PYRIDONE COMPOUNDS AND PREPARATION METHOD THEREFOR, AND APPLICATION

TECHNICAL FIELD

The present disclosure belongs to the technical field of chemical drugs, and relates to a pyridone compound, or an isomer thereof, or a racemate thereof, or a pharmaceutically acceptable salt thereof, and preparation method therefor and application thereof. It acts as a PCSK9 inhibitor. Also related is a method of using it for treating various specific diseases or conditions.

BACKGROUND

Proprotein convertase subtilisin/kexin type 9 (PCSK9), also known as neural apoptosis-regulated convertase 1 (NARC-1), is a prohormone-proprotein convertase belonging to the subtilisin (S8) family of serine proteases. It is expressed in cells with proliferation and differentiation capabilities, comprising hepatocytes, renal interstitial cells, ileal and colonic epithelial cells, and embryonic telencephalic neurons, etc. Studies have found that PCSK9 plays a role in the differentiation of hepatocytes and neural cells. It not only specifically acts on cholesterol biosynthesis or uptake, but also circulating PCSK9 can directly bind to the low-density lipoprotein receptor (LDLR) on the surface of hepatocytes, be internalized by hepatocytes together with LDLR, and promote the degradation of LDLR within hepatocytes, hindering the recycling of LDLR. This leads to an increase in the content of LDL cholesterol (LDL-C) in plasma, and elevated LDL-C content is closely related to human dyslipidemia and cardiovascular-related diseases.

Currently, research is ongoing regarding inhibiting the function of PCSK9 or inhibiting the production of PCSK9. For example, attempts such as inhibiting its function using monoclonal antibodies targeting PCSK9, and inhibiting the production of PCSK9 via RNA interference have been reported. However, for cardiovascular disease patients, there is a need for an effective small molecule to inhibit the function of PCSK9.

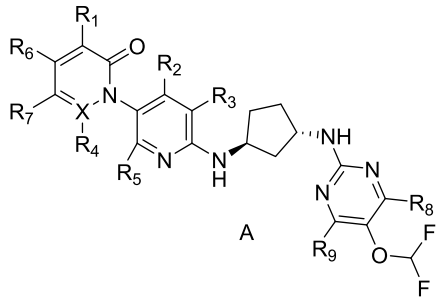
SUMMARY

In view of the problems existing in the prior art, the present application provides a compound represented by general formula (A) or (C), or an isomer thereof, or a racemate thereof, or a pharmaceutically acceptable salt thereof, and preparation method therefor and application

thereof. It acts as a PCSK9 inhibitor. Also provided is a method of using it for treating various specific diseases or conditions.

Specifically, the present disclosure is achieved through the following technical solutions:

A compound represented by general formula (A), or an isomer thereof, or a racemate thereof, or a pharmaceutically acceptable salt thereof, wherein:



A

X is C or N, and when X is N, R_4 is absent;

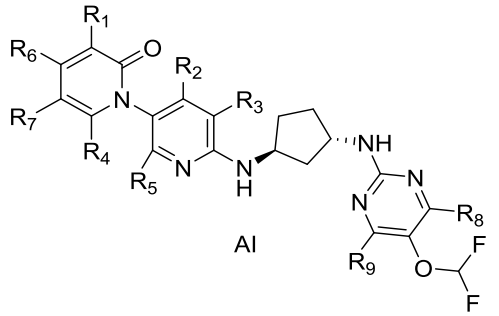
R_1, R_4, R_6, and R_7 are selected from the group consisting of hydrogen, halogen, hydroxyl, substituted or unsubstituted alkyl, cyano, -C(O)-O-alkyl, phenylalkoxy, carboxyl, hydroxymethyl, cycloalkyl, amide, alkyl-substituted amide, Z-C(O)-, and heteroaryl, Z being selected from the group consisting of alkyl and heterocycloalkyl, and a substituent being hydroxyl;

R_2, R_3, and R_5 are each selected from the group consisting of hydrogen, alkyl, alkoxy, cyano, halogen, haloalkyl, amide, hydroxyl, hydroxyl-substituted alkyl, carboxyl, amino, amino-substituted alkyl, alkylcarbonyl, and $-(CH_2)_n-O-(CH_2)_n$-phenyl, and n = 1, 2, or 3;

R_8 and R_9 are each selected from the group consisting of hydrogen, alkyl, halogen, cycloalkyl, alkylthio, alkoxy, aryl, and heteroaryl; and

R_1, R_2, R_3, R_4, R_5, R_6, and R_7 are not all hydrogen simultaneously; or when R_1, R_2, R_3, R_4, R_5, R_6, and R_7 are all hydrogen simultaneously, then R_8 and R_9 are not both hydrogen simultaneously.

The present disclosure further provides a compound represented by general formula (AI), or an isomer thereof, or a racemate thereof, or a pharmaceutically acceptable salt thereof, wherein:



AI

R_1, R_4, R_6, and R_7 are selected from the group consisting of hydrogen, halogen, hydroxyl,

substituted or unsubstituted alkyl, cyano, -C(O)-O-alkyl, phenylalkoxy, carboxyl, hydroxymethyl, cycloalkyl, amide, alkyl-substituted amide, Z-C(O)-, and heteroaryl, Z being selected from the group consisting of alkyl and heterocycloalkyl, and a substituent being hydroxyl;

R_2, R_3, and R_5 are each selected from the group consisting of hydrogen, alkyl, alkoxy, cyano, halogen, haloalkyl, amide, hydroxyl, hydroxyl-substituted alkyl, carboxyl, amino, amino-substituted alkyl, alkylcarbonyl, and $-(CH_2)_n-O-(CH_2)_n$-phenyl, and n = 1, 2, or 3;

R_8 and R_9 are each selected from the group consisting of hydrogen, alkyl, halogen, cycloalkyl, alkylthio, alkoxy, aryl, and heteroaryl; and

R_1, R_2, R_3, R_4, R_5, R_6, and R_7 are not all hydrogen simultaneously; or when R_1, R_2, R_3, R_4, R_5, R_6, and R_7 are all hydrogen simultaneously, then R_8 and R_9 are not both hydrogen simultaneously.

As a preferred technical solution of the present disclosure, in general formula (A) or (AI), R_1, R_2, R_4, R_5, R_6, and R_7 are all hydrogen simultaneously, and R_3 is selected from the group consisting of alkyl, alkoxy, cyano, halogen, haloalkyl, amide, hydroxyl, hydroxyl-substituted alkyl, carboxyl, amino, amino-substituted alkyl, alkylcarbonyl, and $-(CH_2)_n-O-(CH_2)_n$-phenyl, and n = 1, 2, or 3.

As a preferred technical solution of the present disclosure, in general formula (A) or (AI), R_1, R_3, R_4, R_5, R_6, and R_7 are all hydrogen simultaneously, and R_2 is selected from the group consisting of alkyl, alkoxy, cyano, halogen, haloalkyl, amide, hydroxyl, hydroxyl-substituted alkyl, carboxyl, amino, amino-substituted alkyl, alkylcarbonyl, and $-(CH_2)_n-O-(CH_2)_n$-phenyl, and n = 1, 2, or 3.

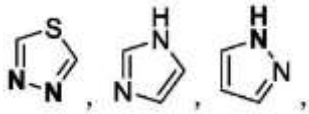
As a preferred technical solution of the present disclosure, in general formula (A) or (AI), the alkyl is selected from the group consisting of methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, n-pentyl, sec-pentyl, 1-ethylpropyl, 2-methylbutyl, tert-pentyl, 1,2-dimethylpropyl, isopentyl, neopentyl, n-hexyl, isohexyl, sec-hexyl, tert-hexyl, neohexyl, 2-methylpentyl, 1,2-dimethylbutyl, and 1-ethylbutyl; the haloalkyl refers to alkyl in which one or more hydrogens are substituted by halogen; the hydroxyl-substituted alkyl refers to alkyl in which one or more hydrogens are substituted by hydroxyl.

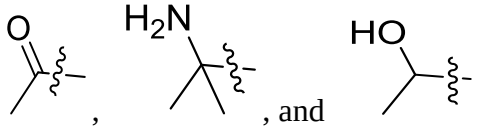
As a preferred technical solution of the present disclosure, in general formula (A) or (AI), the halogen is selected from the group consisting of fluorine, chlorine, bromine, and iodine.

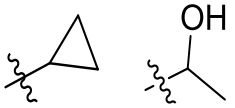
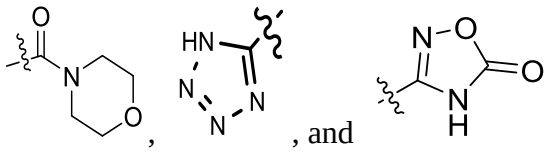
As a preferred technical solution of the present disclosure, in general formula (A) or (AI),

the cycloalkyl is selected from the group consisting of cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl; the heterocycloalkyl refers to cycloalkyl in which one or more carbon atoms are replaced by heteroatoms, the heteroatoms being selected from the group consisting of N, O, and S.

As a preferred technical solution of the present disclosure, in general formula (A) or (AI), the alkoxy is selected from the group consisting of methoxy, ethoxy, n-propoxy, and isopropoxy.

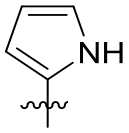
As a preferred technical solution of the present disclosure, in general formula (A) or (AI), the aryl is phenyl; the heteroaryl is preferably selected from the group consisting of: imidazolyl, furanyl, thienyl, thiazolyl, pyrazolyl, oxazolyl, pyrrolyl, tetrazolyl, pyridyl, pyrimidinyl, thiadiazolyl, pyrazinyl, , etc.

As a preferred technical solution of the present disclosure, in general formula (A) or (AI), R_2 or R_3 is selected from the group consisting of F, Cl, Br, methyl, hydroxyl, hydroxymethyl, trifluoromethyl, $-CF_2H$, $-C(O)NH_2$, $-NH_2$, cyano, -COOH, methoxy, $-CH_2-O-CH_2$-phenyl, .

As a preferred technical solution of the present disclosure, in general formula (A) or (AI), R_1 is selected from the group consisting of methyl, hydroxyl, hydroxymethyl, cyano, F, Cl, Br, $-O-CH_2$-phenyl, -COOH, $-COOCH_2CH_3$, , amide, formamide, $CH_3-C(O)-$, .

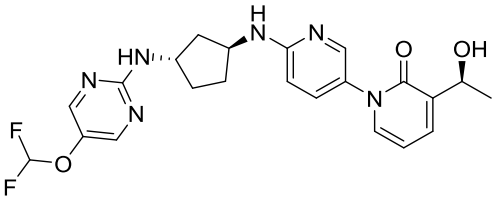
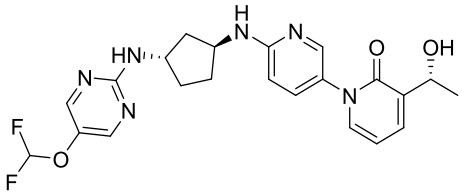
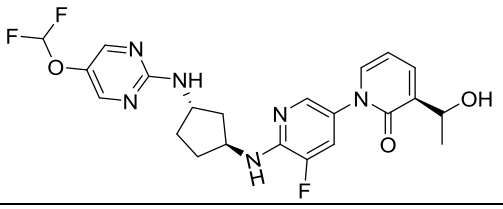
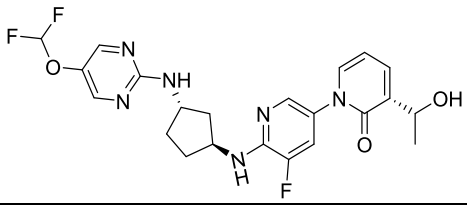
As a preferred technical solution of the present disclosure, in general formula (A) or (AI), R_6 and R_7 are independently H or -COOH.

As a preferred technical solution of the present disclosure, in general formula (A) or (AI), R_4, R_6, and R_7 are independently H.

As a preferred technical solution of the present disclosure, in general formula (A) or (AI), R_8 and R_9 are each independently selected from the group consisting of hydrogen, chlorine, methyl, methoxy, methylthio, ethyl, isopropyl, phenyl, cyclopropyl, and .

As a preferred technical solution of the present disclosure, in general formula (A) or (AI), the compound, or an isomer thereof, or a racemate thereof, or a pharmaceutically acceptable salt thereof is selected from the group consisting of: A1, and A5 to A73.

As a preferred technical solution of the present disclosure, in general formula (A) or (AI), the isomer compound is selected from the group consisting of:

A35A OR A35B		A35B OR A35A	
A43A OR A43B		A43B OR A43A	

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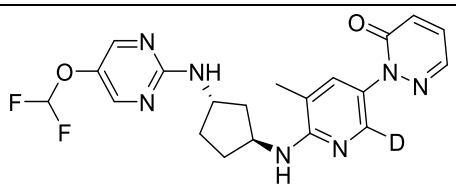
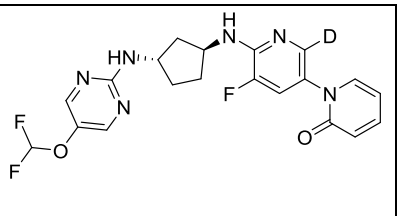
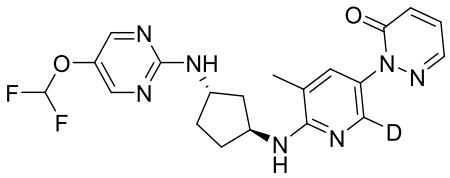
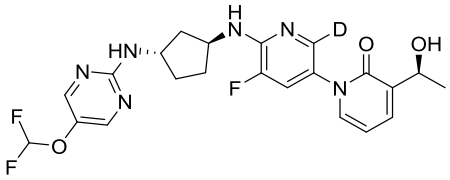
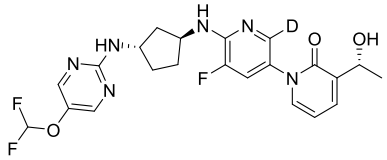
As a preferred technical solution of the present disclosure, in general formula (A) or (AI), the pharmaceutically acceptable salt refers to a salt prepared from the compound, or the isomer thereof, or the racemate thereof, or the pharmaceutically acceptable salt thereof, with a pharmaceutically acceptable acid or base.

