 mmol) were added into a sealed tube, 1,4-dioxane (5 mL) and H_2O (0.5 mL) were added, after replaced with N_2 three times, the reaction solution was heated up to 100 °C and stirred for 16 h. Dichloromethane (20 mL) and saturated saline solution (20 mL) were added to extract, and the organic phase was dried over anhydrous sodium sulfate, and concentrated under reduced pressure to obtain a crude product. The crude product was purified by column chromatography (MeOH/DCM=1/20) to obtain compound **71** (20 mg), white solid.

MS (ESI) m/z 576.64 $[M + H]^+$.

^1H NMR (400 MHz, $\text{MeOD-}d_4$) δ 8.18 (s, 1H), 7.67 (d, $J = 8.3$ Hz, 2H), 7.28 (d, $J = 8.3$ Hz, 2H), 7.17 (t, $J = 8.4$ Hz, 1H), 7.02 – 6.93 (m, 2H), 5.81 (s, 1H), 5.52 (s, 1H), 3.68 (s, 3H), 2.03 (s, 3H), 1.33-1.29 (m, 2H), 1.15 (t, $J = 7.2$ Hz, 3H).

Example 72 *N*-(4-(4-amino-7-methyl-5-(4-(5-oxo-5 λ^6 -thiaspiro [2.3] hexane-5- ylidene) amino) phenyl) -7*H*-pyrrolo [2,3-*d*] pyrimidin-6-yl) -3-fluorophenyl) methacrylamide



Step 1 5-thiaclopril [2.3] hexane 72b

Compound **72a** was synthesized reference to WO2022152705 A1. Compound **72a** (3 g, 7.32 mmol) and sodium sulfide nonahydrate (2.1 g, 8.78 mmol) were placed in a 250 mL thick walled pressure resistant bottle, DMF (15 mL) was added and reacted overnight at 120 °C. After the reaction was completed, H₂O (50 mL) was added and extracted with ethyl acetate three times (10 mL x3), and the organic layers were combined, washed with saturated saline solution, and dried over anhydrous sodium sulfate to obtain a ethyl acetate solution of compound **72b**, which was directly used in the next step.

Step 2 5-amino-5 λ⁶-thiaspiro [2.3] hexane 5-oxide 72c

The ethyl acetate solution of **72b** and ammonium carbamate (856mg, 11.0 mmol) were added into a flask in sequence, and then MeOH (20 mL) and iodobenzene diethyl ester (5.3 g, 16.47mmol) were added. The reaction solution was stirred open at room temperature for 30 min, and then concentrated under reduced pressure to remove the solvent to obtain a crude product. The crude product was purified by column chromatography (MeOH/DCM =1/20) to obtain compound **72c** (500 mg), light brown oil.

MS (ESI) *m/z* 131 [M + H]⁺

Step 3 5- ((4-bromophenyl) imino) -5 λ⁶-thiaspiro [2.3] hexane 5-oxide 72d

Compound **72c** (300 mg, 0.29 mmol), cesium carbonate (1.5 g, 4.58 mmol), 1-bromo-4-iodobenzene (0.65 g, 2.29 mmol), Pd₂(dba)₃ (53 mg, 0.057 mmol), and Xantphos (99 mg, 0.17 mmol) were dissolved in 1,4-dioxane (10 mL), and the reaction solution was heated up to 100 °C to react for 16 h. After the reaction was completed, the reaction solution was filtered through diatomaceous earth, the filter cake was washed with ethyl acetate (100 mL), and saturated saline solution (50 mL) was used for washing. The organic phase was dried over anhydrous sodium sulfate and concentrated under reduced pressure to obtain a crude product. The crude product was purified by column chromatography (PE/EtOAc=4/1 to 3/2) to obtain compound **72d** (310 mg).

MS (ESI) *m/z* 286 [M + H]⁺

Step 4 5- ((4- (4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) phenyl) imino) -5λ⁶-thiaspiro [2.3] hexane 5-oxide 72e

Compound **72d** (310 mg, 1.1 mmol), bis(pinacolato)diboron (330 mg, 1.3 mmol), Pd(dppf)Cl₂ (160 mg, 0.22 mmol), potassium acetate (330 mg, 3.3 mmol), and 1,4-dioxane (10 mL) were added into a round bottom flask, after replaced with argon gas three times, the reaction solution was heated up to 100 °C and stirred for 16 h. After the reaction was completed, it was cooled down to room temperature, water (20 mL) was added and extracted with ethyl acetate (15 mL × 3). The organic phase was washed with saturated saline solution (20 mL), dried over anhydrous sodium sulfate, and concentrated under reduced pressure to obtain a crude product. The crude product was purified by column chromatography (PE/EtOAc=3/2) to obtain compound **72e** (280 mg), light yellow solid.

MS (ESI) *m/z* 333 [M + H]⁺

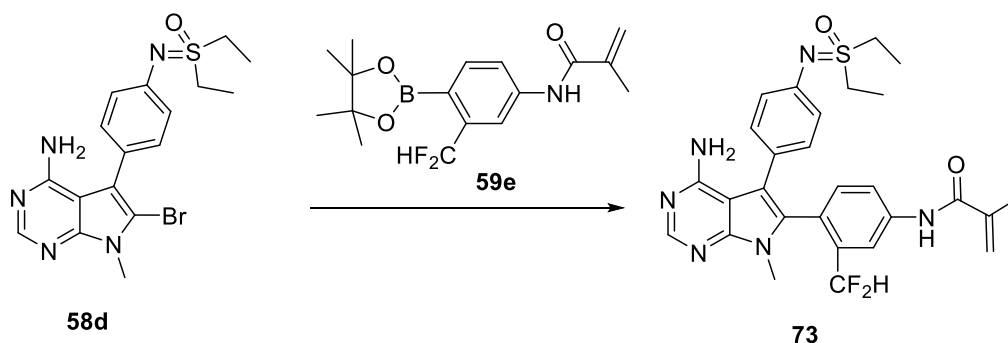
Step 5 *N*- (4- (4-amino-7-methyl-5- (4- (5-oxo-5 λ^6 -thiaspiro [2.3] hex-5-ylidene) amino) phenyl) -7*H*-pyrrolo [2,3-*d*] pyrimidin-6-yl) -3-fluorophenyl) methacrylamide 72

Compound **72e** (50 mg, 0.15 mmol), compound **9e** (50 mg, 0.12 mmol), Pd(PPh₃)₄ (28 mg, 0.025 mmol), K₃PO₄ (80 mg, 0.37 mmol), 1,4-dioxane (2 mL), and H₂O (0.2 mL) were added into a round bottom flask, after replaced with argon gas three times, and the reaction solution was heated up to 100 °C and stirred for 16 h. After the reaction was completed, dichloromethane (20 mL) and saturated saline solution (10 mL) were added and extracted with dichloromethane. The organic phase was dried over anhydrous sodium sulfate and concentrated under reduced pressure to obtain a crude product. The crude product was purified by column chromatography (MeOH/DCM=1/15) to obtain compound **72** (15 mg), white solid.

MS (ESI) *m/z* 531.6 [M + H]⁺

¹H NMR (400 MHz, MeOD-*d*₄) δ 8.21 (s, 1H), 7.74 (dd, *J* = 12.1, 2.1 Hz, 1H), 7.38 (dd, *J* = 8.5, 2.1 Hz, 1H), 7.18 (dt, *J* = 8.3, 4.3 Hz, 3H), 7.10 – 6.89 (m, 2H), 5.83 (s, 1H), 5.57 (d, *J* = 1.6 Hz, 1H), 4.44 – 4.28 (m, 2H), 4.23 – 4.11 (m, 2H), 3.64 (s, 3H), 2.04 (t, *J* = 1.2 Hz, 3H), 1.09 – 0.81 (m, 4H).

Example 73 *N*- (4- (4-amino-5- (4- (diethyl (oxo) - λ^6 - sulfaneylidene) amino) phenyl) -7-methyl- 7*H*-pyrrolo [2,3-*d*] pyrimidin-6-yl) -3- (difluoromethyl) phenyl) methacrylamide

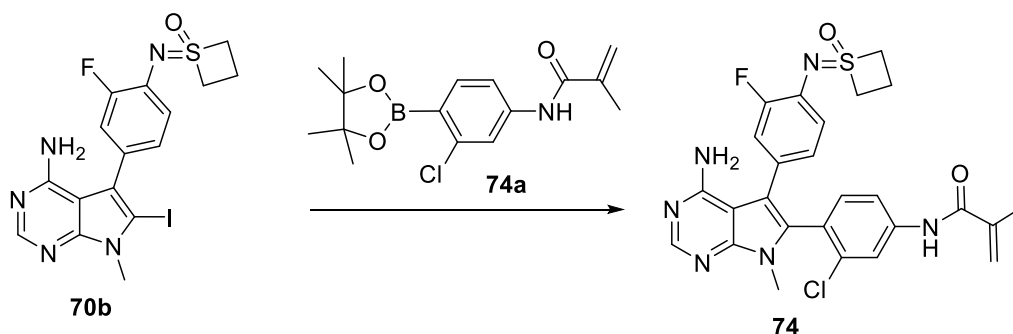


Compound **73** was synthesized with reference to the similar synthetic route and steps of compound **12**, wherein compound **12a** was replaced with compound **58d**, compound **12b** was replaced with compound **59e**.

MS (ESI) *m/z* 553 [M + H]⁺.

¹H NMR (400 MHz, DMSO-*d*₆) δ 10.1 (s, 1H), 8.19 (s, 1H), 8.05 (s, 1H), 7.95 (d, *J*=8.0 Hz, 1H), 7.48 (d, *J*=8.0 Hz, 1H), 6.99 (d, *J*=8.0 Hz, 2H), 6.86 (d, *J*=8.0 Hz, 2H), 6.46 (t, *J*=8.0 Hz, 1H), 6.05 (s, 2H), 5.85 (s, 1H), 5.57 (s, 1H), 3.41 (s, 3H), 3.26-3.23 (m, 4H), 1.96 (s, 3H), 1.23 (s, 6H).

Example 74 *N*- (4- (4-amino-5- (3-fluoro-4- (1-oxo-1 λ^6 -thietan-1-imino) phenyl) -7-methyl-7*H*-pyrrolo [2,3-*d*] pyrimidin-6-yl) -3-chlorophenyl) methacrylamide

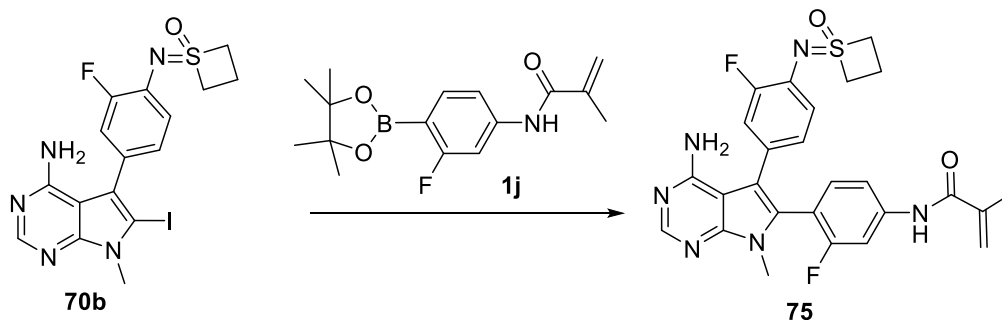


Compound **74** was synthesized with reference to the similar synthetic route and steps of compound **12**, wherein, compound **12a** was replaced with compound **70b**, compound **12b** was replaced with compound **74a**.

5 MS (ESI) m/z 539 $[M + H]^+$.

^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ 10.08 (s, 1H), 8.21 (s, 1H), 8.03 (s, 1H), 7.67 (d, $J=8.0$ Hz, 1H), 7.59-7.56 (m, 3H), 7.35 (t, $J=12.0$ Hz, 1H), 6.14 (s, 2H), 5.84 (s, 1H), 5.58 (s, 1H), 4.29-4.26 (m, 4H), 3.46 (s, 3H), 2.28-2.18 (m, 2H), 1.96 (s, 3H).

10 **Example 75** *N*- (4- (4-amino-5- (3-fluoro-4- (1-oxo-1 λ^6 -thiocyclobutan-1-ylidene) amino) phenyl) -7-methyl-7H-pyrrolo [2,3-*d*] pyrimidin-6-yl) fluorophenyl] methacrylamide



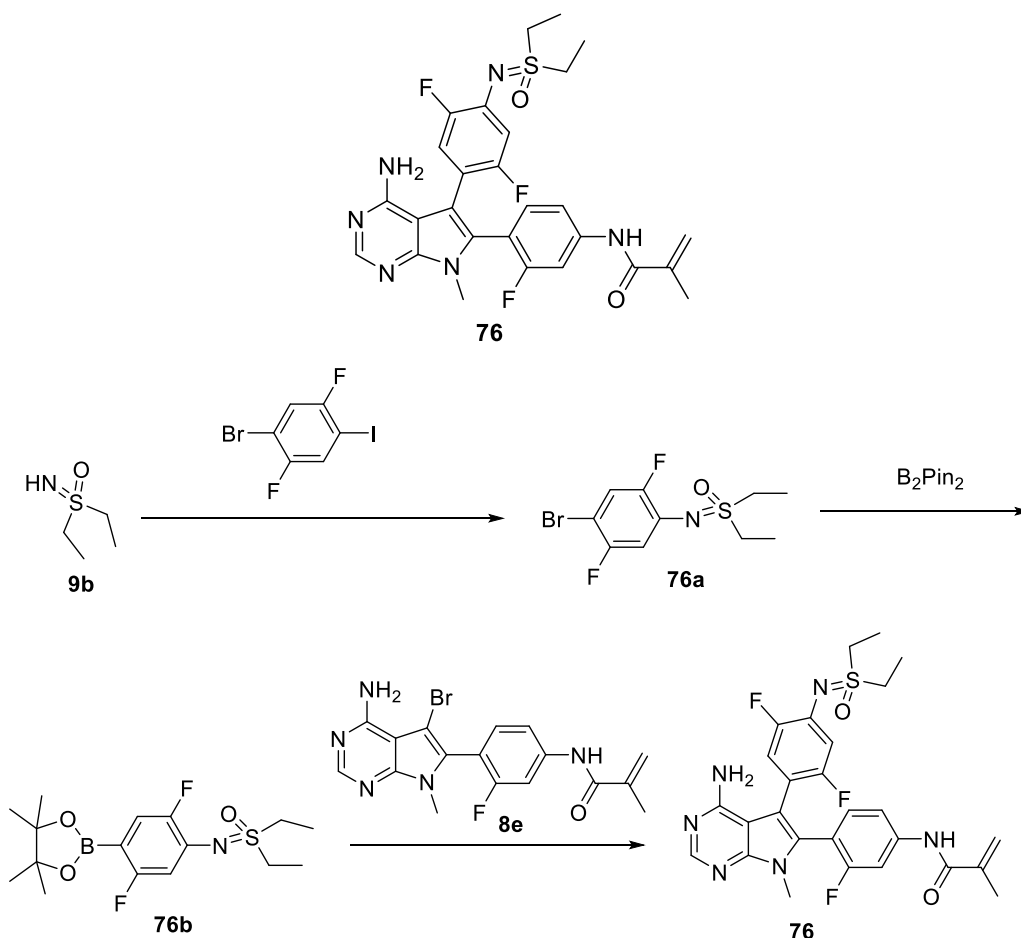
Compound **75** was synthesized with reference to the similar synthetic route and steps of compound **12**, wherein, compound **12a** was replaced with compound **70b**, compound **12b** was replaced with compound **1j**.

15 MS (ESI) m/z 523 $[M + H]^+$.

^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ 10.12 (s, 1H), 8.21 (s, 1H), 7.79 (d, $J=8.0$ Hz, 1H), 7.52 (d, $J=8.0$ Hz, 1H), 7.32 (t, $J=12.0$ Hz, 2H), 7.00-6.89 (m, 2H), 6.12 (s, 2H), 5.84 (s, 1H), 5.59 (s, 1H), 4.31-4.27 (m, 4H), 3.53 (s, 3H), 2.22-2.19 (m, 2H), 1.96 (s, 3H).

20

Example 76 *N*- (4- (4-amino-5- (4- (diethyl (oxo) - λ^6 - sulfaneyliden) amino) -2,5-difluorophenyl) -7-methyl-7H-pyrrolo [2,3-*d*] pyrimidin-6-yl) -3-fluorophenyl] methacrylamide KTH021179



Step 1 ((4-bromo-2,5-difluorophenyl) imino) diethyl - λ^6 -sulfone 76a

At room temperature, compound **9b** (1 g, 8.25 mmol), 5-bromo-1,4-difluoro-2-iodobenzene (3.16 g, 9.91 mmol), tris (dibenzylideneacetone) dipalladium (183.14 mg, 0.19 mmol), 4,5-diphenylphosphine-9,9-dimethyloxanthracene (324.17 mg, 0.56 mmol), and cesium carbonate (3.76 g, 11.55 mmol) were added sequentially to a round bottom flask, 1,4-dioxane (20 mL) was added, followed by vacuum pumping and nitrogen gas purging three times, and heated up to 100 °C and stirred for 3 h. After the reaction was completed, the mixture was cooled down to room temperature and concentrated under reduced pressure to obtain a crude product. The crude product was purified by column chromatography (PE/EtOAc=1/3) to obtain compound **76a** (800 mg), yellow solid.

MS (ESI) m/z 311 $[M + H]^+$.

Step 2 (2,5-difluoro-4- (4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) phenyl) imino diethyl - λ^6 -sulfone 76b

At room temperature, compound **76a** (800 mg, 2.05 mmol), bis(pinacolato)diboron (782.54 mg, 3.08 mmol), potassium acetate (197.49 mg, 54.75 mmol), 1,1'- biphenylphosphine ferrocene palladium chloride (197.49 mg, 0.26 mmol), and 1,4-dioxane (10 mL) were added to a round bottom flask sequentially, followed by vacuum pumping and nitrogen gas purging three times, and heated up to 100 °C and stirred for 1 h. After the reaction was completed, the mixture was cooled down to room temperature and filtered under reduced pressure, the filter cake was washed three

times with dichloromethane, and the filtrate was concentrated under reduced pressure to obtain a crude product. The crude product was purified by column chromatography (PE/EtOAc=1/5) to obtain compound **76b** (700 mg), light yellow solid.

MS (ESI) m/z 360 $[M + H]^+$.

5

Step 3 *N*- (4- (4-amino-5- (4- (diethyl (oxo) - λ^6 - sulfaneylidene) amino) -2,5-difluorophenyl) -7-methyl-7*H*-pyrrolo [2,3-*d*] pyrimidin-6-yl) -3-fluorophenyl) methacrylamide **76**

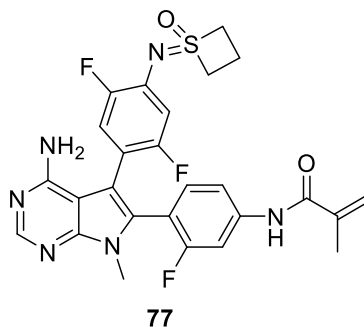
At room temperature, compound **76b** (106 mg, 0.30 mmol), compound **8e** (100 mg, 0.25 mmol), tetrakis (triphenylphosphine) palladium (28.65 mg, 0.025 mmol), potassium phosphate (157.93 mg, 0.74 mmol), 1,4-dioxane (2 mL), and water (0.4 mL) were added to a round bottom flask sequentially, followed by vacuum pumping and nitrogen gas purging three times, and heated up to 90 °C and stirred for 2 h. After the reaction was completed, the mixture was cooled down to room temperature and concentrated under reduced pressure to obtain a crude product. The crude product was purified by column chromatography (DCM/MeOH=15/1) to obtain compound **76** (9.1 mg), white solid.

MS (ESI) m/z 557 $[M + H]^+$.

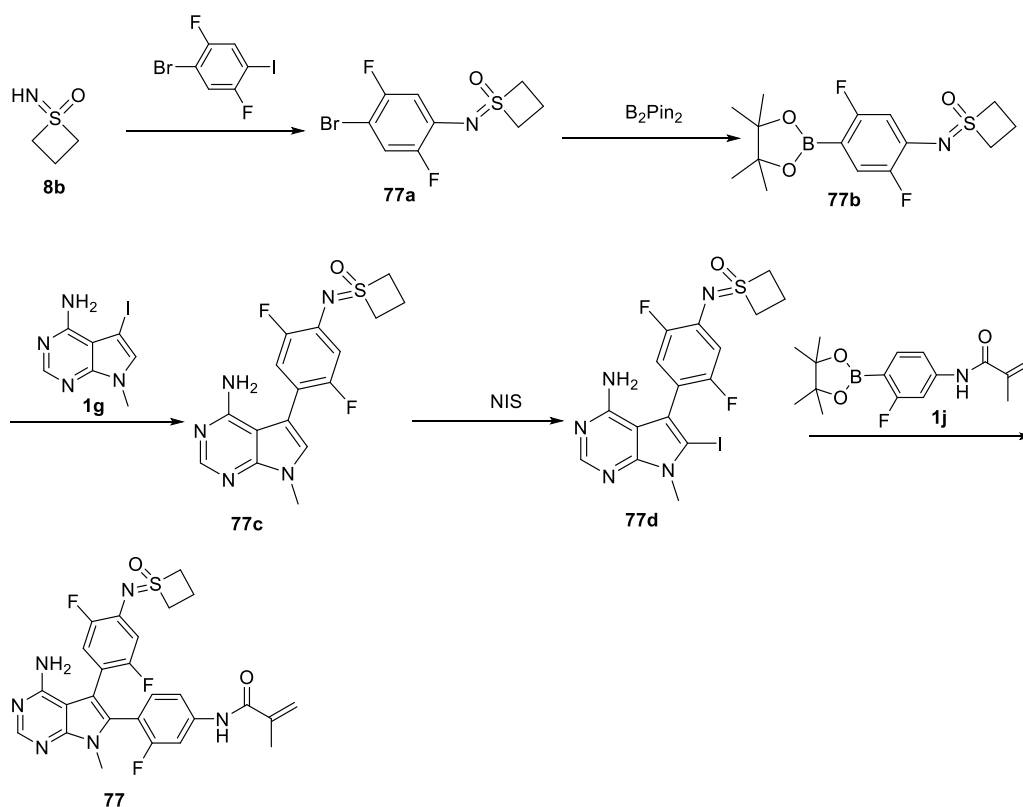
^1H NMR (400 MHz, DMSO- d_6) δ 10.1 (s, 1H), 8.20 (s, 1H), 7.76 (d, $J=8.0$ Hz, 1H), 7.49 (d, $J=8.0$ Hz, 1H), 7.23-7.04 (m, 2H), 6.89 (s, 1H), 6.05 (s, 2H), 5.83 (s, 1H), 5.58 (s, 1H), 3.56 (s, 3H), 3.37-3.34 (m, 4H), 1.96 (s, 3H), 1.27 (s, 6H).

20

Example 77 *N*- (4- (4-amino-5- (2,5-difluoro-4- ((1-oxo-1 λ^6 -thiocyclobutan -1- ylidene) amino) phenyl) -7-methyl-7*H*-pyrrolo [2,3-*d*] pyrimidin-6-yl) -3-fluorophenyl) methacrylamide



25



Step 1 1-((4-bromo-2,5-difluorophenyl) imino) -1 λ^6 -thietane-1-oxide 77a

At room temperature, compound **8b** (1 g, 9.51 mmol), 1-bromo-2,5-difluoro-4-iodobenzene (3.63 g, 11.41 mmol), tris (dibenzylideneacetone) dipalladium (219.77 mg, 0.24 mmol), 4,5-diphenylphosphine-9,9-dimethyloxanthracene (410.82 mg, 0.71 mmol), cesium carbonate (4.34 g, 13.31 mmol), and 1,4-dioxane (20 mL) were added to a round bottom flask sequentially, followed by vacuum pumping and nitrogen gas purging three times, and heated up to 90 °C and stirred for 16 h. After TLC monitored the completion of the reaction, the mixture was cooled down to room temperature and concentrated under reduced pressure to obtain a crude product.

The crude product was purified by column chromatography (PE/EtOAc=3/1) to obtain compound **77a** (630 mg), light yellow solid.

MS (ESI) m/z 295 [M + H]⁺.

Step 2 1-(2,5-difluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) phenyl) imino) -1 λ^6 -thietane-1-oxide 77b

At room temperature, compound **77a** (630 mg, 2.14 mmol), diboronic acid pinacol ester (652.63 mg, 2.57 mmol), 1,1'-biphenylphosphine ferrocene palladium chloride (156.58 mg, 0.214 mmol), potassium acetate (525.05 mg, 5.35 mmol), and 1,4-dioxane (6 mL) were added to a round bottom flask sequentially, followed by vacuum pumping and nitrogen gas purging three times, and heated up to 100 °C and stirred for 1 h. After the reaction was completed, the mixture was concentrated under reduced pressure to obtain a crude product. The crude product was purified by column chromatography (PE/EtOAc=3/1) to obtain compound **77b** (500 mg), brown solid.

MS (ESI) m/z 344[M + H]⁺.

Step 3 1- (4- (4-amino-7-methyl-7*H*-pyrrolo [2,3-*d*] pyrimidin-5-yl) -2,5- difluorophenyl) imino) -1 λ^6 -thietane-1-oxide 77c

At room temperature, compound **77b** (500 mg, 1.45 mmol), compound **1g** (40.20 mg, 0.14 mmol), tetrakis (triphenylphosphine) palladium (167.55 mg, 0.145 mmol), potassium phosphate (923.37 mg, 4.35 mmol), 1,4-dioxane (10 mL), and water (2 mL) were added to a round bottom flask sequentially, followed by vacuum pumping and nitrogen gas purging three times, and heated up to 90 °C and stirred for 3 h. After TLC monitored the completion of the reaction, the mixture was cooled down to room temperature and concentrated under reduced pressure to obtain a crude product. The crude product was purified by column chromatography (DCM/MeOH=15/1) to obtain compound **77c** (300 mg), reddish brown solid.

MS (ESI) m/z 364 [M + H]⁺.

Step 4 1- (4- (4-amino-6-iodo-7-methyl-7*H*-pyrrolo [2,3-*d*] pyrimidin-5-yl) -2,5- difluorophenyl) imino) -1 λ^6 -thietane-1-oxide 77d

At room temperature, compound **77c** (300 mg, 0.83 mmol) was dissolved in dichloromethane (5 mL), and then trifluoroacetic acid (188.36 mg, 1.65 mmol) was added. After it was cooled down to 0 °C, NIS (278.75 mg, 1.24 mmol) was added in batches, and the reaction was carried out at room temperature for 2 h. After the reaction was completed, saturated sodium bicarbonate solution was added and extracted with dichloromethane. The organic phase was concentrated under reduced pressure to obtain a crude product. The crude product was purified by column chromatography (DCM/MeOH=15/1) to obtain compound **77d** (50 mg), light yellow solid.

MS (ESI) m/z 489 [M + H]⁺.

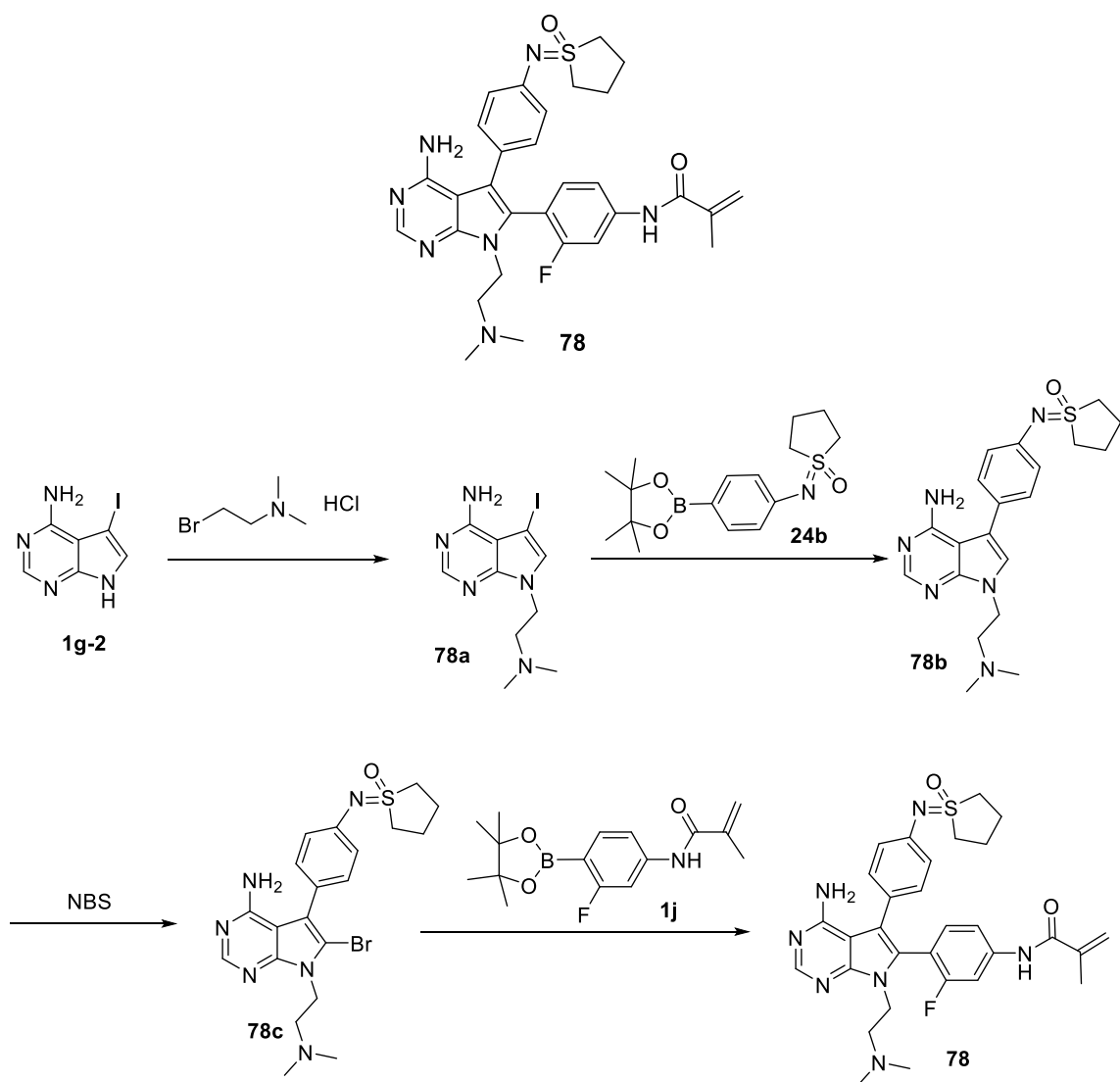
Step 5 *N*- (4- (4-amino-5- (2,5-difluoro-4- (1-oxo-1 λ^6 -thiocyclobutan-1-ylidene) amino) phenyl) -7-methyl-7*H*-pyrrolo [2,3-*d*] pyrimidin-6-yl) -3-fluorophenyl) methacrylamide 77

At room temperature, compound **77d** (50 mg, 0.10 mmol), compound **1j** (37.23 mg, 0.12 mmol), tetrakis (triphenylphosphine) palladium (11.56 mg, 0.01 mmol), potassium phosphate (64.95 mg, 0.31 mmol), 1,4-dioxane (2 mL), and water (0.4 mL) were added to a round bottom flask sequentially, followed by vacuum pumping and nitrogen gas purging three times, and heated up to 90 °C and stirred for 2 h. After the reaction was completed, the mixture was cooled down to room temperature and concentrated under reduced pressure to obtain a crude product. The crude product was purified by column chromatography (DCM/MeOH=15/1) to obtain compound **77** (20 mg), white solid.

MS (ESI) m/z 541 [M + H]⁺.

¹H NMR (400 MHz, DMSO-*d*₆) δ 10.10 (s, 1H), 8.19 (s, 1H), 8.16 (s, 1H), 7.77 (d, *J*=8.0 Hz, 1H), 7.48 (d, *J*=8.0 Hz, 2H), 7.21 (t, *J*=12.0 Hz, 1H), 6.02 (s, 2H), 5.82 (s, 1H), 5.57 (s, 1H), 4.37-4.28 (m, 4H), 3.51 (s, 3H), 2.27-2.21 (m, 2H), 1.98 (s, 3H).

Example 78 *N*- (4- (4-amino-7- (2- (dimethylamino) ethyl) -5- (4- ((1-hydroperoxide -1 λ^6 -thiophene-1-ylidene) amino) phenyl) -7*H*-pyrrolo [2,3-*d*] pyrimidin-6-yl) -3-fluorophenyl) methacrylamide



Step 1 7-(2-(dimethylamino)ethyl)-5-iodo-7H-pyrrolo [2,3-d] pyrimidin-4-amine 78a

At room temperature, compound **1g-2** (1 g, 3.85 mmol), (2-bromomethyl) dimethylamine hydrochloride (872.78 mg, 5.78 mmol), cesium carbonate (2.51 g, 7.7 mmol), and N, N-dimethylformamide (10 mL) were added to a round bottom flask sequentially, and the reaction was stirred at room temperature for 16 h. After TLC monitored the completion of the reaction, the mixture was diluted with water, extracted with ethyl acetate (30 mL $\times$ 3), and washed with saturated saline (30 mL), and the organic phases were combined, dried over anhydrous sodium sulfate and concentrated under reduced pressure to obtain a crude product. The crude product was purified by column chromatography (DCM/MeOH=15/1) to obtain compound **78a** (400 mg), gray solid.

MS (ESI) m/z 332 $[\text{M} + \text{H}]^+$.

Step 2 1-(4-(4-amino-7-(2-(dimethylamino)ethyl)-7H-pyrrolo [2,3-d] pyrimidin -5-yl) phenyl) imino) tetrahydro-1H-1 λ ⁶-thiophene-1-oxide 78b

At room temperature, compound **78a** (400 mg, 1.2 mmol), compound **24b** (423.72 mg, 0.13 mmol), tetrakis (triphenylphosphine) palladium (138.67 mg, 0.12 mmol), potassium phosphate

(764.17 mg, 3.6 mmol), 1,4-dioxane (10 mL), and water (2 mL) were added to a round bottom flask sequentially, followed by vacuum pumping and nitrogen gas purging three times, and heated up to 90 °C and stirred for 3 h. After TLC monitored the completion of the reaction, the mixture was cooled down to room temperature and concentrated under reduced pressure to obtain a crude product. The crude product was purified by column chromatography (DCM/MeOH=15/1) to obtain compound **78b** (210 mg), reddish brown solid.

MS (ESI) m/z 399 $[M + H]^+$.

Step 3 1- (4- (4-amino-6-bromo-7- (2- (dimethylamino) ethyl) -7H-pyrrolo [2,3-*d*] pyrimidin-5-yl) phenyl) imino) tetrahydro-1H-1 λ^6 -thiophene-1-oxide 78c

At room temperature, compound **78b** (210 mg, 0.53 mmol) was dissolved in DMF (5 mL), and it was cooled down to 0 °C, and a solution of NBS in DMF (98.55 mg NBS dissolved in 2 mL DMF) was added dropwise, and then temperature was restored to room temperature to react for additional 2 h. After the reaction was completed, the reaction was quenched by added saturated sodium bisulfite aqueous solution, extracted with dichloromethane, and the organic phase was concentrated to obtain a crude product. The crude product was purified by column chromatography (DCM/MeOH=15/1) to obtain compound **78c** (100 mg), light yellow solid.

MS (ESI) m/z 477 $[M + H]^+$.