As a preferred technical solution of the present disclosure, in general formula (A) or (AI), one or more hydrogen atoms in the compound, or the isomer thereof, or the racemate thereof, or the pharmaceutically acceptable salt thereof, are substituted by the isotope deuterium.

As a preferred technical solution of the present disclosure, in general formula (A) or (AI), the deuterium-substituted compound is selected from the group consisting of:

A5-D		A17-D	

A31D			
A43A OR A43B-D		A43B OR A43A-D	

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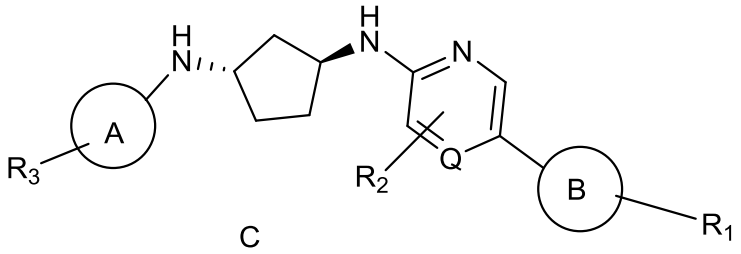
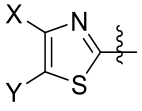
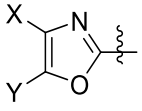
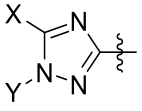
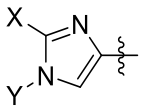
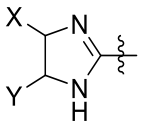
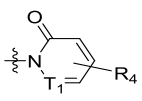
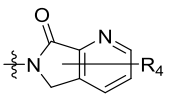
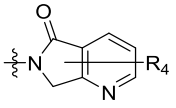
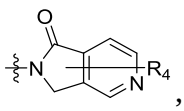
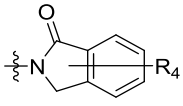
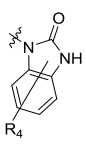
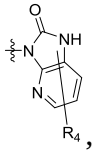
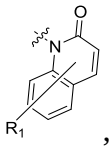
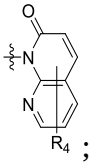
A compound represented by general formula (C), or an isomer thereof, or a racemate thereof, or a pharmaceutically acceptable salt thereof, wherein:



C

ring A is selected from the group consisting of: , , , , and , and X and Y together form a 5- to 7-membered saturated or unsaturated ring, the 5- to 7-membered saturated or unsaturated ring comprises 0, 1, or 2 heteroatoms, the heteroatoms being selected from the group consisting of O, N, and S;

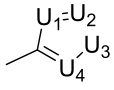
B is selected from the group consisting of , , , , , , , , and ;

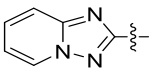
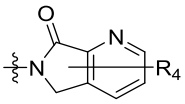
Q is selected from the group consisting of N and CR_{Q1}, R_{Q1} being selected from the group consisting of H and halogen;

T_1 is selected from the group consisting of N and CH;

R_2 is selected from the group consisting of H, alkyl, and halogen, and a number of R_2 is one or more;

R_3 is hydrogen, or R_3 represents that the hydrogen on ring A is further substituted by oxo, alkyl, halogen, alkoxy, alkylthio, haloalkyl, haloalkoxy, cycloalkyl, cycloalkylalkyl, or alkynyl, and a number of R_3 is one or more, or adjacent R_3 together form an alkoxy group ;

R_4 is selected from the group consisting of hydrogen, halogen, hydroxyl, alkoxy, haloalkoxy, substituted or unsubstituted alkyl, cyano, -C(O)-O-alkyl, phenylalkoxy, carboxyl, hydroxymethyl, and cycloalkyl, a substituent being selected from the group consisting of hydroxyl, amide, halogen, and ; U_1, U_2, and U_4 are independently selected from the group consisting of CH and N; U_3 is selected from the group consisting of CH_2 and NH; and a number of R_4 is one or more; and

when ring A is: , ring B is not: .

As a preferred technical solution of the present disclosure, in general formula (C), the alkyl is selected from the group consisting of methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, n-pentyl, sec-pentyl, 1-ethylpropyl, 2-methylbutyl, tert-pentyl, 1,2-dimethylpropyl, isopentyl, neopentyl, n-hexyl, isohexyl, sec-hexyl, tert-hexyl, neohexyl, 2-methylpentyl, 1,2-dimethylbutyl, and 1-ethylbutyl.

As a preferred technical solution of the present disclosure, in general formula (C), the alkoxy is selected from the group consisting of methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, sec-butoxy, and tert-butoxy.

As a preferred technical solution of the present disclosure, in general formula (C), the cycloalkyl is selected from the group consisting of cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl.

As a preferred technical solution of the present disclosure, in general formula (C), the halogen is selected from the group consisting of fluorine, chlorine, bromine, and iodine.

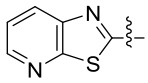
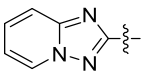
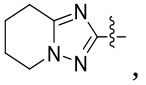
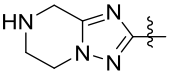
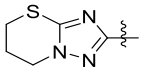
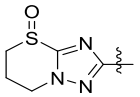
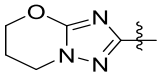
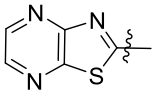
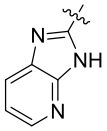
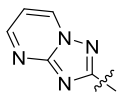
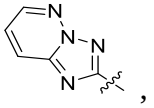
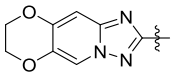
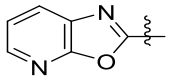
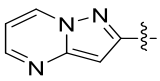
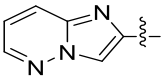
As a preferred technical solution of the present disclosure, in general formula (C), Q is N.

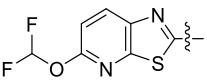
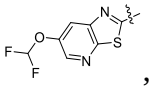
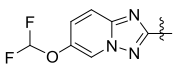
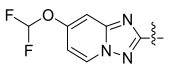
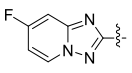
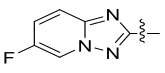
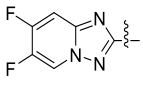
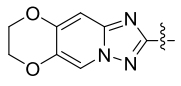
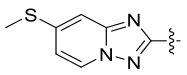
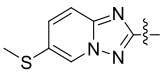
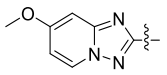
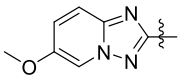
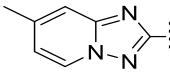
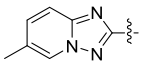
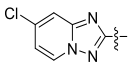
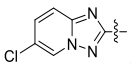
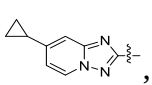
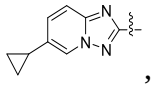
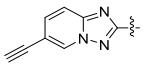
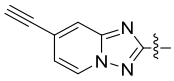
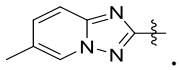
As a preferred technical solution of the present disclosure, in general formula (C), Q is CH, and R_2 is F.

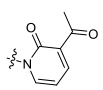
As a preferred technical solution of the present disclosure, in general formula (C), T_1 is N.

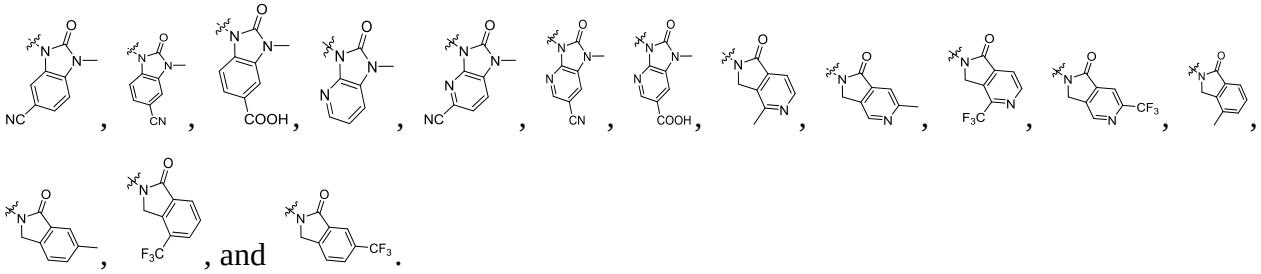
As a preferred technical solution of the present disclosure, in general formula (C), R_3 is selected from the group consisting of hydrogen, methyl, methoxy, cyclopropyl, cyclopropylmethyl, fluorine, chlorine, oxo, and CHF_2-O-.

As a preferred technical solution of the present disclosure, in general formula (C), R_4 is selected from the group consisting of hydrogen, methyl, hydroxyl, hydroxymethyl, cyano, F, Cl, Br, -O-CH_2-phenyl, -COOH, -$COOCH_2CH_3$, , , amide, formamide, CH_3-C(O)-, ethynyl, trifluoromethyl, difluoromethoxy, and methoxy.

As a preferred technical solution of the present disclosure, in general formula (C), ring A is selected from the group consisting of: , , , , , , , , , , , , , , and .

Furthermore, as a preferred technical solution of the present disclosure, in general formula (C), R_3-substituted ring A is selected from the group consisting of: , , , , , , , , , , , , , , , , , , , , and .

Furthermore, as a preferred technical solution of the present disclosure, in general formula (C), the R_4-substituted ring B is selected from the group consisting of: , , , , , , , , , , , , , , , , , , , , ,



As a preferred technical solution of the present disclosure, in general formula (C), the compound, or the isomer thereof, or the racemate thereof, or the pharmaceutically acceptable salt thereof is selected from the group consisting of: C1 to C13, and C15 to C95.

The present disclosure further provides a pharmaceutical composition, comprising a therapeutically effective amount of the compound, or the isomer thereof, or the racemate thereof, or the pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

The present disclosure further provides use of the compound, or the isomer thereof, or the racemate thereof, or the pharmaceutically acceptable salt thereof according to any one of claims 1 to 47 in the manufacture of a medicament for treating a PCSK9 inhibitor-related disease; preferably, the PCSK9 inhibitor-related disease is hypercholesterolemia.

DETAILED DESCRIPTION

For clarity, general terms used in the description of the compound are defined herein.

Unless otherwise indicated, the following terms and phrases used herein are intended to have the following meanings. A specific term or phrase that is not specifically defined should not be considered indefinite or unclear, but should be understood according to its ordinary meaning. When a trade name appears herein, it is intended to refer to the corresponding commercial product or its active ingredient. The term "pharmaceutically acceptable" as used here refers to those compounds, materials, compositions, and/or dosage forms that are, within the scope of sound medical judgment, suitable for use in contact with human and animal tissues without undue toxicity, irritation, allergic reactions, or other problems or complications, and have a reasonable benefit/risk ratio.

The term "pharmaceutically acceptable salt" refers to a salt of the compound of the present disclosure, prepared from the compound of the present disclosure, which has specific substituents as discovered, with a pharmaceutically acceptable acid or base.

In addition to a salt form, the compound provided by the present disclosure may also exist in a prodrug form. The prodrug of the compound described herein readily undergoes chemical

changes under physiological conditions to convert into the compound of the present disclosure. Furthermore, the prodrug can be converted into the compound of the present disclosure through chemical or biochemical methods in an in vivo environment.

Certain compound of the present disclosure may exist in an unsolvated form or solvated form, comprising a hydrated form. In general, the solvated form are equivalent to the unsolvated form, and both are encompassed within the scope of the present disclosure.

The compound of the present disclosure may exist in a specific geometric or stereoisomeric form. The present disclosure contemplates all such compounds, comprising cis and trans isomers, (-)- and (+)- enantiomers, (R)- and (S)- enantiomers, diastereomers, (D)-isomers, (L)-isomers, atropisomers, and their racemic mixtures and other mixtures, such as enantiomerically or diastereomerically enriched mixtures, all of which are encompassed within the scope of the present disclosure. Additional asymmetric carbon atoms may be present in substituents such as alkyl groups. All such isomers and mixtures thereof are encompassed within the scope of the present disclosure.

Optically active (R)- and (S)- isomers, as well as D and L isomers, atropisomers, etc., can be prepared by chiral synthesis or chiral reagents, or by other conventional techniques. If one enantiomer of a compound of the present disclosure is desired, it can be prepared by asymmetric synthesis or by derivation with a chiral auxiliary, wherein the resulting diastereomeric mixture is separated, and the auxiliary group is cleaved to provide the pure desired enantiomer. Alternatively, when the molecule comprises a basic functional group (such as amino) or an acidic functional group (such as carboxyl), diastereomeric salts are formed with an appropriate optically active acid or base, then resolved by conventional methods known in the art to obtain the pure enantiomers, which are then recovered. Furthermore, the separation of enantiomers and diastereomers is usually accomplished using chromatography with a chiral stationary phase, optionally combined with chemical derivatization (e.g., generation of carbamates from amines).

An atom in the molecule of the compound of the present disclosure can be an isotope. Isotopic derivatization often can extend half-life, reduce clearance, improve metabolic stability, and enhance in vivo activity. Moreover, included is an embodiment wherein at least one atom is replaced by an atom having the same atomic number (number of protons) but a different mass number (sum of protons and neutrons). Examples of isotopes comprised in the compounds of the present disclosure comprise hydrogen atom, carbon atom, nitrogen atom, oxygen atom,

phosphorus atom, sulfur atom, fluorine atom, chlorine atom, which comprise ^{2}H, ^{3}H, ^{13}C, ^{14}C, ^{15}N, ^{17}O, ^{18}O, ^{31}P, ^{32}P, ^{35}S, ^{18}F, and ^{36}Cl, respectively. In particular, a radioactive isotope that emits radiation upon decay, such as ^{3}H or ^{14}C, can be used for drug formulation or anatomical testing of the compound in vivo. A stable isotope neither decays nor changes in quantity over time and is non-radioactive, thus it can be used safely. When an atom constituting the molecule of the compound of the present disclosure is an isotope, isotopic conversion can be performed according to general methods by replacing the reagent used in the synthesis with a corresponding isotope-containing reagent.

The compound of the present disclosure may comprise a non-natural proportion of atomic isotopes at one or more atoms constituting the compound. For example, the compound can be labeled with radioactive isotopes, such as deuterium (^{2}H), iodine-125 (^{125}I), or carbon-14 (^{14}C). All isotopic variations of the compound of the present disclosure, whether radioactive or not, are encompassed within the scope of the present disclosure.

Furthermore, in the compound of the present disclosure, one or more hydrogen atoms are substituted by the isotope deuterium (^{2}H). Deuterium substitution of the compound of the present disclosure results in effects such as extended half-life, reduced clearance, improved metabolic stability, and enhanced in vivo activity.

The preparation method for such isotopic derivatives generally comprises: phase transfer catalysis methods. For example, a preferred deuteration method employs a phase transfer catalyst (e.g., tetraalkylammonium salt, NBu_4HSO_4). Using a phase transfer catalyst to exchange the methylene protons of a diphenylmethane compound leads to higher deuterium incorporation compared to reduction with a deuterated silane (e.g., triethylsilyl deuteride) in the presence of an acid (e.g., methanesulfonic acid) or with sodium borodeuteride using a Lewis acid such as aluminum trichloride.

The term "pharmaceutically acceptable carrier" refers to any formulation carrier or medium capable of delivering an effective amount of the active substance of the present disclosure without interfering with the biological activity of the active substance and without toxic side effects to the host or patient. Representative carriers comprise water, oils, vegetable and mineral substances, cream bases, lotion bases, ointment bases, etc. These bases comprise suspending agents, viscosity-increasing agents, transdermal enhancers, etc. Their formulations are well known to those skilled in the art of cosmetics or topical pharmaceuticals. For additional

information on carriers, reference can be made to Remington: The Science and Practice of Pharmacy, 21st Ed., Lippincott, Williams & Wilkins (2005), the content of which is incorporated herein by reference.

The term "excipient" generally refers to carriers, diluents, and/or media required for formulating an effective pharmaceutical composition.

With respect to a drug or pharmacologically active agent, the term "effective amount" or "therapeutically effective amount" refers to a sufficient amount of the drug or agent that is non-toxic but achieves the desired effect. For oral dosage forms in the present disclosure, the "effective amount" of an active substance in the composition refers to the amount required to achieve the desired effect when used in combination with another active substance in the composition. The determination of an effective amount varies from person to person, depending on the age and general condition of the recipient, as well as the specific active substance. A suitable effective amount in an individual case can be determined by those skilled in the art through routine experimentation.

The terms "active ingredient," "therapeutic agent," "active substance," or "active agent" refer to a chemical entity that can effectively treat a targeted disorder, disease, or condition.

"Optional" or "optionally" means that the subsequently described event or circumstance may, but does not have to, occur, and the description includes situations where the event or circumstance occurs and situations where it does not occur.

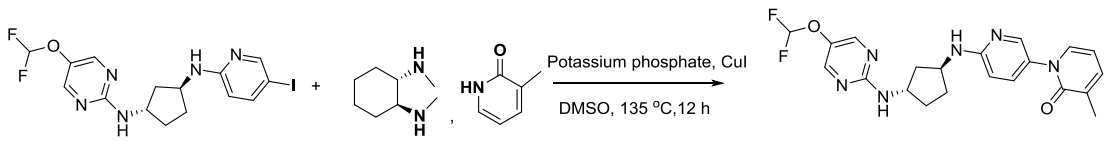
The compound of the present disclosure can be prepared by various synthetic methods well known to those skilled in the art, including the specific embodiments listed below, embodiments formed by combining these with other chemical synthesis methods, and equivalent replacement methods well known to those skilled in the art. Preferred embodiments include, but are not limited to, the examples of the present disclosure.

EXAMPLES

The present application is further described in detail below with reference to examples, but the embodiments of the present application are not limited thereto.

Example A1

Synthesis of 6'-(((1S,3S)-3-((5-(difluoromethoxy)pyrimidin-2-yl)amino)cyclopentyl)amino)-3-methyl-2H-[1,3'-bipyridin]-2-one



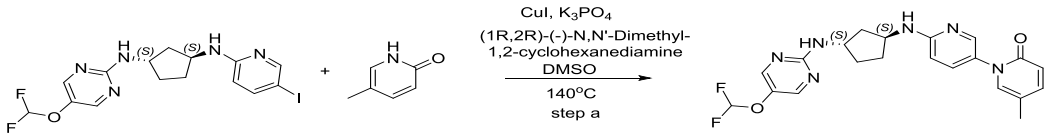
At room temperature, (1S,3S)-N^1-(5-(difluoromethoxy)pyrimidin-2-yl)-N^3-(5-iodopyridin-2-yl)cyclopentane-1,3-diamine (300 mg, 0.67 mmol), 3-methylpyridin-2(1H)-one (146 mg, 1.34 mmol), (1S,2S)-N^1,N^2-dimethylcyclohexane-1,2-diamine (19.0 mg, 0.13 mmol), and potassium phosphate (284.5 mg, 1.34 mmol) were added to DMSO (8 mL). Subsequently, copper(I) iodide (38.2 mg, 0.20 mmol) was added. After completion of addition, the system was purged with nitrogen, and heated to 140 ℃ and reacted for 12 hours.

After completion of the reaction, the mixture was cooled to room temperature, and water (40 mL) was added to the system. The mixture was extracted with ethyl acetate (20 mL × 3). The organic phases were combined, washed with saturated brine (30 mL), dried, filtered, and concentrated under reduced pressure to dryness to obtain a residue. The residue was purified by normal-phase column chromatography (dichloromethane/methanol = 10:1) to obtain 80 mg of a white product, 6'-(((1S,3S)-3-((5-(difluoromethoxy)pyrimidin-2-yl)amino)cyclopentyl)amino)-3-methyl-2H-[1,3'-bipyridin]-2-one (yield: 27.8%).

LC-MS: $[M+H]^+$ = 429. ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.20-8.18 (s, 2H), 7.96-7.93 (d, J = 2.6 Hz, 1H), 7.52-7.43 (m, 3H), 6.91-6.52 (m, 2H), 6.42-6.37 (t, J = 6.8 Hz, 1H), 4.48-4.30 (m, 2H), 2.36-2.24 (m, 2H), 2.18-2.14 (s, 3H), 2.08-1.97 (m, 2H), 1.71-1.56 (m, 2H).

Example A2

Synthesis of 6'-(((1S,3S)-3-((5-(difluoromethoxy)pyrimidin-2-yl)amino)cyclopentyl)amino)-5-methyl-2H-[1,3'-bipyridin]-2-one



(1S,3S)-N^1-(5-(difluoromethoxy)pyrimidin-2-yl)-N^3-(5-iodopyridin-2-yl)cyclopentane-1,3-diamine (300 mg, 0.67 mmol) was dissolved in DMSO (5 mL). 5-Methylpyridin-2(1H)-one (73 mg, 0.67 mmol), copper(I) iodide (25 mg, 0.134 mmol), potassium phosphate (284 mg, 1.34 mmol), and (1R,2R)-(-)-N,N'-dimethyl-1,2-cyclohexanediamine (19 mg, 0.134 mmol) were added. Under nitrogen protection, the mixture was reacted at 140 ℃ for 13 hours.

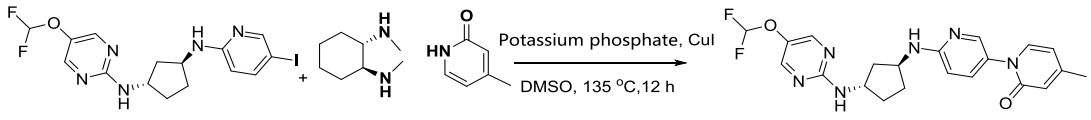
After completion of the reaction, the mixture was cooled to room temperature, quenched

with 10 mL of water, and extracted with ethyl acetate (50 mL × 3). The organic phases were combined, dried over anhydrous sodium sulfate, filtered, and concentrated. The resulting residue was purified by C_{18} column chromatography (water/acetonitrile = 95/5 → acetonitrile) to obtain 130 mg of 6'-(((1S,3S)-3-((5-(difluoromethoxy)pyrimidin-2-yl)amino)cyclopentyl)amino)-5-methyl-2H-[1, 3'-bipyridin]-2-one (yield: 45%).

LC-MS: $[M+H]^+$ = 429. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.23 (s, 2H), 7.90 (d, J = 2.7 Hz, 1H), 7.50 (d, J = 7.2 Hz, 1H), 7.43-7.31 (m, 3H), 7.27-6.83 (m, 2H), 6.51 (d, J = 8.9 Hz, 1H), 6.38 (d, J = 9.2 Hz, 1H), 4.38-4.22 (m, 2H), 2.19-2.05 (m, 2H), 2.03 (d, J = 1.1 Hz, 3H), 1.94-1.79 (m, 2H), 1.58-1.40 (m, 2H).

Example A3

Synthesis of 6'-(((1S,3S)-3-((5-(difluoromethoxy)pyrimidin-2-yl)amino)cyclopentyl)amino)-4-methyl-2H-[1, 3'-bipyridin]-2-one



At room temperature, (1S,3S)-N^1-(5-(difluoromethoxy)pyrimidin-2-yl)-N^3-(5-iodopyridin-2-yl)cyclopentane-1,3-diamine (300 mg, 0.67 mmol), 4-methylpyridin-2(1H)-one (146 mg, 1.34 mmol), (1S,2S)-N^1,N^2-dimethylcyclohexane-1,2-diamine (19.0 mg, 0.13 mmol), and potassium phosphate (284.5 mg, 1.34 mmol) were added to DMSO (8 mL). Subsequently, copper(I) iodide (38.2 mg, 0.20 mmol) was added. After completion of addition, the system was purged with nitrogen, and heated to 140 ℃ and reacted for 12 hours.

After completion of the reaction, the mixture was cooled to room temperature, and water (40 mL) was added to the system. The mixture was extracted with ethyl acetate (20 mL × 3). The organic phases were combined,washed with saturated brine (30 mL), dried, filtered, and concentrated under reduced pressure to dryness to obtain a residue. The residue was purified by normal-phase column chromatography (dichloromethane/methanol = 10:1) to obtain 100 mg of a white product, 6'-(((1S,3S)-3-((5-(difluoromethoxy)pyrimidin-2-yl)amino)cyclopentyl)amino)-4-methyl-2H-[1, 3'-bipyridin]-2-one (yield: 34.7%).

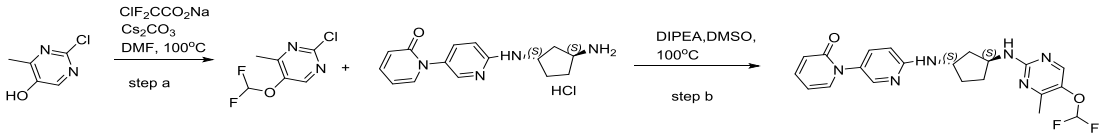
LC-MS: $[M+H]^+$ = 429.

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.24-8.22 (s, 2H), 7.90-7.87 (d, J = 2.7 Hz, 1H),

7.52-7.46 (t, J = 6.6 Hz, 2H), 7.38-7.34 (m, 1H), 7.23-6.84 (m, 2H), 6.53-6.49 (d, J = 8.9 Hz, 1H), 6.26-6.24 (m, 1H), 6.16-6.11 (m, 1H), 4.35-4.25 (m, 2H), 2.20-2.07 (m, 5H), 1.95-1.81 (m, 2H), 1.60-1.44 (m, 2H).

Example A4

Synthesis of 6'-(((1S,3S)-3-((5-(difluoromethoxy)-4-methylpyrimidin-2-yl)amino)cyclopentyl)amino)-2H-[1, 3'-bipyridin]-2-one



Step A: Synthesis of 2-chloro-5-(difluoromethoxy)-4-methylpyrimidine

2-Chloro-4-methylpyrimidin-5-ol (1 g, 7.06 mmol) was dissolved in DMF (20 mL). Cesium carbonate (3 g, 9.19 mmol) was added, and the mixture was reacted under nitrogen protection at room temperature for 1.5 hours. Subsequently, sodium chlorodifluoroacetate (3.5 g, 22.98 mmol) was added, and the mixture was stirred at 100 ℃ for 3.5 hours.

After completion of the reaction, the mixture was cooled to room temperature, quenched with 50 mL of water, and extracted with ethyl acetate (60 mL × 3). The organic phases were combined, dried over anhydrous sodium sulfate, filtered, and concentrated. The resulting residue was purified by silica gel column chromatography (PE/EA = 100/1 to 10/1) to obtain 530 mg of 2-chloro-5-(difluoromethoxy)-4-methylpyrimidine (yield: 38%).

Step B: Synthesis of 6'-(((1S,3S)-3-((5-(difluoromethoxy)-4-methylpyrimidin-2-yl)amino)cyclopentyl)amino)-2H-[1, 3'-bipyridin]-2-one

2-Chloro-5-(difluoromethoxy)-4-methylpyrimidine (317 mg, 1.63 mmol) and 6'-(((1S,3S)-3-aminocyclopentyl)amino)-2H-[1,3'-bipyridin]-2-one hydrochloride (500 mg, 1.63 mmol) were dissolved in DMSO (5 mL) and reacted at 100 ℃ for 6 hours.

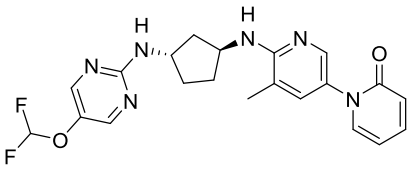
After completion of the reaction, the mixture was cooled to room temperature, quenched with 20 mL of water, and extracted with ethyl acetate (60 mL × 3). The organic phases were combined, dried over anhydrous sodium sulfate, filtered, and concentrated. The resulting residue was purified by silica gel column chromatography (PE/EA = 100/1 to EA) to obtain 80 mg of 6'-(((1S,3S)-3-((5-(difluoromethoxy)-4-methylpyrimidin-2-yl)amino)cyclopentyl)amino)-2H-[1, 3'-bipyridin]-2-one (yield: 11%).