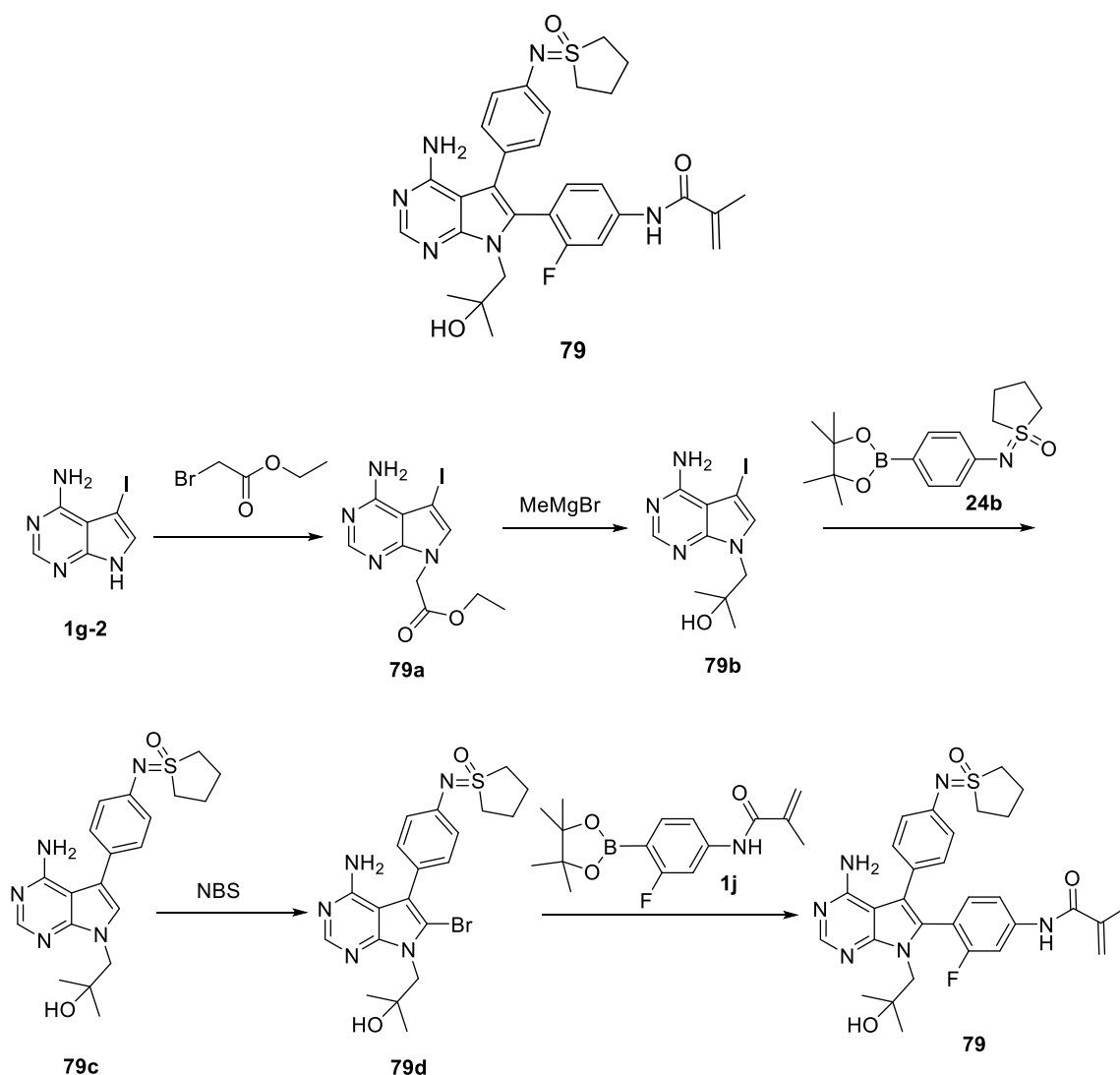
Step 4 N- (4- (4-amino-7- (2- (dimethylamino) ethyl) -5- (4- ((1-hydroperoxide-1 λ^6 -thiophene-1-ylidene) amino) phenyl) -7H-pyrrolo [2,3-*d*] pyrimidin-6-yl) -3- fluorophenyl) methacrylamide 78

At room temperature, compound **78c** (100 mg, 0.21 mmol), compound **1j** (76.9 mg, 0.25 mmol), tetrakis (triphenylphosphine) palladium (24.26 mg, 0.02 mmol), potassium phosphate (133.62 mg, 0.63 mmol), 1,4-dioxane (2 mL), and water (0.4 mL) were added to a round bottom flask sequentially, followed by vacuum pumping and nitrogen gas purging three times, and heated up to 90 °C and stirred for 2 h. After TLC monitored the completion of the reaction, the mixture was cooled down to room temperature and concentrated under reduced pressure to obtain a crude product. The crude product was purified by column chromatography (DCM/MeOH=15/1) to obtain compound **78** (7.7 mg), white solid.

MS (ESI) m/z 576 $[M + H]^+$.

^1H NMR (400 MHz, DMSO- d_6) δ 10.10 (s, 1H), 8.17 (s, 1H), 7.74 (d, $J = 8.0$ Hz, 1H), 7.51 (d, $J = 8.0$ Hz, 1H), 7.31 (t, $J = 12.0$ Hz, 1H), 7.05 (d, $J = 8.0$ Hz, 2H), 6.65 (d, $J = 8.0$ Hz, 2H), 6.02 (s, 2H), 5.82 (s, 1H), 5.57 (s, 1H), 4.16-3.99 (m, 2H), 3.35-3.21 (m, 4H), 2.38-2.30 (m, 2H), 2.21-2.08 (m, 4H), 1.98 (s, 6H), 1.94 (s, 3H).

Example 79 N-(4-(4-amino-7-(2-hydroxy-2-methylpropyl)-5-(4-((1-hydroperoxid-1 λ^6 -thiophene-1-ylidene) amino) phenyl) -7H-pyrrolo [2,3-*d*] pyrimidin -6-yl) -3-fluorophenyl) methacrylamide



Step 1 ethyl 2- (4-amino-5-iodo-7H-pyrrolo [2,3-d] pyrimidin-7-yl) acetate 79a

Compound **1g-2** (1 g, 3.85 mmol), ethyl bromoacetate (963.59 mg, 5.77 mmol), and cesium carbonate (2.51 g, 7.7 mmol) were dissolved in N,N-dimethylformamide (10 mL) and the reaction was carried out at room temperature for 16 h. After the reaction was completed, water (100 mL) was added and extracted with ethyl acetate (30 mL × 3), and washed with saturated saline (30 mL). The organic phases were combined, dried over anhydrous sodium sulfate and concentrated under reduced pressure to obtain a crude product. The crude product was purified by column chromatography (DCM/MeOH=15/1) to obtain compound **79a** (600 mg), gray solid.

MS (ESI) m/z 347 $[M + H]^+$.

Step 2 1- (4-amino-5-iodo-7H-pyrrolo [2,3-d] pyrimidin-7-yl) -2-methylpropyl-2-ol 79b

Compound **79a** (600 mg, 1.67 mmol) was dissolved in tetrahydrofuran (10 mL), followed by vacuum pumping and nitrogen gas purging three times. After it was cooled down to -56 °C, 1.0 M methyl magnesium bromide-tetrahydrofuran solution (8.4 mL, 8.34 mmol) was added slowly dropwise in batches, and the reaction was stirred at -56 °C for additional 2 h. After the reaction was completed, the mixture was warmed up to room temperature naturally, diluted with water,

extracted with ethyl acetate (30 mL × 3), and washed with saturated saline (30 mL), and the organic phases were combined, dried over anhydrous sodium sulfate and concentrated under reduced pressure to obtain a crude product. The crude product was purified by column chromatography (DCM/MeOH=15/1) to obtain compound **79b** (400 mg), light yellow solid.

5 MS (ESI) m/z 333 $[M + H]^+$.

Step 3 1-(4-(4-amino-7-(2-hydroxy-2-methylpropyl) -7H-pyrrolo [2,3-*d*] pyrimidin -5- yl) phenyl) imino) tetrahydro-1H-1 λ^6 -thiophene-1-oxide 79c

To a round bottom flask, compound **79b** (400 mg, 1.2 mmol), compound **24b** (423.72 mg, 0.13 mmol), tetrakis (triphenylphosphine) palladium (138.67 mg, 0.12 mmol), potassium phosphate (764.17 mg, 3.6 mmol), 1,4-dioxane (10 mL), and water (2 mL) were added in sequence, followed by vacuum pumping and nitrogen gas purging three times, and heated up to 90 °C and stirred for 3 h. After the reaction was completed, the mixture was cooled down to room temperature and concentrated under reduced pressure to obtain a crude product. The crude product

10
15 was purified by column chromatography (DCM/MeOH=15/1) to obtain compound **79c** (150 mg), reddish brown solid.

MS (ESI) m/z 400 $[M + H]^+$.

Step 4 1- (4- (4-amino-6-bromo-7- (2-hydroxy-2-methylpropyl) -7H-pyrrolo [2,3-*d*] pyrimidin-5-yl) phenyl) imino) tetrahydro-1H-1 λ^6 -thiophene-1-oxide 79d

Compound **79c** (150 mg, 0.37 mmol) was dissolved in N, N-dimethylformamide (5 mL). After it was cooled down to 0 °C, N-bromosuccinimide (69.93 mg, 0.39 mmol) was added in batches, and the reaction was stirred at room temperature for 2 h. After the reaction was completed, the mixture was concentrated under reduced pressure to obtain a crude product. The

20
25 crude product was purified by column chromatography (DCM/MeOH=15/1) to obtain compound **79d** (100 mg), light yellow solid.

MS (ESI) m/z 478 $[M + H]^+$.

Step 5 N- (4- (4-amino-7- (2-hydroxy-2-methylpropyl) -5- (4- ((1-hydroperoxid-1 λ^6 -thiophene-1-ylidene) amino) phenyl) -7H-pyrrolo [2,3-*d*] pyrimidin-6-yl) -3- fluorophenyl) methacrylamide 79

To a round bottom flask, compound **79d** (100 mg, 0.21 mmol), compound **1j** (70.19 mg, 0.23 mmol), tetrakis (triphenylphosphine) palladium (24.26 mg, 0.02 mmol), potassium phosphate (133.62 mg, 0.63 mmol), 1,4-dioxane (2 mL), and water (0.4 mL) were added in sequence,

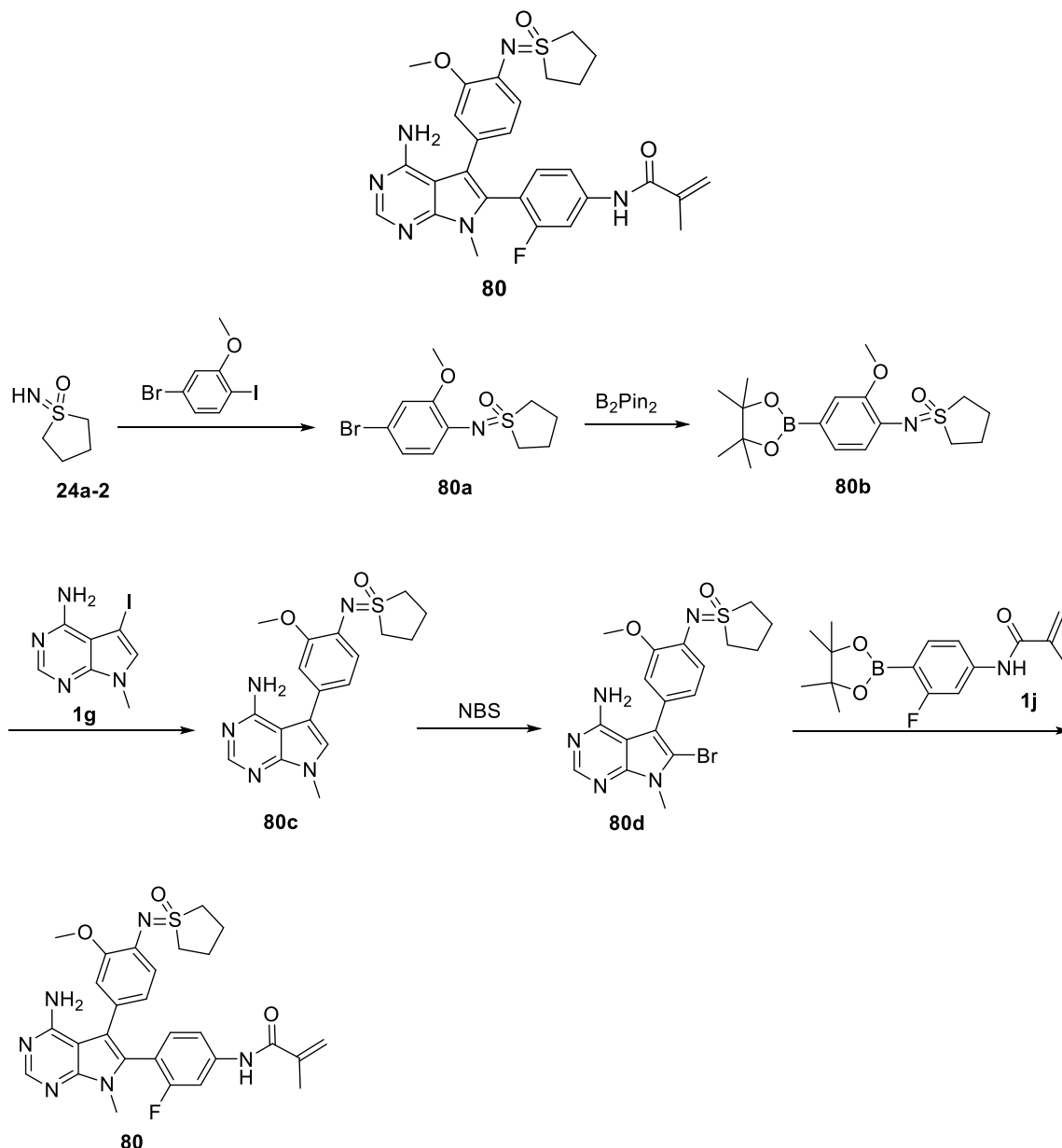
30
35 followed by vacuum pumping and nitrogen gas purging three times, and heated up to 90 °C and reacted for 2 h. After the reaction was completed, the mixture was cooled down to room temperature and concentrated under reduced pressure to obtain a crude product. The crude product was purified by column chromatography (DCM/MeOH=15/1) to obtain compound **79** (13.4 mg), white solid.

40 MS (ESI) m/z 577 $[M + H]^+$.

^1H NMR (400 MHz, DMSO- d_6) δ 10.06 (s, 1H), 8.17 (s, 1H), 7.71 (d, $J=8.0$ Hz, 1H), 7.47 (d, $J=8.0$ Hz, 1H), 7.27 (t, $J=12.0$ Hz, 1H), 7.28-7.03 (m, 2H), 6.88-6.84 (m, 2H), 6.02 (s, 2H), 5.80

(s, 1H), 5.56 (s, 1H), 4.91 (s, 1H), 4.16-3.99 (m, 2H), 3.28-3.21 (m, 4H), 2.22-2.02 4 (m, 4H), 1.94 (s, 3H), 0.88 (s, 6H).

Example 80 *N*- (4- (4-amino-5- (3-methoxy-4- ((1-hydroperoxid-1 λ^6 -thiophene -1-ylidene) amino) phenyl) -7-methyl-7*H*-pyrrolo [2,3-*d*] pyrimidin-6-yl) -3-fluorophenyl) methacrylamide



Step 1 1- ((4-bromo-2-methoxyphenyl) imino) tetrahydro-1*H*-1 λ^6 -thiophene-1- oxide **80a**

At room temperature, compound **24a-2** (1 g, 8.4 mmol), 4-bromo-1-iodo-2-methoxybenzene (3.14 g, 10.08 mmol), tris (dibenzylideneacetone) dipalladium (192.3 mg, 0.21 mmol), 4,5-diphenylphosphine-9,9-dimethyloxaanthracene (364.53 mg, 0.63 mmol), cesium carbonate (3.83 g, 11.76 mmol), and 1,4-dioxane (20 mL) were added to a round bottom flask sequentially, followed by vacuum pumping and nitrogen gas purging three times, and heated up to 90 °C and

stirred for 3 h. After TLC monitored the completion of the reaction, the mixture was cooled down to room temperature and concentrated under reduced pressure to obtain a crude product. The crude product was purified by column chromatography (PE/EtOAc=1/3) to obtain compound **80a** (1.2 g), yellow solid.

5 MS (ESI) m/z 303 $[M + H]^+$.

Step 2 1- ((2-methoxy-4- (4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) phenyl) imino) tetrahydro-1H-1 λ^6 -thiophene-1-oxide 80b

10 To a round bottom flask, compound **80a** (1.2 g, 3.96 mmol), bis(pinacolato)diboron (1.21 g, 4.75 mmol), potassium acetate (971.59 mg, 9.9 mmol), 1,1'- biphenylphosphine ferrocene palladium chloride (285.36 mg, 0.39 mmol), and 1,4-dioxane (20 mL) were added in sequence, followed by vacuum pumping and nitrogen gas purging three times, and heated up to 100 °C and stirred for 1 h. After the reaction was completed, the mixture was cooled down to room temperature and filtered under reduced pressure, the filter cake was washed with dichloromethane
15 three times, and all filtrates were combined, concentrated under reduced pressure to obtain a crude product. The crude product was purified by column chromatography (PE/EtOAc=1/5) to obtain compound **80b** (1 g), light yellow solid.

MS (ESI) m/z 352 $[M + H]^+$.

20 **Step 3 1- (4- (4-amino-7-methyl-7H-pyrrolo [2,3-*d*] pyrimidin-5-yl) -2- methoxyphenyl) imino) tetrahydro-1H-1 λ^6 -thiophene-1-oxide 80c**

To a round bottom flask, compound **80b** (1 g, 2.84 mmol), compound **1g** (654.10 mg, 2.37 mmol), tetrakis (triphenylphosphine) palladium (273.87 mg, 0.237 mmol), potassium phosphate (1.51 g, 7.11 mmol), 1,4-dioxane (20 mL), and water (4 mL) were added in sequence, followed by
25 vacuum pumping and nitrogen gas purging three times, and heated up to 90 °C and reacted for 3 h. After TLC monitored the completion of the reaction, the mixture was cooled down to room temperature and concentrated under reduced pressure to obtain a crude product. The crude product was purified by column chromatography (DCM/MeOH=15/1) to obtain compound **80c** (430 mg), reddish brown solid.

30 MS (ESI) m/z 372 $[M + H]^+$.

Step 4 1- (4- (4-amino-6-bromo-7-methyl-7H-pyrrolo [2,3-*d*] pyrimidin-5-yl) -2- methoxyphenyl) imino) tetrahydro-1H-1 λ^6 -thiophene-1-oxide 80d

35 Compound **80c** (430 mg, 1.16mmol) was dissolved in N, N-dimethylformamide (5 mL), and it was cooled down down to 0 °C, and then N-bromosuccinimide (217.13 mg, 1.22 mmol) was added in batches, and heated up to room temperature and reacted for 2 h. After the reaction was completed, the mixture was concentrated under reduced pressure to obtain a crude product. The crude product was purified by column chromatography (DCM/MeOH=15/1) to obtain compound **80d** (300 mg), light yellow solid.

40 MS (ESI) m/z 450 $[M + H]^+$.

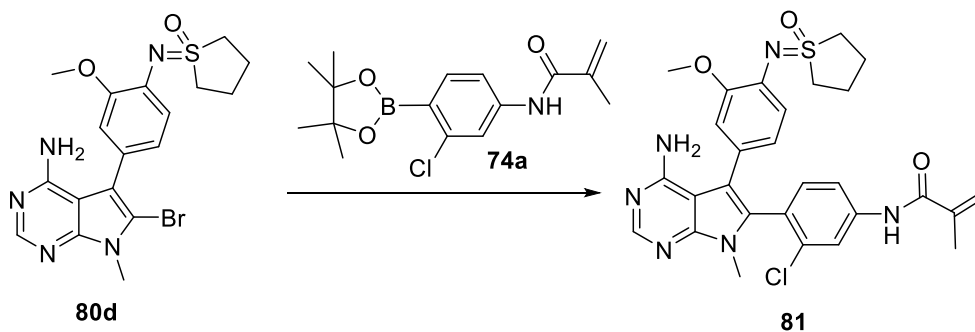
Step 5 N- (4- (4-amino-5- (3-methoxy-4- ((1-hydroperoxid-1 λ^6 -thiophene-1-ylidene) amino) phenyl) -7-methyl-7H-pyrrolo [2,3-*d*] pyrimidin-6-yl) -3-fluorophenyl) methacrylamide **80**

To a round bottom flask, compound **80d** (100 mg, 0.22 mmol), compound **1j** (77.08 mg, 0.24 mmol), tetrakis (triphenylphosphine) palladium (25.42 mg, 0.022 mmol), potassium phosphate (140.1 mg, 0.66 mmol), 1,4-dioxane (2 mL), and water (0.4 mL) were added in sequence, followed by vacuum pumping and nitrogen gas purging three times, and heated up to 90 °C and reacted for 2 h. After the reaction was completed, the mixture was cooled down to room temperature and concentrated under reduced pressure to obtain a crude product. The crude product was purified by column chromatography (DCM/MeOH=15/1) to obtain compound **80** (17.4mg), white solid.

MS (ESI) m/z 549 $[M + H]^+$.

^1H NMR (400 MHz, DMSO- d_6) δ 10.11 (s, 1H), 8.19 (s, 1H), 7.78 (d, $J=8.0$ Hz, 1H), 7.48 (d, $J=8.0$ Hz, 1H), 7.29 (t, $J=12.0$ Hz, 1H), 6.85 (d, $J=8.0$ Hz, 1H), 6.73-6.65 (m, 2H), 6.12 (s, 2H), 5.82 (s, 1H), 5.57 (s, 1H), 3.60 (s, 3H), 3.53 (s, 3H), 3.31-3.16 (m, 4H), 2.16-2.09 (m, 4H), 1.95 (s, 3H).

Example 81 N- (4- (4-amino-5- (3-methoxy-4- ((1-hydroperoxid-1 λ^6 -thiophene-1-ylidene) amino) phenyl) -7-methyl-7H-pyrrolo [2,3-*d*] pyrimidin-6-yl) -3-chlorophenyl) methacrylamide

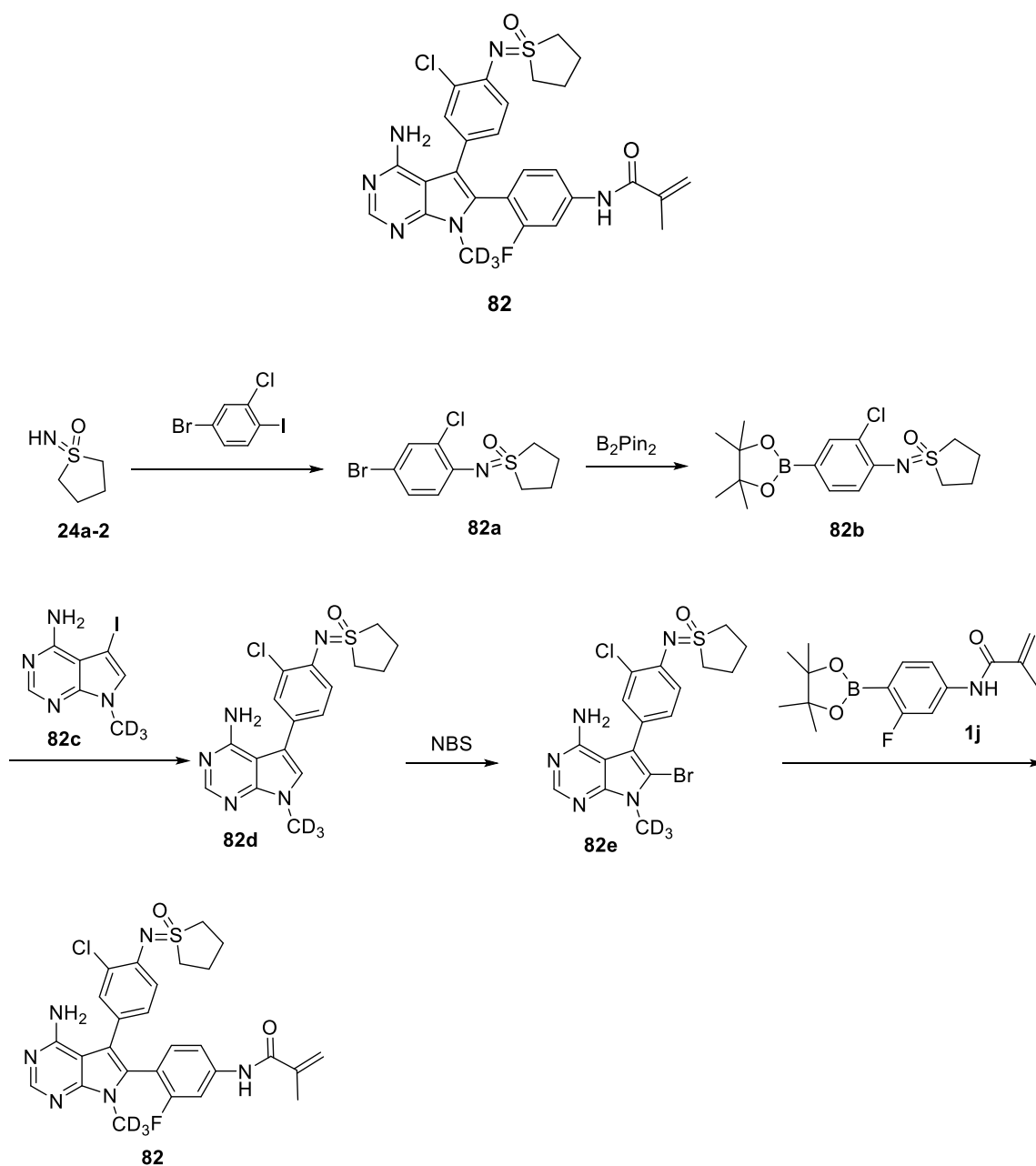


Compound **81** was synthesized with reference to the similar synthetic route and steps of compound **12**, wherein, compound **12a** was replaced with compound **80b**, compound **12b** was replaced with compound **74a**.

MS (ESI) m/z 566 $[M + H]^+$.

^1H NMR (400 MHz, DMSO- d_6) δ 10.08 (s, 1H), 8.19 (s, 1H), 8.02 (d, $J=8.0$ Hz, 1H), 7.64 (d, $J=8.0$ Hz, 1H), 7.35 (t, $J=20.0$ Hz, 2H), 6.84 (d, $J=8.0$ Hz, 2H), 6.72-6.66 (m, 4H), 6.12 (s, 2H), 5.83 (s, 1H), 5.57 (s, 1H), 4.31-4.27 (m, 4H), 3.59 (s, 3H), 3.46 (s, 3H), 1.94 (s, 3H).

Example 82 N- (4- (4-amino-5- (3-chloro-4- ((1-oxide tetrahydro-1 λ^6 -thiophene-1-ylidene) amino) phenyl) -7- (methyl- d_3) -7H-pyrrolo [2,3-*d*] pyrimidin-6-yl) -3- fluorophenyl) methacrylamide



Step 1 1-((4-bromo-2-chlorophenyl) imino) tetrahydro-1H-1 λ^6 -thiophene-1-oxide 82a

- 5 To a round bottom flask, compound **24a-2** (1 g, 8.4 mmol), 4-bromo-2-chloro-1-iodobenzene (3.18 g, 10.08 mmol), tris (dibenzylideneacetone) dipalladium (153.84 mg, 0.17 mmol), 4,5- diphenylphosphine-9,9-dimethyloxanthracene (364.53 mg, 0.50 mmol), cesium carbonate (3.56 g, 10.92 mmol), and 1,4-dioxane (10 mL) were added in sequence, followed by vacuum pumping and nitrogen gas purging three times, and heated up to 90 °C and reacted for 3 h.
- 10 After the reaction was completed, it was cooled down to room temperature, and the mixture was concentrated under reduced pressure to obtain a crude product. The crude product was purified by column chromatography (PE/EtOAc=1/3) to obtain compound **82a** (1.2 g), yellow solid.

MS (ESI) m/z 307 $[\text{M} + \text{H}]^+$.

Step 2 1- ((2-chloro-4- (4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) phenyl) imino) tetrahydro-1H-1 λ^6 -thiophene-1-oxide 82b

To a round bottom flask, **82a** (1.2 g, 3.9 mmol), bis(pinacolato)diboron (1.19 g, 4.68 mmol), potassium acetate (956.86 mg, 9.75 mmol), 1,1'- biphenylphosphine ferrocene palladium chloride (285.36 mg, 0.39 mmol), and 1,4-dioxane (20 mL) were added sequentially, followed by vacuum pumping and nitrogen gas purging three times, and heated up to 100 °C and reacted for 1 h. After the reaction was completed, the mixture was cooled down to room temperature and filtered under reduced pressure, the filter cake was washed with dichloromethane three times, and all filtrates were combined and concentrated under reduced pressure to obtain a crude product. The crude product was purified by column chromatography (PE/EtOAc=1/5) to obtain compound **82b** (1 g), light yellow solid.

MS (ESI) m/z 356 [M + H]⁺.

Step 3 1- (4- (4-amino-7- (methyl- d_3) -7H-pyrrolo [2,3-*d*] pyrimidin-5-yl) -2-chlorophenyl) imino) tetrahydro-1H-1 λ^6 -thiophene-1-oxide 82d

To a round bottom flask, compound **82b** (1 g, 2.82 mmol), compound **82c** (709.09 mg, 2.56 mmol), tetrakis (triphenylphosphine) palladium (325.87 mg, 0.282 mmol), potassium phosphate (1.80 g, 8.46 mmol), 1,4-dioxane (10 mL), and water (2 mL) were added in sequence, followed by vacuum pumping and nitrogen gas purging three times, and heated up to 90 °C and reacted for 3 h. After the reaction was completed, the mixture was cooled down to room temperature and concentrated under reduced pressure to obtain a crude product. The crude product was purified by column chromatography (DCM/MeOH=15/1) to obtain compound **82d** (530 mg), reddish brown solid.

MS (ESI) m/z 379 [M + H]⁺.

Step 4 1- (4- (4-amino-6-bromo-7- (methyl- d_3) -7H-pyrrolo [2,3-*d*] pyrimidin-5-yl) -2-chlorophenyl) imino) tetrahydro-1H-1 λ^6 -thiophene-1-oxide 82e

Compound **82d** (530 mg, 1.40 mmol) was dissolved in N, N-dimethylformamide (6 mL). After it was cooled down to 0 °C, NBS (261.63 mg, 1.47 mmol) was added in batches, and it was heated up to room temperature and reacted for 2 h. After the reaction was completed, the mixture was concentrated under reduced pressure to obtain a crude product. The crude product was purified by column chromatography (DCM/MeOH=15/1) to obtain compound **82e** (460 mg), yellow solid.

MS (ESI) m/z 457 [M + H]⁺.

Step 5 N- (4- (4-amino-5- (3-chloro-4- ((1-hydroperoxid-1 λ^6 -thiophene-1-ylidene) amino) phenyl) -7- (methyl- d_3) -7H-pyrrolo [2,3-*d*] pyrimidin-6-yl) -3-fluorophenyl) methacrylamide 82

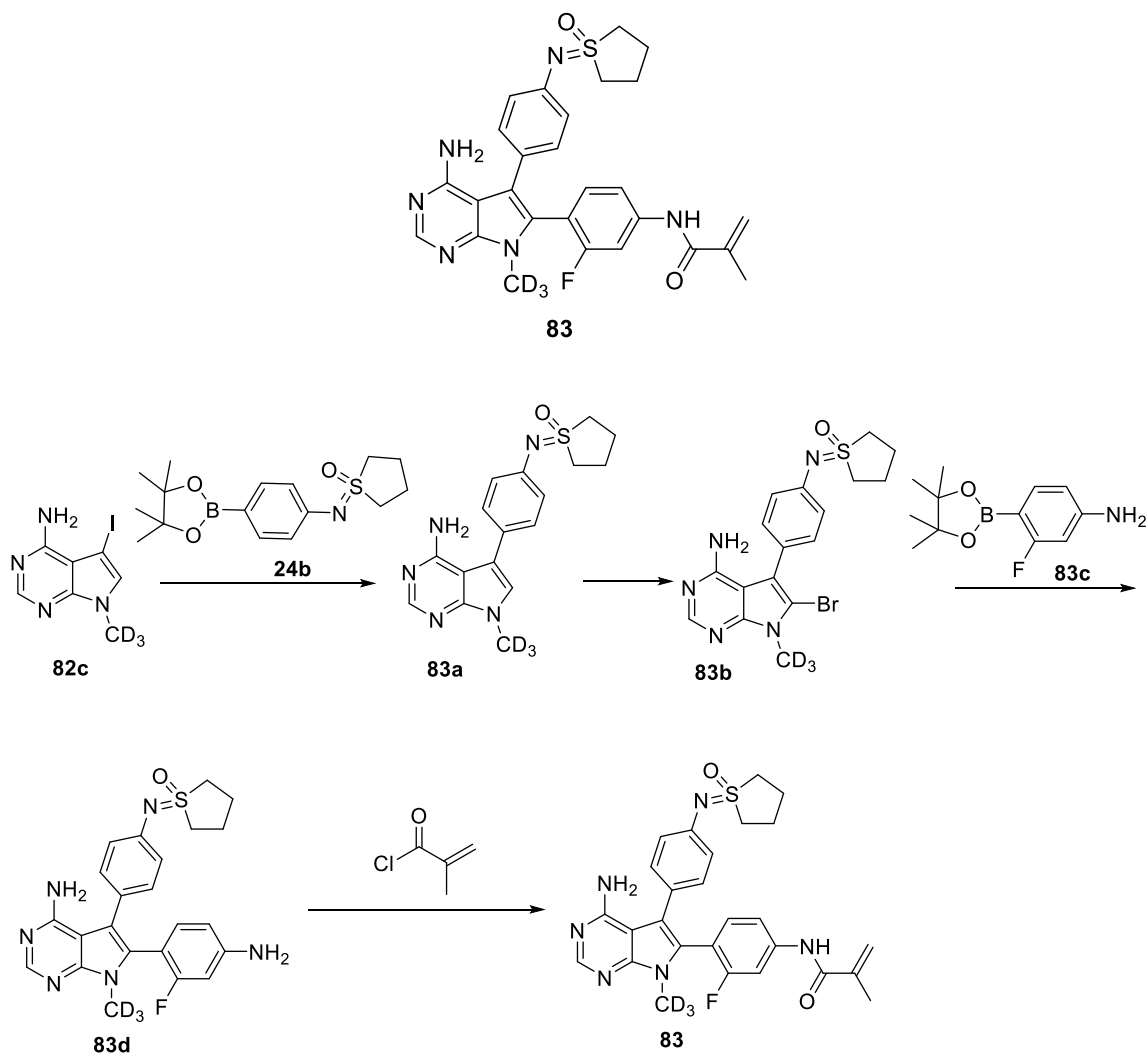
To a round bottom flask, compound **82e** (100 mg, 0.22 mmol), compound **1j** (73.85 mg, 0.24 mmol), tetrakis (triphenylphosphine) palladium (25.42 mg, 0.022 mmol), potassium phosphate (140.1 mg, 0.66 mmol), 1,4-dioxane (2 mL), and water (0.4 mL) were added in sequence, followed by vacuum pumping and nitrogen gas purging three times, and heated up to 90 °C and reacted for 2 h. After the reaction was completed, the mixture was cooled down to room

temperature and concentrated under reduced pressure to obtain a crude product. The crude product was purified by column chromatography (DCM/MeOH=15/1) to obtain compound **82** (15.7mg), white solid.

MS (ESI) m/z 556 $[M + H]^+$.

¹H NMR (400 MHz, DMSO-*d*₆) δ 10.11 (s, 1H), 8.19 (s, 1H), 7.78 (d, $J=8.0$ Hz, 1H), 7.51 (d, $J=8.0$ Hz, 1H), 7.29 (t, $J=20.0$ Hz, 1H), 7.17 (s, 1H), 7.07 (s, 1H), 7.01 (s, 1H), 6.11-5.95 (m, 2H), 5.83 (s, 1H), 5.58 (s, 1H), 3.40-3.37 (m, 4H), 2.22-2.12 (m, 4H), 1.95 (s, 3H).

Example 83 *N*- (4- (4-amino-7- (methyl-*d*₃) -5- (4- (1-oxotetrahydro-1 λ^6 -thiophene -1-imino) phenyl) -7*H*-pyrrolo [2,3-*d*] pyrimidin-6-yl) -3-fluorophenyl) methacrylamide



Step 1 1- (4- (4-amino-7- (methyl-*d*₃) -7*H*-pyrrolo [2,3-*d*] pyrimidin-5-yl) phenyl) imino) tetrahydro-1*H*-1 λ^6 -thiophene-1-oxide **83a**

To a reaction flask, compound **82c** (18.9 g, 62 mmol), compound **24b** (16.8 g, 52 mmol), Pd(PPh₃)₄ (6.0 g, 5.2 mmol), K₃PO₄ (33 g, 156 mmol), 1,4-dioxane (300 mL), and H₂O (30 mL) were added, after replaced with argon gas three times, the reaction solution was heated up to 70 °C and stirred for 16 h. Dioxane was removed by distilled under reduced pressure, water (50 mL) and DCM (200 mL) were added, and it was stirred, filtered through diatomaceous earth, extracted,

and concentrated under reduced pressure to obtain crude product. The crude product was purified by column chromatography (MeOH/DCM=1/20) to obtain compound **83a** (9.3 g), light yellow solid.

¹H NMR (400 MHz, CDCl₃) δ 8.33 (s, 1H), 7.34 (d, *J* = 8.4 Hz, 2H), 7.14 (*d*, *J* = 8.4 Hz, 2H), 6.88 (s, 1H), 5.12 (s, 2H), 3.50-3.40 (m, 2H), 3.25-3.18 (m, 2H), 2.40-2.20 (m, 4H).