LC-MS: $[M+H]^+$ = 429. ^1H NMR (400 MHz, DMSO-d_6) δ 8.08 (s, 1H), 7.92 (d, J = 2.7 Hz, 1H), 7.60 (d, J = 6.8 Hz, 1H), 7.47 (t, J = 7.9 Hz, 1H), 7.43-7.31 (m, 2H), 7.22-6.78 (m, 2H),

6.52 (d, J = 8.9 Hz, 1H), 6.44 (d, J = 9.2 Hz, 1H), 6.27 (t, J = 6.7 Hz, 1H), 4.39-4.23 (m, 2H), 2.24 (s, 3H), 2.18-2.03 (m, 2H), 1.96-1.79 (m, 2H), 1.56-1.42 (m, 2H).

Example A5

Synthesis of 6'-(((1S,3S)-3-((5-(difluoromethoxy)pyrimidin-2-yl)amino)cyclopentyl)amino)-5'-methyl-2H-[1,3'-bipyridin]-2-one



Step A: Synthesis of 6'-chloro-5'-methyl-2H-[1,3'-bipyridin]-2-one

Under nitrogen protection at room temperature, pyridin-2(1H)-one (1.045 g, 11.0 mmol, 1.1 eq), 2-chloro-5-iodo-3-methylpyridine (2.5 g, 10.0 mmol, 1.0 eq), copper(I) iodide (0.286 g, 1.5 mmol, 0.15 eq), (1S,2S)-N^1,N^2-dimethylcyclohexane-1,2-diamine (0.427 g, 3.0 mmol, 0.3 eq), and potassium phosphate (4.245 g, 20.0 mmol, 2.0 eq) were dissolved in dimethyl sulfoxide (40 mL) and reacted at 120 ℃ for 14 hours.

After completion of the reaction, cold water (100 mL) was added to quench the reaction, followed by extraction with ethyl acetate (100 mL × 3). The organic phases were combined, dried over anhydrous sodium sulfate, filtered, and concentrated. The resulting residue was purified by silica gel column chromatography (eluent: ethyl acetate/n-hexane = 5/10) to obtain 1.0 g of a yellow solid, 6'-chloro-5'-methyl-2H-[1,3'-bipyridin]-2-one (yield: 45%). LC-MS: $[M+H]^+$ = 221.

Step B: Synthesis of 6'-(((1S,3S)-3-((5-(difluoromethoxy)pyrimidin-2-yl)amino)cyclopentyl)amino)-5'-methyl-2H-[1,3'-bipyridin]-2-one

Under nitrogen protection at room temperature, 6'-chloro-5'-methyl-2H-[1,3'-bipyridin]-2-one (0.33 g, 1.5 mmol, 1.2 eq), (1S,3S)-N^1-(5-(difluoromethoxy)pyrimidin-2-yl)cyclopentane-1,3-diamine (0.305 g, 1.25 mmol, 1.0 eq), methanesulfonato(2-di-tert-butylphosphino-2',4',6'-triisopropyl-1,1'-biphenyl)(2'-amino-1,1'-biphenyl-2-yl)palladium(II) (0.2 g, 0.25 mmol, 0.2 eq), and potassium tert-butoxide (0.281 g, 2.5 mmol, 2.0 eq) were dissolved in 1,4-dioxane (5 mL), and the mixture was heated to 110 ℃ and reacted overnight.

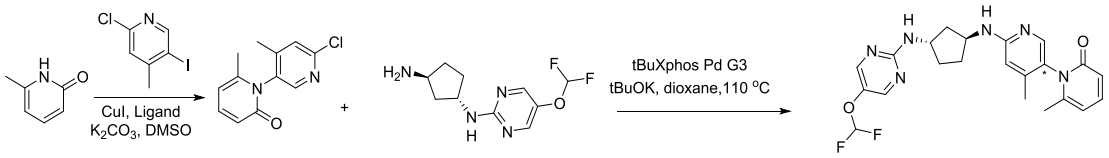
After completion of the reaction, water (50 mL) was added, followed by extraction with

ethyl acetate (50 mL × 3). The organic phases were combined, dried over anhydrous sodium sulfate, filtered, and concentrated. The resulting residue was purified by silica gel column chromatography (eluent: ethyl acetate/methanol = 1/10) to obtain 0.130 g of 6'-(((1S,3S)-3-((5-(difluoromethoxy)pyrimidin-2-yl)amino)cyclopentyl)amino)-5'-methyl-2H-[1,3'-bipyridin]-2-one (yield: 20%). LC-MS: $[M+H]^+$ = 429.

NMR data: ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.23 (s, 2H), 7.83 (d, J = 2.6 Hz, 1H), 7.58 (dd, J = 6.9, 2.1 Hz, 1H), 7.54-7.42 (m, 2H), 7.28 (dd, J = 2.6, 1.0 Hz, 1H), 7.03 (t, J = 74.0 Hz, 1H), 6.50-6.40 (m, 1H), 6.26 (td, J = 6.7, 1.4 Hz, 1H), 5.95 (d, J = 7.0 Hz, 1H), 4.53 (h, J = 7.0 Hz, 1H), 4.34 (p, J = 7.0 Hz, 1H), 2.27-2.03 (m, 5H), 1.94 (t, J = 7.1 Hz, 2H), 1.63-1.48 (m, 2H).

Example A6

Synthesis of 6'-(((1S,3S)-3-((5-(difluoromethoxy)pyrimidin-2-yl)amino)cyclopentyl)amino)-4',6-dimethyl-2H-[1,3'-bipyridin]-2-one



Step A: Synthesis of 6'-chloro-4',6-dimethyl-2H-[1,3'-bipyridin]-2-one

Under nitrogen protection at room temperature, 6-methylpyridin-2(1H)-one (2.0 g, 18.35 mmol, 1.0 eq), 2-chloro-5-iodo-4-methylpyridine (5.0 g, 20.2 mmol, 1.1 eq), copper(I) iodide (1.05 g, 5.5 mmol, 0.3 eq), 8-hydroxyquinoline (0.88 g, 6.05 mmol, 0.33 eq), and potassium carbonate (8.88 g, 64.22 mmol, 3.5 eq) were dissolved in dimethyl sulfoxide (74 mL) and reacted at 140 ℃ overnight.

After completion of the reaction, cold water (150 mL) was added to quench the reaction, followed by extraction with ethyl acetate (100 mL × 3). The organic phases were combined, dried over anhydrous sodium sulfate, filtered, and concentrated. The resulting residue was purified by silica gel column chromatography (eluent: ethyl acetate/n-hexane = 5/10) to obtain 0.407 g of a yellow solid, 6'-chloro-4',6-dimethyl-2H-[1,3'-bipyridin]-2-one (yield: 10%). LC-MS: $[M+H]^+$ = 235.

Step B: Synthesis of 6'-(((1S,3S)-3-((5-(difluoromethoxy)pyrimidin-2-yl)amino)cyclopentyl)amino)-4',6-dimethyl-2H-[1,3'-bipyridin]-2-one

Under nitrogen protection at room temperature, 6'-chloro-4',6-dimethyl-2H-[1,3'-bipyridin]-2-one (0.407 g, 1.74 mmol, 1.2 eq),

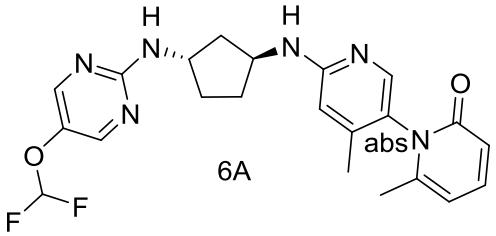
(1S,3S)-N^1-(5-(difluoromethoxy)pyrimidin-2-yl)cyclopentane-1,3-diamine (0.472 g, 1.45 mmol, 1.0 eq), methanesulfonato(2-di-tert-butylphosphino-2',4',6'-triisopropyl-1,1'-biphenyl)(2'-amino-1,1'-biphenyl-2-yl)palladium(II) (0.231 g, 0.29 mmol, 0.2 eq), and potassium tert-butoxide (0.325 g, 2.9 mmol, 2.0 eq) were dissolved in 1,4-dioxane (6 mL), and the mixture was heated to 110 ℃ and reacted overnight.

After completion of the reaction, the organic solvent was directly dried by rotary evaporation. The resulting residue was purified by silica gel column chromatography (eluent: ethyl acetate/methanol = 1/10) to obtain 0.36 g of 6'-(((1S,3S)-3-((5-(difluoromethoxy)pyrimidin-2-yl)amino)cyclopentyl)amino)-4',6-dimethyl-2H-[1,3'-bipyridin]-2-one (yield: 56%). LC-MS: $[M+H]^+$ = 443.

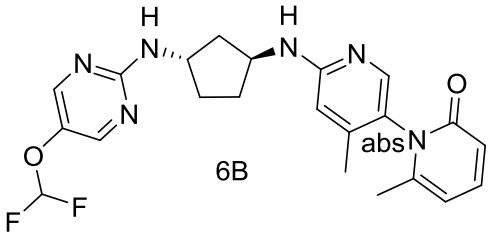
NMR data: ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.23 (s, 2H), 7.65 (s, 1H), 7.47 (dd, J = 7.2, 3.6 Hz, 1H), 7.39 (dd, J = 9.2, 6.8 Hz, 1H), 7.21-6.84 (m, 1H), 6.76 (d, J = 6.9 Hz, 1H), 6.42 (s, 1H), 6.32 (d, J = 9.2 Hz, 1H), 6.23 (d, J = 6.8 Hz, 1H), 4.30 (dtd, J = 12.1, 7.1, 3.9 Hz, 2H), 2.12 (dtd, J = 12.4, 8.6, 7.7, 3.7 Hz, 2H), 1.92-1.85 (m, 5H), 1.81 (s, 3H), 1.51 (dtd, J = 18.5, 10.6, 9.8, 4.1 Hz, 2H).

After Pre-HPLC separation, using column model IG-3: 4.6*250mm*5um, mobile phase n-hexane/ethanol = 20:80, flow rate 0.6 mL/min, column temperature 35 ℃, 22 mg of product with HPLC retention time 12 minutes and purity 96.16% was obtained, named 6A. NMR data: ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.23 (s, 2H), 7.65 (s, 1H), 7.47 (d, J = 7.3 Hz, 1H), 7.40 (dd, J = 9.2, 6.8 Hz, 1H), 7.12 (d, J = 74.1 Hz, 1H), 6.76 (d, J = 6.9 Hz, 1H), 6.42 (s, 1H), 6.32 (d, J = 9.1 Hz, 1H), 6.23 (dt, J = 6.8, 1.2 Hz, 1H), 4.29 (p, J = 6.6 Hz, 2H), 2.12 (dq, J = 9.7, 5.3, 4.6 Hz, 2H), 1.96-1.79 (m, 8H), 1.51 (tdd, J = 15.8, 12.9, 11.1, 5.3 Hz, 2H).

32 mg of product with HPLC retention time 15.1 minutes and purity 80.37% was obtained, named 6B. NMR data: ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.23 (s, 2H), 7.65 (s, 1H), 7.47 (d, J = 7.2 Hz, 1H), 7.39 (dd, J = 9.2, 6.7 Hz, 1H), 7.03 (s, 1H), 6.76 (d, J = 6.9 Hz, 1H), 6.42 (s, 1H), 6.32 (d, J = 9.1 Hz, 1H), 6.23 (d, J = 6.8 Hz, 1H), 4.31 (h, J = 7.1, 6.6 Hz, 2H), 2.18-2.07 (m, 2H), 1.89 (d, J = 11.4 Hz, 5H), 1.81 (s, 3H), 1.51 (td, J = 17.8, 16.3, 6.9 Hz, 2H).



6A

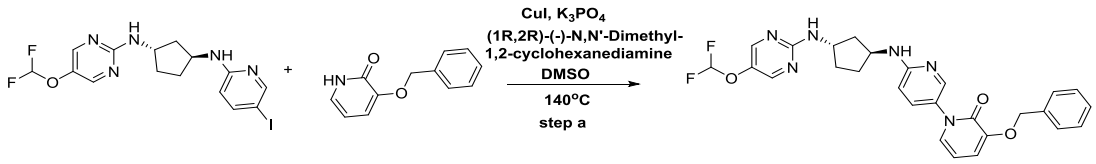


6B

wherein, * represents a racemate, and abs indicates absolute configuration.

Example A7

Synthesis of 3-(benzyloxy)-6'-(((1S,3S)-3-((5-(difluoromethoxy)pyrimidin-2-yl)amino)cyclopentyl)amino)-2H-[1,3'-bipyridin]-2-one



Step A: Synthesis of 3-(benzyloxy)-6'-(((1S,3S)-3-((5-(difluoromethoxy)pyrimidin-2-yl)amino)cyclopentyl)amino)-2H-[1,3'-bipyridin]-2-one

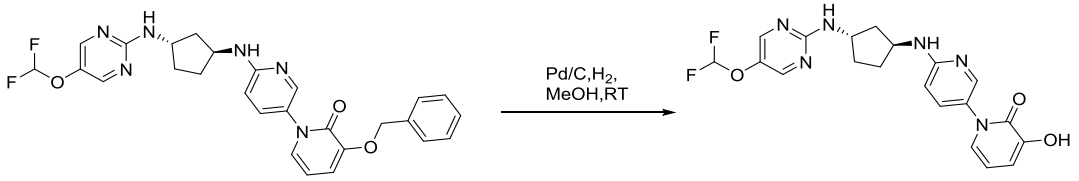
(1S,3S)-N^1-(5-(difluoromethoxy)pyrimidin-2-yl)-N^3-(5-iodopyridin-2-yl)cyclopentane-1,3-diamine (500 mg, 1.12 mmol) was dissolved in DMSO (5 mL). 3-(benzyloxy)pyridin-2(1H)-one (449 mg, 2.24 mmol), copper(I) iodide (85 mg, 0.447 mmol), potassium phosphate (309 mg, 2.24 mmol), and (1R,2R)-(-)-N,N'-dimethyl-1,2-cyclohexanediamine (32 mg, 0.224 mmol) were added. Under nitrogen protection, the mixture was reacted at 140 ℃ for 16 hours.

After completion of the reaction, the mixture was cooled to room temperature, quenched with 10 mL of water, and extracted with ethyl acetate (50 mL × 3). The organic phases were combined, dried over anhydrous sodium sulfate, filtered, and concentrated. The resulting residue was purified by C_{18} column chromatography (water/acetonitrile = 95/5 → acetonitrile) to obtain 0.35 g of 3-(benzyloxy)-6'-(((1S,3S)-3-((5-(difluoromethoxy)pyrimidin-2-yl)amino)cyclopentyl)amino)-2H-[1,3'-bipyridin]-2-one (yield: 60%).

LC-MS: $[M+H]^+$ = 521. NMR data: ^{1}H NMR (400 MHz, DMSO-d_6) δ: 8.23 (s, 2H), 7.92 (d, J = 2.7 Hz, 1H), 7.53-7.28 (m, 7H), 7.24-6.81 (m, 4H), 6.52 (d, J = 8.9 Hz, 1H), 6.18 (t, J = 7.2 Hz, 1H), 5.04 (s, 2H), 4.38-4.25 (m, 2H), 2.22-2.05 (m, 2H), 1.96-1.80 (m, 2H), 1.61-1.41 (m, 2H).

Example A8

Synthesis of 6'-(((1S,3S)-3-((5-(difluoromethoxy)pyrimidin-2-yl)amino)cyclopentyl)amino)-3-hydroxy-2H-[1,3'-bipyridin]-2-one



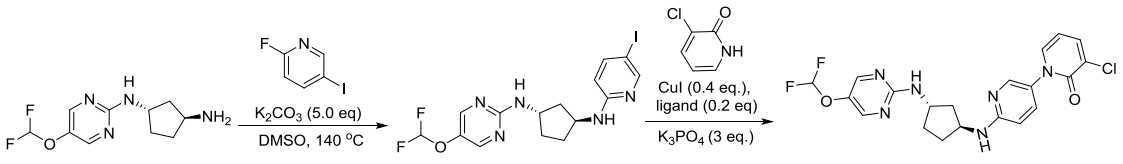
Under nitrogen protection, 3-(benzyloxy)-6'-(((1S,3S)-3-((5-(difluoromethoxy)pyrimidin-2-yl)amino)cyclopentyl)amino)-2H-[1,3'-bipyridin]-2-one (200 mg, 0.384 mmol) was dissolved in methanol (5 mL). 10% Pd/C (40 mg) was added, and the mixture was reacted under a hydrogen atmosphere at room temperature for 12 hours.

After completion of the reaction, the solid was filtered off, and the filtrate was concentrated. The resulting residue was purified by C_{18} column chromatography (water/acetonitrile = 100/0 → 10/90) to obtain 0.12 g of 6'-(((1S,3S)-3-((5-(difluoromethoxy)pyrimidin-2-yl)amino)cyclopentyl)amino)-3-hydroxy-2H-[1,3'-bipyridin]-2-one (yield: 72.7%).

LC-MS: $[M+H]^+$ = 431. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 9.14 (s, 1H), 8.22 (s, 2H), 7.93 (d, J = 2.7 Hz, 1H), 7.52-7.32 (m, 2H), 7.22-6.79 (m, 3H), 6.79-6.68 (m, 1H), 6.53 (d, J = 8.9 Hz, 1H), 6.16 (t, J = 7.1 Hz, 1H), 4.38-4.21 (m, 2H), 2.21-2.03 (m, 2H), 1.96-1.78 (m, J = 6.7 Hz, 2H), 1.62-1.40 (m, 2H).

Example A9

Synthesis of 3-chloro-6'-(((1S,3S)-3-((5-(difluoromethoxy)pyrimidin-2-yl)amino)cyclopentyl)amino)-2H-[1,3'-bipyridin]-2-one



Step A: Synthesis of (1S,3S)-N^1-(5-(difluoromethoxy)pyrimidin-2-yl)-N^3-(5-iodopyridin-2-yl)cyclopentane-1,3-diamine

Under nitrogen protection at room temperature, (1S,3S)-N^1-(5-(difluoromethoxy)pyrimidin-2-yl)cyclopentane-1,3-diamine (7.32 g, 30.0 mmol, 1.0 eq), 2-fluoro-5-iodopyridine (8.03 g, 36 mmol, 1.2 eq), and potassium carbonate (20.73 g, 150 mmol, 5.0 eq) were dissolved in dimethyl sulfoxide (140 mL) and reacted at 140 ℃ overnight.

After completion of the reaction, cold water (200 mL) was added to quench the reaction,

followed by extraction with ethyl acetate (250 mL × 3). The organic phases were combined, dried over anhydrous sodium sulfate, filtered, and concentrated. The resulting residue was purified by silica gel column chromatography (eluent: ethyl acetate/n-hexane = 5/10) to obtain 10 g of a white solid, (1S,3S)-N^1-(5-(difluoromethoxy)pyrimidin-2-yl)-N^3-(5-iodopyridin-2-yl)cyclopentane-1,3-diamine (yield: 75%). LC-MS: $[M+H]^+$ = 448.

Step B: Synthesis of 3-chloro-6'-(((1S,3S)-3-((5-(difluoromethoxy)pyrimidin-2-yl)amino)cyclopentyl)amino)-2H-[1,3'-bipyridin]-2-one

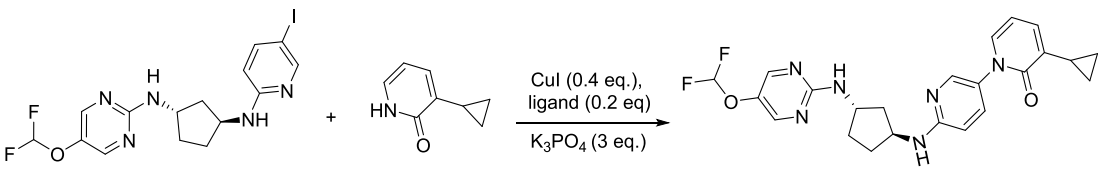
Under nitrogen protection at room temperature, (1S,3S)-N^1-(5-(difluoromethoxy)pyrimidin-2-yl)-N^3-(5-iodopyridin-2-yl)cyclopentane-1,3-diamine (0.448 g, 1.0 mmol, 1.0 eq), 3-chloropyridin-2(1H)-one (0.260 g, 2.0 mmol, 2.0 eq), copper(I) iodide (0.076 g, 0.4 mmol, 0.4 eq), N^1,N^2-dimethylcyclohexane-1,2-diamine (0.029 g, 0.2 mmol, 0.2 eq), and potassium phosphate (0.673 g, 3.0 mmol, 3.0 eq) were dissolved in dimethyl sulfoxide (4 mL), and the mixture was heated to 140 ℃ and reacted overnight.

After completion of the reaction, cold water (50 mL) was added to quench the reaction, followed by extraction with ethyl acetate (50 mL × 3). The organic phases were combined, dried over anhydrous sodium sulfate, filtered, and concentrated. The resulting residue was purified by silica gel column chromatography (eluent: ethyl acetate) to obtain 0.1 g of 3-chloro-6'-(((1S,3S)-3-((5-(difluoromethoxy)pyrimidin-2-yl)amino)cyclopentyl)amino)-2H-[1,3'-bipyridin]-2-one (yield: 22%).

LC-MS: $[M+H]^+$ = 449. NMR data: ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.23 (s, 2H), 7.95 (d, J = 2.7 Hz, 1H), 7.81 (dd, J = 7.3, 1.9 Hz, 1H), 7.65 (dd, J = 6.8, 1.9 Hz, 1H), 7.53-7.39 (m, 2H), 7.22-6.84 (m, 2H), 6.53 (d, J = 8.9 Hz, 1H), 6.30 (t, J = 7.1 Hz, 1H), 4.31 (h, J = 6.7 Hz, 2H), 2.12 (dq, J = 12.1, 7.2 Hz, 2H), 1.88 (tdd, J = 13.2, 10.5, 6.3 Hz, 2H), 1.59-1.43 (m, 2H).

Example A10

Synthesis of 3-cyclopropyl-6'-(((1S,3S)-3-((5-(difluoromethoxy)pyrimidin-2-yl)amino)cyclopentyl)amino)-2H-[1,3'-bipyridin]-2-one



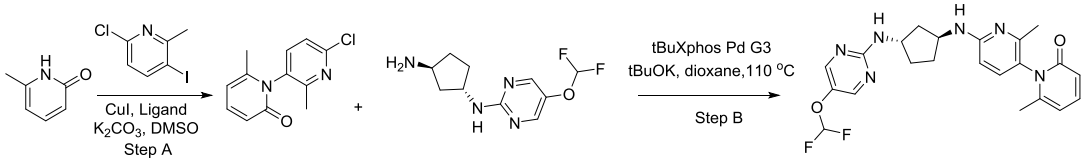
Under nitrogen protection at room temperature, (1S,3S)-N^1-(5-(difluoromethoxy)pyrimidin-2-yl)-N^3-(5-iodopyridin-2-yl)cyclopentane-1,3-diamine (0.224 g, 0.5 mmol, 1.0 eq), 3-cyclopropylpyridin-2(1H)-one (0.10 g, 0.735 mmol, 1.5 eq), copper(I) iodide (0.038 g, 0.2 mmol, 0.4 eq), N^1,N^2-dimethylcyclohexane-1,2-diamine (0.015 g, 0.1 mmol, 0.2 eq), and potassium phosphate (0.320 g, 1.5 mmol, 3.0 eq) were dissolved in dimethyl sulfoxide (2 mL), and the mixture was heated to 140 ℃ and reacted overnight.

After completion of the reaction, cold water (25 mL) was added to quench the reaction, followed by extraction with ethyl acetate (50 mL × 3). The organic phases were combined, dried over anhydrous sodium sulfate, filtered, and concentrated. The resulting residue was purified by silica gel column chromatography (eluent: ethyl acetate) to obtain 0.077 g of 3-cyclopropyl-6'-(((1S,3S)-3-((5-(difluoromethoxy)pyrimidin-2-yl)amino)cyclopentyl)amino)-2H-[1,3'-bipyridin]-2-one (yield: 31%).

LC-MS: $[M+H]^+$ = 455. NMR data: ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.23 (s, 2H), 7.91 (d, J = 2.7 Hz, 1H), 7.48 (d, J = 7.2 Hz, 1H), 7.43-7.36 (m, 2H), 7.22-6.85 (m, 3H), 6.52 (d, J = 8.9 Hz, 1H), 6.17 (t, J = 6.8 Hz, 1H), 4.30 (p, J = 6.6 Hz, 2H), 2.18-2.08 (m, 2H), 2.01 (ddd, J = 8.5, 5.3, 3.1 Hz, 1H), 1.95-1.83 (m, 2H), 1.51 (ddd, J = 18.9, 13.8, 7.3 Hz, 2H), 0.88-0.81 (m, 2H), 0.67-0.60 (m, 2H).

Example A11

Synthesis of 6'-(((1S,3S)-3-((5-(difluoromethoxy)pyrimidin-2-yl)amino)cyclopentyl)amino)-2',6-dimethyl-2H-[1,3'-bipyridin]-2-one



Step A: Synthesis of 6'-chloro-2',6-dimethyl-2H-[1,3'-bipyridin]-2-one

Under nitrogen protection at room temperature, 6-methylpyridin-2(1H)-one (2.0 g, 18.35 mmol, 1.0 eq), 6-chloro-3-iodo-2-methylpyridine (5.0 g, 20.2 mmol, 1.1 eq), copper(I) iodide (1.05 g, 5.5 mmol, 0.3 eq), 8-hydroxyquinoline (0.88 g, 6.05 mmol, 0.33 eq), and potassium carbonate (8.88 g, 64.22 mmol, 3.5 eq) were dissolved in dimethyl sulfoxide (40 mL) and reacted at 140 ℃ overnight.

After completion of the reaction, cold water (150 mL) was added to quench the reaction, followed by extraction with ethyl acetate (100 mL × 3). The organic phases were combined, dried over anhydrous sodium sulfate, filtered, and concentrated. The resulting residue was

purified by silica gel column chromatography (eluent: ethyl acetate/n-hexane = 5/10) to obtain 0.203 g of a yellow solid, 6'-chloro-2',6-dimethyl-2H-[1,3'-bipyridin]-2-one (yield: 5%). LC-MS: $[M+H]^+$ = 235.

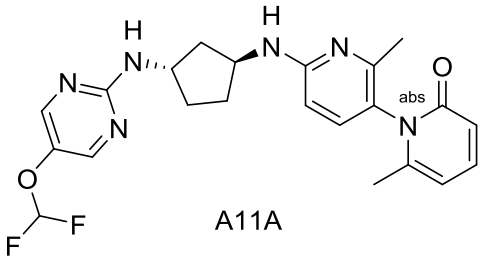
Step B: Synthesis of 6'-(((1S,3S)-3-((5-(difluoromethoxy)pyrimidin-2-yl)amino)cyclopentyl)amino)-2',6-dimethyl-2H-[1,3'-bipyridin]-2-one

Under nitrogen protection at room temperature, 6'-chloro-2',6-dimethyl-2H-[1,3'-bipyridin]-2-one (0.203 g, 0.86 mmol, 1.2 eq), (1S,3S)-N^1-(5-(difluoromethoxy)pyrimidin-2-yl)cyclopentane-1,3-diamine (0.24 g, 0.72 mmol, 1.0 eq), methanesulfonato(2-di-tert-butylphosphino-2',4',6'-triisopropyl-1,1'-biphenyl)(2'-amino-1,1'-biphenyl-2-yl)palladium(II) (0.12 g, 0.15 mmol, 0.2 eq), and potassium tert-butoxide (0.16 g, 1.45 mmol, 2.0 eq) were dissolved in 1,4-dioxane (8 mL), and the mixture was heated to 110 ℃ and reacted overnight.

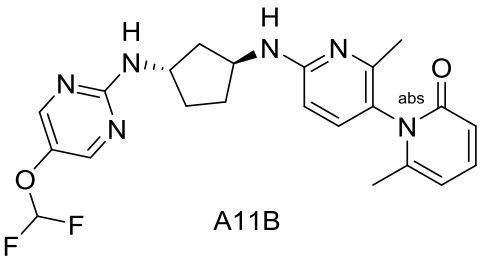
After completion of the reaction, the organic solvent was directly dried by rotary evaporation. The resulting residue was purified by silica gel column chromatography (eluent: ethyl acetate/methanol = 1/10) to obtain 0.18 g of 6'-(((1S,3S)-3-((5-(difluoromethoxy)pyrimidin-2-yl)amino)cyclopentyl)amino)-2',6-dimethyl-2H-[1,3'-bipyridin]-2-one.