Step 2 1- (4- (4-amino-6-bromo-7- (methyl-*d*₃) -7*H*-pyrrolo [2,3-*d*] pyrimidin-5-yl) phenyl) imino) tetrahydro-1*H*-1 λ⁶-thiophene-1-oxide **83b**

Compound **83a** (7.0 g, 20 mmol) was dissolved in DMF (30 mL), and a solution of NBS (3.8 g, 21 mmol) in DMF (30 mL) was added dropwise at 0 °C. The reaction solution was stirred at 0 °C for 1 h, and then quenched with saturated Na₂S₂O₃ aqueous solution (30 mL). Water (20 mL) was added, and it was stirred for half an hour to precipitate a solid, filtered, washed with water, washed with ethyl acetate, and dried to obtain compound **83b** (5.8 g), yellow solid.

¹H NMR (400 MHz, CDCl₃) δ 8.29 (s, 1H), 7.33 (d, *J* = 8.4 Hz, 2H), 7.16 (*d*, *J* = 8.4 Hz, 2H), 4.98 (s, 2H), 3.52-3.43 (m, 2H), 3.28-3.20 (m, 2H), 2.42-2.22 (m, 4H).

Step 3 1- (4- (4-amino-6- (4-amino-2-fluorophenyl) -7- (methyl-*d*₃) -7*H*-pyrrolo [2,3-*d*] pyrimidin-5-yl) phenyl) imino) tetrahydro-1*H*-1 λ⁶-thiophene-1-oxide **83d**

To a reaction flask, compound **83b** (5.0 g, 12 mmol), **83c** (4.27 g, 18 mmol), Pd(PPh₃)₄ (1.39 g, 1.2 mmol), K₃PO₄ (7.6 g, 36 mmol), dioxane (60 mL), and water (6 mL) were added, after replaced with argon gas three times, the reaction solution was heated up to 90 °C and stirred for 16 h, and then Dichloromethane (40 mL) and H₂O (40 mL) were added, stirred for half an hour, filtered, washed with water, and washed with dichloromethane to obtain compound **83d** (4.0 g), gray solid.

¹H NMR (400 MHz, CDCl₃) δ 8.32 (s, 1H), 7.13 (d, *J* = 8.4 Hz, 2H), 6.98 (d, *J* = 8.4 Hz, 2H), 6.85 (t, *J* = 8.2 Hz, 1H), 6.42 (dd, *J* = 11.4, 2.4 Hz, 1H), 6.35 (dd, *J* = 8.2, 2.4 Hz, 1H), 5.01 (s, 2H), 3.89 (s, 2H), 3.46-3.36 (m, 2H), 3.24-3.14 (m, 2H), 2.40-2.18 (m, 4H).

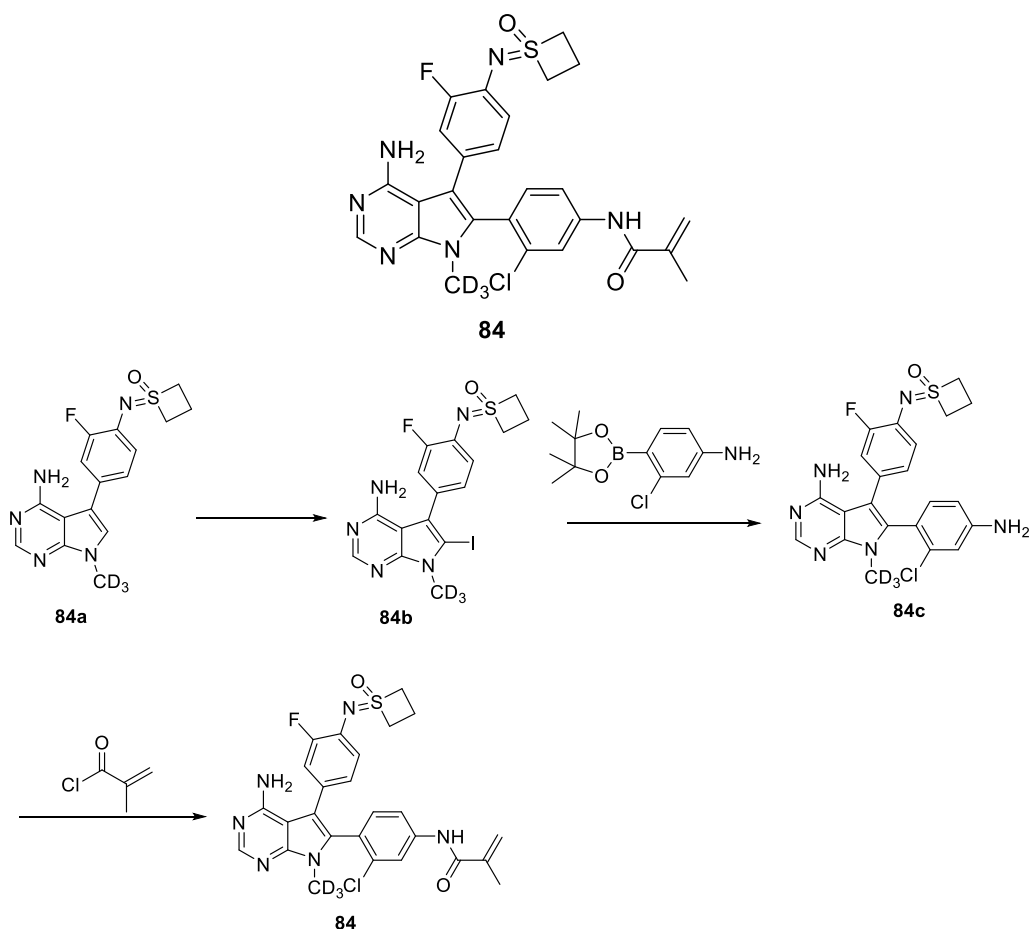
Step 4 *N*- (4- (4-amino-7- (methyl-*d*₃) -5- (4- (1-oxotetrahydro-1 λ⁶- thiophene-1-imino) phenyl) -7*H*-pyrrolo [2,3-*d*] pyrimidin-6-yl) -3-fluorophenyl) methacrylamide **83**

Compound **83d** (4.2 g, 9.3 mmol), pyridine (5 mL), and DMF (20 mL) were added to a reaction flask, a solution of methacryloyl chloride (1.36 g, 13 mmol) in DMF (20 mL) was added dropwise at 0 °C, and it was heated up to room temperature to react for 1 h. The reaction was quenched with added water, extracted with ethyl acetate (200 mL × 3), washed with saturated saline solution, and concentrated under reduced pressure to obtain a crude product. The crude product was purified by column chromatography (MeOH/DCM=1/20) to obtain compound **83** (2.9 g), white solid.

MS (ESI) *m/z* 522 [M + H]⁺.

¹H NMR (400 MHz, CDCl₃) δ 8.36 (s, 1H), 7.70 (dd, *J* = 11.8, 1.8 Hz, 1H), 7.57 (s, 1H), 7.17-6.93 (m, 6H), 5.80 (s, 1H), 5.51 (d, *J* = 1.6 Hz, 1H), 5.00 (s, 2H), 3.49-3.35 (m, 2H), 3.24-3.14 (m, 2H), 2.40-2.19 (m, 4H), 2.07 (s, 3H).

Example 84 *N*- (4- (4-amino-5- (3-fluoro-4- (1-oxo-1 λ^6 -thietan-1-imino) phenyl) -7- (methyl-*d*₃) -7*H*-pyrrolo [2,3-*d*] pyrimidin-6-yl) -3-chlorophenyl) methacrylamide



Step 1 1- (4- (4-amino-6-iodo-7- (methyl-*d*₃) -7*H*-pyrrolo [2,3-*d*] pyrimidin-5-yl) -2-fluorophenyl) imino) -1 λ^6 -thietane-1-oxide **84b**

Compound **84a** (216 mg, 0.6 mmol) was dissolved in dichloromethane (6 mL), trifluoroacetic acid (0.14 mL, 1.8 mmol) was added at 0 °C, and NIS (168 mg, 0.72 mmol) was added in batches. The reaction solution was heated up to room temperature and stirred for 1.5 h, and then quenched with added Na₂S₂O₃ (sat. 3 mL), extracted with water (10 mL), dichloromethane, and concentrated under reduced pressure to obtain a crude product. The crude product was purified by column chromatography (MeOH/DCM=1/20) to obtain compound **84b** (light yellow solid, 183 mg, 64%).

¹H NMR (400 MHz, CDCl₃) δ 8.24 (s, 1H), 7.21-7.06 (m, 3H), 5.11 (s, 2H), 4.41-4.26 (m, 4H), 2.43-2.32 (m, 2H).

Step 2 1- (4- (4-amino-6- (4-amino-2-chlorophenyl) -7- (methyl-*d*₃) -7*H*-pyrrolo [2,3-*d*] pyrimidin-5-yl) -2-fluorophenyl) imino) -1 λ^6 -thietane-1-oxide **84c**

To a reaction flask, compound **84b** (183 mg, 0.4 mmol), 3-chloro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) aniline (150 mg, 0.6 mmol), Pd(PPh₃)₄ (45 mg, 0.04 mmol), K₃PO₄ (0.25 g, 1.2 mmol), dioxane (4 mL), and water (0.4 mL) were added, after replaced with argon gas three times, the reaction solution was heated up to 80 °C and stirred for 16 h, and then extracted

with dichloromethane (40 mL) and H₂O (10 mL). The crude product was concentrated under reduced pressure and purified by column chromatography (MeOH/DCM=1/20) to obtain compound **84c** (light yellow solid, 106 mg, 58%).

¹H NMR (400 MHz, CDCl₃) δ 8.36 (s, 1H), 7.05-6.88 (m, 4H), 6.77 (d, *J* = 2.4 Hz, 1H), 6.50 (dd, *J* = 8.3, 2.4 Hz, 1H), 5.02 (s, 2H), 4.38-4.20 (m, 4H), 3.86 (s, 2H), 2.41-2.28 (m, 2H).

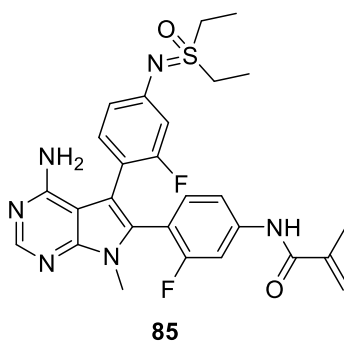
Step 3 N- (4- (4-amino-5- (3-fluoro-4- (1-oxo-1 λ⁶-thietan-1-imino) phenyl) -7- (methyl-d₃) -7H-pyrrolo [2,3-d] pyrimidin-6-yl) -3-chlorophenyl) methacrylamide **84**

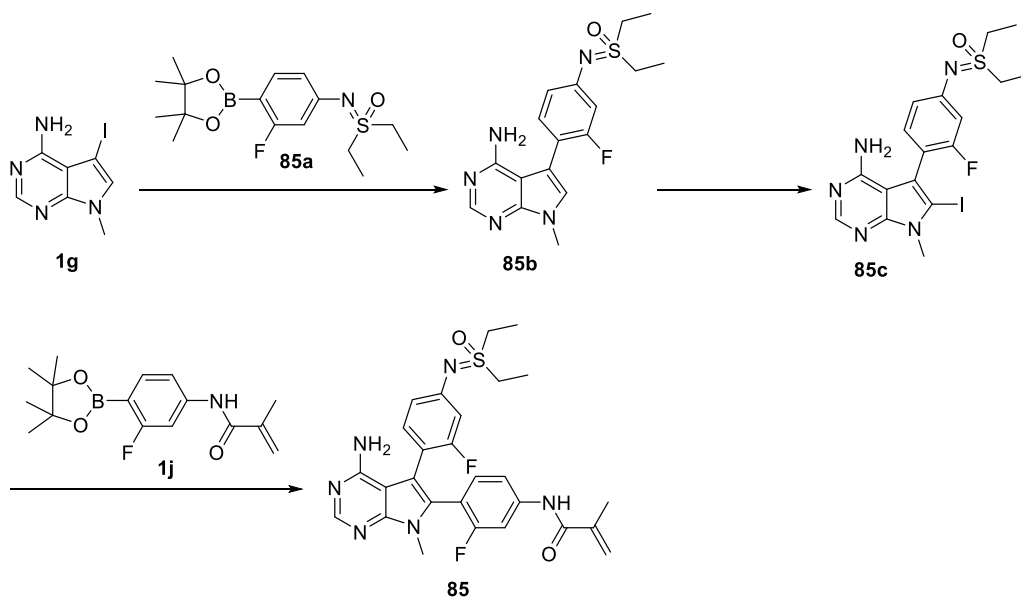
Compound **84c** (50 mg, 0.1 mmol), pyridine (0.5 mL), and DMF (2 mL) were added to a reaction flask, a solution of methacryloyl chloride (14 mg, 0.13 mmol) in DMF (2 mL) was added dropwise at 0 °C, and heated up to room temperature to react for 1 h. The reaction was quenched with added water, extracted with ethyl acetate (100 mL × 3), washed with saturated saline solution, and concentrated under reduced pressure to obtain a crude product. The crude product was purified by column chromatography (MeOH/DCM=1/20) to obtain compound **84** (38 mg), white solid.

MS (ESI) *m/z* 542 [M + H]⁺.

¹H NMR (400 MHz, CDCl₃) δ 8.35 (s, 1H), 7.89 (d, *J* = 2.2 Hz, 1H), 7.73 (s, 1H), 7.37 (dd, *J* = 8.4, 2.2 Hz, 1H), 7.11 (d, *J* = 8.4 Hz, 1H), 6.99 (t, *J* = 8.4 Hz, 1H), 6.92 (d, *J* = 10.0 Hz, 2H), 5.80 (s, 1H), 5.50 (d, *J* = 1.6 Hz, 1H), 5.13 (s, 2H), 4.34-4.20 (m, 4H), 2.37-2.27 (m, 2H).

Example 85 N- (4- (4-amino-5- (4- (diethyl (oxo) - λ⁶- sulfaneylidene) amino) -2-fluorophenyl) -7-methyl-7H-pyrrolo [2,3-d] pyrimidin-6-yl) -3-fluorophenyl) methacrylamide





Step 1 1 (4- (4-amino-7-methyl-7H-pyrrolo [2,3-d] pyrimidin-5-yl) -3-fluorophenyl imino) diethyl - λ⁶-sulfone 85b

To the reaction flask, compound **85a** (500 mg, 1.54 mmol), 1,4-dioxane (5 mL), H₂O (1 mL), compound **1g** (383 mg, 1.40 mmol), potassium phosphate (890 mg, 4.2 mmol), and Pd(PPh₃)₄ (162 mg, 0.14 mmol) were added in sequence, after replaced with nitrogen gas three times, heated up to 90 °C and reacted for 3 h. New spots were observed in TLC monitoring, and the reaction solution was diluted with ethyl acetate and H₂O. After filtrated through diatomaceous earth, it was extracted with ethyl acetate, the organic phase was washed with saturated saline solution, dried over anhydrous sodium sulfate, concentrated under reduced pressure, and purified by column chromatography (DCM/MeOH=10/1) to obtain compound **85b** (262 mg), yellow solid.

MS (ESI) *m/z* 362 [M + H]⁺

Step 2 4- (4-amino-6-iodo-7-methyl-7H-pyrrolo [2,3-d] pyrimidin-5-yl) -3- fluorophenyl imino) diethyl - λ⁶-sulfone 85c

Compound **85b** (262 mg, 0.72 mmol) was dissolved in anhydrous DCM (3 mL), TFA (246 mg, 2.16 mmol) and NIS (163 mg, 0.72 mmol) were added at 0 °C for 1 h, and then the reaction was quenched with added sodium thiosulfate solution, extracted with saturated sodium bicarbonate aqueous solution and dichloromethane, the organic layers were combined, and washed with saturated salt water once. The organic phase was dried over anhydrous sodium sulfate, concentrated under reduced pressure, and purified by column chromatography (PE/EA=1:1) to obtain compound **85c** (176 mg), yellow solid.

MS (ESI) *m/z* 488 [M + H]⁺

Step 3 N- (4- (4-amino-5- (4- (diethyl (oxo) - λ⁶- sulfaneylidene) amino) -2-fluorophenyl) -7- methyl-7H-pyrrolo [2,3-d] pyrimidin-6-yl) -3-fluorophenyl) methacrylamide 85

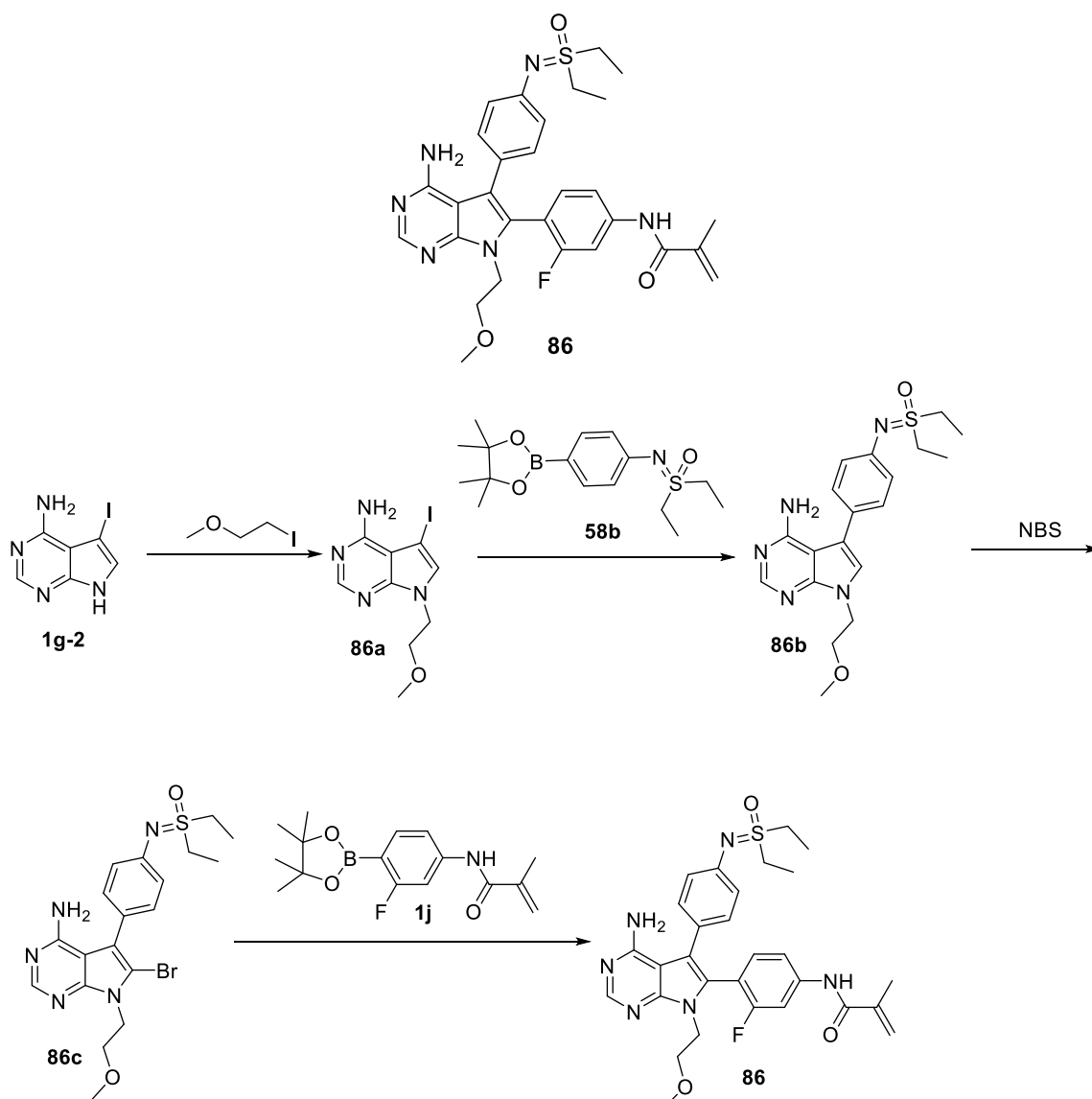
To a reaction flask, compound **85c** (176 mg, 0.36 mmol), 1,4-dioxane (4 mL), water (1 mL), compound **1j** (132 mg, 0.433 mmol), Pd(PPh₃)₄ (42 mg, 0.036 mmol), and potassium phosphate (82.8 mg, 0.39 mmol) were added, after replaced with nitrogen gas three times, the reaction was

carried out at 90 °C for 3 h. The reaction solution was diluted with added Ethyl acetate (10 mL) and H₂O (10 mL), filtered through diatomaceous earth, and extracted with ethyl acetate, and the organic phase was washed with saturated saline solution, dried over anhydrous sodium sulfate, concentrated under reduced pressure, and purified by column chromatography (DCM/MeOH=10/1) to obtain compound **85** (57.5 mg), white solid.

MS (ESI) m/z 539.2 [M + H]⁺.

¹H NMR (400 MHz, MeOD-d₄) δ 8.17 (s, 1H), 7.64 (dd, J = 12.2, 1.9 Hz, 1H), 7.42 – 7.34 (m, 2H), 7.29 – 7.19 (m, 3H), 5.83 (s, 1H), 5.56 (s, 1H), 3.84 (s, 3H), 3.23 (m, 4H), 2.05 (s, 3H), 1.29 (t, J = 7.4 Hz, 6H).

Example 86 *N*- (4- (4-amino-5- (4- (diethyl (oxo) - λ^6 - sulfaneylidene) amino) phenyl) -7- (2-methoxyethyl) -7H-pyrrolo [2,3-*d*] pyrimidin-6-yl) -3-fluorophenyl) methacrylamide



Step 1 5-iodo-7- (2-methoxyethyl) -7H-pyrrolo [2,3-*d*] pyrimidin-4-amine **86a**

To a reaction flask, compound **1g-2** (500 mg, 1.92 mmol), DMF (5 mL), cesium carbonate (1.25 g, 3.84 mmol) and 1-iodo-2-methoxyethane (429 mg, 2.31 mmol) were added sequentially, the reaction was carried out at room temperature for 2 h. H₂O (50 mL) was added and extracted with ethyl acetate, and the organic phase was washed with saturated saline solution, dried over anhydrous sodium sulfate, concentrated under reduced pressure, and purified by column chromatography (DCM/MeOH=10/1) to obtain compound **86a** (464 mg).

MS (ESI) m/z 319 [M + H]⁺

Step 2 (4- (4-amino-7- (2-methoxyethyl) -7H-pyrrolo [2,3-*d*] pyrimidin-5-yl) phenyl) imino) diethyl - λ^6 -sulfone **86b**

To a reaction flask, compound **86a** (440 mg, 1.38 mmol), 1,4-dioxane (5 mL), water (1 mL), compound **58b** (537 mg, 1.66 mmol), Pd(PPh₃)₄ (160 mg, 0.138 mmol), and potassium phosphate (292 mg, 1.38 mmol) were added in sequence, after replaced with nitrogen gas three times, the reaction was carried out at 90 °C for 2 h. After the reaction was completed, it was cooled down to room temperature, and the reaction solution was diluted with added ethyl acetate and H₂O. After filtrated through diatomaceous earth to extract with EA, and the organic phase was washed with saturated saline solution, dried over anhydrous sodium sulfate, concentrated under reduced pressure, and purified by column chromatography (DCM/MeOH=10/1) to obtain compound **86b** (140 mg), white solid.

MS (ESI) m/z 388 [M + H]⁺

Step 3 (4- (4-amino-6-bromo-7- (2-methoxyethyl) -7H-pyrrolo [2,3-*d*] pyrimidin -5-yl) phenyl) imino) diethyl-6-sulfone **86c**

Compound **86b** (92 mg, 0.24 mmol) was dissolved in anhydrous DMF (4 mL), NBS (44 mg, 0.25 mmol) was added at 0 °C, and the reaction was carried out at 0 °C for 1 h, and then the reaction was quenched with added sodium thiosulfate solution, extracted with added H₂O (40 mL) and ethyl acetate 3 times, and the organic phase was dried over anhydrous sodium sulfate, concentrated under reduced pressure, and purified by column chromatography (DCM/MEOH=10/1) to obtain compound **86c** (87 mg), yellow oil.

MS (ESI) m/z 467 [M + H]⁺

Step 4 *N*- (4- (4-amino-5- (4- (diethyl (oxo) - λ^6 - sulfaneylidene) amino) phenyl) -7- (2-methoxyethyl) -7H-pyrrolo [2,3-*d*] pyrimidin-6-yl) -3-fluorophenyl) methacrylamide **86**

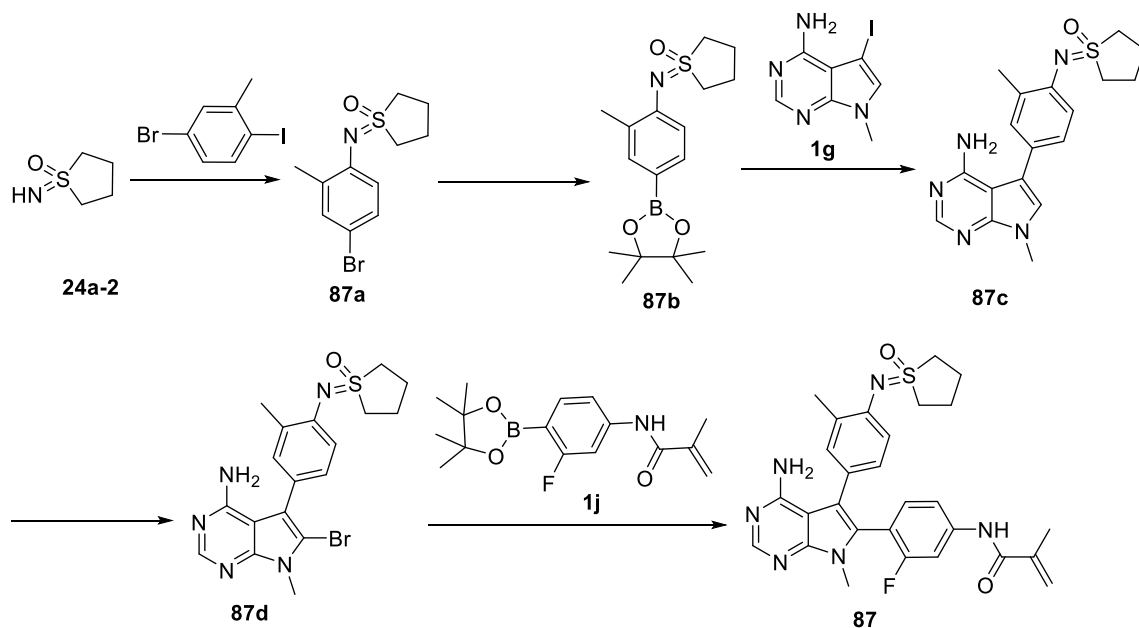
To a reaction flask, compound **86c** (87 mg, 0.19 mmol), 1,4-dioxane (2.4 mL), water (0.6 mL), compound **1j** (68 mg, 0.22 mmol), potassium phosphate (119 mg, 0.56 mmol), and Pd(PPh₃)₄ (22 mg, 0.019 mmol) were added in sequence, after replaced with nitrogen gas three times, the reaction was carried out at 90 °C for 3 h. After the reaction was completed, it was cooled down to room temperature, and the reaction solution was diluted with ethyl acetate and H₂O. After filtered through diatomaceous earth, it was extracted with ethyl acetate, and the organic phase was washed with saturated saline solution, dried over anhydrous sodium sulfate, concentrated under reduced pressure, and purified by column chromatography (DCM/MeOH=10/1) to obtain compound **86** (9.1 mg), white solid.

MS (ESI) m/z 565.38 [M + H]⁺.

¹H NMR (400 MHz, MeOD-d₄) δ 8.19 (s, 1H), 7.69 (dd, *J* = 12.0, 2.0 Hz, 1H), 7.39 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.25 (t, *J* = 8.3 Hz, 1H), 7.14 (d, *J* = 8.2 Hz, 2H), 7.05 (d, *J* = 8.6 Hz, 2H), 5.83 (s, 1H), 5.57 (s, 1H), 4.38 (s, 1H), 4.21 (s, 1H), 3.59 (s, 1H), 3.50 (s, 1H), 3.29 (d, *J* = 7.4 Hz, 4H), 3.16 (d, *J* = 8.9 Hz, 3H), 2.04 (s, 3H), 1.46 – 1.29 (m, 6H).

5

Example 87 *N*-(4-(4-amino-7-methyl-5-(3-methyl-4-((1-tetrahydro-1 λ ⁶-thiophene-1-ylidene) amino) phenyl) -7*H*-pyrrolo [2,3-*d*] pyrimidin-6-yl) -3-fluorophenyl) methacrylamide

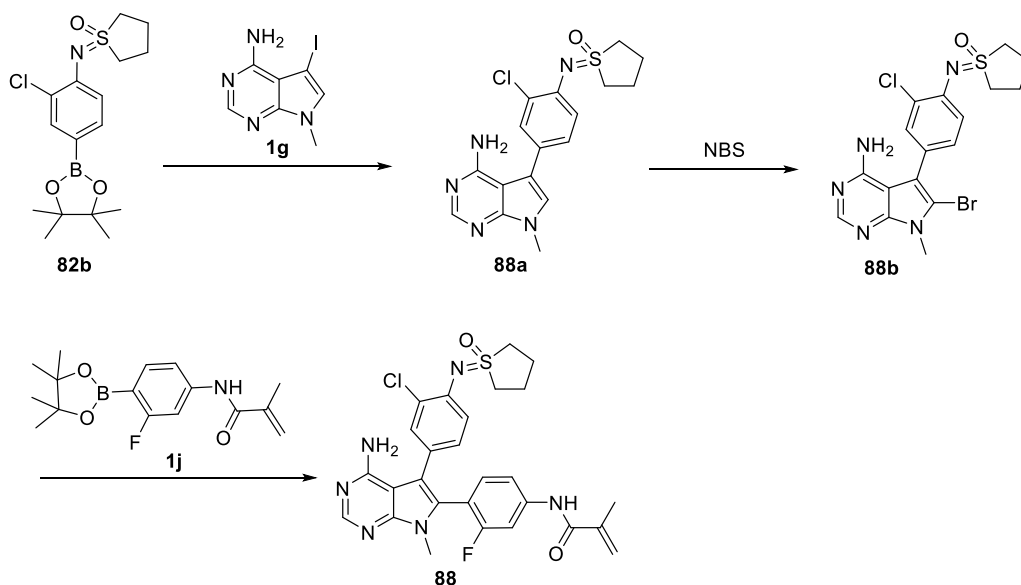


10 Compound **87** was synthesized with reference to the similar synthetic route and steps of compound **82**, wherein, 4-bromo-2-chloriodobenzene was replaced with 4-bromo-1-iodo-2-methylbenzene.

MS (ESI) *m/z* 533.35[M + H]⁺.

15 ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.03 (s, 1H), 8.11 (s, 1H), 7.69 (dd, *J* = 12.4, 1.9 Hz, 1H), 7.41 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.20 (t, *J* = 8.4 Hz, 1H), 7.02 – 6.76 (m, 3H), 5.75 (s, 1H), 5.50 (s, 1H), 3.44 (s, 3H), 3.18 (m, 4H), 2.18 – 1.99 (m, 7H), 1.88 (s, 3H).

20 **Example 88** *N*-(4-(4-amino-5-(3-chloro-4-((1-oxide tetrahydro-1 λ ⁶-thiophene-1-ylidene) amino) phenyl) -7-methyl-7*H*-pyrrolo [2,3-*d*] pyrimidin-6-yl) -3-fluorophenyl) methacrylamide

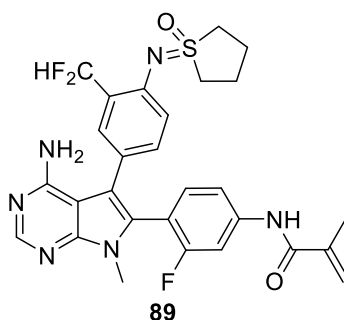


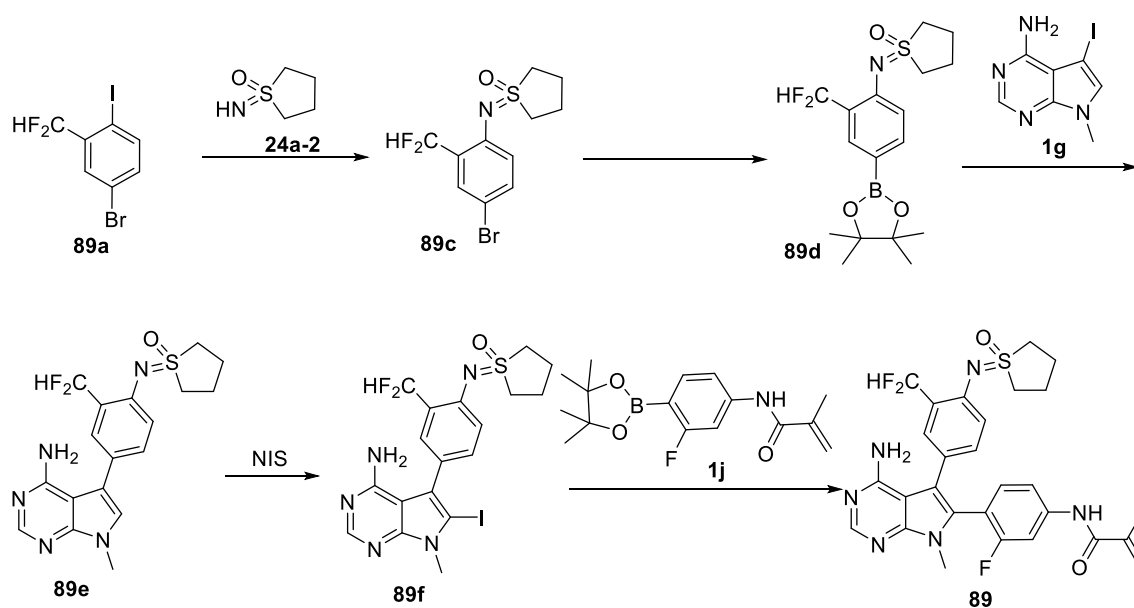
Compound **88** was synthesized with reference to the similar synthetic route and steps of compound **87**, wherein, compound **87b** was replaced with compound **82b**.

MS (ESI) m/z 553.3 $[M + H]^+$.

- 5 ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 10.12 (s, 1H), 8.19 (s, 1H), 7.77 (dd, $J = 12.4, 1.8$ Hz, 1H), 7.50 (dd, $J = 8.5, 1.9$ Hz, 1H), 7.29 (t, $J = 8.4$ Hz, 1H), 7.16 (d, $J = 1.9$ Hz, 1H), 7.07 (d, $J = 8.2$ Hz, 1H), 7.02 (dd, $J = 8.2, 1.9$ Hz, 1H), 5.83 (s, 1H), 5.58 (s, 1H), 3.51 (s, 3H), 3.28 (m, 4H), 2.17 (m, 4H), 1.95 (s, 3H).