LC-MS: $[M+H]^+$ = 443. NMR data: ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.26–8.21 (s, 2H), 7.52–7.44 (dd, J = 7.2, 2.3 Hz, 1H), 7.42–7.35 (dd, J = 9.2, 6.8 Hz, 1H), 7.23–7.02 (m, 2H), 6.86–6.75 (m, 1H), 6.41–6.29 (dd, J = 24.5, 8.9 Hz, 2H), 6.25–6.20 (m, 1H), 4.36–4.22 (m, 2H), 2.22–2.05 (m, 2H), 1.95–1.84 (m, 8H), 1.59–1.44 (m, 2H).

After Pre-SFC separation (method: column model IG-3: 4.6*250mm*5um, mobile phase n-hexane/ethanol = 20:80, flow rate 0.6 mL/min, column temperature 35 ℃), 25 mg of the front peak (RT = 10.53 min, purity 99%, named A11A) and 35 mg of the rear peak (RT=12.985 min, purity 76%, named A11B) were obtained.



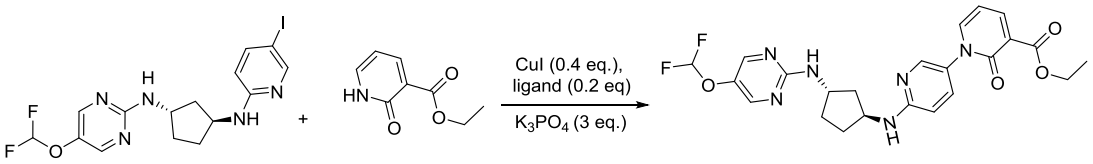
A11A



A11B

Example A12

Synthesis of ethyl 6'-(((1S,3S)-3-((5-(difluoromethoxy)pyrimidin-2-yl)amino)cyclopentyl)amino)-2-oxo-2H-[1,3'-bipyridine]-3-carboxylate



Step A: Synthesis of ethyl 6'-(((1S,3S)-3-((5-(difluoromethoxy)pyrimidin-2-yl)amino)cyclopentyl)amino)-2-oxo-2H-[1,3'-bipyridine]-3-carboxylate

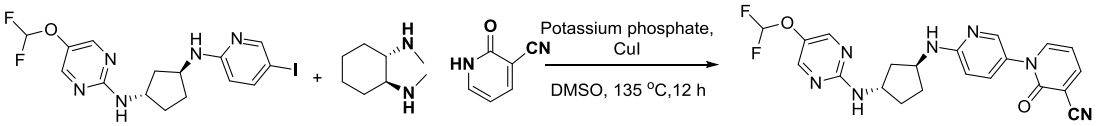
Under nitrogen protection at room temperature, (1S,3S)-N^1-(5-(difluoromethoxy)pyrimidin-2-yl)-N^3-(5-iodopyridin-2-yl)cyclopentane-1,3-diamine (0.642 g, 1.5 mmol, 1.0 eq), ethyl 2-oxo-1,2-dihydropyridine-3-carboxylate (0.502 g, 3 mmol, 2 eq), copper(I) iodide (0.114 g, 0.6 mmol, 0.4 eq), N^1,N^2-dimethylcyclohexane-1,2-diamine (0.043 g, 0.3 mmol, 0.2 eq), and potassium phosphate (0.320 g, 1.5 mmol, 3.0 eq) were dissolved in dimethyl sulfoxide (6 mL), and the mixture was heated to 140 ℃ and reacted overnight.

After completion of the reaction, cold water (25 mL) was added to quench the reaction, followed by extraction with ethyl acetate (50 mL × 3). The organic phases were combined, dried over anhydrous sodium sulfate, filtered, and concentrated. The resulting residue was purified by silica gel column chromatography (eluent: ethyl acetate) to obtain 0.19 g of ethyl 6'-(((1S,3S)-3-((5-(difluoromethoxy)pyrimidin-2-yl)amino)cyclopentyl)amino)-2-oxo-2H-[1,3'-bipyridine]-3-carboxylate.

LC-MS: $[M+H]^+$ = 487. NMR data: ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.23 (s, 2H), 8.06 (dd, J = 7.1, 2.2 Hz, 1H), 8.00–7.87 (m, 2H), 7.48 (d, J = 7.2 Hz, 1H), 7.41 (dd, J = 8.9, 2.7 Hz, 1H), 7.21–6.85 (m, 2H), 6.53 (d, J = 8.9 Hz, 1H), 6.36 (t, J = 6.9 Hz, 1H), 4.31 (h, J = 6.7 Hz, 2H), 4.21 (q, J = 7.1 Hz, 2H), 2.13 (ddt, J = 14.6, 12.4, 7.1 Hz, 2H), 1.88 (tdd, J = 13.3, 10.6, 6.4 Hz, 2H), 1.51 (ddd, J = 18.6, 13.9, 7.2 Hz, 2H), 1.25 (t, J = 7.1 Hz, 3H).

Example A13

Synthesis of 6'-(((1S,3S)-3-((5-(difluoromethoxy)pyrimidin-2-yl)amino)cyclopentyl)amino)-2-oxo-2H-[1,3'-bipyridine]-3-carbonitrile



Step A: Synthesis of

6'-(((1S,3S)-3-((5-(difluoromethoxy)pyrimidin-2-yl)amino)cyclopentyl)amino)-2-oxo-2H-[1,3'-bipyridine]-3-carbonitrile

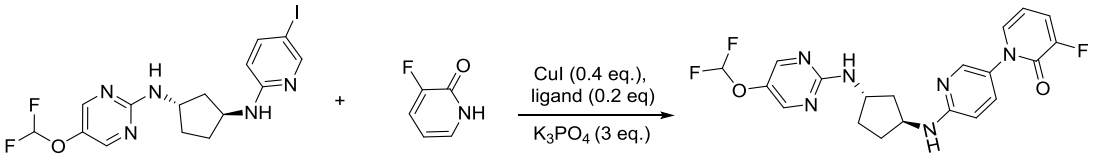
At room temperature, (1S,3S)-N^1-(5-(difluoromethoxy)pyrimidin-2-yl)-N^3-(5-iodopyridin-2-yl)cyclopentane-1,3-diamine (300 mg, 0.67 mmol), 2-oxo-1,2-dihydropyridine-3-carbonitrile (161 mg, 1.34 mmol), (1S,2S)-N^1,N^2-dimethylcyclohexane-1,2-diamine (19.0 mg, 0.13 mmol), and potassium phosphate (284.5 mg, 1.34 mmol) were added to DMSO (8 mL). Subsequently, copper(I) iodide (38.2 mg, 0.20 mmol) was added. After completion of addition, the system was purged with nitrogen, and then heated to 140 ℃ and reacted for 12 hours.

After completion of the reaction, the mixture was cooled to room temperature, and water (40 mL) was added to the system. The mixture was extracted with ethyl acetate (20 mL × 3). The organic phases were combined, washed with saturated brine (30 mL), dried, filtered, and concentrated under reduced pressure to dryness to obtain a residue. The residue was purified by normal-phase column chromatography (dichloromethane/methanol = 10:1) to obtain 18 mg of 6'-(((1S,3S)-3-((5-(difluoromethoxy)pyrimidin-2-yl)amino)cyclopentyl)amino)-2-oxo-2H-[1,3'-bipyridine]-3-carbonitrile.

LC-MS: $[M+H]^+$ = 440. NMR data: ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.24–8.20 (m, 3H), 8.06–8.03 (dd, J = 6.8, 2.1 Hz, 1H), 7.99–7.96 (d, J = 2.7 Hz, 1H), 7.51–7.42 (m, 2H), 7.23–6.84 (m, 2H), 6.57–6.51 (d, J = 9.0 Hz, 1H), 6.49–6.43 (t, J = 7.0 Hz, 1H), 4.37–4.26 (m, 2H), 2.20–2.07 (m, 2H), 1.96–1.81 (m, 2H), 1.60–1.43 (m, 2H).

Example A14

Synthesis of 6'-(((1S,3S)-3-((5-(difluoromethoxy)pyrimidin-2-yl)amino)cyclopentyl)amino)-3-fluoro-2H-[1,3'-bipyridin]-2-one



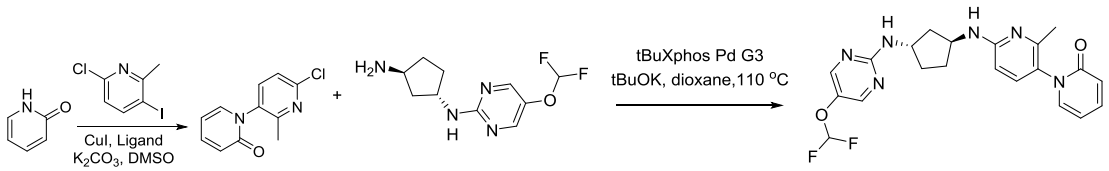
Under nitrogen protection at room temperature, (1S,3S)-N^1-(5-(difluoromethoxy)pyrimidin-2-yl)-N^3-(5-iodopyridin-2-yl)cyclopentane-1,3-diamine (0.448 g, 1.0 mmol, 1.0 eq), 3-fluoropyridin-2(1H)-one (0.226 g, 2.0 mmol, 2.0 eq), copper(I) iodide (0.076 g, 0.4 mmol, 0.4 eq), N^1,N^2-dimethylcyclohexane-1,2-diamine (0.029 g, 0.2 mmol, 0.2 eq), and potassium phosphate (0.673 g, 3.0 mmol, 3.0 eq) were dissolved in dimethyl sulfoxide (4 mL), and the mixture was heated to 140 ℃ and reacted overnight.

After completion of the reaction, cold water (50 mL) was added to quench the reaction, followed by extraction with ethyl acetate (50 mL × 3). The organic phases were combined, dried over anhydrous sodium sulfate, filtered, and concentrated. The resulting residue was purified by silica gel column chromatography (eluent: ethyl acetate) to obtain 6'-(((1S,3S)-3-((5-(difluoromethoxy)pyrimidin-2-yl)amino)cyclopentyl)amino)-3-fluoro-2H-[1,3'-bipyridin]-2-one. LC-MS: $[M+H]^+$ = 433.

NMR data: ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.23 (s, 2H), 7.96 (d, J = 2.7 Hz, 1H), 7.54–7.39 (m, 4H), 7.22–6.84 (m, 2H), 6.54 (d, J = 8.9 Hz, 1H), 6.24 (td, J = 7.3, 4.8 Hz, 1H), 4.31 (h, J = 6.8, 6.3 Hz, 2H), 2.19–2.06 (m, 2H), 1.88 (tdd, J = 13.2, 10.4, 6.3 Hz, 2H), 1.58–1.45 (m, 2H).

Example A15

Synthesis of 6'-(((1S,3S)-3-((5-(difluoromethoxy)pyrimidin-2-yl)amino)cyclopentyl)amino)-2'-methyl-2H-[1,3'-bipyridin]-2-one



Step A: Synthesis of 6'-chloro-2'-methyl-2H-[1,3'-bipyridin]-2-one

Under nitrogen protection at room temperature, pyridin-2(1H)-one (2.0 g, 21.0 mmol, 1.0 eq), 6-chloro-3-iodo-2-methylpyridine (5.85 g, 23.1 mmol, 1.1 eq), copper(I) iodide (1.21 g, 6.3 mmol, 0.3 eq), 8-hydroxyquinoline (1.0 g, 6.9 mmol, 0.33 eq), and potassium carbonate (10.1 g, 74.7 mmol, 3.5 eq) were dissolved in dimethyl sulfoxide (40 mL) and reacted at 140 ℃ for 2 hours.

After completion of the reaction, cold water (150 mL) was added to quench the reaction, followed by extraction with ethyl acetate (100 mL × 3). The organic phases were combined, dried over anhydrous sodium sulfate, filtered, and concentrated. The resulting residue was purified by silica gel column chromatography (eluent: ethyl acetate/n-hexane = 5/10) to obtain 0.17 g of a yellow solid, 6'-chloro-2'-methyl-2H-[1,3'-bipyridin]-2-one (yield: 3.6%). LC-MS: $[M+H]^+$ = 221.

Step B: Synthesis of 6'-(((1S,3S)-3-((5-(difluoromethoxy)pyrimidin-2-yl)amino)cyclopentyl)amino)-2'-methyl-2H-[1,3'-bipyridin]-2-one

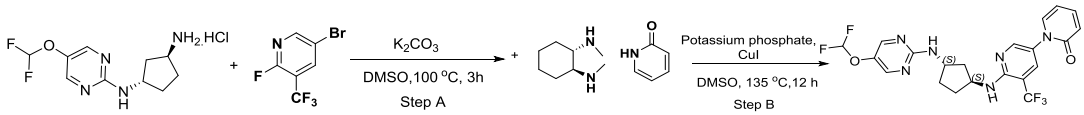
Under nitrogen protection at room temperature, 6'-chloro-2'-methyl-2H-[1,3'-bipyridin]-2-one (0.17 g, 0.77 mmol, 1.0 eq), (1S,3S)-N^1-(5-(difluoromethoxy)pyrimidin-2-yl)cyclopentane-1,3-diamine (0.207 g, 0.84 mmol, 1.1 eq), methanesulfonato(2-di-tert-butylphosphino-2',4',6'-triisopropyl-1,1'-biphenyl)(2'-amino-1,1'-biphenyl-2-yl)palladium(II) (0.12 g, 0.15 mmol, 0.2 eq), and potassium tert-butoxide (0.17 g, 1.54 mmol, 2.0 eq) were dissolved in 1,4-dioxane (8 mL), and the mixture was heated to 110 ℃ and reacted overnight.

After completion of the reaction, the organic solvent was directly dried by rotary evaporation. The resulting residue was purified by silica gel column chromatography (eluent: ethyl acetate/methanol = 1/10) to obtain 6'-(((1S,3S)-3-((5-(difluoromethoxy)pyrimidin-2-yl)amino)cyclopentyl)amino)-2'-methyl-2H-[1,3'-bipyridin]-2-one. LC-MS: $[M+H]^+$ = 429.

NMR data: ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.42–7.38 (s, 2H), 6.69–6.62 (m, 3H), 6.40–6.33 (m, 1H), 6.22–5.85 (m, 2H), 5.66–5.59 (d, J = 9.6 Hz, 1H), 5.56–5.50 (d, J = 8.6 Hz, 1H), 5.46–5.41 (t, J = 6.7 Hz, 1H), 3.52–3.39 (m, 2H), 1.37–1.23 (m, 2H), 1.20–1.13 (s, 3H), 1.10–0.99 (t, J = 6.8 Hz, 2H), 0.77–0.60 (m, 2H).

Example A16

Synthesis of 6'-(((1S,3S)-3-((5-(difluoromethoxy)pyrimidin-2-yl)amino)cyclopentyl)amino)-5'-(trifluoromethyl)-2H-[1,3'-bipyridin]-2-one



Step A: Synthesis of (1S,3S)-N^1-(5-bromo-3-(trifluoromethyl)pyridin-2-yl)-N^3-(5-(difluoromethoxy)pyrimidin-2-yl)cyclopentane-1,3-diamine

At room temperature, 5-bromo-2-fluoro-3-(trifluoromethyl)pyridine (500.0 mg, 2.05 mmol) and (1S,3S)-N^1-(5-(difluoromethoxy)pyrimidin-2-yl)cyclopentane-1,3-diamine hydrochloride (626 mg, 2.25 mmol) were dissolved in DMSO (10 mL). Subsequently, K_2CO_3 (1.7 g, 12.3 mmol) was added. After completion of addition, the system was heated to 100 ℃ and reacted for 3 hours.

After completion of the reaction, the mixture was cooled to room temperature, and water (40 mL) was added to the system. The mixture was extracted with ethyl acetate (20 mL × 3). The

organic phases were combined, washed with saturated brine (30 mL), dried, filtered, and dried by rotary evaporation to obtain a residue. The resulting residue was purified by normal-phase column chromatography (n-hexane/ethyl acetate = 1:2) to obtain 600 mg of a white product, (1S,3S)-N^1-(5-bromo-3-(trifluoromethyl)pyridin-2-yl)-N^3-(5-(difluoromethoxy)pyrimidin-2-yl)cyclopentane-1,3-diamine (yield: 62%). LC-MS: $[M+H]^+$ = 468.

Step B: Synthesis of 6'-(((1S,3S)-3-((5-(difluoromethoxy)pyrimidin-2-yl)amino)cyclopentyl)amino)-5'-(trifluoromethyl)-2H-[1,3'-bipyridin]-2-one

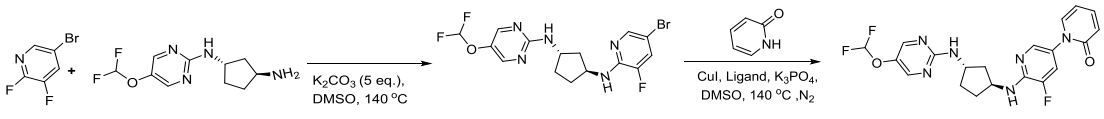
At room temperature, (1S,3S)-N^1-(5-bromo-3-(trifluoromethyl)pyridin-2-yl)-N^3-(5-(difluoromethoxy)pyrimidin-2-yl)cyclopentane-1,3-diamine (300 mg, 0.64 mmol), pyridin-2(1H)-one (122 mg, 1.28 mmol), (1S,2S)-N^1,N^2-dimethylcyclohexane-1,2-diamine (18.2 mg, 0.13 mmol), and potassium phosphate (408.5 mg, 1.92 mmol) were added to DMSO (8 mL). Subsequently, copper(I) iodide (24.6 mg, 0.128 mmol) was added. After completion of addition, the system was purged with nitrogen, and heated to 140 ℃ and reacted for 12 hours.

After completion of the reaction, the mixture was cooled to room temperature, and water (40 mL) was added to the system. The mixture was extracted with ethyl acetate (20 mL × 3). The organic phases were combined, washed with saturated brine (30 mL), dried, filtered, and dried by rotary evaporation to obtain a residue. The resulting residue was purified by normal-phase column chromatography (dichloromethane/methanol = 10:1) to obtain 6'-(((1S,3S)-3-((5-(difluoromethoxy)pyrimidin-2-yl)amino)cyclopentyl)amino)-5'-(trifluoromethyl)-2H-[1,3'-bipyridin]-2-one. LC-MS: $[M+H]^+$ = 483.

NMR data: ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.31–8.28 (d, J = 2.5 Hz, 1H), 8.25–8.22 (s, 2H), 7.90–7.87 (d, J = 2.5 Hz, 1H), 7.71–7.66 (dd, J = 7.0, 2.1 Hz, 1H), 7.53–7.46 (m, 2H), 7.23–6.84 (t, J = 74.0 Hz, 1H), 6.49–6.45 (d, J = 9.2 Hz, 1H), 6.35–6.28 (m, 2H), 4.76–4.65 (m, 1H), 4.39–4.29 (m, 1H), 2.18–2.06 (m, 2H), 2.04–1.90 (m, 2H), 1.70–1.49 (m, 2H).

Example A17

Synthesis of 6'-(((1S,3S)-3-((5-(difluoromethoxy)pyrimidin-2-yl)amino)cyclopentyl)amino)-5'-fluoro-2H-[1,3'-bipyridin]-2-one



Step A: Synthesis of

(1S,3S)-N^1-(5-bromo-3-fluoropyridin-2-yl)-N^3-(5-(difluoromethoxy)pyrimidin-2-yl)cyclopentane-1,3-diamine

Under nitrogen protection at room temperature, 5-bromo-2,3-difluoropyridine (0.464 g, 2.4 mmol, 1.2 eq), (1S,3S)-N^1-(5-(difluoromethoxy)pyrimidin-2-yl)cyclopentane-1,3-diamine (0.488 g, 2 mmol, 1.0 eq), and potassium carbonate (1.4 g, 10.0 mmol, 5.0 eq) were dissolved in dimethyl sulfoxide (8 mL) and reacted at 140 ℃ for 14 hours.

After completion of the reaction, cold water (50 mL) was added to quench the reaction, followed by extraction with ethyl acetate (50 mL × 3). The organic phases were combined, dried over anhydrous sodium sulfate, filtered, and concentrated. The resulting residue was purified by silica gel column chromatography (eluent: ethyl acetate/n-hexane = 5/10) to obtain 0.641 g of a yellow solid, (1S,3S)-N^1-(5-bromo-3-fluoropyridin-2-yl)-N^3-(5-(difluoromethoxy)pyrimidin-2-yl)cyclopentane-1,3-diamine (yield: 77%). LC-MS: $[M+H]^+$ = 418.

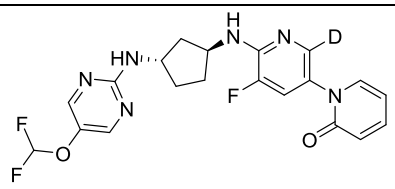
Step B: Synthesis of 6'-(((1S,3S)-3-((5-(difluoromethoxy)pyrimidin-2-yl)amino)cyclopentyl)amino)-5'-fluoro-2H-[1,3'-bipyridin]-2-one

Under nitrogen protection at room temperature, (1S,3S)-N^1-(5-bromo-3-fluoropyridin-2-yl)-N^3-(5-(difluoromethoxy)pyrimidin-2-yl)cyclopentane-1,3-diamine (0.641 g, 1.537 mmol, 1.0 eq), pyridin-2(1H)-one (0.292 g, 3.08 mmol, 2.0 eq), copper(I) iodide (0.117 g, 0.615 mmol, 0.4 eq), N^1,N^2-dimethylcyclohexane-1,2-diamine (0.044 g, 0.307 mmol, 0.2 eq), and potassium phosphate (0.98 g, 4.6 mmol, 3.0 eq) were dissolved in dimethyl sulfoxide (6 mL), and the mixture was heated to 140 ℃ and reacted overnight.

After completion of the reaction, cold water (50 mL) was added to quench the reaction, followed by extraction with ethyl acetate (50 mL × 3). The organic phases were combined, dried over anhydrous sodium sulfate, filtered, and concentrated. The resulting residue was purified by silica gel column chromatography (eluent: ethyl acetate) to obtain 6'-(((1S,3S)-3-((5-(difluoromethoxy)pyrimidin-2-yl)amino)cyclopentyl)amino)-5'-fluoro-2H-[1,3'-bipyridin]-2-one. LC-MS: $[M+H]^+$ = 433.

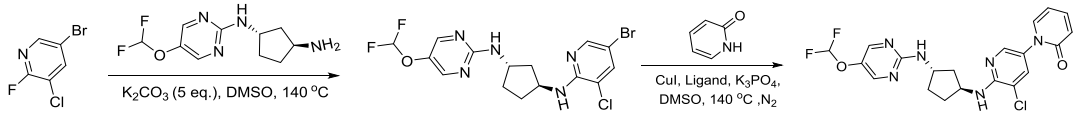
NMR data: ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.23 (s, 2H), 7.84 (d, J = 2.1 Hz, 1H), 7.64 (dd, J = 6.9, 2.1 Hz, 1H), 7.60–7.42 (m, 3H), 7.22–6.84 (m, 2H), 6.50–6.42 (m, 1H), 6.28 (td, J = 6.7, 1.4 Hz, 1H), 4.50 (h, J = 6.9 Hz, 1H), 4.33 (p, J = 6.8 Hz, 1H), 2.18–2.07 (m, 2H), 1.99–1.89 (m, 2H), 1.65–1.49 (m, 2H).

Following the preparation methods of Compound A17 and Compound A34, Compound A17-D was prepared:

A17-D		NMR Data：^{1}H NMR: δ 8.21 (s, 2H), 7.61 (dd, *J* = 1.5, 6.9 Hz, 1H), 7.55 - 7.46 (m, 2H), 7.19 - 6.75 (m, 1H), 6.46 (d, *J* = 8.9 Hz, 1H), 6.31 (dt, *J* = 1.3, 6.7 Hz, 1H), 4.47 (quin, *J* = 6.8 Hz, 1H), 4.29 (quin, *J* = 6.7 Hz, 1H), 2.19 - 2.03 (m, 2H), 2.00 - 1.84 (m, 2H), 1.65 - 1.46 (m, 2H)

Example A18

Synthesis of 5'-chloro-6'-(((1S,3S)-3-((5-(difluoromethoxy)pyrimidin-2-yl)amino)cyclopentyl)amino)-2H-[1, 3'-bipyridin]-2-one



Step A: Synthesis of (1S,3S)-N^1-(5-bromo-3-chloropyridin-2-yl)-N^3-(5-(difluoromethoxy)pyrimidin-2-yl)cyclopentane-1,3-diamine

Under nitrogen protection at room temperature, 5-bromo-3-chloro-2-fluoropyridine (0.502 g, 2.4 mmol, 1.2 eq), (1S,3S)-N^1-(5-(difluoromethoxy)pyrimidin-2-yl)cyclopentane-1,3-diamine (0.488 g, 2 mmol, 1.0 eq), and potassium carbonate (1.4 g, 10.0 mmol, 5.0 eq) were dissolved in dimethyl sulfoxide (8 mL) and reacted at 140 ℃ for 14 hours.

After completion of the reaction, cold water (50 mL) was added to quench the reaction, followed by extraction with ethyl acetate (50 mL × 3). The organic phases were combined, dried over anhydrous sodium sulfate, filtered, and concentrated. The resulting residue was purified by silica gel column chromatography (eluent: ethyl acetate/n-hexane = 5/10) to obtain 0.706 g of a yellow solid, (1S,3S)-N^1-(5-bromo-3-chloropyridin-2-yl)-N^3-(5-(difluoromethoxy)pyrimidin-2-yl)cyclopentane-1,3-diamine (yield: 82%). LC-MS: $[M+H]^+$ = 434.

Step B: Synthesis of 5'-chloro-6'-(((1S,3S)-3-((5-(difluoromethoxy)pyrimidin-2-yl)amino)cyclopentyl)amino)-2H-[1, 3'-bipyridin]-2-one

Under nitrogen protection at room temperature, (1S,3S)-N^1-(5-bromo-3-chloropyridin-2-yl)-N^3-(5-(difluoromethoxy)pyrimidin-2-yl)cyclopentane-1,3-diamine (0.706 g, 1.627 mmol, 1.0 eq), pyridin-2(1H)-one (0.31 g, 3.25 mmol, 2.0 eq), copper(I) iodide (0.124 g, 0.65 mmol, 0.4 eq), N^1,N^2-dimethylcyclohexane-1,2-diamine (0.046 g, 0.325 mmol, 0.2 eq), and potassium phosphate (1.04 g, 4.9 mmol, 3.0 eq) were dissolved in

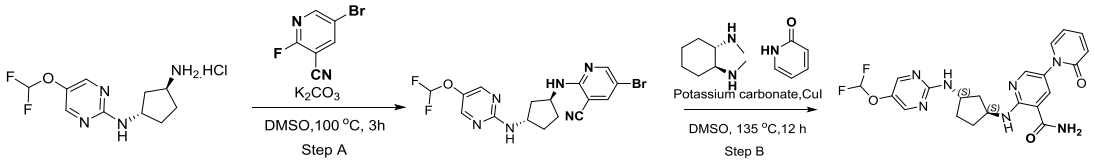
dimethyl sulfoxide (6.5 mL), and the mixture was heated to 140 ℃ and reacted overnight.

After completion of the reaction, cold water (50 mL) was added to quench the reaction, followed by extraction with ethyl acetate (50 mL × 3). The organic phases were combined, dried over anhydrous sodium sulfate, filtered, and concentrated. The resulting residue was purified by silica gel column chromatography (eluent: ethyl acetate) to obtain 5'-chloro-6'-(((1S,3S)-3-((5-(difluoromethoxy)pyrimidin-2-yl)amino)cyclopentyl)amino)-2H-[1,3'-bipyridin]-2-one. LC-MS: $[M+H]^+$ = 449.