- 10 **Example 89** *N*-(4-(4-amino-5-(3-(difluoromethyl)-4-((1-tetrahydro-1 λ^6 -thiophene-1-ylidene)amino)phenyl)-7-methyl-7H-pyrrolo[2,3-*d*]pyrimidin-6-yl)-3-fluorophenyl) methacrylamide



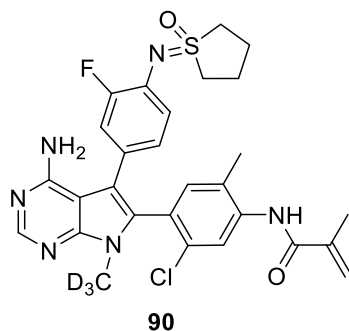


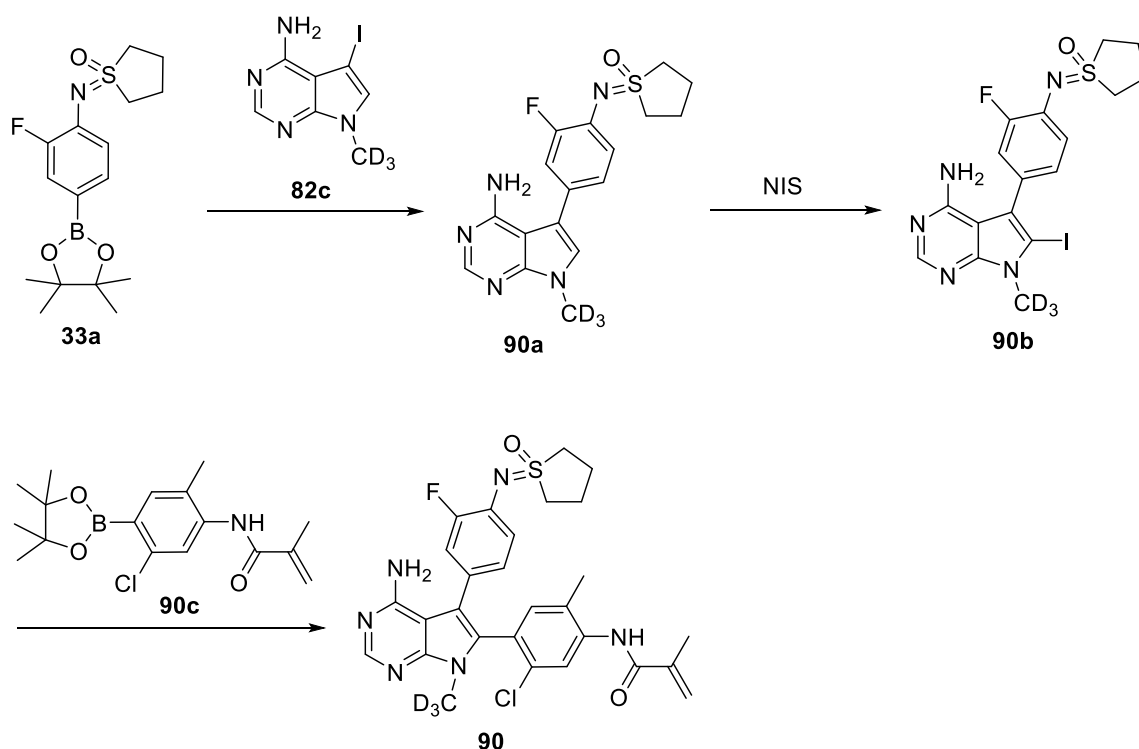
Compound **89** was synthesized with reference to the similar synthetic route and steps of compound **77**, wherein, 1-bromo-2,5-difluoro-4-iodobenzene was replaced with compound **89a**. Compound **89a** was synthesized with reference to WO 2023/001794A1.

5 MS (ESI) m/z 569.15 $[M + H]^+$.

^1H NMR (400 MHz, MeOD- d_4) δ 8.19 (s, 1H), 7.72 (dd, $J = 12.1, 1.8$ Hz, 1H), 7.44 – 7.34 (m, 2H), 7.24 – 6.83 (m, 4H), 5.81 (s, 1H), 5.55 (s, 1H), 3.62 (s, 3H), 3.46 – 3.39 (m, 2H), 3.27 – 3.19 (m, 2H), 2.27 (m, 4H), 2.02 (s, 3H).

10 **Example 90** *N*- (4- (4-amino-5- (3-fluoro-4- ((1-tetrahydro-1 λ^6 -thiophene-1-ylidene) amino) phenyl) -7- (methyl- d_3) -7*H*-pyrrolo [2,3-*d*] pyrimidin-6-yl) -5-chloro-2-methylphenyl) methacrylamide



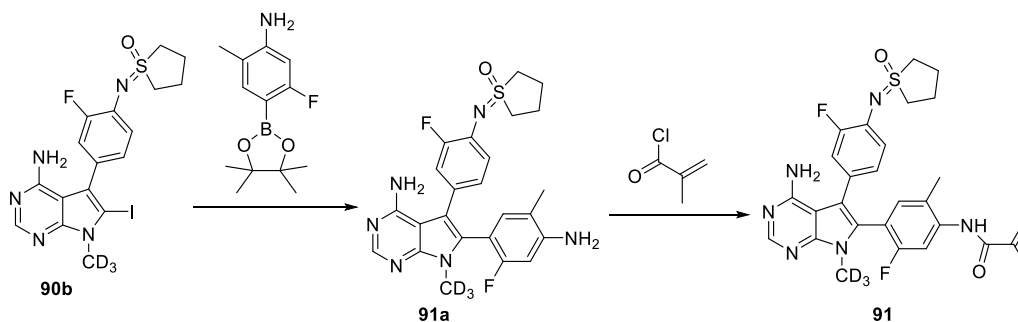


Compound **90** was synthesized with reference to the similar synthetic route and steps of compound **85**, wherein, compound **85a** was replaced with compound **33a**, and compound **1g** was replaced with compound **82c** in step 1, and compound **1j** was replaced with compound **90c** in step 3.

MS (ESI) m/z 570.0 $[M + H]^+$.

^1H NMR (400 MHz, DMSO- d_6) δ 9.39 (s, 1H), 8.20 (s, 1H), 7.65 (s, 1H), 7.32 (s, 1H), 7.11 – 6.81 (m, 3H), 5.88 (s, 1H), 5.55 (s, 1H), 3.45 – 3.36 (m, 2H), 3.27 (dd, $J = 13.2, 6.6$ Hz, 2H), 2.23 – 2.07 (m, 7H), 1.97 (s, 3H).

Example 91 *N*-(4-(4-amino-5-(3-fluoro-4-((1-(tetrahydro-1 λ^6 -thiophene-1-ylidene)amino)phenyl)-7-(methyl- d_3)-7H-pyrrolo [2,3-*d*] pyrimidin-6-yl)-5-fluoro-2-methylphenyl) methacrylamide



Step 1 1-(4-(4-amino-6-(4-amino-2-fluoro-5-methylphenyl)-7-(methyl- d_3)-7H-pyrrolo [2,3-*d*] pyrimidin-5-yl)-2-fluorophenyl) imino) tetrahydro-1H-1 λ^6 -thiophene-1-oxide **91a**

Compound **90b** (210 mg, 0.43 mmol), 5-fluoro-2-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (160 mg, 0.63 mmol), Pd(PPh₃)₄ (49 mg, 0.04 mmol), and potassium phosphate (270 mg, 1.29 mmol) were dissolved in 1,4-dioxane (8 mL) and water (2 mL), after replaced with nitrogen gas three times, the reaction was refluxed at 90 °C for 12 h. The reaction solution was cooled down to room temperature, filtered through diatomaceous earth, concentrated under reduced pressure to remove the solvent, extracted with DCM/H₂O three times, and the organic layers were combined, washed with saturated saline solution, dried over anhydrous sodium sulfate, concentrated under reduced pressure, purified by column chromatography (DCM/MeOH=40/1) to obtain compound **91a** (100 mg), light yellow solid.

MS (ESI) *m/z* 485.90 [M + H]⁺.

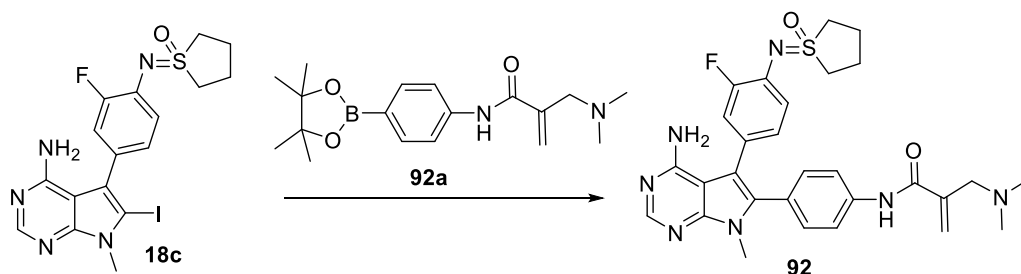
Step 2 *N*- (4- (4-amino-5- (3-fluoro-4- ((1-tetrahydro-1λ⁶-thiophene-1-ylidene) amino) phenyl) -7- (methyl-*d*₃) -7*H*-pyrrolo [2,3-*d*] pyrimidin-6-yl) -5-fluoro-2- methylphenyl) methacrylamide **91**

Compound **91a** (44 mg, 0.09 mmol) was dissolved with anhydrous DMF (10 mL), and pyridine (0.5 mL) was added dropwise. Methacryloyl chloride (11 mg, 0.11 mmol) was dissolved in anhydrous DMF (1 mL), and the solution of methacryloyl chloride in DMF was added dropwise to the DMF solution of compound **91a** at 0 °C, and the reaction was carried out for 1 h, quenched with water, extracted with DCM/H₂O three times, and the organic layers were combined, washed with saturated saline solution, dried over anhydrous sodium sulfate, concentrated under reduced pressure, and purified by reverse column chromatography to obtain compound **91** (13 mg), white solid.

MS (ESI) *m/z* 553.88 [M + H]⁺.

¹H NMR (400 MHz, CDCl₃) δ 8.39 (s, 1H), 8.15 (d, *J* = 11.6 Hz, 1H), 7.48 (s, 1H), 7.13 (t, *J* = 8.5 Hz, 1H), 7.01 – 6.86 (m, 3H), 5.88 (s, 1H), 5.55 (d, *J* = 1.8 Hz, 1H), 5.06 (s, 2H), 3.46 (dt, *J* = 13.3, 6.8 Hz, 2H), 3.25 (dt, *J* = 13.0, 6.6 Hz, 2H), 2.34 (q, *J* = 7.7 Hz, 4H), 2.20 (s, 3H), 2.12 (s, 3H).

Example 92 *N*- (4- (4-amino-5- (3-fluoro-4- ((1-tetrahydro-1λ⁶-thiophene-1-ylidene) amino) phenyl) -7-methyl-7*H*-pyrrolo [2,3-*d*] pyrimidin-6-yl) phenyl) -2- (dimethylamino) methyl acrylamide

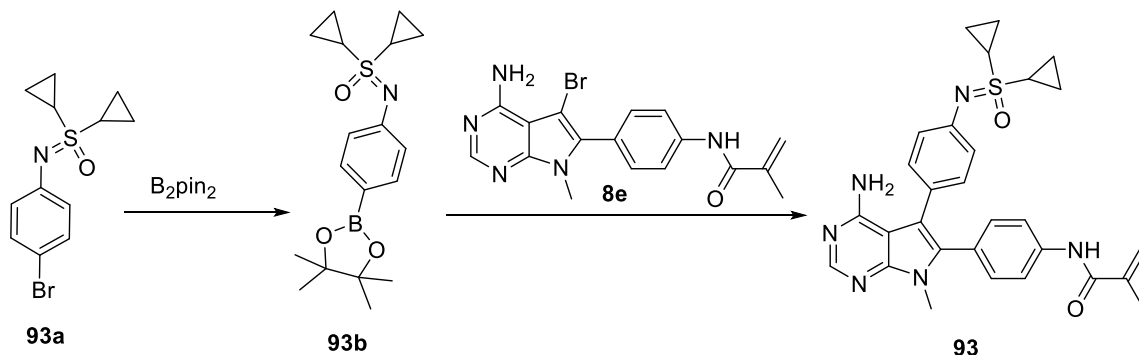


Compound **92** was synthesized with reference to the similar synthetic route and steps of compound **12**, wherein, compound **12a** was replaced with compound **18c**, compound **12b** was replaced with compound **92a**.

MS (ESI) *m/z* 562 [M + H]⁺.

¹H NMR (400 MHz, DMSO-*d*₆) δ 11.25 (s, 1H), 8.19 (s, 1H), 7.67 (d, *J*=8.0 Hz, 2H), 7.32 (d, *J*=8.0 Hz, 2H), 7.05 (t, *J*=12.0 Hz, 1H), 6.99-6.91 (m, 2H), 6.12 (s, 2H), 6.03 (s, 1H), 5.59 (s, 1H), 4.22 (s, 2H), 3.41-3.23 (m, 4H), 2.51-2.47 (m, 4H), 2.25 (s, 3H), 0.88 (s, 6H).

5 **Example 93** *N*- (4- (4-amino-5- (4- ((dicyclopropyl (oxo)-λ⁶- sulfaneylidene) amino) phenyl)-7- methyl-7*H*-pyrrolo [2,3-*d*] pyrimidin-6-yl) phenyl) methacrylamide

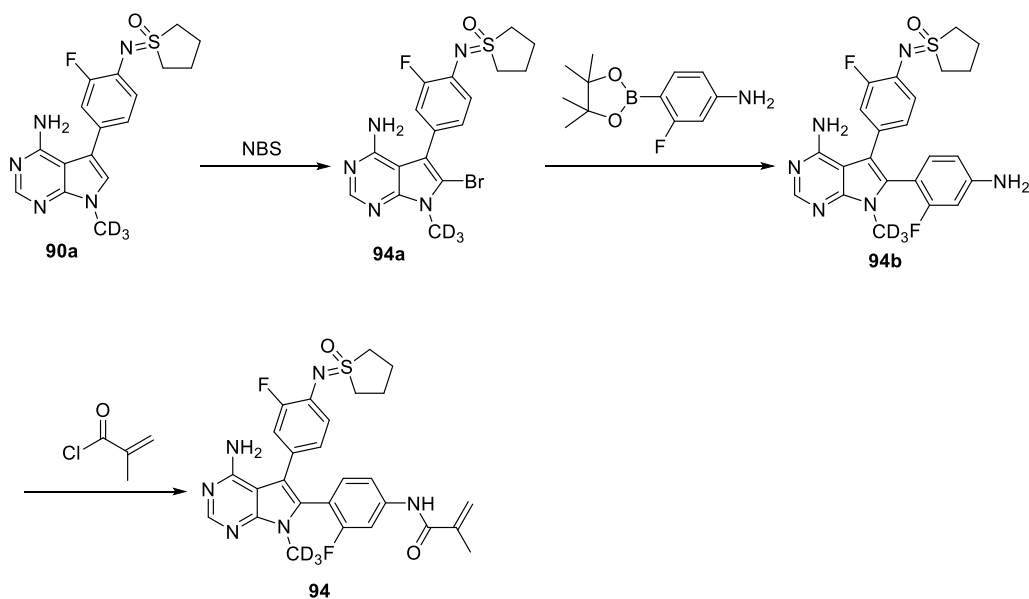


Compound **93** was synthesized with reference to the similar synthetic route and steps of compound **11**, wherein, compound **11c** was replaced with compound **93a**.

10 MS (ESI) *m/z* 527.2 [M + H]⁺.

¹H NMR (400 MHz, CDCl₃) δ 8.34 (s, 1H), 7.61 - 7.50 (m, 3H), 7.23 (d, *J*=8.46, 2H), 7.10-6.94 (m, 2H), 5.81 (s, 1H), 5.50 (s, 1H), 5.17 (br. s., 2H), 3.77 - 3.69 (s, 3H), 2.57 - 2.45 (m, 2H), 2.08 (s, 3H), 1.39 - 1.16 (m, 4H), 1.11 - 0.97 (m, 4H)

15 **Example 94** *N*- (4-amino-5- (3-fluoro-4- (1-oxotetrahydro-1 λ⁶-thiophene-1-ylidene) amino) phenyl) -7- (methyl-*d*₃) -7*H*-pyrrolo [2,3-*d*] pyrimidin-6-yl) -3-fluorophenyl) methacrylamide



20 **Step 1** 1- (4- (4-amino-6-bromo-7- (methyl-*d*₃) -7*H*-pyrrolo [2,3-*d*] pyrimidin-5-yl) -2-fluorophenyl) imino) tetrahydro-1*H*-1 λ⁶-thiophene-1-oxide **94a**

Compound **90a** (2.1 g, 5.79 mmol) was dissolved with anhydrous DMF (10 mL), NBS (1.08 g, 6.08 mmol) was added at 0 °C, and the reaction was carried out for 2 h, and then quenched with added sodium thiosulfate solution, and extracted with dichloromethane, and the organic layers were combined, and washed with saturated salt water once. The organic phase was dried over anhydrous sodium sulfate, concentrated under reduced pressure, and purified by column chromatography (DCM/MeOH=30/1) to obtain compound **94a** (1.4 g), yellow solid.

MS (ESI) m/z 441 $[M + H]^+$.

Step 2 1- (4- (4-amino-6- (4-amino-2-fluorophenyl) -7- (methyl- d_3) -7H-pyrrolo [2,3-*d*] pyrimidin-5-yl) -2-fluorophenyl) imino) tetrahydro-1H-1 λ^6 -thiophene-1-oxide 94b

Compound **94a** (1.4 g, 3.17 mmol), 3-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) aniline (1.13 g, 4.76 mmol), Pd(PPh₃)₄ (366 mg, 0.32 mmol), and potassium phosphate (2.02 g, 9.52 mmol) were dissolved in 1,4-dioxane (20 mL) and water (2 mL), after replaced with nitrogen three times, the reaction was refluxed at 100 °C for 12 h. The reaction solution was cooled down to room temperature, filtered through diatomaceous earth, concentrated under reduced pressure to remove the solvent, extracted with DCM/H₂O three times, and the organic layers were combined, washed with saturated saline solution and dried over anhydrous sodium sulfate, concentrated under reduced pressure, purified by column chromatography (DCM/MeOH=40/1) to obtain compound **94b** (1.33 mg), white solid.

MS (ESI) m/z 472 $[M + H]^+$.

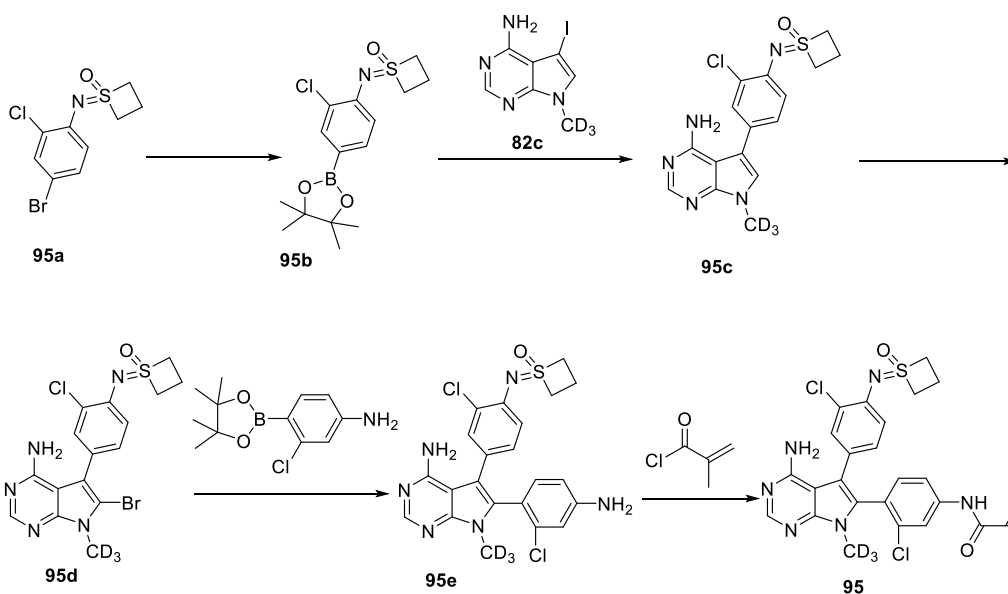
Step 3 N- (4- (4-amino-5- (3-fluoro-4- ((1-tetrahydro-1 λ^6 -thiophene-1-ylidene) amino) phenyl) -7- (methyl- d_3) -7H-pyrrolo [2,3-*d*] pyrimidin-6-yl) -3-fluorophenyl) methacrylamide 94

Compound **94b** (610 mg, 1.29 mmol) was dissolved with anhydrous DMF (10 mL), methacryloyl chloride (162 mg, 4.76 mmol) was added at 0 °C, the reaction was carried out for 1 h, and then quenched with water, extracted with dichloromethane, and the organic layers were combined, and washed with saturated salt once. The organic phase was dried over anhydrous sodium sulfate, concentrated under reduced pressure, and purified by column chromatography (DCM/MeOH=20/1) to obtain compound **94** (140 mg), white solid.

MS (ESI) m/z 540.2 $[M + H]^+$.

¹H NMR (400 MHz, CDCl₃) δ 8.30 (s, 1H), 7.65 (dd, J = 11.6, 2.1 Hz, 1H), 7.54 (s, 1H), 7.04 (ddd, J = 8.6, 5.4, 3.3 Hz, 2H), 6.98 (t, J = 8.0 Hz, 1H), 6.86 (d, J = 9.7 Hz, 2H), 5.74 (s, 1H), 5.45 (d, J = 1.6 Hz, 1H), 4.96 (s, 2H), 3.36 (d, J = 6.3 Hz, 2H), 3.18 (s, 2H), 2.24 (d, J = 8.1 Hz, 4H), 2.00 (t, J = 1.2 Hz, 3H).

Example 95 N- (4- (4-amino-5- (3-chloro-4- ((1-oxo-1 λ^6 -thietan-1-ylidene) amino) phenyl) -7- (methyl- d_3) -7H-pyrrolo [2,3-*d*] pyrimidin-6-yl) -3-chlorophenyl) methacrylamide



Step 1 1- (2-chloro-4- (4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) phenyl) imino) -1 λ⁶-thietane-1-oxide **95b**

Compound **95a** (4 g, 13.58 mmol), bis(pinacolato)diboron (4.14 g, 16.29 mmol), Pd(dppf)Cl₂ (1.99 g, 2.72 mmol), and potassium acetate (3.99 g, 40.73 mmol) were added to 1,4-dioxane (50 mL), after replaced with argon gas three times, the reaction solution was heated up to 90 °C and stirred for 16 h. Water (100 mL) was added and extracted with DCM (100 mL × 3). The organic phase was washed with saturated saline solution (200 mL), dried over anhydrous sodium sulfate, and concentrated under reduced pressure to obtain a crude product. The crude product was purified by column chromatography (PE/EtOAc=3/2) to obtain compound **95b** (4.17 g), light yellow solid.

MS (ESI) *m/z* 342 [M + H]⁺

Step 2 1- (4- (4-amino-7- (methyl-d₃) -7H-pyrrolo [2,3-d] pyrimidin-5-yl) -2-chlorophenyl) imino) -1 λ⁶-thietane-1-oxide **95c**

Compound **95b** (3.57 g, 10.45 mmol), compound **82c** (3.76 g, 13.58 mmol), tetrakis (triphenylphosphine) palladium (1.21 g, 1.04 mmol), and potassium phosphate (6.65 g, 31.35 mmol) were dissolved in 1,4-dioxane (30 mL) and water (3 mL), after replaced with nitrogen three times, the reaction was carried out at 70 °C overnight. After the reaction was completed, it was cooled down to room temperature, filtered through diatomaceous earth, concentrated under reduced pressure to remove the solvent, extracted with DCM/H₂O three times, and the organic layers were combined, and washed with saturated sodium chloride once, and the organic phase was dried over anhydrous sodium sulfate, concentrated under reduced pressure, and purified by column chromatography (DCM/MeOH=30/1) to obtain compound **95c** (2.91 g), yellow solid.

MS (ESI) *m/z* 365 [M + H]⁺.

Step 3 1- (4- (4-amino-6-bromo-7- (methyl-d₃) -7H-pyrrolo [2,3-d] pyrimidin-5-yl) -2-chlorophenyl) imino) -1 λ⁶-thietane-1-oxide **95d**

Compound **95c** (1 g, 2.74 mmol) was dissolved with anhydrous DMF (10 mL), NBS (512 mg, 2.88 mmol) was added at 0 °C, and the reaction was carried out for 2 h, and then quenched with sodium thiosulfate solution, extracted with EA/H₂O 4 times, and the organic layers were combined, washed with saturated salt water once, dried over anhydrous sodium sulfate, concentrated under reduced pressure, and purified by column chromatography (DCM/MEOH=30/1) to obtain compound **95d** (800 mg), yellow solid.

MS (ESI) *m/z* 443 [M + H]⁺.

Step 4 1- ((4- (4-amino-6- (4-amino-2-chlorophenyl) -7- (methyl-*d*₃) -7*H*-pyrrolo [2,3-*d*] pyrimidin-5-yl) -2-chlorophenyl) imino) -1 λ⁶-thietane-1-oxide **95e**

Compound **95d** (800 mg, 1.80 mmol), 3-chloro-4- (4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) aniline (686 mg, 2.70 mmol), tetrakis (triphenylphosphine) palladium (208 mg, 0.18 mmol), and potassium phosphate (1.15 g, 5.41 mmol) were dissolved in 1,4-dioxane (20 mL) and water (2 mL), after replaced with nitrogen gas three times, the reaction was refluxed at 100 °C for 12 h. The reaction solution was cooled down to room temperature, filtered through diatomaceous earth, concentrated under the reduced pressure to remove the solvent, extracted with DCM/H₂O three times, and the organic layers were combined, washed with saturated saline solution, dried over anhydrous sodium sulfate. concentrated under the reduced pressure, and purified by column chromatography (DCM/MEOH=40/1) to obtain compound **95e** (376 mg), white solid.

MS (ESI) *m/z* 490 [M + H]⁺.

Step 5 *N*- (4- (4-amino-5- (3-chloro-4- ((1-oxo-1 λ⁶-thietan-1-ylidene) amino) phenyl) -7- (methyl-*d*₃) -7*H*-pyrrolo [2,3-*d*] pyrimidin-6-yl) -3-chlorophenyl) methacrylamide **95**

Compound **95e** (376 mg, 0.77 mmol) was dissolved with anhydrous DMF (10 mL), methacryloyl chloride (96 mg, 0.92 mmol) was added at 0 °C, the reaction was carried out for 1 h, and then quenched with water, extracted with dichloromethane, and the organic layers were combined, washed with saturated salt once, and the organic phase was dried over anhydrous sodium sulfate, concentrated under reduced pressure, and purified by column chromatography (DCM/MEOH=20/1) to obtain compound **95** (60 mg), white solid.

MS (ESI) *m/z* 558 [M + H]⁺.

¹H NMR (400 MHz, CDCl₃) δ 8.37 (s, 1H), 7.89 (d, *J* = 2.1 Hz, 1H), 7.55 (s, 1*H*), 7.38 (dd, *J* = 8.3, 2.2 Hz, 1H), 7.29 (s, 1H), 7.14 (d, *J* = 8.3 Hz, 1H), 7.06 (d, *J* = 8.1 Hz, 1H), 7.02 (s, 1H), 5.81 (s, 1H), 5.52 (d, *J* = 1.6 Hz, 1H), 5.02 (s, 2H), 4.33 – 4.19 (m, 4H), 2.44 – 2.31 (m, 2H), 2.07 (t, *J* = 1.3 Hz, 3H).

Example 96 *N*- (4- (4-amino-5- (3-fluoro-4- ((methyl (*oxo*) (phenyl) - λ⁶- sulfaneylidene) amino) phenyl) -7- (methyl-*d*₃) -7*H*-pyrrolo [2,3-*d*] pyrimidin-6-yl) -3-fluorophenyl) methacrylamide

Compound **96b** (5.76 g, 37.11 mmol), cesium carbonate (18.15 g, 55.66 mmol), 1-bromo-3-fluoro-4-iodobenzene (11.17 g, 37.11 mmol), Pd₂(dba)₃ (1.02 g, 1.11 mmol), and Xantphos (1.29 g, 2.23 mmol) were added to 1,4-dioxane (100 mL), the reaction solution was heated up to 100 °C to react for 16 h. The reaction solution was filtered through diatomaceous earth, and the filter cake was washed with ethyl acetate (300 mL), and saturated saline solution (500 mL) was used for washing. The organic phase was dried over anhydrous sodium sulfate and concentrated under reduced pressure to obtain a crude product. The crude product was purified by column chromatography (PE/EtOAc=4/1 to 3/2) to obtain compound **96c** (11.14 g), light yellow solid.

MS (ESI) m/z 328 [M + H]⁺

Step 3 (2-fluoro-4- (4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) phenyl imino) (methyl phenyl - λ⁶-sulfone 96d

Compound **96c** (2 g, 6.09 mmol), bis(pinacolato)diboron (1.86 mg, 7.31 mmol), Pd(dppf)Cl₂ (892 mg, 1.22 mmol), and potassium acetate (1.79 g, 18.28 mmol) were added to 1,4-dioxane (30 mL), after replaced with argon gas three times, and the reaction solution was heated up to 90 °C and stirred for 16 h. Water (100 mL) as added and extracted with DCM (50 mL × 3). The organic phase was washed with saturated saline solution (200 mL), dried over anhydrous sodium sulfate, and concentrated under reduced pressure to obtain a crude product. The crude product was purified by column chromatography (PE/EtOAc=3/2) to obtain compound **96d** (2.08 g), light yellow solid.

MS (ESI) m/z 376 [M + H]⁺

Step 4 (4- (4-amino-7-methyl-d₃) -7H-pyrrolo [2,3-*d*] pyrimidin-5-yl) -2- fluorophenyl imino) (methyl phenyl - λ⁶-sulfone 96e

Compound **96d** (2.08 g, 5.54 mmol), compound **82c** (2.00 g, 7.21 mmol), tetrakis (triphenylphosphine) palladium (640 mg, 0.55 mmol), and potassium phosphate (4.20 g, 19.83 mmol) were added in 1,4-dioxane (30 mL) and water (3 mL), after replaced with nitrogen gas three times, the reaction was carried out at 70 °C overnight. After the reaction was completed, it was cooled down to room temperature, filtered through diatomaceous earth, concentrated under reduced pressure to remove the solvent, extracted with DCM/H₂O three times, and the organic layers were combined, washed with saturated sodium chloride once, dried over anhydrous sodium sulfate, concentrated under reduced pressure, and purified by column chromatography (DCM/MeOH=30/1) to obtain compound **96e** (1.26 g), yellow solid.

MS (ESI) m/z 399 [M + H]⁺.

Step 5 (4- (4-amino-6-bromo-7-methyl-d₃) -7H-pyrrolo [2,3-*d*] pyrimidin-5-yl) -2- fluorophenyl imino) (methyl phenyl - λ⁶-sulfone 96f

Compound **96e** (1.26 g, 3.16 mmol) was dissolved with anhydrous DMF (15 mL), NBS (591 mg, 3.32 mmol) was added at 0 °C, the reaction was carried out for 2 h, and then quenched with sodium thiosulfate solution, extracted with dichloromethane, and the organic layers were combined, and washed with saturated salt water once, and the organic phase was dried over

anhydrous sodium sulfate, concentrated under reduced pressure, and purified by column chromatography (DCM/MEOH=30/1) to obtain compound **96f** (726 g), yellow solid.

MS (ESI) m/z 477 $[M + H]^+$.

Step 6 (4- (4-amino-6- (4-amino-2-fluorophenyl) -7-methyl- d_3) -7H-pyrrolo [2,3- d] pyrimidin-5-yl) -2-fluorophenyl imino) (methyl) phenyl - λ^6 -sulfone **96g**

Compound **96f** (726 mg, 1.52 mmol), 3-fluoro-4- (4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) aniline (578 mg, 2.28 mmol), tetrakis (triphenylphosphine) palladium (176 mg, 0.15 mmol), and potassium phosphate (967 mg, 4.56 mmol) were added in 1,4-dioxane (20 mL) and water (2 mL), after replaced with nitrogen gas three times, the reaction was refluxed at 100 °C for 12 h. The reaction solution was cooled down to room temperature, and filtered through diatomaceous earth, concentrated under reduced pressure to remove the solvent, extracted with DCM/H₂O three times, and the organic layers were combined, washed with saturated saline solution, dried over anhydrous sodium sulfate, concentrated under reduced pressure, and purified by column chromatography (DCM/ MEOH=40/1) to obtain compound **96g** (550 mg), white solid.

MS (ESI) m/z 508 $[M + H]^+$.

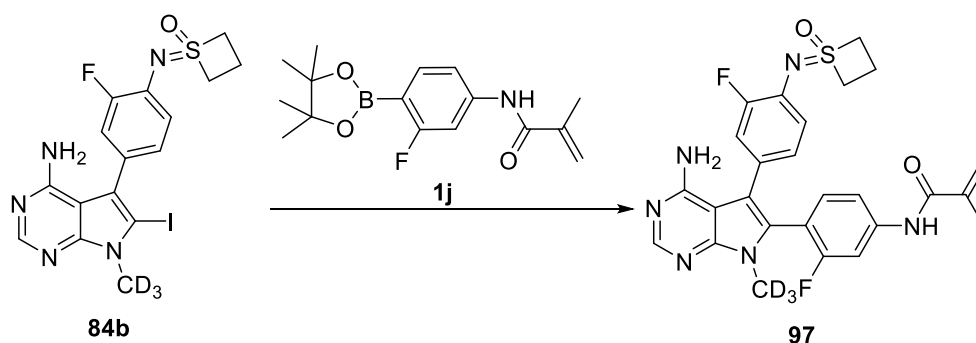
Step 7 N- (4- (4-amino-5- (3-fluoro-4- ((methyl (oxo) (phenyl) - λ^6 - sulfaneylidene) amino) phenyl) -7- (methyl- d_3) -7H-pyrrolo [2,3- d] pyrimidin-6-yl) -3-fluorophenyl) methacrylamide **96**

Compound **96g** (550 mg, 1.08 mmol) was dissolved with anhydrous DMF (10 mL), methacryloyl chloride (136 mg, 1.30 mmol) was added at 0 °C, and the reaction was carried out for 1 h, and then quenched with water, extracted with dichloromethane, and the organic layers were combined, washed with saturated salt once, and the organic phase was dried over anhydrous sodium sulfate, concentrated under reduced pressure, and purified by column chromatography (DCM/MEOH=20/1) to obtain compound **96** (25 mg), white solid.

MS (ESI) m/z 576 $[M + H]^+$.

¹H NMR (400 MHz, CDCl₃) δ 8.34 (s, 1H), 8.00 (dd, J = 7.2, 1.7 Hz, 2H), 7.64 (d , J = 7.3 Hz, 2H), 7.60 – 7.54 (m, 3H), 7.05 (d , J = 8.3 Hz, 1H), 6.98 (d , J = 8.0 Hz, 1H), 6.87 (d , J = 11.3 Hz, 1H), 6.77 (s, 1H), 5.82 (s, 1H), 5.53 (d , J = 1.6 Hz, 1H), 4.95 (s, 2H), 3.29 (s, 3H), 2.09 (d , J = 0.6 Hz, 3H).

Example 97 N- (4- (4-amino-5- (3-fluoro-4- ((1-oxo-1 λ^6 -thiophene-1-ylidene) amino) phenyl) -7- (methyl- d_3) -7H-pyrrolo [2,3- d] pyrimidin-6-yl) -3-fluorophenyl) methacrylamide



reduced pressure to obtain crude product compound **98b** (0.20 g), which was directly used in the next step.

MS (ESI) m/z 409.10 $[M + H]^+$.

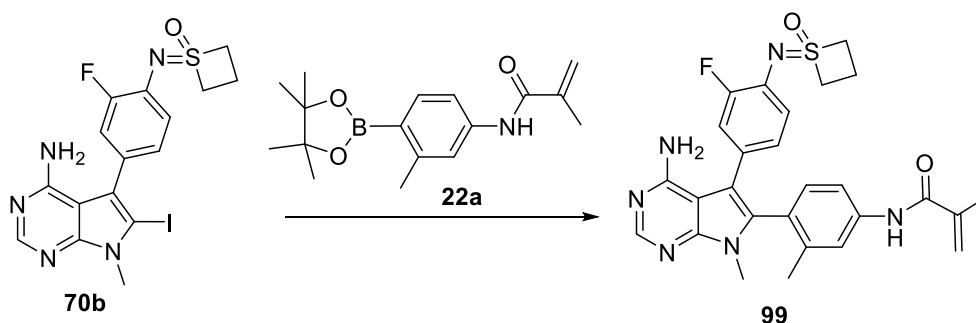
Step 3 *N*- (4- (4-amino-7- (methyl- d_3) -5- (4- ((1-oxo-1 λ^6 -thiophene-1-ylidene) amino) phenyl) -7*H*-pyrrolo [2,3-*d*] pyrimidin-6-yl) -3-fluorophenyl) methacrylamide **98**

Compound **98b** (0.20 g, 0.49 mmol) was dissolved in 1,4-dioxane (5 mL) and H₂O (1 mL), compound **1j** (0.17 g, 0.54 mmol), potassium phosphate (320 mg, 1.50 mmol), and tetrakis (triphenylphosphine) palladium (0.036 g, 0.05 mmol) were added, and the reaction was carried out at 90 °C for 14 h under N₂ protection. After TLC monitored the completion of the reaction, it was extracted with ethyl acetate (50 mL $\times$ 3), and the organic phases were combined and concentrated under reduced pressure to obtain a crude product. The crude product was purified by column chromatography (DCM/MeOH=10/1) to obtain compound **98** (22.0 mg).

MS (ESI) m/z 508.10 $[M + H]^+$.

¹H NMR (400 MHz, CDCl₃) δ 8.37 (d, J = 7.8 Hz, 1H), 7.73 (dd, J = 11.5, 2.0 Hz, 1H), 7.61 (s, 1H), 7.23 – 7.04 (m, 4H), 6.97 (d, J = 8.1 Hz, 2H), 5.83 (s, 1H), 5.54 (d, J = 1.6 Hz, 1H), 5.10 (s, 2H), 4.24 (dd, J = 9.3, 7.2 Hz, 4H), 2.55 – 2.30 (m, 2H), 2.09 (d, J = 1.3 Hz, 3H).

Example 99 *N*- (4- (4-amino-5- (3-fluoro-4- ((1-oxo-1 λ^6 -thiophene-1-ylidene) amino) phenyl) -7-methyl-7*H*-pyrrolo [2,3-*d*] pyrimidin-6-yl) -3-methylphenyl) methacrylamide

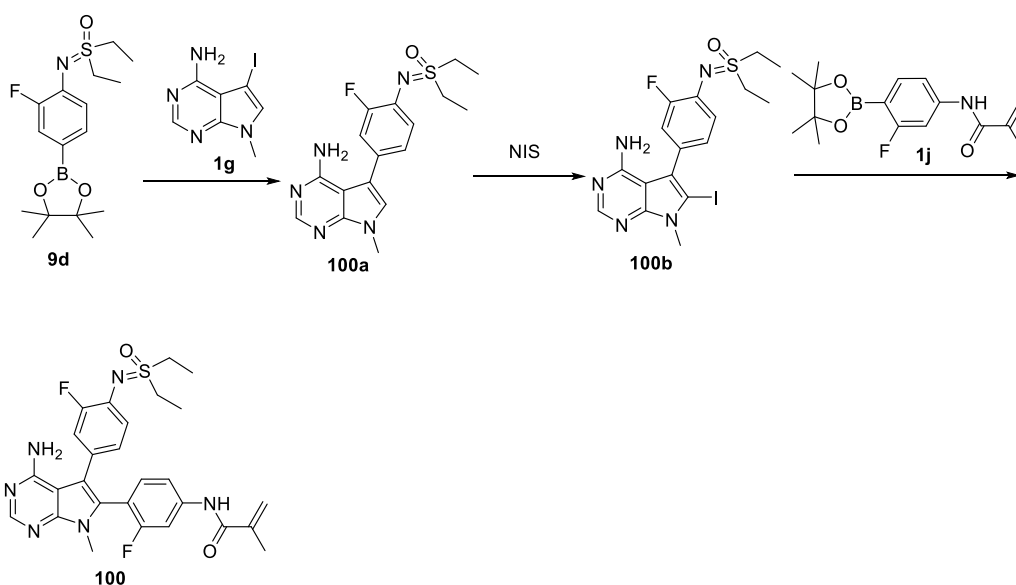


Compound **99** was synthesized with reference to the similar synthetic route and steps of compound **12**, wherein, compound **12a** was replaced with compound **70b**, compound **12b** was replaced with compound **22a**.

MS (ESI) m/z 519.2 $[M + H]^+$.

¹H NMR (400 MHz, CDCl₃) δ 8.30 (s, 1H), 7.43 (d, J = 2.8 Hz, 2H), 7.35 (dd, J = 8.2, 2.3 Hz, 1H), 7.10 (d, J = 8.3 Hz, 1H), 6.91 (d, J = 8.3 Hz, 1H), 6.85 – 6.77 (m, 2H), 5.73 (s, 1H), 5.42 (d, J = 1.6 Hz, 1H), 4.95 (s, 2H), 4.20 (q, J = 8.4, 8.0 Hz, 4H), 3.45 (s, 3H), 2.26 (t, J = 8.3 Hz, 2H), 2.02 – 1.90 (m, 6H).

Example 100 *N*- (4- (4-amino-5- (4- (diethyl (oxo) -1 λ^6 - sulfaneylidene) amino) -3-fluorophenyl) -7-methyl-7*H*-pyrrolo [2,3-*d*] pyrimidin-6-yl) -3-fluorophenyl) methacrylamide

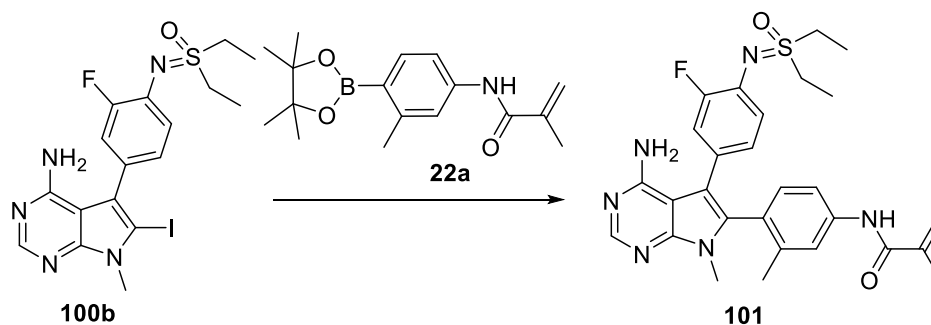


Compound **100** was synthesized with reference to the similar synthetic route and steps of compound **85**, wherein, compound **85a** was replaced with compound **9d**.

MS (ESI) m/z 538.2 $[M + H]^+$.

- 5 ^1H NMR (400 MHz, CDCl_3) δ 8.30 (s, 1H), 7.64 (dd, $J = 11.6, 2.1$ Hz, 1H), 7.50 (s, 1H), 7.13 (t, $J = 8.5$ Hz, 1H), 7.06 – 6.96 (m, 2H), 6.85 (d, $J = 10.4$ Hz, 2H), 5.74 (s, 1H), 5.45 (q, $J = 1.6$ Hz, 1H), 4.95 (s, 2H), 3.58 (d, $J = 1.1$ Hz, 3H), 3.15 (tq, $J = 14.3, 7.2$ Hz, 4H), 1.97 (s, 3H), 1.37 (t, $J = 7.5$ Hz, 6H).

- 10 **Example 101** *N*- (4- (4-amino-5- (4- (diethyl (oxo) -1 λ^6 - sulfaneylidene) amino) -3-fluorophenyl) -7-methyl-7*H*-pyrrolo [2,3-*d*] pyrimidin-6-yl) -3-methylphenyl) methacrylamide

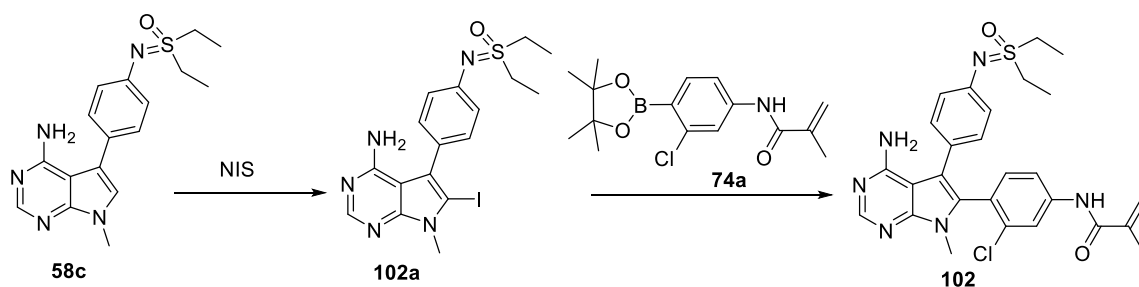


- 15 Compound **101** was synthesized with reference to the similar synthetic route and steps of compound **12**, wherein, compound **12a** was replaced with compound **100b**, compound **12b** was replaced with compound **22a**.

MS (ESI) m/z 535.3 $[M + H]^+$.

- 20 ^1H NMR (400 MHz, CDCl_3) δ 8.36 (s, 1H), 7.50 (d, $J = 2.5$ Hz, 2H), 7.41 (dd, $J = 8.1, 2.2$ Hz, 1H), 7.17 (dt, $J = 8.4, 4.3$ Hz, 2H), 6.85 (d, $J = 9.5$ Hz, 2H), 5.80 (s, 1H), 5.49 (d, $J = 1.8$ Hz, 1H), 5.09 (s, 2H), 3.52 (s, 3H), 3.20 (m, 4H), 2.08 (t, $J = 1.2$ Hz, 3H), 2.00 (s, 3H), 1.43 (t, $J = 7.5$ Hz, 6H).

Example 102 *N*- (4- (4-amino-5- (4- (diethyl (oxo) -1 λ^6 - sulfaneylidene) amino) phenyl) -7-methyl-7*H*-pyrrolo [2,3-*d*] pyrimidin-6-yl) -3-chlorophenyl) methacrylamide

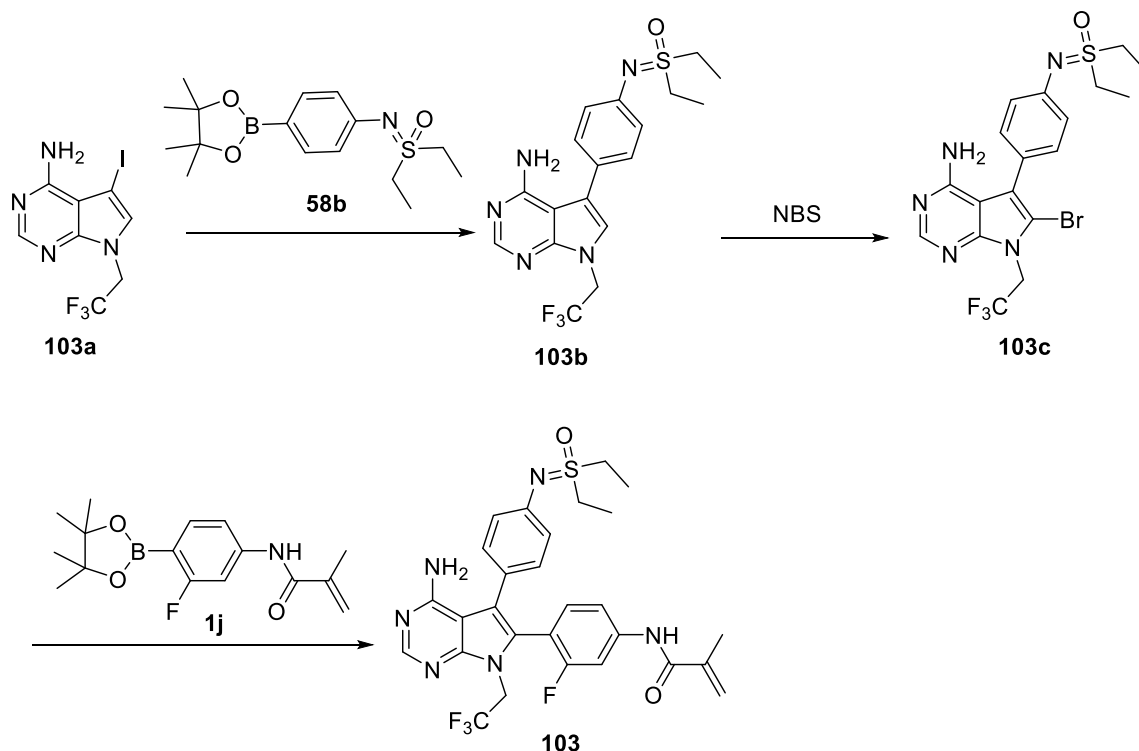


Compound **102** was synthesized with reference to the similar synthetic route and steps of compound **77**, wherein, compound **12a** was replaced with compound **58c**, compound **1j** was replaced with compound **74a**.

MS (ESI) m/z 537.3 $[\text{M} + \text{H}]^+$.

^1H NMR (400 MHz, CDCl_3) δ 8.39 (s, 1H), 7.89 (d, $J = 2.2$ Hz, 1H), 7.61 (s, 1H), 7.37 (dd, $J = 8.3, 2.2$ Hz, 1H), 7.14 (m, 3H), 7.03 (d, $J = 8.0$ Hz, 2H), 5.83 (s, 1H), 5.54 (s, 1H), 5.08 (s, 2H), 3.61 (s, 3H), 3.31 – 3.10 (m, 4H), 2.10 (s, 3H), 1.43 (t, $J = 7.4$ Hz, 6H).

Example 103 *N*- (4- (4-amino-5- (4- (diethyl (oxo) -1 λ^6 - sulfaneylidene) amino) phenyl) -7- (2,2,2-trifluoroethyl) -7*H*-pyrrolo [2,3-*d*] pyrimidin-6-yl) -3-fluorophenyl) methacrylamide

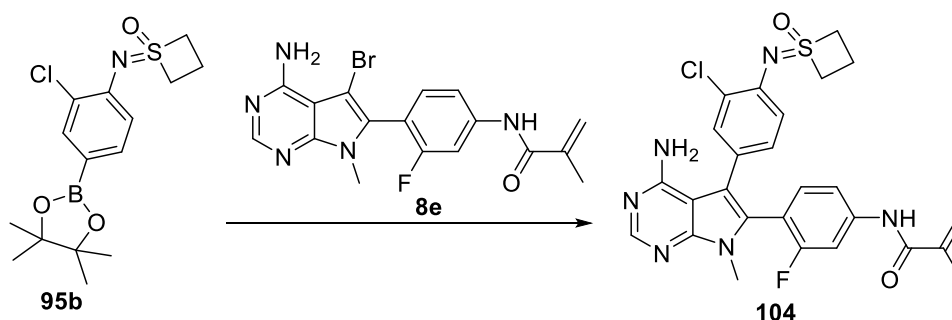


Compound **103** was synthesized with reference to the similar synthetic route and steps of compound **85**, wherein, in step 1, compound **1g** was replaced with compound **103a**, compound **58d** was replaced with compound **85a**.

MS (ESI) m/z 589.3 $[M + H]^+$.

¹H NMR (400 MHz, CDCl₃) δ 8.41 (s, 1H), 7.77 (d, J = 11.5 Hz, 1H), 7.62 (s, 1H), 7.23 – 6.94 (m, 6H), 5.83 (s, 1H), 5.55 (s, 1H), 5.11 (s, 2H), 3.24 (m, 4H), 2.10 (s, 3H), 1.65 (s, 2H), 1.44 (t, J = 7.5 Hz, 6H).

Example 104 *N*- (4- (4-amino-5- (3-chloro-4- ((1-oxo-1 λ^6 -thiophene-1-ylidene) amino) phenyl) -7-methyl-7*H*-pyrrolo [2,3-*d*] pyrimidin-6-yl) -3-fluorophenyl) methacrylamide

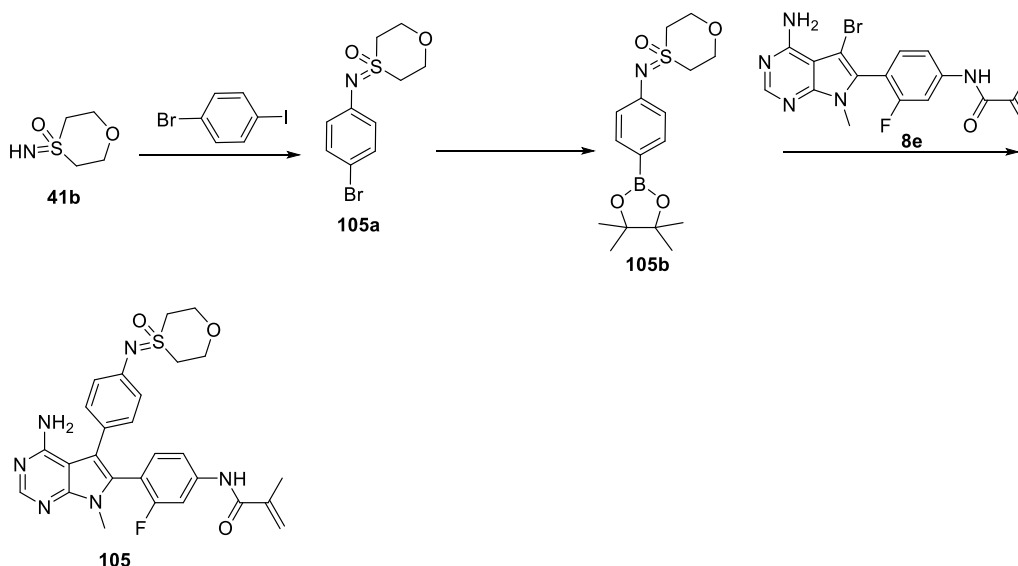


Compound **104** was synthesized with reference to the similar synthetic route and steps of compound **31**, wherein, compound **24b** was replaced with compound **95b**, compound **9e** was replaced with compound **8e**.

MS (ESI) m/z 539.1 $[M + H]^+$.

¹H NMR (400 MHz, CDCl₃) δ 8.37 (s, 1H), 7.73 (dd, J = 11.6, 2.0 Hz, 1H), 7.58 (s, 1H), 7.29 (s, 3H), 7.14 – 6.97 (m, 3H), 5.81 (s, 1H), 5.52 (q, J = 1.6 Hz, 1H), 5.00 (s, 1H), 4.42 – 4.15 (m, 3H), 2.47 – 2.28 (m, 3H), 1.59 (s, 6H).

Example 105 *N*- (4- (4-amino-7-methyl-5- (4- (4-oxo-1,4 λ^6 -oxathiohexane-4-ylidene) amino) phenyl) -7*H*-pyrrolo [2,3-*d*] pyrimidin-6-yl) -3-fluorophenyl) methacrylamide

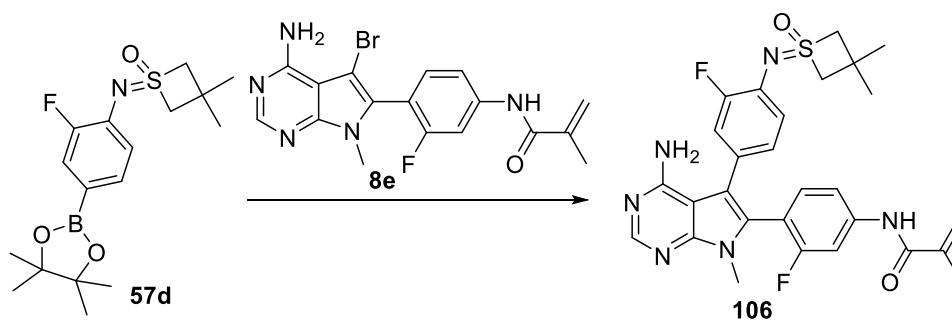


Compound **105** was synthesized with reference to the similar synthetic route and steps of compound **8**, wherein, compound **8b** was replaced with compound **41b**.

MS (ESI) m/z 535.2 $[M + H]^+$.

^1H NMR (400 MHz, $CDCl_3$) δ 8.39 (s, 1H), 7.71 (dd, $J = 11.5, 2.0$ Hz, 1H), 7.59 (s, 1H), 7.19 – 7.05 (m, 6H), 5.83 (s, 1H), 5.55 (q, $J = 1.5$ Hz, 1H), 5.04 (s, 2H), 4.22 (dt, $J = 12.8, 4.3$ Hz, 2H), 4.12 (m, 2H), 3.68 (d, $J = 1.1$ Hz, 4H), 3.48 – 3.36 (m, 3H), 3.30 (m, 3H).

Example 106 *N*-(4-(4-amino-5-(4-((3,3-dimethyl-1-oxo-1 λ^6 -thiocyclobutan-1-ylidene)amino)-3-fluorophenyl)-7-methyl-7H-pyrrolo [2,3-*d*] pyrimidin-6-yl)-3-fluorophenyl) methacrylamide

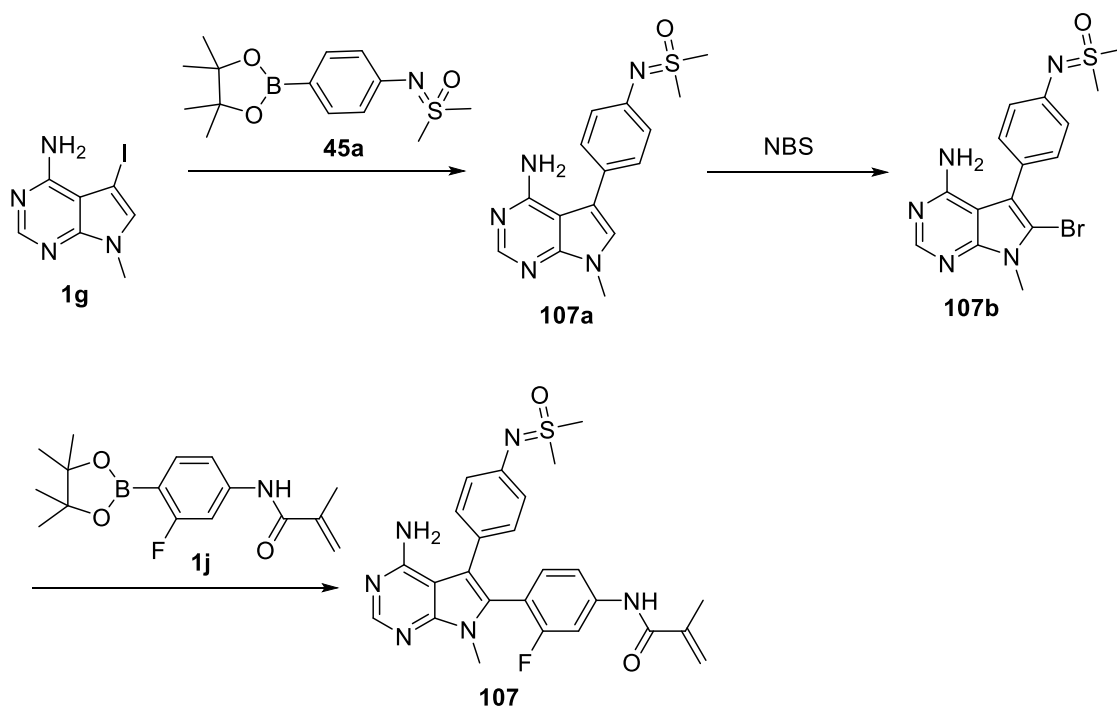


Compound **106** was synthesized with reference to the similar synthetic route and steps of compound **8**, wherein, compound **8d** was replaced with compound **57d**.

MS (ESI) m/z 551.1 $[M + H]^+$.

^1H NMR (400 MHz, $CDCl_3$) δ 8.39 (s, 1H), 7.76 (dd, $J = 11.6, 2.1$ Hz, 1H), 7.60 (s, 1H), 7.17 – 7.02 (m, 3H), 6.96 (d, $J = 9.9$ Hz, 2H), 5.84 (s, 1H), 5.55 (d, $J = 1.8$ Hz, 1H), 5.04 (s, 2H), 4.20 – 4.01 (m, 4H), 3.68 (d, $J = 1.1$ Hz, 2H), 2.10 (s, 2H), 1.56 (m, 4H), 1.30 (d, $J = 9.4$ Hz, 4H).

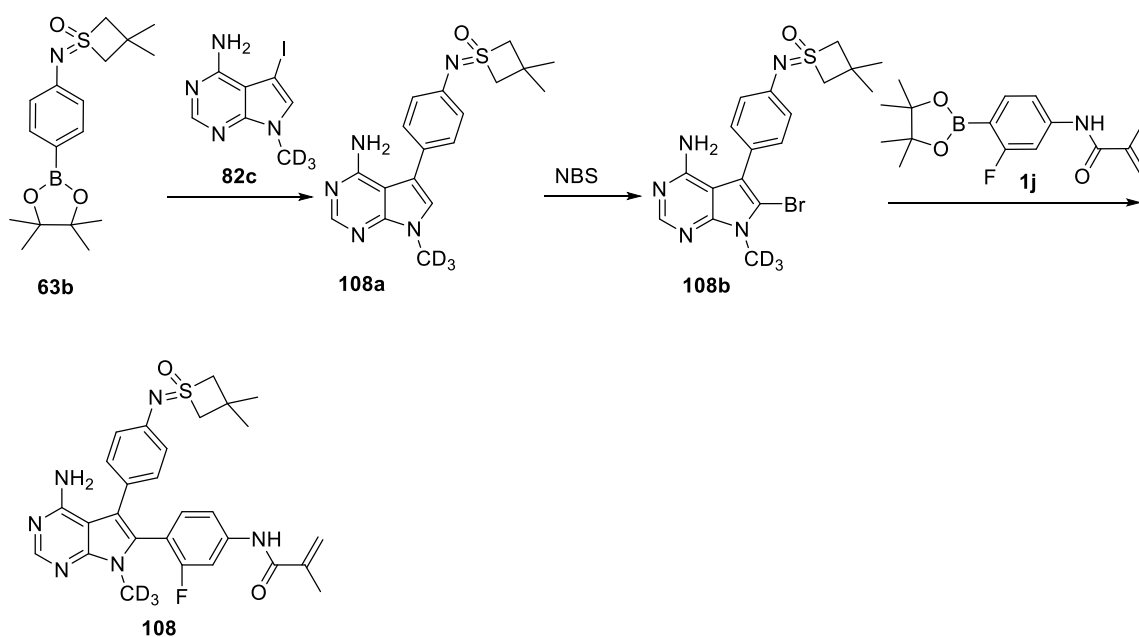
Example 107 *N*-(4-(4-amino-5-(4-(dimethyl (oxo) -1 λ^6 -sulfaneylidene) amino) phenyl)-7-methyl-7H-pyrrolo [2,3-*d*] pyrimidin-6-yl)-3-fluorophenyl) methacrylamide



It was synthesized with reference to the similar synthetic route and steps of compound **85**. MS (ESI) m/z 493.2 $[M + H]^+$.

^1H NMR (400 MHz, CDCl_3) δ 8.29 (s, 1H), 7.63 (d, $J = 11.7$ Hz, 1H), 7.49 (s, 1H), 7.11 – 6.85 (m, 5H), 5.73 (s, 1H), 5.45 (s, 1H), 5.28 (s, 1H), 4.96 (s, 2H), 3.59 (s, 3H), 2.00 (s, 3H), 1.19 (s, 6H).

Example 108 *N*- (4- (4-amino-5- (4- ((3,3-dimethyl-1-oxo-1 λ^6 -thiophene-1-ylidene) amino) phenyl) -7- (methyl- d_3) -7*H*-pyrrolo [2,3-*d*] pyrimidin-6-yl) -3-fluorophenyl) methacrylamide

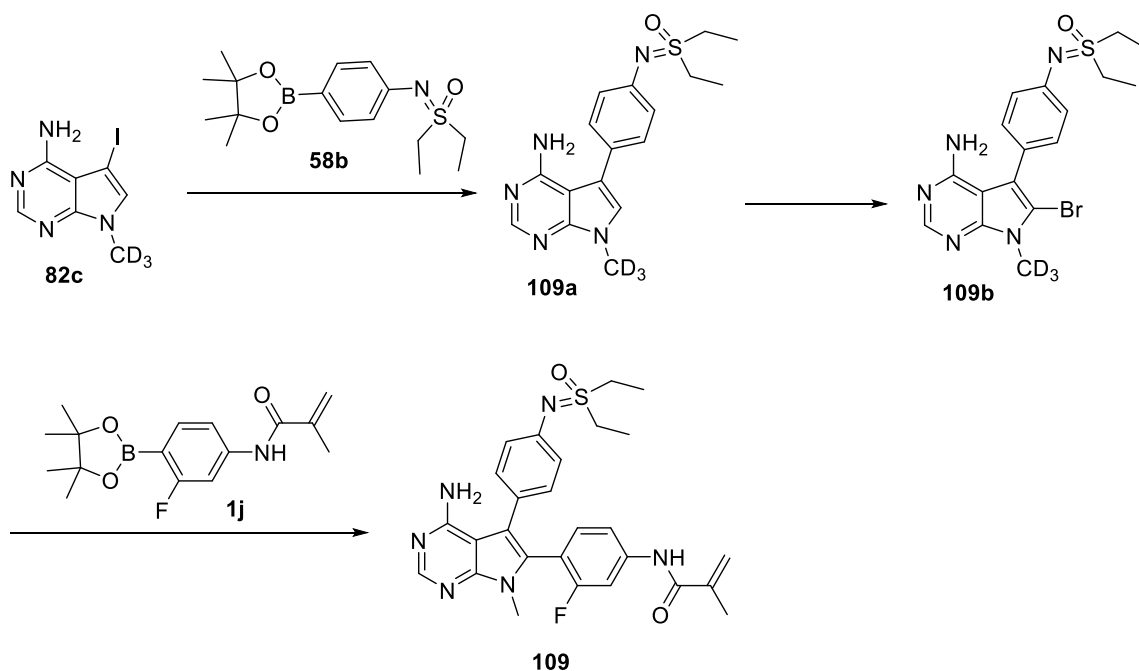


Compound **108** was synthesized with reference to the similar synthetic route and steps of compound **85**, wherein, in step 1, compound **85a** was replaced with compound **63b**, compound **1g** was replaced with compound **82c**.

MS (ESI) m/z 536.9 $[M + H]^+$.

5 ^1H NMR (400 MHz, $CDCl_3$) δ 8.36 (s, 1H), 7.71 (dd, $J = 11.8, 1.8$ Hz, 1H), 7.56 (s, 1H), 7.17 – 7.03 (m, 4H), 6.94 (d, $J = 8.1$ Hz, 2H), 5.80 (s, 1H), 5.52 (d, $J = 1.6$ Hz, 1H), 5.02 (s, 2H), 4.05 – 3.90 (m, 4H), 2.05 (d, $J = 10.4$ Hz, 3H), 1.54 (s, 3H), 1.52 (s, 3H).

10 **Example 109** *N*-(4-(4-amino-5-(4-(diethyl(oxo)- λ^6 -sulfaneylidene)amino)phenyl)-7-(methyl- d_3)-7H-pyrrolo [2,3-*d*] pyrimidin-6-yl)-3-fluorophenyl) methacrylamide

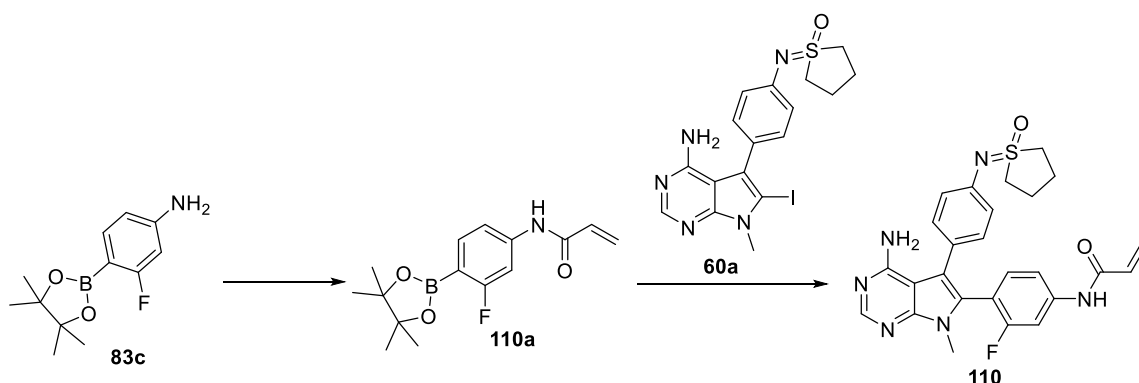


Compound **109** was synthesized with reference to the similar synthetic route and steps of compound **58**, wherein, in step 1, compound **1g** was replaced with compound **82c**.

MS (ESI) m/z 542.10 $[M + H]^+$.

15 ^1H NMR (400 MHz, $CDCl_3$) δ 8.27 (s, 1H), 7.94-7.82 (m, 1H), 7.57-7.42 (m, 2H), 7.38-7.24 (m, 3H), 5.79 (s, 1H), 5.72 (s, 1H), 5.00 (s, 2H), 2.61 (q, 4H), 2.07 (s, 3H), 1.22 (t, 6H).

Example 110 *N*-(4-(4-amino-7-methyl-5-(4-(1-tetrahydro-1 λ^6 -thiophene-1-ylidene)amino)phenyl)-7H-pyrrolo [2,3-*d*] pyrimidin-6-yl)-3-fluorophenyl) acrylamide



Step 1 *N*- (3-fluoro-4- (4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) phenyl) acrylamide 110a

Compound **83c** (100 mg, 0.42 mmol), acrylic acid (45 mg, 0.63 mmol), and triethylamine (127 mg, 1.26 mmol) were dissolved in THF (5 mL), and then T3P (50% DMF solution) (0.63 mmol) was added, and the reaction was carried out at room temperature for 2 h, then concentrated under reduced pressure to remove the solvent, extracted with DCM/H₂O three times, and the organic layers were combined, and washed once with saturated sodium chloride, and the organic phase was dried over anhydrous sodium sulfate, concentrated under reduced pressure, and purified by column chromatography (PE/EA=5/1) to obtain compound **110a** (80 mg), yellow solid.

MS (ESI) *m/z* 292.02 [M + H]⁺.

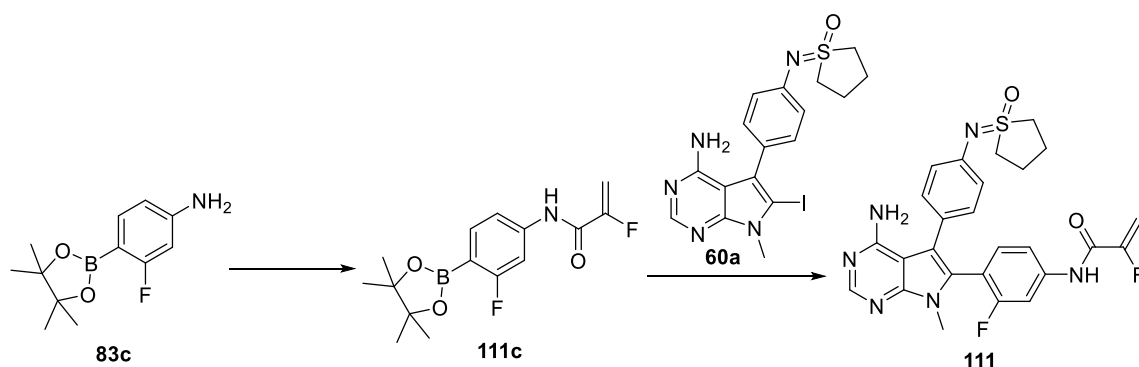
Step 2 *N*- (4- (4-amino-7-methyl-5- (4- (1-tetrahydro-1λ⁶-thiophene-1-ylidene) amino) phenyl) -7*H*-pyrrolo [2,3-*d*] pyrimidin-6-yl) -3-fluorophenyl) acrylamide 110

Compound **110a** (80 mg, 0.17 mmol), compound **60a** (59 mg, 0.20 mmol), Pd(dppf)Cl₂ (25 mg, 0.034 mmol), and potassium phosphate (108 mg, 0.51 mmol) were dissolved in 1,4-dioxane (2 mL) and water (0.5 mL), after replaced with nitrogen gas three times, the reaction was refluxed at 90 °C for 6 h. The reaction solution was cooled down to room temperature, filtered through diatomaceous earth, concentrated under reduced pressure to remove the solvent, extracted with DCM/H₂O three times, and the organic layers were combined and washed with saturated saline solution, and the organic phase was dried over anhydrous sodium sulfate, concentrated under reduced pressure, and purified by column chromatography (DCM/MEOH=40/1) to obtain compound **110** (40 mg), yellow solid.

MS (ESI) *m/z* 505.03 [M + H]⁺.

¹H NMR (400 MHz, CDCl₃) δ 8.28 (s, 1H), 7.66 (d, *J* = 11.3 Hz, 1H), 7.48 (s, 1H), 7.08 – 7.01 (m, 3H), 6.99 (d, *J* = 7.8 Hz, 1H), 6.91 (d, *J* = 8.1 Hz, 2H), 6.39 (d, *J* = 16.8 Hz, 1H), 6.18 (dd, *J* = 16.9, 10.2 Hz, 1H), 5.75 (d, *J* = 10.2 Hz, 1H), 4.97 (s, 2H), 3.58 (s, 3H), 3.36 (dd, *J* = 13.0, 6.6 Hz, 2H), 3.12 (dt, *J* = 12.7, 6.6 Hz, 2H), 2.33 – 2.13 (m, 4H).

Example 111 *N*- (4- (4-amino-7-methyl-5- (4- (1-tetrahydro-1λ⁶-thiophene-1-ylidene) amino) phenyl) -7*H*-pyrrolo [2,3-*d*] pyrimidin-6-yl) -3-fluorophenyl) -2-fluoroacrylamide



Step 1 2-fluoro-*N*-(3-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) phenyl) acrylamide 111c

Compound **83c** (100 mg, 0.42 mmol), 2-fluoroacrylic acid (57 mg, 0.63 mmol), and triethylamine (127 mg, 1.26 mmol) was dissolved in THF (5 mL), and then T3P (50% DMF solution) (0.63 mmol) was added, and the reaction was carried out at room temperature for 2 h, concentrated under reduced pressure to remove the solvent, extracted with DCM/H₂O three times, and the organic layers were combined, and washed with saturated salt twice, and the organic phase was dried over anhydrous sodium sulfate, concentrated under reduced pressure, and purified by column chromatography (PE/EA=5/1) to obtain compound **111c** (85 mg), yellow solid.

MS (ESI) *m/z* 310.02 [M + H]⁺.

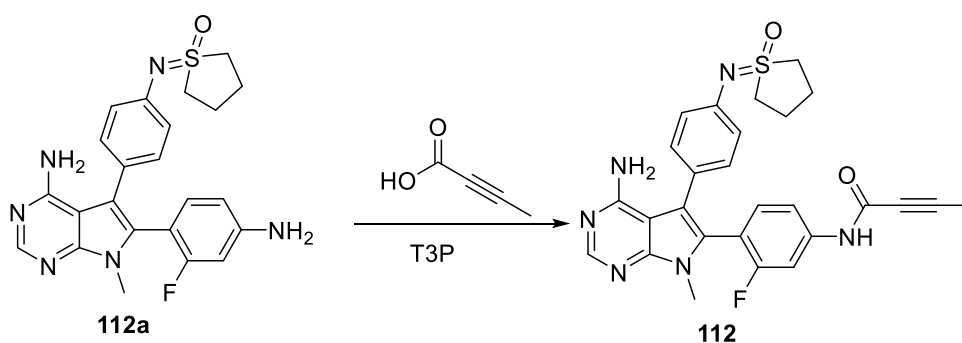
Step 2 *N*-(4-(4-amino-7-methyl-5-(4-(1-hydroperoxide-1 λ^6 -thiophene-1-ylidene) amino) phenyl) -7*H*-pyrrolo [2,3-*d*] pyrimidin-6-yl) -3-fluorophenyl) -2- fluoroacrylamide 111

Compound **111c** (30 mg, 0.097 mmol), compound **60a** (56 mg, 0.12 mmol), Pd(dppf)Cl₂ (14 mg, 0.019 mmol), and potassium phosphate (61 mg, 0.29 mmol) were dissolved in 1,4-dioxane (2 mL) and water (0.5 mL), after replaced with nitrogen gas three times, the reaction was refluxed at 90 °C for 6 h. The reaction solution was cooled down to room temperature, filtered through diatomaceous earth, concentrated under reduced pressure to remove the solvent, extracted with DCM/H₂O three times, and the organic layers were combined, washed with saturated saline solution, dried over anhydrous sodium sulfate, concentrated under reduced pressure, purified by column chromatography (DCM/MEOH=40/1) to obtain compound **111** (4 mg), white solid.

MS (ESI) *m/z* 523.10 [M + H]⁺.

¹H NMR (400 MHz, CDCl₃) δ 8.29 (s, 1H), 7.93 (d, *J* = 5.4 Hz, 1H), 7.70 – 7.59 (m, 1H), 7.12 – 6.97 (m, 4H), 6.91 (d, *J* = 8.1 Hz, 2H), 5.79 (dd, *J* = 47.8, 3.6 Hz, 1H), 5.23 (dd, *J* = 15.1, 3.5 Hz, 1H), 4.99 (s, 2H), 3.59 (s, 3H), 3.35 (dt, *J* = 12.6, 6.4 Hz, 2H), 3.12 (dt, *J* = 12.9, 6.6 Hz, 2H), 2.38 – 2.11 (m, 4H).

Example 112 *N*-(4-(4-amino-7-methyl-5-(4-((1-tetrahydro-1 λ^6 -thiophene-1-ylidene) amino) phenyl) -7*H*-pyrrolo [2,3-*d*] pyrimidin-6-yl) -3-fluorophenyl) but-2-ynamide

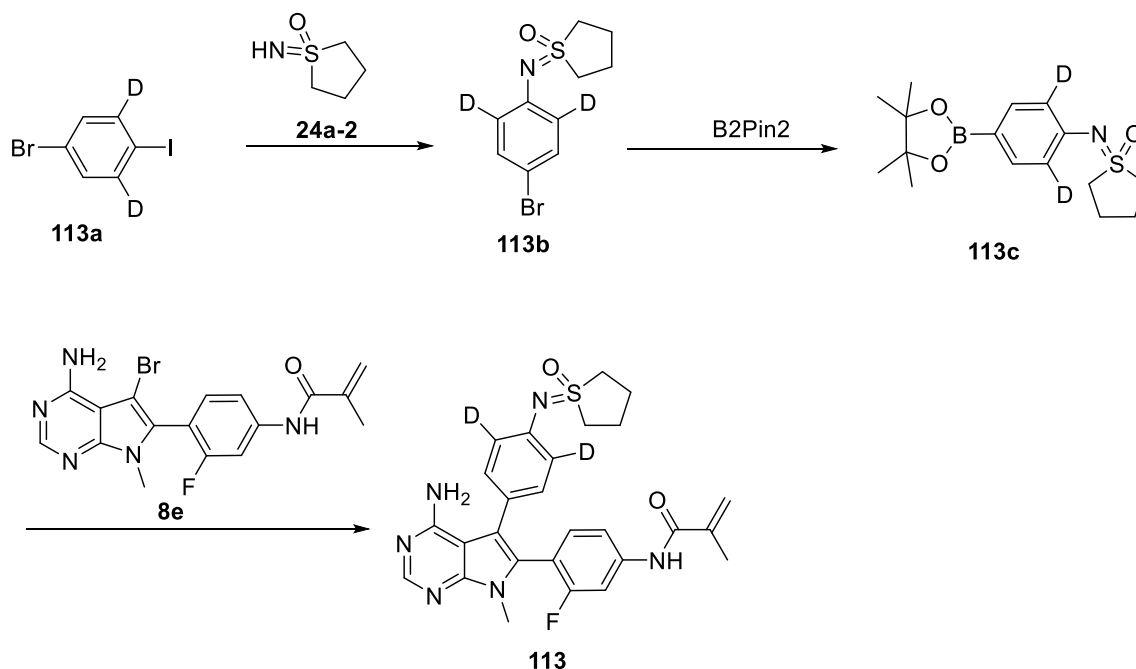


Compound **112a** (100 mg, 0.22 mmol), 2-butynoic acid (27 mg, 0.33 mmol), and triethylamine (67 mg, 0.66 mmol) were dissolved in THF (5 mL), and then T3P (50% DMF solution) (0.33 mmol) was added, and the reaction was carried out at room temperature for 2 h, then concentrated under reduced pressure to remove the solvent, extracted with DCM/H₂O three times, and the organic layers were combined, washed with saturated sodium chloride once, dried over anhydrous sodium sulfate, concentrated under reduced pressure, and purified by column chromatography (DCM/MeOH=40/1) to obtain compound **112** (10 mg), white solid.

MS (ESI) m/z 517.20 $[M + H]^+$.

¹H NMR (400 MHz, CDCl₃) δ 8.28 (s, 1H), 7.53 (d, J = 10.3 Hz, 2H), 7.04 (d, J = 7.8 Hz, 2H), 7.00 – 6.95 (m, 2H), 6.91 (d, J = 8.0 Hz, 2H), 4.97 (s, 2H), 3.59 – 3.56 (m, 3H), 3.35 (dt, J = 13.2, 6.5 Hz, 2H), 3.13 (dt, J = 12.9, 6.6 Hz, 2H), 2.32 – 2.09 (m, 5H).

Example 113 *N*- (4- (4-amino-7-methyl-5- (4- (1-tetrahydro-1 λ ⁶-thiophene-1-ylidene) amino) phenyl-3,5-d₂)-7*H*-pyrrolo [2,3-*d*] pyrimidin-6-yl) -3-fluorophenyl) methacrylamide

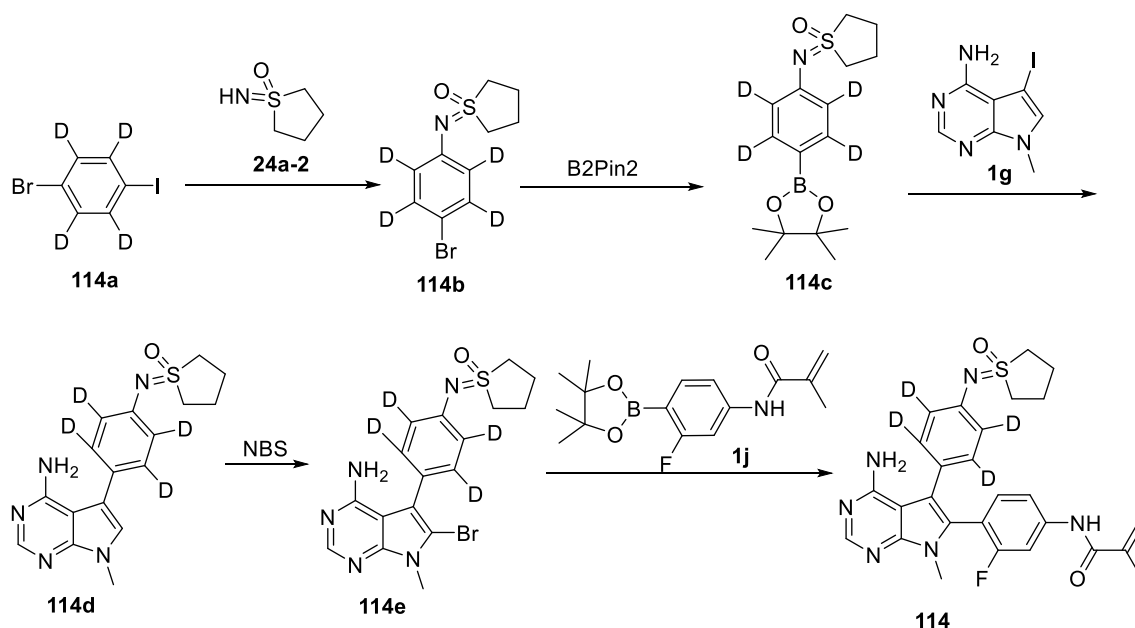


Compound **113** was synthesized with reference to the similar synthetic route and steps of compound **105**, wherein, in step 1, p-bromiodobenzene was replaced with compound **113a**.

MS (ESI) m/z 521.2 $[M + H]^+$

^1H NMR (400 MHz, $\text{MeOD-}d_4$) δ 8.18 (s, 1H), 7.71 (dd, $J = 12.1, 2.0$ Hz, 1H), 7.35 (dd, $J = 8.4, 2.0$ Hz, 1H), 7.15 (t, $J = 4.1$ Hz, 3H), 5.81 (s, 1H), 5.54 (d, $J = 1.1$ Hz, 1H), 3.61 (s, 3H), 3.42 (m, 2H), 3.25 – 3.20 (m, 2H), 2.37 – 2.30 (m, 2H), 2.22 (m, 2H), 2.02 (s, 3H).

Example 114 *N*- (4- (4-amino-7-methyl-5- (4- ((1-oxide tetrahydro-1 λ^6 - thiophene-1-ylidene) amino) phenyl-2,3,5,6- d_4) -7*H*-pyrrolo [2,3-*d*] pyrimidin-6-yl) -3-fluorophenyl) methacrylamide



Step 1 1- ((4-bromophenyl-2,3,5,6- d_4) imino) tetrahydro-1*H*-1 λ^6 -thiophene-1-oxide 114b

Compound **114a** was synthesized with reference to Organic Letters (2021), 23 (5), 1554-1560. To the reaction flask, compound **114a** (1.13 g, 3.95 mmol), anhydrous 1,4-dioxane (11 mL), compound **24a-2** (471 mg, 3.95 mmol), Xantphos (171 mg, 0.30 mmol), cesium carbonate (1.80 g, 5.53 mmol), and $\text{Pd}_2(\text{dba})_3$ (90 mg, 0.099 mmol) were added in sequence, after replaced with nitrogen gas three times, the reaction was refluxed at 100 °C for 3 h. TLC showed the formation of new dots, the reaction was diluted with ethyl acetate and H_2O , filtered through diatomaceous earth, extracted with ethyl acetate, and the organic phase was washed with saturated saline solution, dried over anhydrous sodium sulfate, concentrated under reduced pressure, and purified by silica gel column chromatography (PE/EA=1/1) to obtain compound **114b** (775 mg), light yellow oil.

MS (ESI) m/z 278 $[\text{M} + \text{H}]^+$.

Step 2 1- (4- (4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) phenyl-2,3,5,6- d_4) imino) tetrahydro-1*H*-1 λ^6 -thiophene-1-oxide 114c

To the reaction flask, compound **114b** (725 mg, 2.61 mmol), anhydrous 1,4-dioxane (8 mL), bis(pinacolato)diboron (993 mg, 3.91 mmol), potassium acetate (768 mg, 7.83 mmol), and $\text{Pd}(\text{dppf})\text{Cl}_2$ (189 mg, 0.261 mmol) were added in sequence, after replaced with nitrogen gas three

times, the reaction was heated up to 90 °C for 4 h. TLC showed the formation of new dots, and after the reaction was completed, the reaction solution was cooled down to room temperature, diluted with ethyl acetate and H₂O, filtered through diatomaceous earth, extracted with ethyl acetate, and the organic phase was washed with saturated saline solution, dried over anhydrous sodium sulfate, concentrated under reduced pressure, and purified by silica gel column chromatography (PE/EA=1/1) to obtain compound **114c** (532 mg), yellow solid.

MS (ESI) m/z 326 [M + H]⁺.

Step 3 1- (4- (4-amino-7-methyl-7H-pyrrolo [2,3-*d*] pyrimidin-5-yl) phenyl- 2,3,5,6 -*d*4) imino) tetrahydro-1H-1 λ⁶-thiophene-1-oxide 114d

To a reaction flask, compound **114c** (467 mg, 1.44 mmol), 1,4-dioxane (5 mL), H₂O (1 mL), compound **1g** (359 mg, 1.31 mmol), potassium phosphate (1.66 g, 7.8 mmol), and Pd(PPh₃)₄ (300 mg, 0.26 mmol) were added in sequence, after replaced with nitrogen gas three times, the reaction was carried at 90 °C for 5 h. TLC showed the formation of new dots, and after the reaction was completed, the reaction solution was cooled down to room temperature, diluted with dichloromethane and H₂O, filtered through diatomaceous earth, extracted with dichloromethane, and the organic phase was washed with saturated saline solution, dried over anhydrous sodium sulfate, concentrated under reduced pressure, and purified by silica gel column chromatography (DCM/MeOH=10/1) to obtain compound **114d** (144 mg), yellow solid.

MS (ESI) m/z 346 [M + H]⁺.

Step 4 1- (4- (4-amino-6-bromo-7-methyl-7H-pyrrolo [2,3-*d*] pyrimidin-5-yl) phenyl-2,3,5,6-*d*4) imino) tetrahydro-1H-1 λ⁶-thiophene-1-oxide 114e

Compound **114d** (94 mg, 0.27 mmol) was dissolved in DMF (2 mL), and a solution of NBS in DMF (51 mg of NBS dissolved in 2 mL of DMF) was added dropwise in an ice water bath, and reacted under ice water bath for 1 h, and TLC showed the formation of new spots. The reaction was quenched with added saturated NaHSO₃ solution (10 mL) and H₂O (20 mL), extracted with dichloromethane (20 mL x 3), and the organic phases were combined, washed with saturated saline solution, dried over anhydrous sodium sulfate, concentrated under reduced pressure, and purified by silica gel column chromatography to obtain **114e** (70 mg), yellow solid.

MS (ESI) m/z 425 [M + H]⁺.

Step 5 N- (4- (4-amino-7-methyl-5- (4- ((1-oxide tetrahydro-1 λ⁶-thiophene -1-ylidene) amino) phenyl-2,3,5,6-*d*4) -7H-pyrrolo [2,3-*d*] pyrimidin-6-yl) -3- fluorophenyl) methacrylamide 114

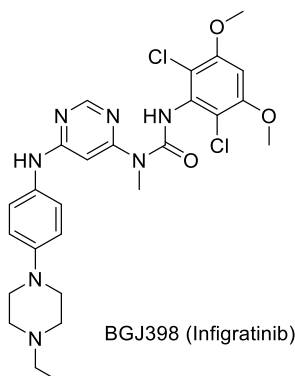
To a reaction flask, compound **114c** (70 mg, 0.16 mmol), 1,4-dioxane (4 mL), water (1 mL), compound **1j** (60 mg, 0.20 mmol), potassium phosphate (104 mg, 0.49 mmol), and Pd(PPh₃)₄ (9 mg, 0.016 mmol) were added in sequence, after replaced with nitrogen gas three times, the reaction was refluxed at 90 °C for 5 h. TLC showed the formation of new spots, and after the reaction was completed, it was cooled down to room temperature, and the reaction solution was diluted with dichloromethane and H₂O. After filtered through diatomaceous earth, it was extracted

with dichloromethane, and the organic phase was washed with saturated saline solution, dried over anhydrous sodium sulfate, concentrated under reduced pressure, and purified by silica gel column chromatography (DCM/MeOH=10/1) to obtain compound **114** (5.0 mg), white solid.

MS (ESI) m/z 523.2 $[M + H]^+$.

- 5 ^1H NMR (400 MHz, DMSO- d_6) δ 10.11 (s, 1H), 8.20 (s, 1H), 7.77 (dd, $J = 12.4, 1.9$ Hz, 1H), 7.50 (dd, $J = 8.5, 1.9$ Hz, 1H), 7.28 (t, $J = 8.4$ Hz, 1H), 5.84 (s, 1H), 5.59 (s, 1H), 3.54 (s, 3H), 3.38 (d, $J = 6.7$ Hz, 2H), 3.28 – 3.22 (m, 2H), 2.26 – 2.06 (m, 4H), 1.97 (s, 3H).

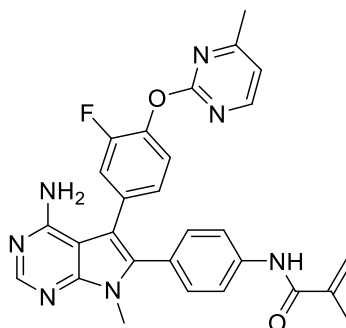
Internal control compound BGJ398



10

This compound was purchased commercially, manufacturer: MCE, item number: HY-13311

Control compound I



15

It was synthesized with reference to WO2020231990A1.

Test Example 1: the test of compounds on cell viability of Ba/F3 Cells

In this experiment, the inhibitory effect of compounds on cell proliferation was studied by detecting their effects on in vitro cell viability of Ba/F3 cell lines (Ba/F3-TL-FGFR1, Ba/F3-TL-FGFR2, Ba/F3-TL-FGFR3). BGJ398 is an internal control compound in this project, a cell line stably expresses the fusion protein of the intracellular kinase domain of TEL-FGFR subtype obtained by transfection into Ba/F3 cells (Hefei PreceDo Biomedical Technology Co., Ltd.) for testing.

20 The cell line was cultured in a incubator under the culture condition of 37 °C and 5% CO₂, regularly passaged, and cells in logarithmic growth phase were taken for plating. The test

25

compounds and the internal control compound BGJ398 were prepared into a 10 mM solution using DMSO.

Preparation of compound stock plate (tube): It was diluted with DMSO from the highest concentration to the lowest concentration in a 4-fold gradient, for a total of 9 concentrations, and the internal control compound was diluted with 4-fold diluent, for a total of 9 concentrations. Then, the preparation of the compound working solution: 98 μ L cell culture medium was added to a flat bottomed 96 well transparent drug plate, and 2 μ L compound was aspirated from the compound stock plate and added to the cell culture medium in 96 well transparent drug plate. 2 μ L DMSO was added to the solvent control. After the compound or DMSO was added, and then mixed well by blowed with a pipette.

Cell plating and administration: Suspension cells were plated according to the following steps: 1) cells were stained with trypan blue, and live cells were counted to ensure a cell viability rate of over 90%; 2) the cell concentration was adjusted to an appropriate level; 3) 95 μ L cell suspension (2000 cells/cell) was added to each well of the detection cell plate of compounds, and culture medium without cells (containing 0.1%) was added to the Min control well; 4) administration in cell plate for compounds detection: 5 μ L of 20 $\times$ compound working solution was taken and added to the cell culture plate as shown in Table 1. 5 μ L DMSO cell culture medium mixture was added to the Max control. The final concentration of DMSO was 0.1%; 5) the culture plate was cultured in a 37 $^{\circ}$ C, 5% CO₂ incubator for 72 h.

It was performed according to the instructions of the PromegaCellTiter Glo luminescent cell viability assay kit (Promega-G7573): 1) the CellTiter Glo buffer was thawed and placed to room temperature; 2) the CellTiter Glo substrate was placed to room temperature; 3) CellTiter Glo buffer was added to a bottle of CellTiter Glo substrate to dissolve the substrate and prepare CellTiter Glo working solution; 4) slow vortex oscillation for sufficient dissolution; 5) the cell culture plate was taken out and placed for 10 min for equilibrated to room temperature; 6) 50 μ L (equivalent to half the volume of cell culture medium in each well) of CellTiter Glo working solution was added to each well; 7) the culture plate was shaken on the track shaker for 2 min to induce cell lysis; 8) the culture plate was placed at room temperature for 10 min to stabilize the luminescence signal; 9) the luminous signal was detected on the SpectraMaxParadigm reader.

The data on inhibition rate of cell proliferation was processed using the following formula:

$$\text{Inhibition Rate (Inh\%)} = 100 - (\text{RLU}_{\text{Drug}} - \text{RLU}_{\text{Min}}) / (\text{RLU}_{\text{Max}} - \text{RLU}_{\text{Min}}) * 100\%.$$

The inhibition rates of compounds at different concentrations were calculate in EXCEL, then GraphPad Prism software was used to make inhibition rate curves and calculate relevant parameters, including maximum and minimum cell inhibition rates, IC₅₀ values.

Table 1 Results of proliferation inhibition of test compounds on Ba/F3 cell lines (Ba/F3-TEL-FGFR₁, Ba/F3-TEL-FGFR₂, Ba/F3-TEL-FGFR₃)

Compound number	Ba/F3 cell		
	FGFR2 (IC ₅₀ nM)	FGFR1 (IC ₅₀ nM)	FGFR3 (IC ₅₀ nM)
BGJ398	4.2	11.3	6.7
Control compound I	2.5	1323	1615
1	2.3	656.1	869.2

2	11.2	1509	846.5
3	699.7	-	-
4	9.9	2371	3361
5	29.3	-	-
6	9.3	-	-
7	2.4	626.8	544.9
8	0.7	600.3	-
9	14.9	-	-
10	106.6	-	-
11	171.8	-	-
12	275.7	-	-
13	0.6	-	-
14	9.9	-	-
15	15.4	-	-
16	50.1	-	-
17	4616	-	-
18	21.5	-	-
19	2982	-	-
20	86.7	-	-
21	0.8	-	-
22	2.7	716.7	-
23	0.7	568.2	-
24	2.1	1909	-
25	38.7	-	-
26	4.5	-	109.6
27	26.0	-	-
28	0.9	-	-
29	1209	-	-
30	1442	-	-
31	8.3	2094	-
32	0.4	-	-
33	11.2	2310	1292
34	17.9	-	-

35	4.4	-	-
36	53.5	-	-
37	32.0	-	-
38	246.9	-	-
39	10.2	-	-
40	7.7	-	-
41	123.6	-	-
42	32.9	-	-
43	14.2	-	-
44	216.4	-	-
45	83.1	-	-
46	161.7	-	-
47	2.7	-	-
48	0.9	625.1	577.3
49	12.8	-	-
50	7.6	-	-
51	19.1	-	-
52	2.3	-	-
53	10.2	-	-
54	2.8	-	-
55	3.0	-	-
56	12.6	-	-
57	17.4	-	-
58	3.0	2026	441.7
59	7.8	1316	-
60	13.1	-	-
61	150.2	-	-
62	9.2	-	-
63	1.1	395.9	-
64	658.3	-	-
65	120.9	-	-
66	27.8	-	-
67	105.0	-	-

68	0.5	-	-
69	11.4	-	-
70	2.7	774.6	-
71	2.5	-	-
72	2.2	-	-
73	11.1	-	-
74	0.5	299.6	-
75	0.8	700.9	-
76	6.1	-	-
77	4.7	883.7	-
78	585.1	-	-
79	61.1	-	-
80	46.0	-	-
81	18.1	-	-
82	0.8	484.1	-
83	1.1	660.7	319.2
84	0.8	250.4	-
85	907.3	-	-
86	67.4	-	-
87	2.1	665.7	-
88	1.5	561.1	215.9
89	6.5	685.9	-
90	3.6	-	173.8
91	23.9	-	-
92	0.8	-	-
93	31.7	-	-
94	1.1	625.4	204.7
95	0.7	483.6	-
96	29.8	-	-
97	1.9	479.8	-
98	0.6	416.1	-
99	2.7	-	-
100	1.9	823.2	414.4

101	4.7	-	-
102	0.6	-	-
103	13.9	-	-
104	0.9	640.1	-
105	20.9	-	-
106	2.2	-	-
107	15.6	3629	-
108	2.5	-	-
109	4.5	-	-
110	2.0	-	-
111	<0.15	-	-
112	2.0	-	-
113	1.8	-	-
114	1.2	-	-

-: Not tested

As can be seen from the above table, the compounds of the present invention have a good inhibitory effect on the proliferation in Ba/F3-TEL-FGFR2 cells, and exhibit high selectivity on Ba/F3-TEL-FGFR1 and Ba/F3-TEL-FGFR3.

5

Test Example 2: Human Liver Microsomes Stability Test

Human liver microsomes stability test was performed by co-incubating compounds with human liver microsomes in vitro. Firstly, a 10 mM stock solution of the test compound in DMSO solvent was prepared, and then the compound was diluted with methanol to a 0.15 mM working solution. A certain amount PBS, 12mM MgCl₂, human liver microsomes (Corning), and compound working solution were mixed to achieve a compound concentration of 1.0 μM, a human liver microsome concentration of 0.5 mg/mL, and the MgCl₂ concentration of 3 mM in the reaction system. A deep well plate was taken, 270 μL microsomal buffer mixture solution was added to each well, and then 30 μL preheated 10 mM NADPH solution was added to initiate the reaction, and it was incubated at 37 °C. At 0, 5, 15, 30, and 60 min of incubation, 200 μL methanol: acetonitrile = 1: 1 containing an internal standard was added to the corresponding well to terminate the reaction. After the reaction was terminated at the last 60 min, the deep well plate was subjected to vortex vibration for 5 min (600 rpm/min), and then centrifugated for 10 min. After centrifugation, the supernatant was taken, and purified water was added at a 1:1 ratio for LC-MS/MS detection, and the peak area ratio of the compound to the internal standard at each time point was obtained, and the peak area ratio of the compound at 5, 15, 30, and 60 min was compared with the peak area ratio at 0 minute to calculate the remaining percentage of the compound at each time point, and T_{1/2} was calculated using Graphpad 7 software.

25

Table 2 Results of human liver microsomes stability test

Compound	Remaining percentage of compound after 60 min of incubation (%)	T _{1/2} (min)	CL _{int} (mL/min/kg)
Control compound I	36.4	42.0	29.7
2	54.0	69.3	18.0
4	61.6	85.6	14.6

The experimental results showed that compared with the control compound I, the compound of the present invention exhibited better liver metabolic stability and better druggability.

Test Example 3: Pharmacokinetic Test in Rats

5 Rat pharmacokinetic experiments were performed using male SD rats, 180-220g, provided by Beijing Vital River Laboratory Animal Technology Co., Ltd. 3 rats that were fasted overnight were taken, and administered orally by gavage (10 mg/kg). Blood samples were collected before administration, as well as 5, 15, 30 min and 1, 2, 4, 6, 8, 24 h after administration; another 3 rats were taken and administered intravenously (1 mg/kg), blood samples were collected before
10 administration, as well as 5, 15, 30 min and 1, 2, 4, 6, 8, 24 h after administration. Blood sample was centrifuged at 6800g, 2-8 °C for 6 min, and plasma was collected, and stored at -80 °C. Plasma of each time point was taken, 10 times the amount of 50% methanol acetonitrile solution containing internal standard was added, and mixed by vortex for 5 min, centrifuged at 18000 rpm at 4 °C for 10 min, and the supernatant was taken directly for LC-MS/MS analysis. The main
15 pharmacokinetic parameters were analyzed using WinNonlin8.2 software for non compartmental model analysis.

Table 3: pharmacokinetic test in rats results of test compounds

Compound	Pharmacokinetic parameters in rats (Oral gavage administration) (10 mg/kg)			
	C _{max} (ng/mL)	T _{max} (hr)	AUC _{0-t} (h*ng/mL)	T _{1/2} (hr)
Control compound I	141	0.67	606	0.85
8	352	0.25	630	1.81
24	270	0.25	871	1.43
33	306	0.42	778	1.32
48	212	0.83	883	3.44
58	604	0.50	1423	3.18
63	556	0.5	1696	2.59
83	414	0.33	1483	1.87

The results of pharmacokinetic test in rats showed that the compounds in the present invention have high oral exposure, good pharmacokinetic properties, and good druggability.

Test Example 4: Manual Patch Clamp Technique for Detecting the Effect of Test Compounds on Stable Overexpressed hERG Channel Current

4.1. Preparation of Test Compound

5 A small amount of compound 24 was weighed, and prepared into a 31.346 mM stock solution using DMSO. The test compound stock solution was diluted with DMSO to 10 mM, 3.33 mM, 1 mM, 0.33 mM, and 0.1 mM diluent in sequence. The test compound diluents were diluted with extracellular fluid containing 0.5% F68 in sequence to prepare working solutions of 30 μ M, 10 μ M, 3 μ M, 1 μ M and 0.3 μ M, and 0.3% DMSO was ensured. All concentrations were dissolved without visible precipitation.

10 A small amount of control compound I was weighed, and prepared into a 31.311 mM stock solution using DMSO. The test compound stock solution was diluted with DMSO to 10 mM, 3.33 mM, 1 mM, 0.33 mM, and 0.1 mM diluent in sequence. The test compound diluents were diluted with extracellular fluid containing 0.5% F68 in sequence to prepare working solutions with concentrations of 30 μ M, 10 μ M, 3 μ M, 1 μ M and 0.3 μ M, and 0.3% DMSO was ensured. All concentrations were dissolved without visible precipitation.

15 The positive control Cisapride was prepared into a 10 mM stock solution using DMSO. Cisapride stock solution was diluted with DMSO to 1 mM, 333.33 μ M, 33.33 μ M, 3.33 μ M, 0.33 μ M, and 0.033 μ M diluent in sequence. Cisapride diluent was diluted with extracellular fluid in sequence to prepare working solutions of 1000 nM, 100 nM, 10 nM, 1 nM and 0.1 nM, and 0.3% DMSO was ensured. All concentrations were dissolved without visible precipitation.

4.2 Cell Culture

25 The HEK-293 cell line stably expressing hERG potassium channels was cultured in DMEM medium containing 10% fetal bovine serum and 0.8 mg/mL G418 at a temperature of 37 °C and a carbon dioxide concentration of 5%. Cells were inoculated into 6 cm cell culture dishes, with a total of 2.5×10^5 cells per dish (final volume: 5 mL). To maintain the electrophysiological activity of cells, the cell density must not exceed 80%. Before patch clamp detection, cells were isolated with TrypLE™ Express, 4×10^3 cells were spread onto cover glass, and cultured in a 24 well plate (final volume: 500 μ L) for 18 h, and then experimental test was performed.

30

4.3. Patch Clamp Detection

35 The voltage stimulation protocol for recording hERG currents using whole cell patch clamp was as follows: when a whole cell seal was formed, the cell membrane voltage was clamped at -80 mV. The clamping voltage was reduced from -80 mV to -50 mV and maintained for 0.5 s (as a leakage current detection), and then stepped up to 30 mV and maintained for 2.5 s, and then quickly restored to -50 mV and maintained for 4 s to excite the tail current of the hERG channel. Data was collected repeatedly every 10 s to observe the effect of the drug on hERG tail current. The experimental data was collected by IPA amplifier (Sutter Instrument) and stored in SutterPatch (with Igor Pro) software.

40 When the hERG current recorded by the whole cell was stabilized, administration began, and each drug concentration acted for about 5 min (or until the current was stabilized), and then the next concentration was detected, multiple concentrations were detected for each test compound. The cover glass covered with cells was placed in the recording bath under an inverted microscope,

the blank control solution and the test compound working solution sequentially flowed through the recording bath from low concentration to high concentration using gravity perfusion to act on the cells, liquid exchange was performed using a peristaltic pump during recording. The current of each cell detected in the extracellular fluid without the compound serves as its own control group.

- 5 Each concentration should be independently tested twice using at least two cells. All electrophysiological tests were performed at room temperature.

4.4 Test Results

- 10 The inhibitory effects of compound **24** and control compound I on hERG channels were detected in two independent replicate tests, and the IC₅₀ values of the test compounds on hERG current were calculated by fitting the concentration effect curve. The test results were as follows:

Table 4. Inhibition rates and IC₅₀ results of compound I and compound 24 on hERG current

Compound	HERG current inhibition rate% (Mean ± SE)					n	IC ₅₀
	0.3 μM	1 μM	3 μM	10 μM	30 μM		
Control compound I	6.28% ± 0.31%	16.23% ± 0.51%	28.98% ± 0.56%	64.51% ± 1.31%	89.42% ± 0.20%	2	6.046 μM
24	-1.24% ± 1.48%	7.73% ± 0.87%	10.17% ± 0.62%	32.17% ± 2.92%	14.21% ± 2.95%	2	>10 μM

- 15 The experimental results show that compared with the control compound I, the compound of the present invention have weak inhibition on hERG and have good safety.

Test Example 5: In Vitro Evaluation of The Inhibitory Effect of The Test Compound on Cytochrome P450 Enzyme

5.1 Experimental Materials

- 20 5.1.1 Human liver microsomes

Vendor	CAS	Cat No.	Lot No.	Concentration
CORNING	NA	452161	1151001	20 mg/mL

5.1.2 Positive control

Name	Vendor	Cat No.	Lot No.	Concentration of stock solution	Solvent
α-naphthoflavone	SIGMA	604-59-1	SLBN2386V	0.3 mM	DMSO
Sulfamethoxazole	J&K	178125	LP20Q121	10 mM	DMSO
Omeprazole	TCI	73590-58-6	X5JEB	100 mM	DMSO
Quinidine	Energy Chemical	56-54-2	99OXROHQ	10 mM	DMSO
Ketoconazole	J&K	973125	LI30P36	2.5 mM	DMSO

5.1.3 Probe substrate

Name	Vendor	Cat No.	Lot No.	Concentration of stock	Solvent
------	--------	---------	---------	------------------------	---------

				solution	
Phenacetin	aladdin	NA	F2101248	30mM	DMSO
Diclofenac acid	TCI	D3748	U5XOJ	10mM	DMSO
S-methomyl	MCE	HY-B1184	117020	35mM	DMSO
Dextromethorphan hydrobromide	National Institute for Food and Drug Control	6700-34-1	100201-201204	5 mM	DMSO
Testosterone	aladdin	NA	F2126139	80mM	DMSO
Midazolam	National Institute for Food and Drug Control	59467-70-8	171265-201402	5 mM	DMSO

5.1.4 Internal standard

Name	Vendor	Cat No.	Lot No.
Toluene sulfonamide	Supelco	T0891	SLCK4822
Verapamil	TCI	V0118	RFMWJ

5.1.5 Other reagents

Name	Vendor	Cat No.	Lot No.
NADPH	MCE	HY-F0003	139299
Phosphate buffered saline (PBS)	Yuanpei	B320KJ	K211021

Termination solution containing internal standard: toluene sulfonamide concentration of 20.0 ng/mL, verapamil concentration of 10.0 ng/mL

5.2 Experimental Preparation

Preparation of positive control inhibitor and compound working solution: 16 μ L inhibitor stock solution or compound stock solution for each CYP subtype were taken and added to 24 μ L DMSO. Then, they were diluted gradually three times with diluent to obtain different concentrations of test sample/positive control inhibitor working solution (7 concentrations each except for blank)

Preparation of substrates for each CYP subtype: Preparation of substrates for each CYP subtype: for CYP1A2, CYP2C9, CYP3A4 (midazolam), and CYP2D6, 8 μ L substrate stock solution was added to 1992 μ L PBS; for CYP2C19, 40 μ L substrate stock solution and 160 μ L human liver microsomes (20.0 mg/mL) were added to 1800 μ L of PBS; for CYP3A4 (testosterone), 40 μ L substrate stock solution was added to 1960 μ L PBS.

Preparation of liver microsomal working solution: 300 μ L human liver microsomes (20.0 mg/mL) was taken and added to 29700 μ L PBS and mixed well, and the concentration of the prepared human liver microsomal working solution was 0.200 mg/mL.

Preparation of 4 x NADPH working solution: A certain weight of NADPH tetrasodium salt was weighted and dissolved to a suitable volume of PBS to obtain NADPH working solution, with a concentration of 8.00 mM.

Preparation of test sample group working solution: The human liver microsomal working solution was divided into 96 well plates at 796 μL per well, and then 4 μL test sample working solution was added.

Preparation of positive control group working solution: The human liver microsomal working solution was divided into 96 well plates at 199 μL per well, and then 1 μL positive control inhibitor working solution was added.

Blank solvent working solution preparation: The human liver microsomal working solution was divided into 96 well plates at 199 μL per well, and then 1 μL DMSO was added.

5.3 Experimental steps

(a) 30 μL test sample/positive control inhibitor working solution or 30 μL blank solvent working solution per well were transferred into a 96 well plate, and 15 μL substrate working solution of different enzyme subtypes transferred into each well, and mixed evenly.

(b) The above incubation plates and 4 $\times$ NADPH working solution were preheated at 37 $^{\circ}\text{C}$ for 5 min.

(c) 15 μL preheated 4 $\times$ NADPH working solution per well was transferred into the incubation plate, and the reaction initiated, and continued to be incubated at 37 $^{\circ}\text{C}$. The incubation time is as follows:

CYP	Substrate	Final concentration (μM)	Inhibitor	Final highest concentration (μM)	Liver microsomal concentration (mg/mL)	Incubation time (min)
1A2	Phenacetin	30.0	α - naphthoflavone	0.300	0.100	10
2C9	Diclofenac acid	10.0	Sulfamethoxazole	10.0	0.100	10
2C19	S-meifentuin	35.0	Omeprazole	100	0.500	45
2D6	Dextromethorphan	5.00	Quinidine	10.0	0.100	20
3A4	Testosterone	80.0	Ketoconazole	2.50	0.100	5
3A4	Midazolam	5.00	Ketoconazole	2.50	0.1	5

(d) After the reaction time was reached, 180 μL termination solution was added to terminate the reaction.

(e) The incubation plate was vibrated at 600 rpm for 10 min, and then centrifuged at 6000 rpm for 15 min.

(f) After centrifugation, 80 μL supernatant was taken and added to 120 μL ultrapure water, and after it was mixed evenly, LC-MS/MS was used to analyze the metabolites of the probe substrate.

Table 5 Inhibition tests results of control compound I and the compounds of the present invention on CYP subtypes

Compound	IC ₅₀ (μM)					
	1A2	2C9	2C19	2D6	3A4 (Testosterone)	3A4 (Testosterone)

Control compound I	>10	1.68	7.78	1.50	11.84	10.85
9	-	-	-	24.61	-	13.52
24	>10	29	19.37	14.27	10.68	-
33	-	-	-	9.52	-	19.19
56	-	-	-	5.54	-	13.23
58	>10	29.68	5.42	9.81	>10	-
83	>10	14.40	14.13	8.77	11.57	-

-: Not tested

The experimental results indicate that compared with the control compound I, the compounds of the present invention have weaker inhibitory effects on CYP subtypes and have lower potential drug interaction risks.

5

Test Example 6: In Vitro Evaluation of Rat Liver Cells Metabolic Stability of Test Compound

6.1 Rat liver cells and reagents

Species	Strain	Cat No.	Lot No.	Gender	Supplier
Rat	SD	M00005	DVB	Male	BioIVT

10

Reagent	Vendor	Cat No.
Isotonic percoll	Cytiva	10303640
HEPES	Sigma	RNBH8969
DPBS	Gibco	2224922
FBS	Corning	35-076-CV
Human-insulin	Gibco	12585-014
Dexamethasone	NICBPB	-
Williams E Medium	Gibco	2336217
GlutaMAX (100x)	Gibco	22777239

6.2 Experimental Design

6.2.1 Preparation of compound working solution

Test compound and control drug verapamil powder were prepared into 10 mm stock solution using DMSO, and they were diluted with 50% acetonitrile/50% water to 100 μ M working solution before use.

15

6.2.2 Preparation of liver cells

1) 49.5 mL Williams E Medium and 0.5 mL glutaMAX were mixed as incubation medium. The liver cell resuscitation solution and incubation solution were preheated in a 37 °C water bath for at least 15 min before use.

20

2) A tube of liver cells stored at ultra-low temperature was taken and ensured that they remain in a low-temperature frozen state before resuscitation. The liver cells were placed quickly in a 37 °C water bath and shaken gently until all ice crystals were dispersed.

3) The contents of the liver cells tubes were poured into a centrifuge tube containing 50 mL of resuscitation medium, and they were centrifuged at 100 g for 10 min. After centrifugation, the resuscitation medium was aspirated, and sufficient incubation medium was added to obtain a cell suspension with a cell density of approximately 1.0×10^6 cells/mL.

4) AO/PI staining was used to count liver cells and determine viable cell density, the survival rate of liver cells must be greater than 75%. The liver cell suspension was diluted with incubation medium to a viable cell density of 0.5×10^6 cells/mL.

6.3 Experimental Methods

1) 198 μ L live cell suspension was transferred to a 96 well deep well plate, and the deep well plate was placed on a vortex and preheat in the incubator for 10 min.

2) 2 μ L 100 μ M test compound or positive control compound was added to each well for reaction initiation, and the deep well plate was placed back on the incubator vortex.

3) The incubation plate was placed into the incubator for incubation. 25 μ L suspension was taken at 0.5, 15, 30, 60, 90, and 120 min, and 6-fold (150 μ L) acetonitrile containing internal standard quencher (100 nM alprazolam, 200 nM caffeine, and 100 nM toluenesulfonylbutamide) was added to a new 96 well plate to terminate the reaction. The plate was vortexed for 5 min and centrifuged at 3220 rpm and 4 $^{\circ}$ C for 45 min to precipitate the protein. 100 μ L of supernatant was transferred to the sample plate, and 100 μ L pure water was added and mixed well for UPLC-MS/MS analysis. All incubation systems were conducted in a dual parallel manner.

6.4 Data Analysis and Experimental Results

All data was calculated using Microsoft Excel software. Peak area was detected by extracting ion chromatogram. In vitro half-life ($T_{1/2}$) and in vitro clearance rate (in μ L/min/ 10^6 cells) of the parent drug were detected by linearly fitting of the natural logarithm of the elimination percentage of the parent drug versus time.

Table 6 Results of rat liver cell stability test

Compound	Remaining percentage of compound after 60 min of incubation (%)	in vitro $t_{1/2}$ (min)	in vitro CL_{int} (μ L/min/ 10^6 cells)
Control compound I	18.14	24.52	56.66
23	24.45	28.65	48.40
24	37.55	37.34	37.13
83	35.86	37.15	37.31

The experimental results showed that compared with the control compound I, the compounds in the present invention exhibited better liver cell metabolic stability and better druggability.

Test Example 7: The Test of The Proliferation Inhibitory Activity of Compounds on SNU16 and A204 Cells

CCK-8 (Bimake/B34304) colorimetric method was used to detect the in vitro proliferation inhibitory effect of compounds on suspended or adherent cells in this experiment. The specific experimental steps were as follows:

1) Cell plating: SNU16 and A204 tumor cells (cells from Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences) in the logarithmic growth phase were digested and

centrifuged for trypan blue counting, and the cells were seeded into a transparent 96 well plate at a density of 4000 cells/100 μ l/well. Blank control group: only culture medium was added.

2) Preparation of working solution: The test compound and internal control compound BGJ398 were both prepared into 10 mM stock solutions using DMSO. The test compound and control compound stock solution were diluted with the corresponding culture medium required for cell culture (with or without solvent DMSO) to obtain a series of working solutions, with concentrations of twice the final concentration. The solvent DMSO contents in each concentration group were consistent with that of the solvent control group. The final concentration of A204 cells started at 10 μ M and was diluted twice. The final concentration of SNU-16 cells started at 1 μ M and was diluted 4-fold.

3) Co-incubation: After 24 h of plate plating, 100 μ l/well mother solution of compound with series concentration was added to a 96 well plate and mixed well, then co-cultured for 72 h. All groups should have at least 4 replicates, with 10 concentrations of each compound. Blank control group: Only culture medium was added, and no cells or drugs were added, to eliminate interference from the contrast color of the culture medium.

4) Measurement of absorbance: 30 μ l of CCK8/culture medium (1: 2) mixed system was added to each well, and co-cultured for 2 h, then shaken thoroughly to make it uniform, and the absorbance values at A450 and A650 were measured on a BioTek Synergy H1 enzyme-linked immunosorbent assay reader.

5) Process of data: The raw data of A450-A650 was obtained, the cell survival rates of each treatment well were obtained, and a nonlinear regression model was used to calculate the IC₅₀ values of the compound on different cells.

Calculation of cell survival rate: Cell survival rate (%)=[(As-Ac)/(Ab-Ac)] $\times$ 100%] (As: experimental well; Ab: Solvent control well; Ac: Blank well).

Table 7 Results of proliferation inhibition of test compounds on SNU16 and A204 cell lines

Compound number	Cells	
	SNU16(IC ₅₀ nM)	A204(IC ₅₀ nM)
BGJ398	4.3	100
Control compound I	13.2	3220
1	5.57	1314
7	5.43	582.7
8	1.34	618
21	1.72	332.7
22	4.97	1606
23	2.4	617.6
24	1.59	678.9
26	3.36	285.4
32	9.56	2250

35	4.91	406.4
48	13.8	1350
58	9.52	1271
63	8.71	459.7
68	1.65	267.4
74	1.19	595
83	1.89	627.1
87	7.74	3595
88	5.01	858.4
97	2.66	763.7
98	1.81	845.4
100	4.78	642.2
102	2.63	502
104	5.51	1018
109	9.38	1045

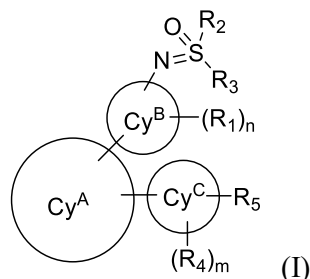
As can be seen from the above table, the compounds of the present invention have a good proliferation inhibitory effect on SNU-16 cells and weak proliferation inhibitory activity on A204 cells, which showed high selectivity.

- 5 All references mentioned in the present invention are cited as references in this application, as if each reference were cited separately. In addition, it should be understood that after reading the above teaching content of the present invention, those skilled in the art can make various changes or modifications to the present invention, and these equivalent forms also fall within the scope of the claims attached to this application.

10

Claims

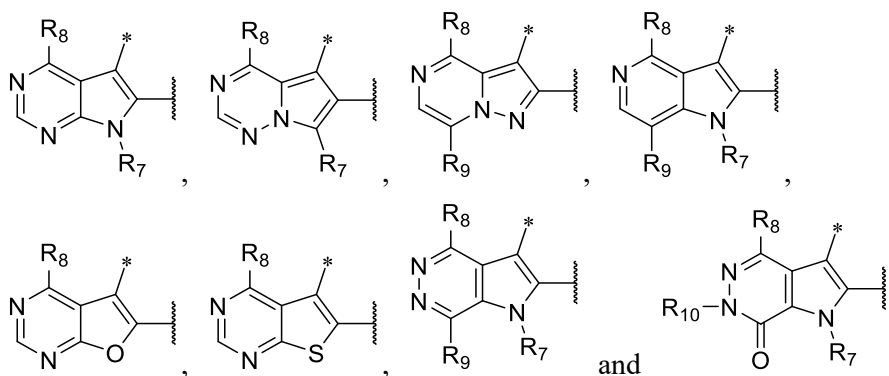
1. A compound as shown in formula (I), a tautomer, a stereoisomer, a hydrate, a solvate, or a pharmaceutically acceptable salt thereof:



5

wherein, n and m are each independently 0, 1, 2, or 3;

Cy^A is selected from the group consisting of:



10

wherein denotes a bond connected to Cy^B, and denotes a bond connected to Cy^C;

Cy^B is selected from the group consisting of: C₆₋₁₀ aryl and 5-12 membered heteroaryl;

Cy^C is selected from the group consisting of: C₆₋₁₀ aryl, 5-12-membered heteroaryl, saturated or partially unsaturated C₃₋₆ carbocyclyl and saturated or partially unsaturated 4-12-membered heterocyclyl;

15

R₁ is selected from the group consisting of: H, D, halogen, CN, OH, NH₂, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkyl, C₁₋₆ haloalkoxy, C₁₋₆ alkylamino, C₂₋₄ alkenyl, C₁₋₄ haloalkenyl, C₂₋₄ alkynyl, C₁₋₄ haloalkynyl, C₃₋₆ saturated or partially unsaturated carbocyclyl, C₃₋₆ halogenated saturated or partially unsaturated carbocyclyl, C₃₋₆ saturated or partially unsaturated carbocyclyl-O-, SF₅ and 4-12 membered heterocyclyl;

20

R₂ and R₃ are each independently selected from the group consisting of: C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkyl, C₁₋₆ haloalkoxy, C₁₋₆ alkylamino, C₃₋₆ saturated or partially unsaturated carbocyclyl and 4-12-membered heterocyclyl; wherein R₂ and R₃ can be the same or different;

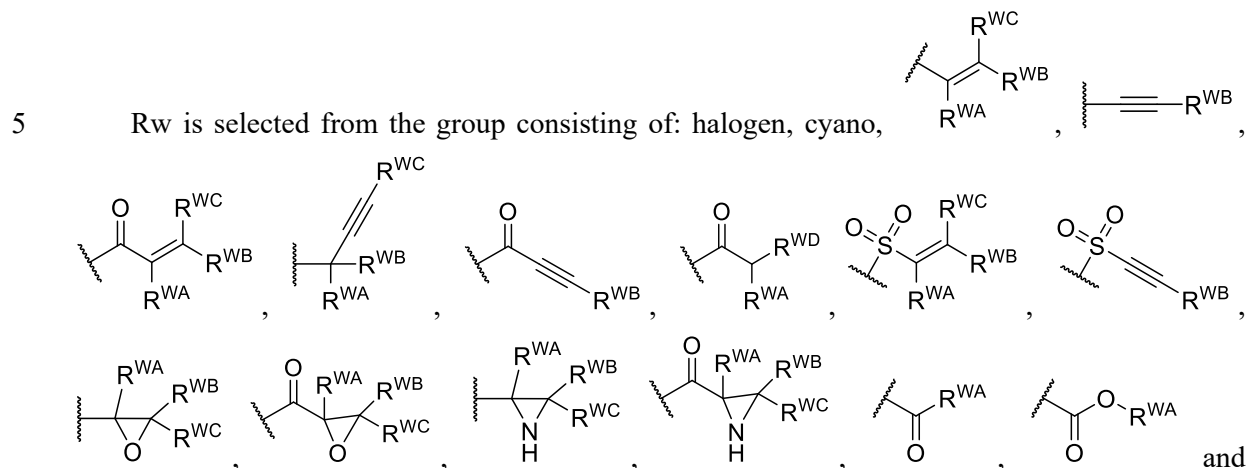
or R₂ and R₃ together with the sulfur atom to which they are connected form a 4-12-membered heterocyclyl;

25

R₄ is selected from the group consisting of: H, D, halogen, CN, OH, NH₂, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkyl, C₁₋₆ haloalkoxy, C₁₋₆ alkylamino, C₂₋₄ alkenyl, C₁₋₄ haloalkenyl, C₂₋₄ alkynyl, C₁₋₄ haloalkynyl, C₃₋₆ saturated or partially unsaturated carbocyclyl, C₃₋₆ halogenated saturated or partially unsaturated carbocyclyl, C₃₋₆ carbocyclyl-O-, SF₅ and 4-12-membered heterocyclyl;

R₅ is -L-R_w, wherein L is selected from the group consisting of: covalent bond, -C₁₋₄ alkyl-, -NR₆-, -C₁₋₄ alkyl NR₆-;

R₆ is selected from the group consisting of: H, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkyl and C₁₋₆ haloalkoxy;



5-12-membered nitrogen-containing heterocyclyl;

10 R^{WA}, R^{WB}, and R^{WC} are each independently selected from the group consisting of: H, D, halogen, CN, C(O)Ra, C(O)ORa, NRaRb, C(O)NRaRb, C(O)NRaORb, or selected from the group consisting of: C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkyl, C₁₋₆ haloalkoxy, phenyl, 3 to 7-membered saturated or partially unsaturated heterocyclyl with 1 to 2 heteroatoms independently selected from nitrogen, oxygen and sulfur, and 5 to 6-membered heteroaryl with 1 to 4 heteroatoms independently selected from nitrogen, oxygen and sulfur; and the R^{WA}, R^{WB}, and R^{WC} can each be independently substituted with 1, 2, or 3 substituents selected from the group consisting of: C₁₋₆ alkylamino and C₁₋₆ alkoxy;

or R₆ and R_w together form a ring; and the ring is selected from the group consisting of: 5-12 membered heteroaryl and 4-12 membered heterocyclyl;

20 R₇ is selected from the group consisting of: H, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkyl, C₁₋₆ haloalkoxy, C₁₋₆ alkylamino, C₂₋₄ alkenyl, C₁₋₄ haloalkenyl, C₂₋₄ alkynyl, C₁₋₄ haloalkynyl, C₃₋₆ saturated or partially unsaturated carbocyclyl, C₃₋₆ halogenated saturated or partially unsaturated carbocyclyl, C₆₋₁₀ aryl, 5-12 membered heteroaryl, 4-12-membered heterocyclyl; or R₄ and R₇, as well as the atoms between them, together form a ring, and the ring is selected from the group consisting of: C₆₋₈ saturated or partially unsaturated carbocyclyl, C₆₋₁₀ aryl, 6-12 membered heteroaryl and 6-12 membered saturated or partially unsaturated heterocyclyl;

25 R₈ is selected from the group consisting of: H, OH, NH₂, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkyl, C₁₋₆ haloalkoxy and C₁₋₆ alkylamino;

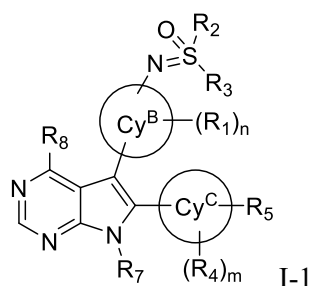
R₉ is selected from the group consisting of: H, D, halogen, CN, NH₂, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkyl, C₁₋₆ haloalkoxy and C₁₋₆ alkylamino;

30 unless otherwise specified, each of the above-mentioned alkyl, alkoxy, haloalkyl, haloalkoxy, alkylamino, alkenyl, haloalkenyl, alkynyl, haloalkynyl, saturated or partially unsaturated carbocyclyl, halogenated saturated or partially unsaturated carbocyclyl, saturated or partially unsaturated heterocyclyl, aryl and heteroaryl can be substituted with one or more Ra;

Ra and Rb are each independently selected from H, D, halogen, CN, oxo (=O), OH, NH₂, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkyl, C₁₋₆ haloalkoxy, C₁₋₆ alkylamino, C₂₋₄ alkyenyl, C₁₋₄ haloalkenyl, C₂₋₄ alkynyl, C₁₋₄ haloalkynyl, C₃₋₆ saturated or partially unsaturated carbocyclyl, C₃₋₆ halogenated saturated or partially unsaturated carbocyclyl, C₃₋₆ saturated or partially unsaturated carbocyclyl-O-, 4-12 membered heterocyclyl;

wherein, the heterocyclyl is a saturated or partially unsaturated non-aromatic group; the carbocyclyl or heterocyclyl can be optionally in the form of a monocycle, bridged ring, spirocycle, or fused ring.

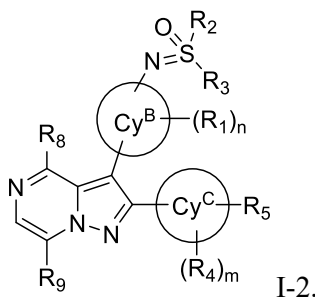
2. The compound according to claim 1, or a tautomer, a stereoisomer, a hydrate, a solvate, or a pharmaceutically acceptable salt thereof, wherein, the compound has a structure as shown in formula (I-1):



wherein, R₁, R₂, R₃, R₄, R₅, R₇, R₈, Cy^B and Cy^C are as defined in claim 1;

or R₇, R₄, and atoms to which they connected together form a 5-12 membered carbocyclyl or heterocyclyl.

3. The compound according to claim 1, or a tautomer, a stereoisomer, a hydrate, a solvate, or a pharmaceutically acceptable salt thereof, wherein, the compound has a structure as shown in formula (I-2):



In another preferred embodiment, R₈ is selected from the group consisting of H, NH₂, C₁₋₆ alkyl, and C₁₋₆ alkylamino.

In another preferred embodiment, R₉ is selected from the group consisting of: H, D, halogen, CN, C₁₋₆ alkyl and C₁₋₆ haloalkyl.

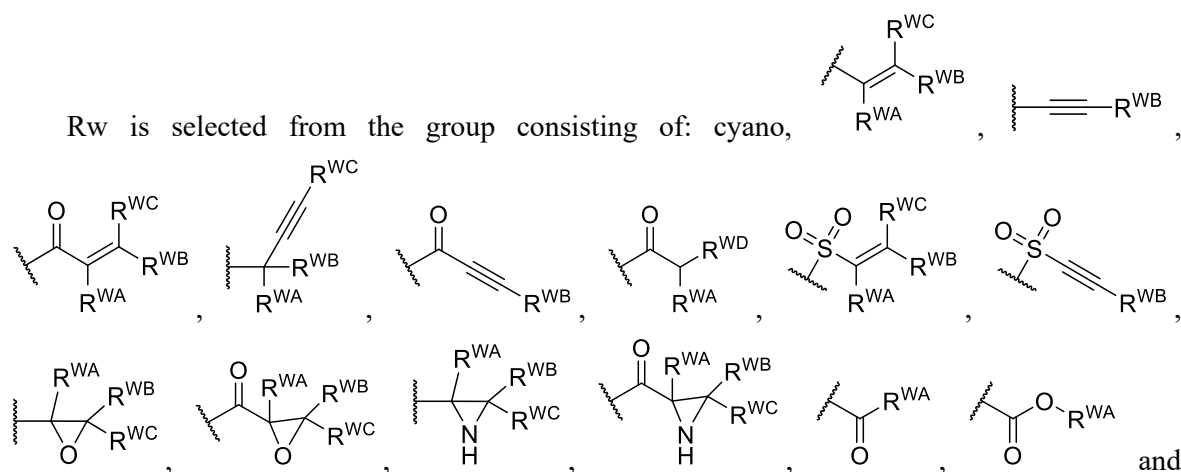
4. The compound according to claim 1, or a tautomer, a stereoisomer, a hydrate, a solvate, or a pharmaceutically acceptable salt thereof, wherein, Cy^B is selected from the group consisting of: phenyl and 5-7 membered heteroaryl.

In another preferred embodiment, Cy^B is selected from the group consisting of: phenyl, pyridyl, pyrimidinyl, pyridazinyl, pyrrolyl, furanyl, thienyl, imidazolyl, pyrazolyl, thiazolyl, triazolyl, and oxazolyl.

- 5 5. The compound according to claim 1, or a tautomer, a stereoisomer, a hydrate, a solvate, or a pharmaceutically acceptable salt thereof, wherein, Cy^C is selected from the group consisting of: phenyl, 5-7 membered heteroaryl, saturated or partially unsaturated C₃₋₆ saturated or partially unsaturated carbocyclyl, and saturated or partially unsaturated 4-7 membered heterocyclyl.

- 10 In another preferred embodiment, Cy^C is selected from the group consisting of: phenyl, pyridyl, pyrimidinyl, pyridazinyl, pyrrolyl, furanyl, thiophenyl, imidazolyl, pyrazolyl, thiazolyl, triazolyl, oxazolyl, and 5-7 membered saturated or partially unsaturated heterocyclyl.

- 15 6. The compound according to claim 1, or a tautomer, a stereoisomer, a hydrate, a solvate, or a pharmaceutically acceptable salt thereof, wherein, R₅ is -L-R_w, wherein L is selected from the group consisting of: covalent bonds, -C₁₋₄ alkyl, and -NR₆-; R₆ is selected from the group consisting of: H, and C₁₋₆ alkyl;



- 20 5-7 membered nitrogen-containing heterocyclyl;

R^{WA}, R^{WB}, and R^{WC} are each independently selected from the group consisting of: H, D, halogen, C₁₋₆ alkyl, and C₁₋₆ haloalkyl; and R^{WA}, R^{WB}, and R^{WC} can each be independently substituted with 1, 2, or 3 substituents selected from the group consisting of: C₁₋₆ alkylamino and C₁₋₆ alkoxy;

- 25 or R₆ and R_w together form a ring; and the ring is selected from the group consisting of: 5-7 membered heteroaryl and 4-7 membered heterocyclyl.

7. The compound according to claim 1, or a tautomer, a stereoisomer, a hydrate, a solvate, or a pharmaceutically acceptable salt thereof, wherein,

- 30 R₁ is selected from the group consisting of: H, D, halogen, CN, OH, NH₂, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkyl, C₁₋₆ haloalkoxy, C₁₋₆ alkylamino, C₂₋₄ alkenyl, C₁₋₄ haloalkenyl, C₂₋₄ alkynyl, C₁₋₄ haloalkynyl and SF₅;

R₂ and R₃ are each independently selected from the group consisting of: C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkyl, C₁₋₆ haloalkoxy and C₁₋₆ alkylamino; wherein, R₂ and R₃ can be the same or different;

or R₂ and R₃ together with the sulfur atom to which they are connected form a 3-7 membered heterocyclyl (preferably a 4-6 membered heterocyclyl);

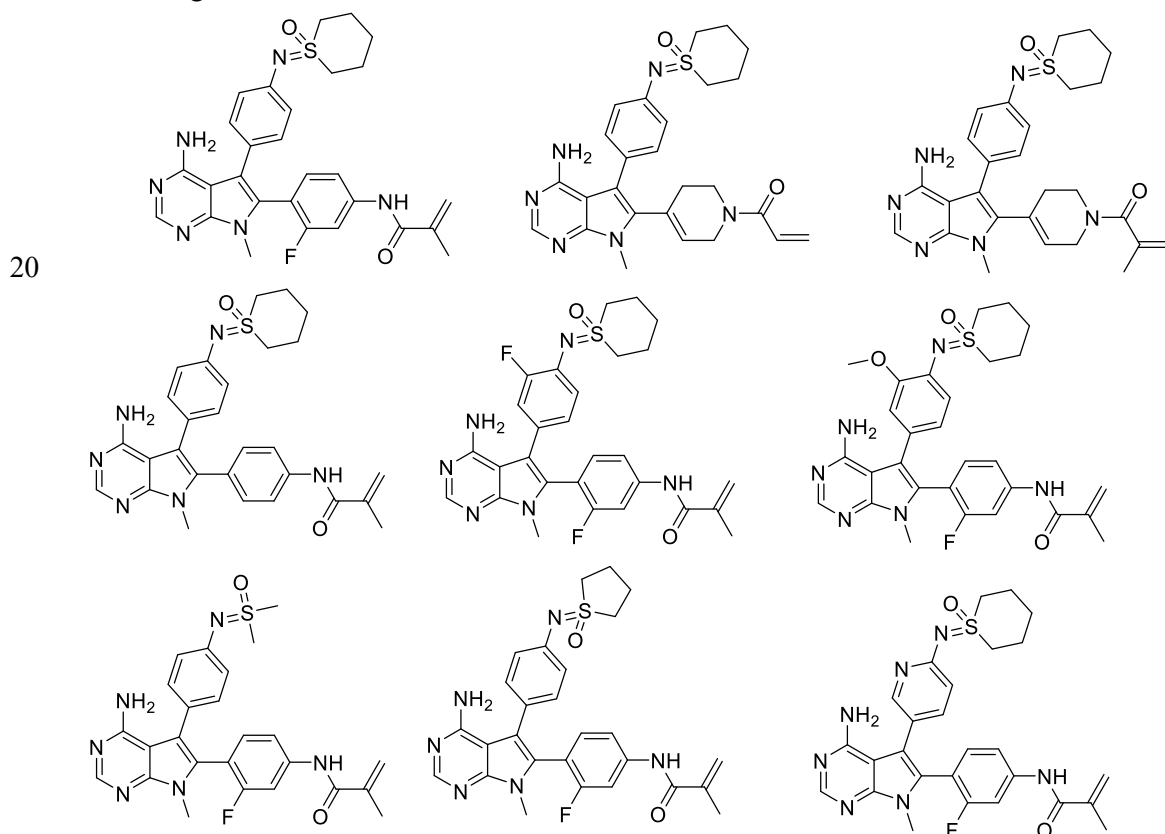
R₄ is selected from the group consisting of: H, D, halogen, CN, OH, NH₂, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkyl, C₁₋₆ haloalkoxy and C₁₋₆ alkylamino.

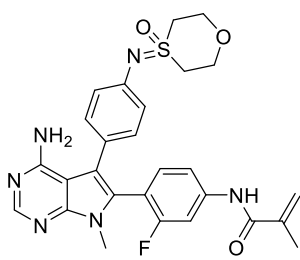
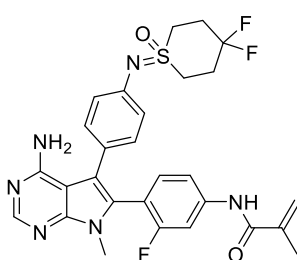
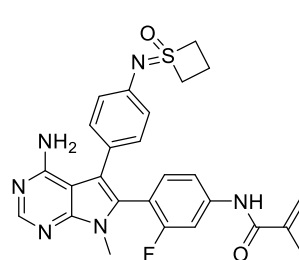
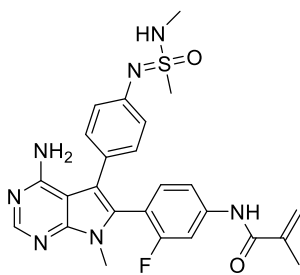
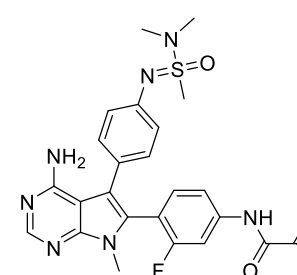
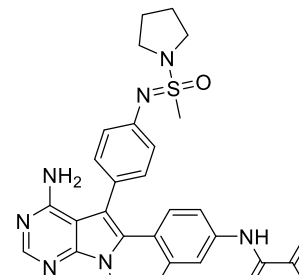
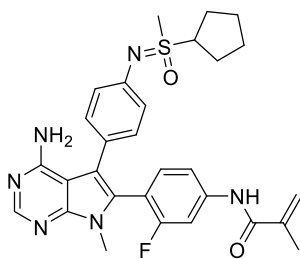
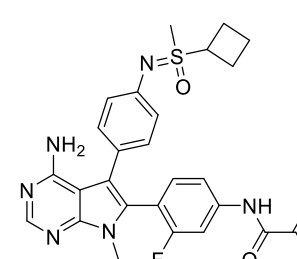
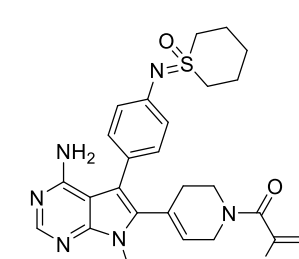
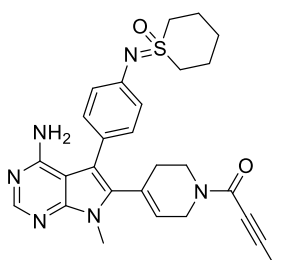
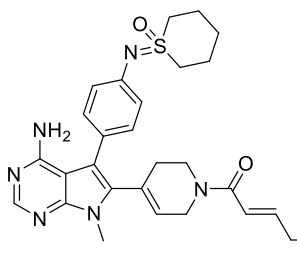
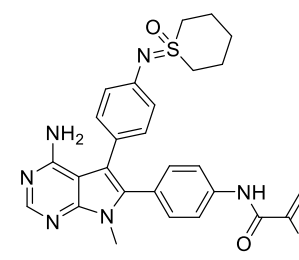
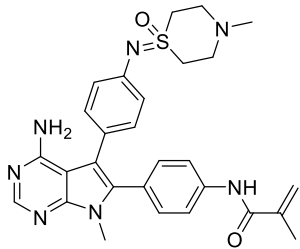
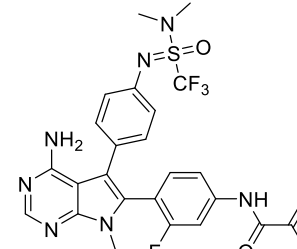
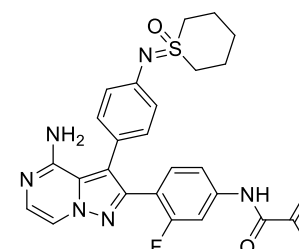
In another preferred embodiment, R₁ is selected from the group consisting of: H, D, halogen, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkyl and C₁₋₆ haloalkoxy;

R₂ and R₃ are each independently selected from the group consisting of: C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₁₋₆ alkylamino and C₁₋₆ haloalkylamino; wherein, R₂ and R₃ can be the same or different; or R₂ and R₃ together with the sulfur atom to which they are connected form a 4-8 membered heterocyclyl;

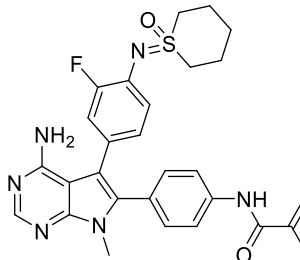
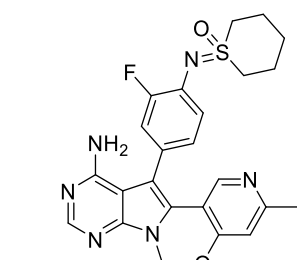
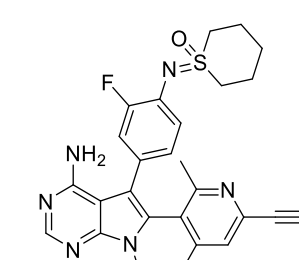
R₄ is selected from the group consisting of: H, D, halogen, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkyl, and C₁₋₆ haloalkoxy.

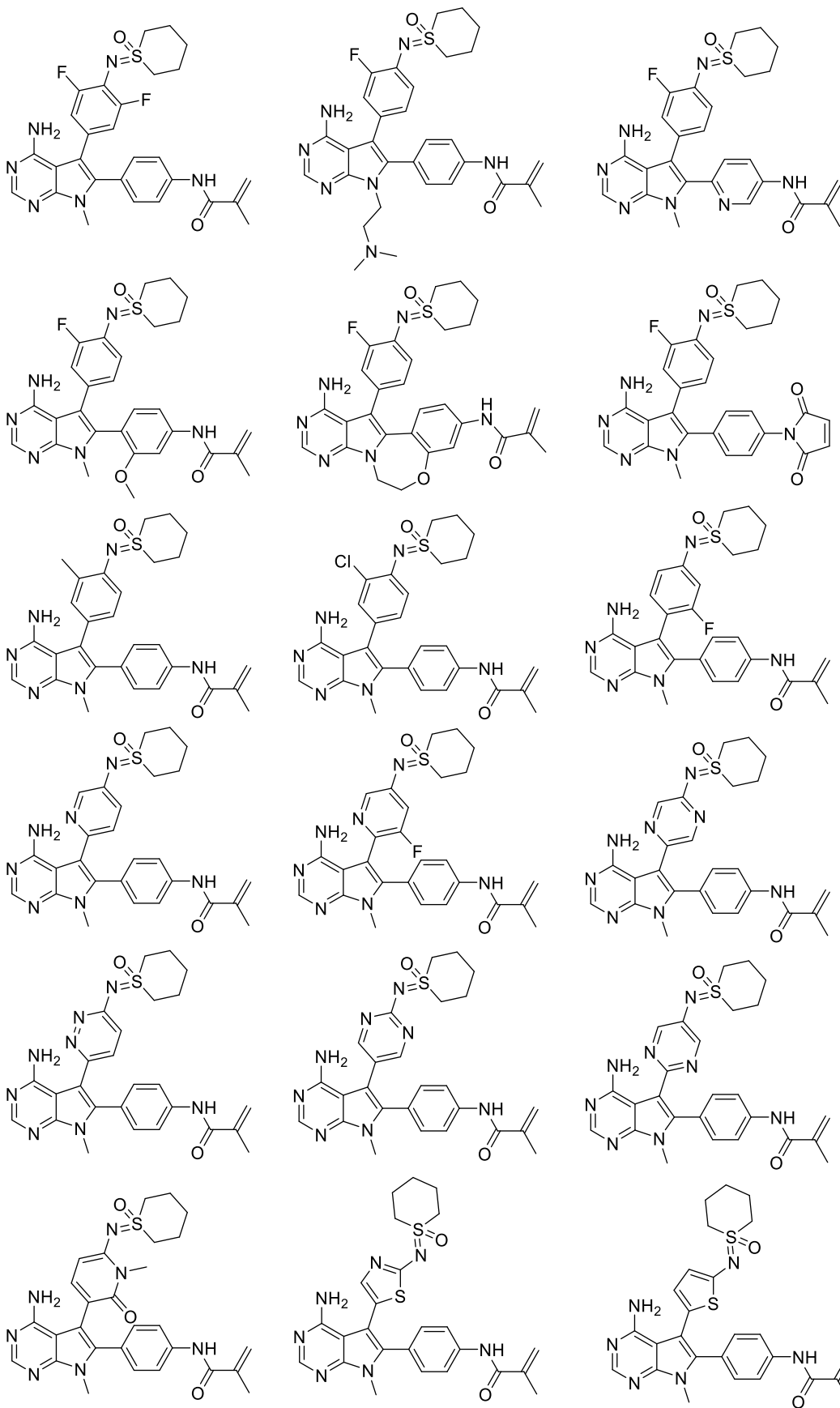
8. The compound according to claim 1, or a tautomer, a stereoisomer, a hydrate, a solvate, or a pharmaceutically acceptable salt thereof, wherein the compound is selected from the group consisting of:

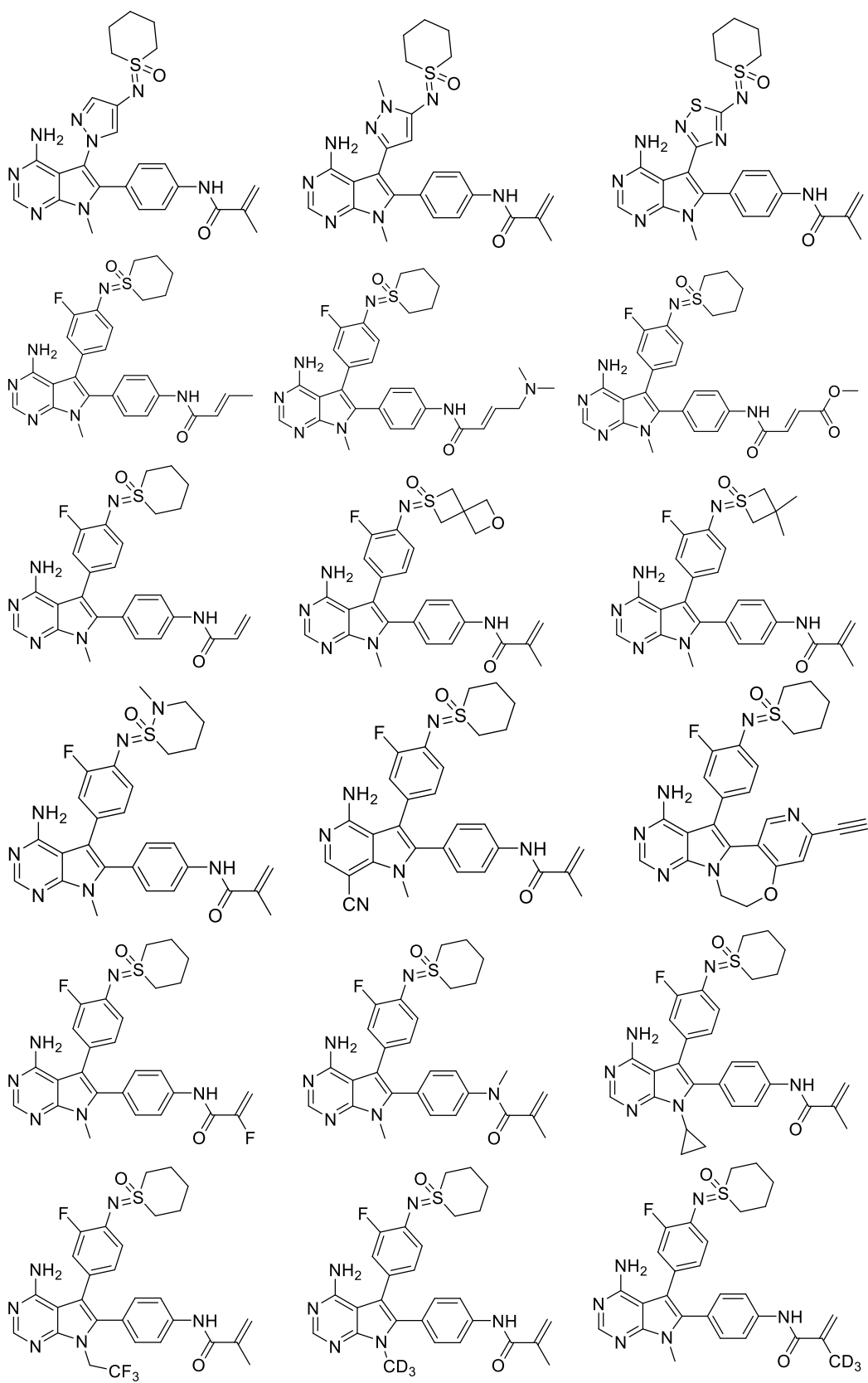


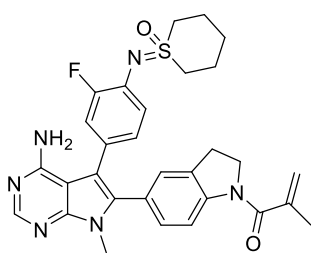
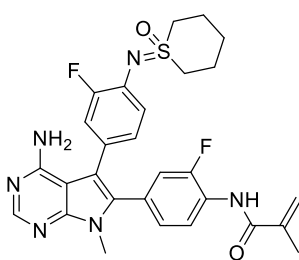
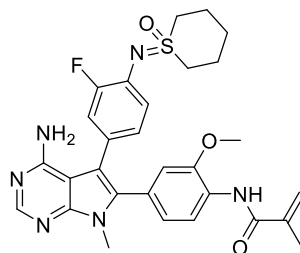
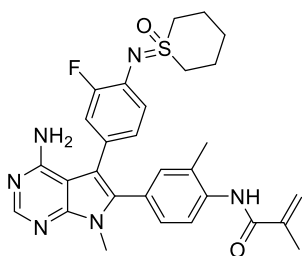
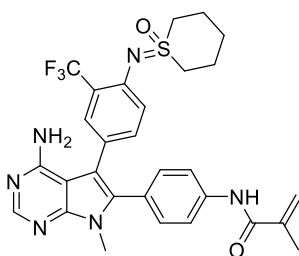
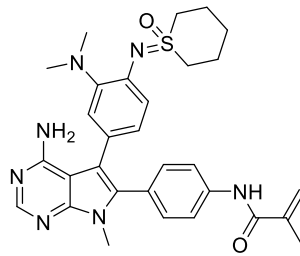
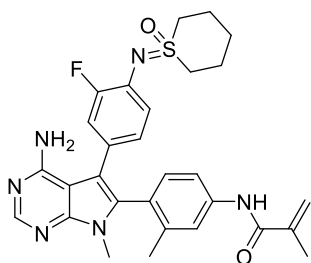
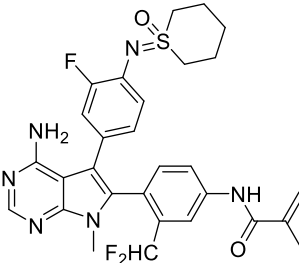
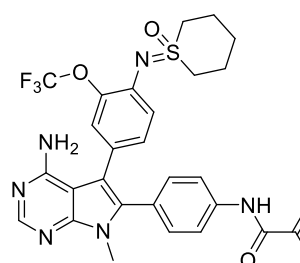
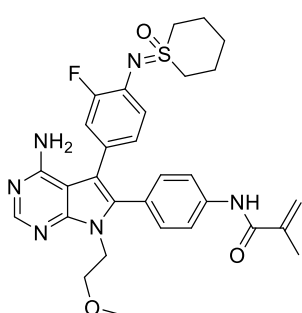
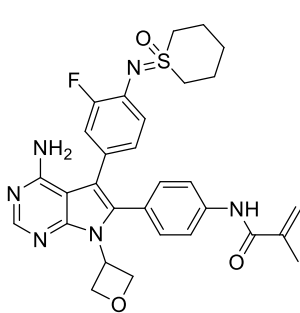
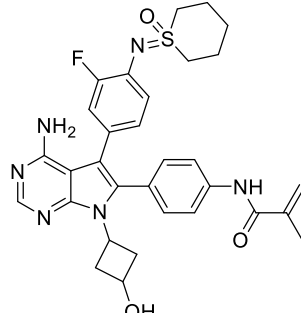
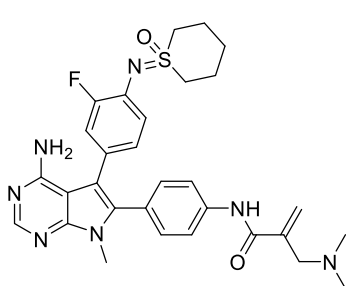
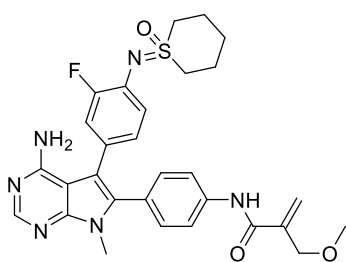
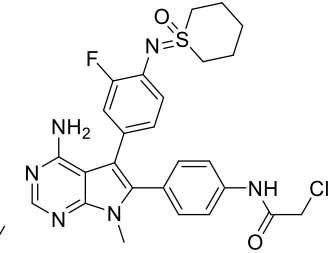


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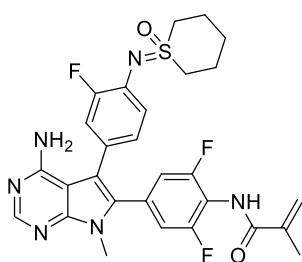
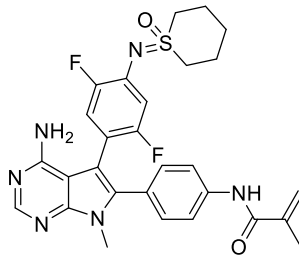
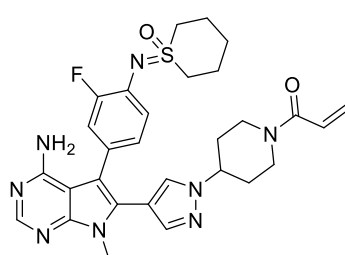


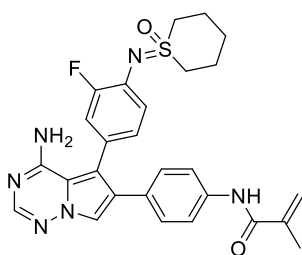
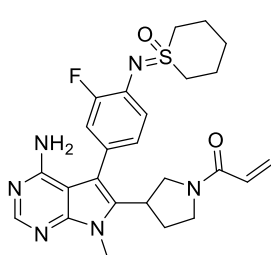
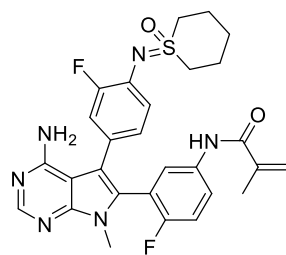
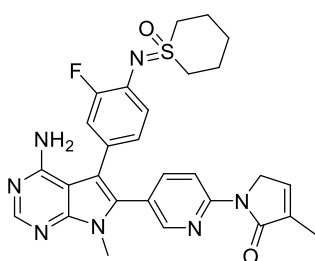
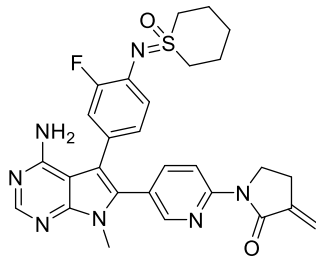
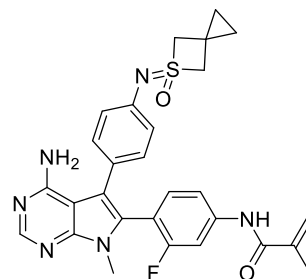
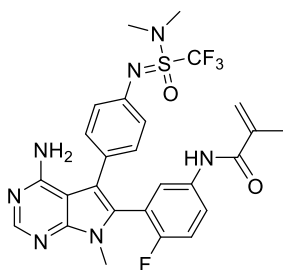
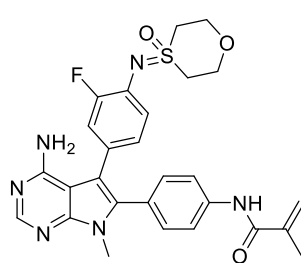
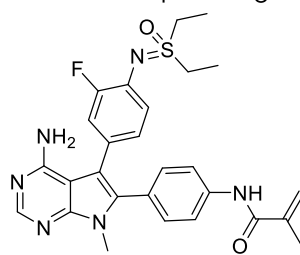
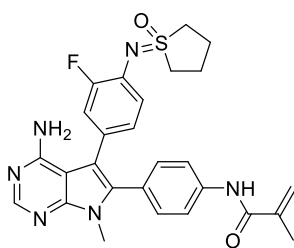
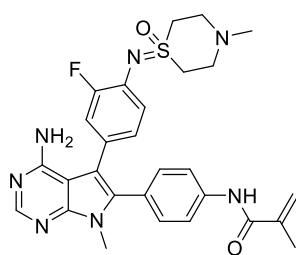
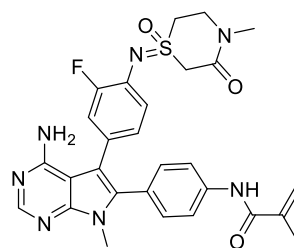
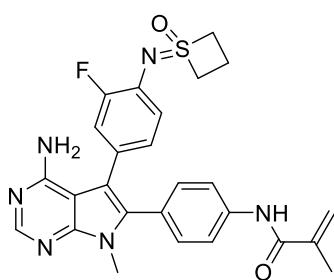
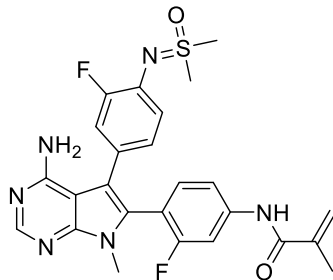
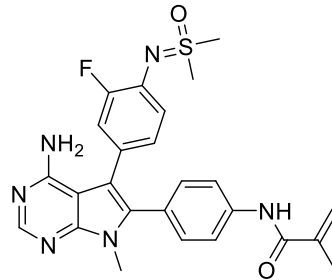




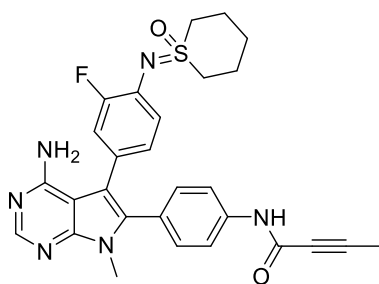
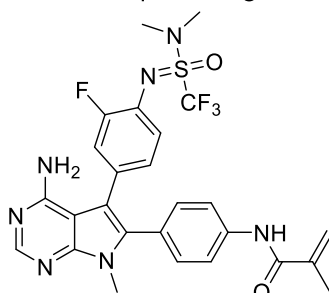
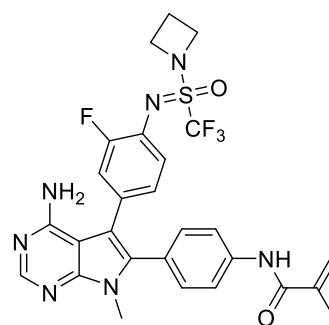


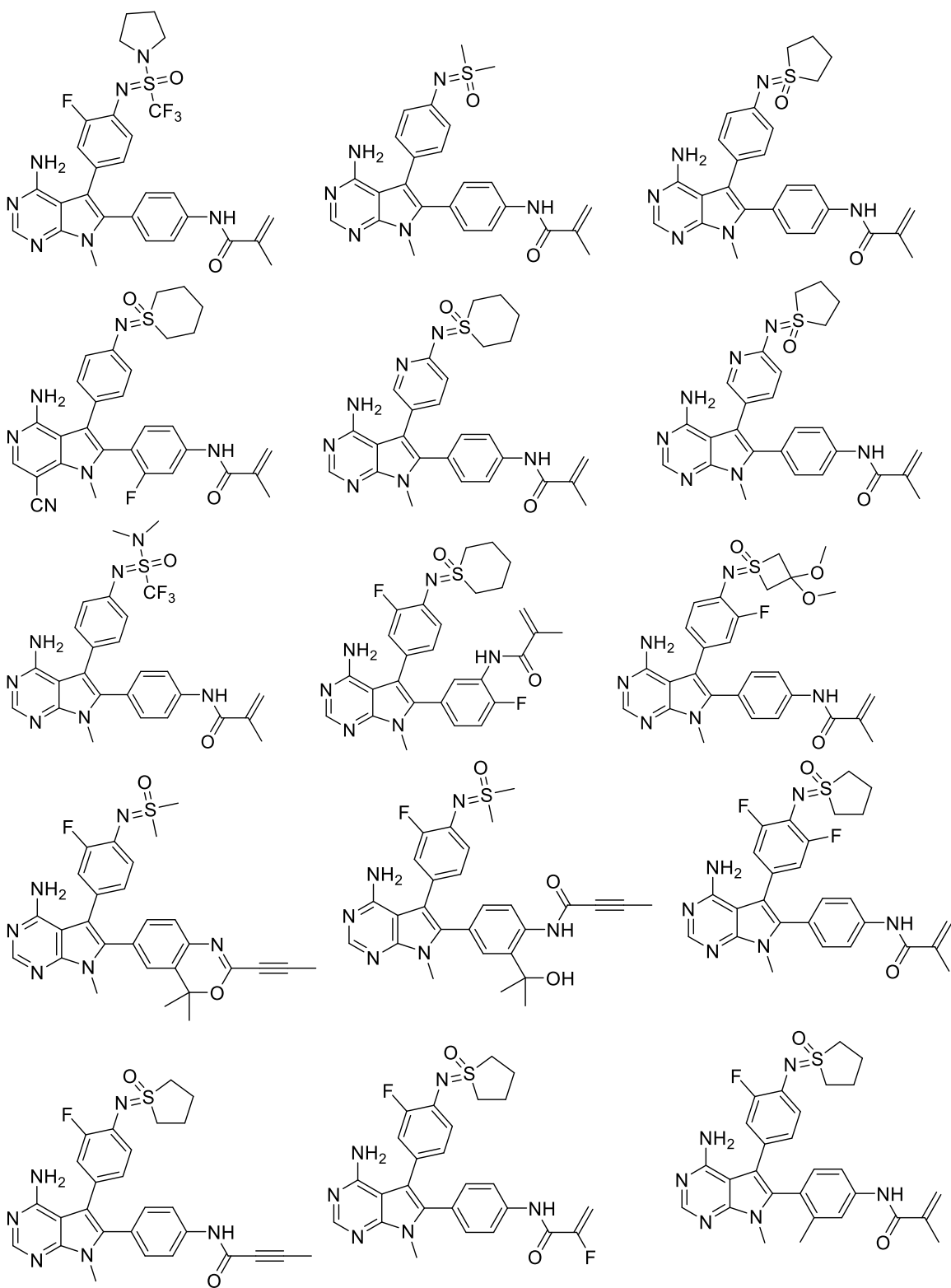
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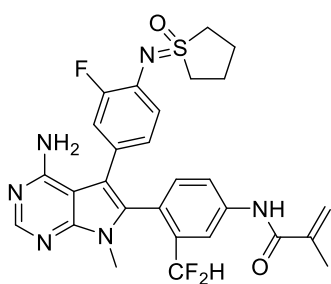
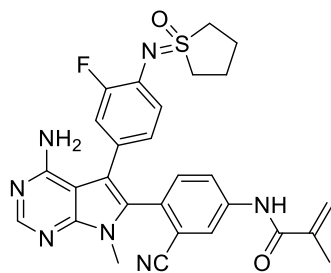
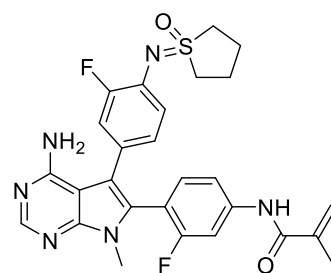
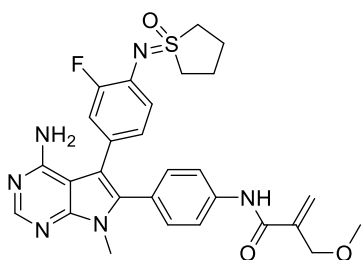
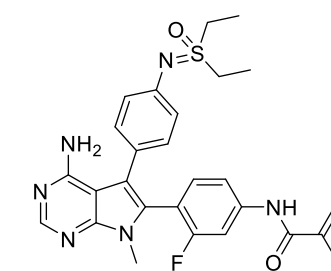
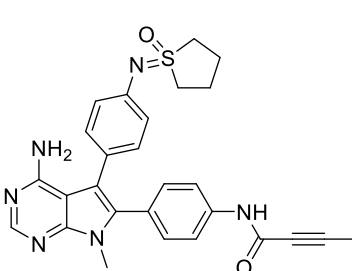
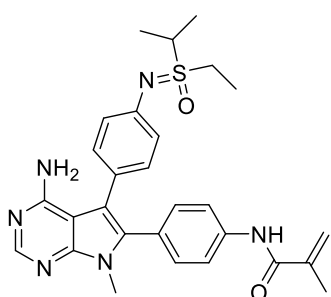
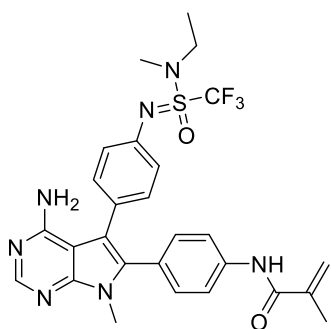
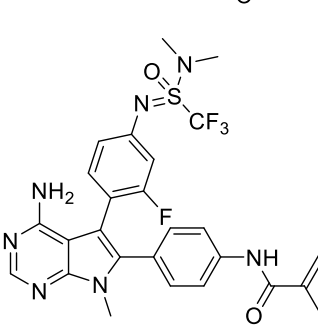
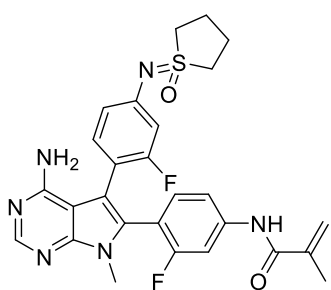
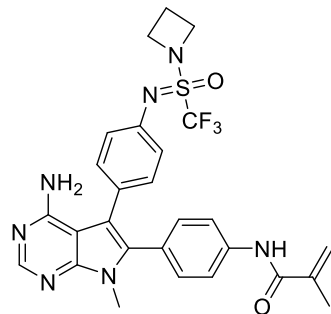
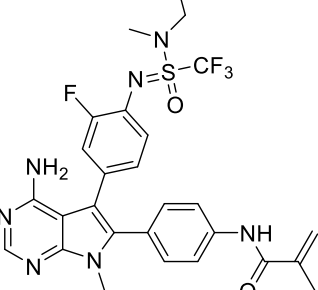
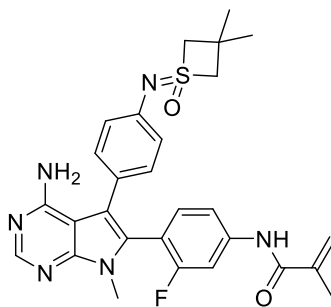
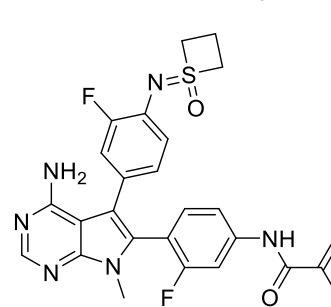
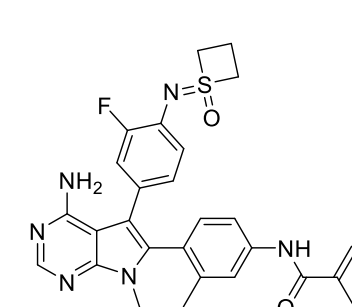


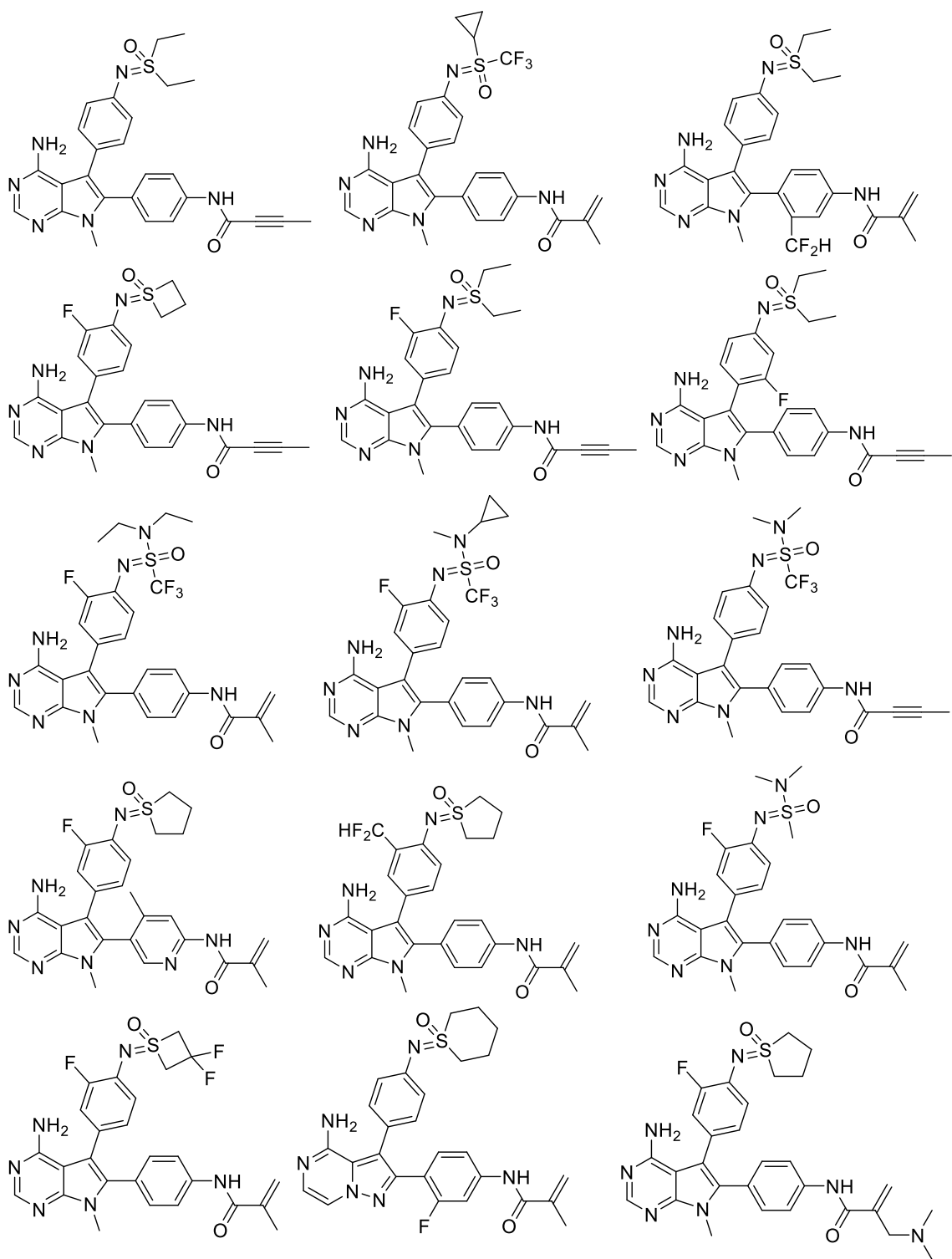


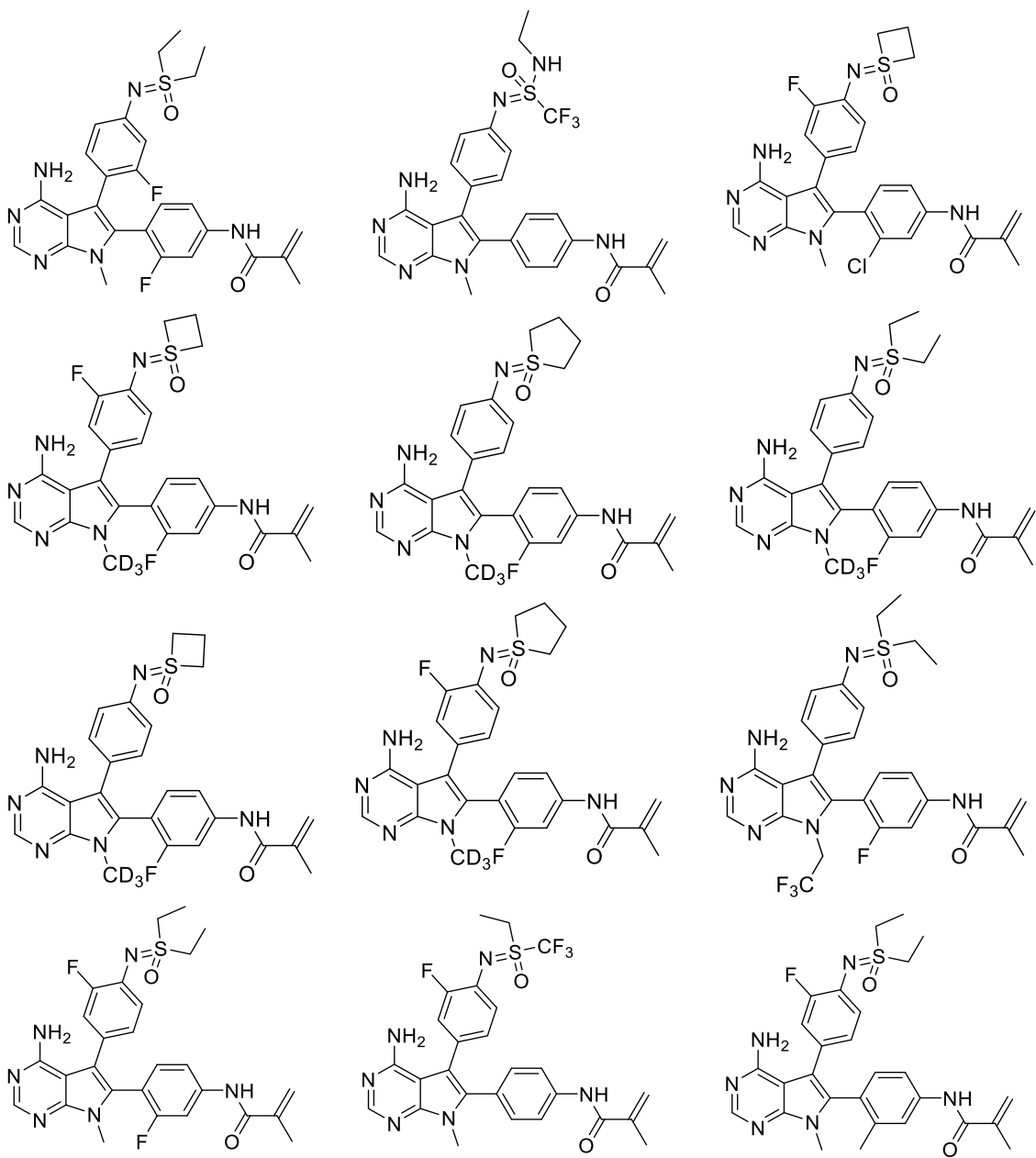
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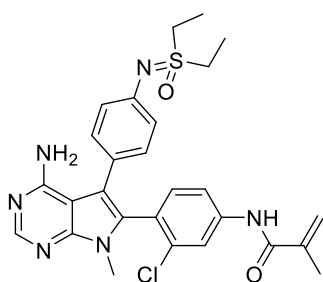
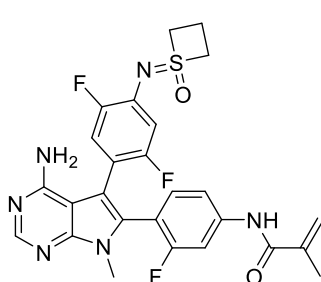
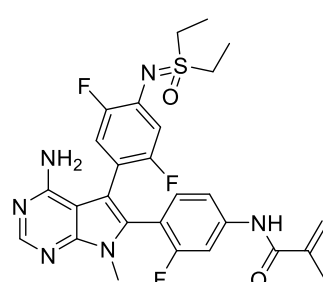
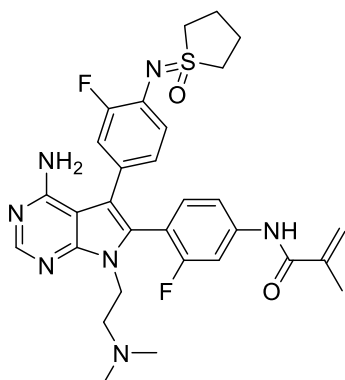
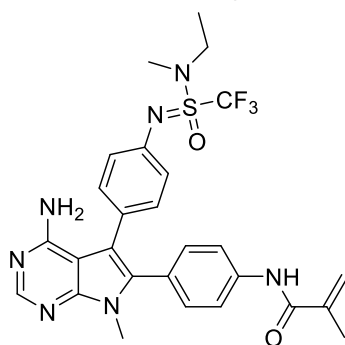
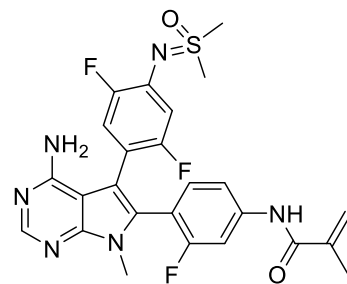
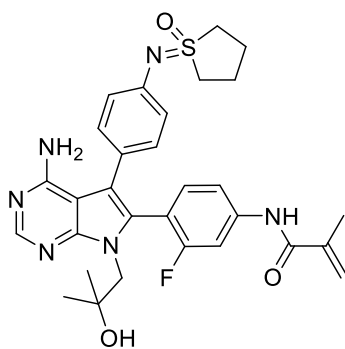
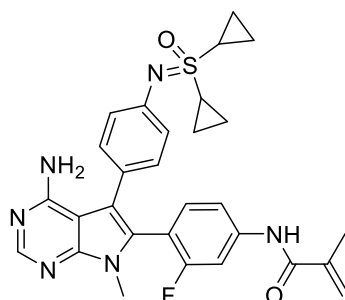
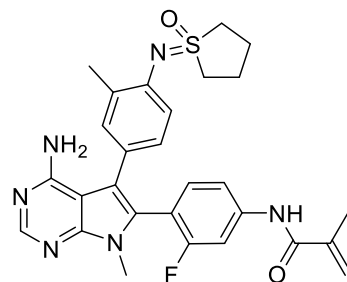
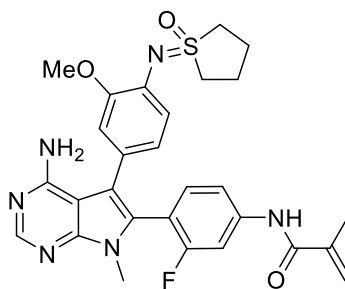
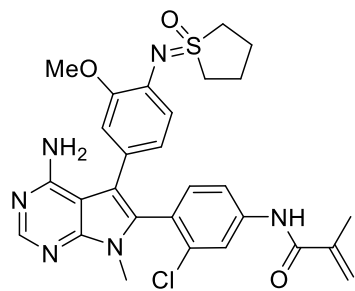
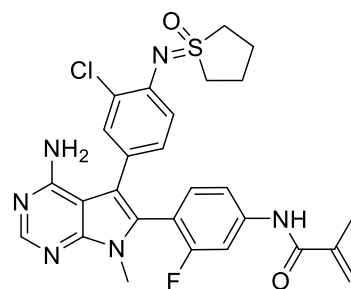
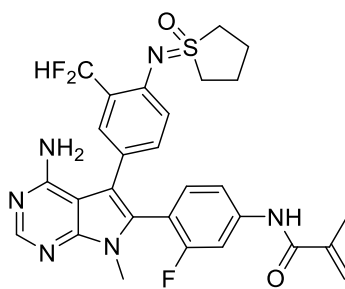
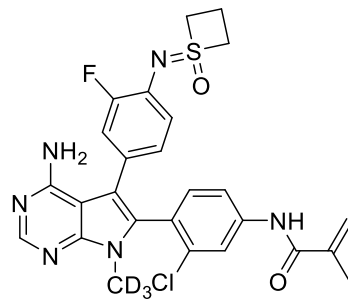
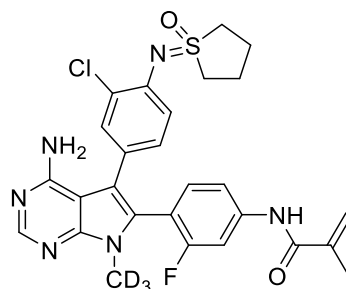












pharmaceutical composition for treating or preventing diseases or conditions associated with abnormal activity or expression levels of FGFR.

In another preferred embodiment, the disease or condition is specifically associated with a subtype of FGFR; preferably, the FGFR subtype is selected from the group consisting of: FGFR2.

5