NMR data: ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.23 (s, 2H), 8.00 (d, J = 2.3 Hz, 1H), 7.76 (d, J = 2.3 Hz, 1H), 7.64 (dd, J = 6.9, 2.1 Hz, 1H), 7.49 (ddd, J = 8.7, 6.7, 2.0 Hz, 2H), 7.03 (t, J = 74.0 Hz, 1H), 6.54 (d, J = 7.3 Hz, 1H), 6.49–6.43 (m, 1H), 6.29 (td, J = 6.7, 1.4 Hz, 1H), 4.56 (p, J = 7.1 Hz, 1H), 4.33 (q, J = 6.8 Hz, 1H), 2.12 (qt, J = 7.5, 3.6 Hz, 2H), 2.01–1.90 (m, 2H), 1.67–1.50 (m, 2H).

Example A19

Synthesis of 6'-(((1S,3S)-3-((5-(difluoromethoxy)pyrimidin-2-yl)amino)cyclopentyl)amino)-2-oxo-2H-[1,3'-bipyridine]-5'-carboxamide



Step A: Synthesis of 5-bromo-2-(((1S,3S)-3-((5-(difluoromethoxy)pyrimidin-2-yl)amino)cyclopentyl)amino)nicotinonitrile

At room temperature, 5-bromo-2-fluoronicotinonitrile (500 mg, 2.5 mmol) and (1S,3S)-N^1-(5-(difluoromethoxy)pyrimidin-2-yl)cyclopentane-1,3-diamine hydrochloride (770 mg, 2.75 mmol) were dissolved in DMSO (10 mL). Subsequently, K_2CO_3 (1.38 g, 10.0 mmol) was added. After completion of addition, the system was heated to 100 ℃ and reacted for 30 minutes.

After completion of the reaction, the mixture was cooled to room temperature, and water (40 mL) was added to the system. The mixture was extracted with ethyl acetate (20 mL × 3). The organic phases were combined, washed with saturated brine (30 mL), dried, filtered, and concentrated under reduced pressure to dryness to obtain a residue. The residue was purified by normal-phase column chromatography (n-hexane/ethyl acetate = 1:2) to obtain 700 mg of 5-bromo-2-(((1S,3S)-3-((5-(difluoromethoxy)pyrimidin-2-yl)amino)cyclopentyl)amino)nicotino

nitrile (yield: 66%). LC-MS: $[M+H]^+$ = 425.

Step B: Synthesis of 6'-(((1S,3S)-3-((5-(difluoromethoxy)pyrimidin-2-yl)amino)cyclopentyl)amino)-2-oxo-2H-[1,3'-bipyridine]-5'-carboxamide

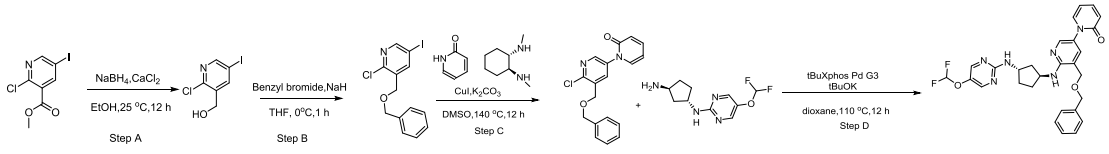
At room temperature, 5-bromo-2-(((1S,3S)-3-((5-(difluoromethoxy)pyrimidin-2-yl)amino)cyclopentyl)amino)nicotinonitrile (300 mg, 0.70 mmol), pyridin-2(1H)-one (134 mg, 1.40 mmol), (1S,2S)-N^1,N^2-dimethylcyclohexane-1,2-diamine (20.0 mg, 0.14 mmol), and potassium carbonate (195.2 mg, 1.40 mmol) were added to DMSO (8 mL). Subsequently, copper(I) iodide (27.1 mg, 0.14 mmol) was added. After completion of addition, the system was purged with nitrogen, and heated to 140 ℃ and reacted for 12 hours.

After completion of the reaction, the mixture was cooled to room temperature, and water (40 mL) was added to the system. The mixture was extracted with ethyl acetate (20 mL × 3). The organic phases were combined, washed with saturated brine (30 mL), dried, filtered, and concentrated under reduced pressure to dryness to obtain a residue. The residue was purified by normal-phase column chromatography (dichloromethane/methanol = 10:1) to obtain 6'-(((1S,3S)-3-((5-(difluoromethoxy)pyrimidin-2-yl)amino)cyclopentyl)amino)-2-oxo-2H-[1,3'-bipyridine]-5'-carboxamide. LC-MS: $[M+H]^+$ = 458.

NMR data: ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.96–8.90 (d, J = 6.8 Hz, 1H), 8.28–8.22 (s, 2H), 8.20–8.18 (d, J = 2.5 Hz, 1H), 8.09–8.00 (m, 2H), 7.70–7.65 (dd, J = 6.9, 2.1 Hz, 1H), 7.55–7.43 (m, 3H), 7.24–6.84 (t, J = 74.0 Hz, 1H), 6.51–6.45 (d, J = 9.2 Hz, 1H), 6.36–6.29 (td, J = 6.7, 1.4 Hz, 1H), 4.57–4.47 (q, J = 6.7 Hz, 1H), 4.36–4.27 (q, J = 7.0 Hz, 1H), 2.28–2.07 (m, 2H), 2.04–1.93 (m, 1H), 1.91–1.81 (m, 1H), 1.65–1.40 (m, 2H).

Example A20

Synthesis of 5'-((benzyloxy)methyl)-6'-(((1S,3S)-3-((5-(difluoromethoxy)pyrimidin-2-yl)amino)cyclopentyl)amino)-2H-[1,3'-bipyridin]-2-one



Step A: Synthesis of (2-chloro-5-iodopyridin-3-yl)methanol

Under nitrogen protection at room temperature, methyl 2-chloro-5-iodonicotinate (1.0 g, 3.3 mmol) and anhydrous calcium chloride (1.3 g, 11.5 mmol) were dissolved in anhydrous ethanol

(20 mL). The mixture was stirred for 15 minutes, then sodium borohydride solid (0.51 g, 13.2 mmol) was added in batches. The mixture was reacted at room temperature overnight.

After completion of the reaction, saturated aqueous ammonium chloride solution (150 mL) was added to quench the reaction, followed by extraction with ethyl acetate (100 mL × 3). The organic phases were combined, dried over anhydrous sodium sulfate, filtered, and concentrated. The resulting residue was used directly in the next step without further purification, obtaining 0.85 g of a yellow solid, (2-chloro-5-iodopyridin-3-yl)methanol (yield: 94.4%). LC-MS: $[M+H]^+$ = 270.

Step B: Synthesis of 3-((benzyloxy)methyl)-2-chloro-5-iodopyridine

Under nitrogen protection at room temperature, (2-chloro-5-iodopyridin-3-yl)methanol (0.85 g, 3.1 mmol) was dissolved in anhydrous tetrahydrofuran (20 mL). The system was then cooled to 0 ℃, and sodium hydride (0.16 g, 4.0 mmol, 60% content) was added in batches. After stirring for 15 minutes, benzyl bromide (0.68 g, 3.7 mmol) was added, and the mixture was reacted at 0 ℃ for one hour.

After completion of the reaction, saturated aqueous ammonium chloride solution (150 mL) was added to quench the reaction, followed by extraction with ethyl acetate (100 mL × 3). The organic phases were combined, dried over anhydrous sodium sulfate, filtered, and concentrated. The resulting residue was purified by silica gel column chromatography (eluent: ethyl acetate/n-hexane = 1/20) to obtain 0.95 g of a yellow solid, 3-((benzyloxy)methyl)-2-chloro-5-iodopyridine (yield: 84%). LC-MS: $[M+H]^+$ = 360.

Step C: Synthesis of 5'-((benzyloxy)methyl)-6'-chloro-2H-[1,3'-bipyridin]-2-one

At room temperature, 3-((benzyloxy)methyl)-2-chloro-5-iodopyridine (0.95 g, 2.6 mmol), pyridin-2(1H)-one (0.5 g, 5.2 mmol), (1S,2S)-N^1,N^2-dimethylcyclohexane-1,2-diamine (0.075 g, 0.52 mmol), and potassium phosphate (0.73 g, 5.2 mmol) were added to DMSO (20 mL). Subsequently, copper(I) iodide (0.1 g, 0.52 mmol) was added. After completion of addition, the system was purged with nitrogen, and heated to 140 ℃ and reacted for 12 hours.

After completion of the reaction, the mixture was cooled to room temperature, and water (40 mL) was added to the system. The mixture was extracted with ethyl acetate (40 mL × 3). The organic phases were combined, washed with saturated brine (100 mL), dried, filtered, and concentrated under reduced pressure to dryness to obtain a residue. The resulting residue was purified by normal-phase column chromatography (ethyl acetate/n-hexane = 4:1) to obtain 200 mg of a white product, 5'-((benzyloxy)methyl)-6'-chloro-2H-[1,3'-bipyridin]-2-one (yield: 23.2%). LC-MS: $[M+H]^+$ = 327.

Step D: Synthesis of 5'-((benzyloxy)methyl)-6'-(((1S,3S)-3-((5-(difluoromethoxy)pyrimidin-2-yl)amino)cyclopentyl)amino)-2H-[1,3'-bipyridin]-2-one

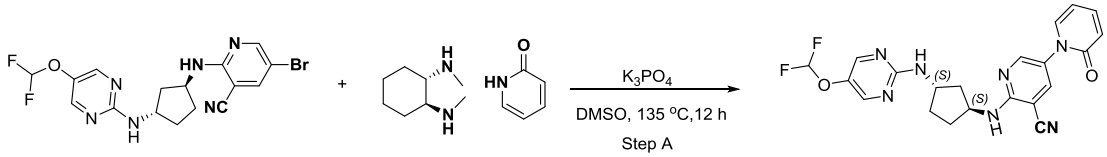
Under nitrogen protection at room temperature, 5'-((benzyloxy)methyl)-6'-chloro-2H-[1,3'-bipyridin]-2-one (0.2 g, 0.6 mmol), (1S,3S)-N^1-(5-(difluoromethoxy)pyrimidin-2-yl)cyclopentane-1,3-diamine (0.179 g, 0.72 mmol), methanesulfonato(2-di-tert-butylphosphino-2',4',6'-triisopropyl-1,1'-biphenyl)(2'-amino-1,1'-biphenyl-2-yl)palladium(II) (0.097 g, 0.12 mmol), and potassium tert-butoxide (0.27 g, 2.4 mmol) were dissolved in 1,4-dioxane (8 mL), and the mixture was heated to 110 ℃ and reacted overnight.

After completion of the reaction, the organic solvent was directly dried by rotary evaporation. The resulting residue was purified by silica gel column chromatography (eluent: ethyl acetate/methanol = 1/10) to obtain 5'-((benzyloxy)methyl)-6'-(((1S,3S)-3-((5-(difluoromethoxy)pyrimidin-2-yl)amino)cyclopentyl)amino)-2H-[1,3'-bipyridin]-2-one. LC-MS: $[M+H]^+$ = 535.

NMR data: ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.24–8.21 (s, 2H), 7.97–7.94 (d, J = 2.6 Hz, 1H), 7.64–7.60 (m, 1H), 7.52–7.44 (m, 3H), 7.41–7.27 (m, 5H), 7.23–6.84 (t, J = 74.0 Hz, 1H), 6.48–6.43 (m, 1H), 6.31–6.25 (td, J = 6.7, 1.4 Hz, 1H), 5.96–5.90 (d, J = 6.9 Hz, 1H), 4.60–4.46 (d, J = 22.1 Hz, 5H), 4.34–4.26 (m, 1H), 2.21–2.04 (m, 2H), 1.99–1.83 (m, 2H), 1.60–1.43 (m, 2H).

Example A21

Synthesis of 6'-(((1S,3S)-3-((5-(difluoromethoxy)pyrimidin-2-yl)amino)cyclopentyl)amino)-2-oxo-2H-[1,3'-bipyridine]-5'-carbonitrile



At room temperature, 5-bromo-2-(((1S,3S)-3-((5-(difluoromethoxy)pyrimidin-2-yl)amino)cyclopentyl)amino)nicotinonitrile (300 mg, 0.70 mmol), pyridin-2(1H)-one (134 mg, 1.40 mmol), (1S,2S)-N^1,N^2-dimethylcyclohexane-1,2-diamine (20.0 mg, 0.14 mmol), and potassium phosphate (300 mg, 1.40 mmol) were added to DMSO (8 mL). Subsequently, copper(I) iodide (27.1 mg, 0.14 mmol) was added. After completion of addition, the system was purged with

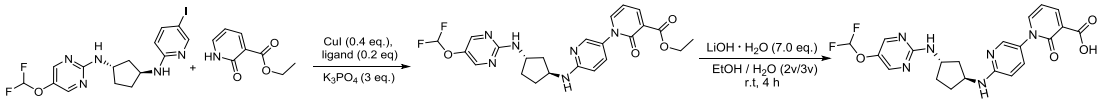
nitrogen, and heated to 140 ℃ and reacted for 12 hours.

After completion of the reaction, the mixture was cooled to room temperature, and water (40 mL) was added to the system. The mixture was extracted with ethyl acetate (20 mL × 3). The organic phases were combined, washed with saturated brine (30 mL), dried, filtered, and concentrated under reduced pressure to dryness to obtain a residue. The resulting residue was purified by normal-phase column chromatography (dichloromethane/methanol = 10:1) to obtain 6'-(((1S,3S)-3-((5-(difluoromethoxy)pyrimidin-2-yl)amino)cyclopentyl)amino)-2-oxo-2H-[1,3'-bipyridine]-5'-carbonitrile. LC-MS: $[M+H]^+$ = 440.

NMR data: ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.32–8.29 (d, J = 2.6 Hz, 1H), 8.25–8.22 (s, 2H), 8.08–8.06 (d, J = 2.7 Hz, 1H), 7.68–7.64 (dd, J = 7.0, 2.0 Hz, 1H), 7.53–7.46 (m, 2H), 7.37–7.33 (d, J = 7.2 Hz, 1H), 7.23–6.84 (t, J = 74.0 Hz, 1H), 6.50–6.45 (m, 1H), 6.34–6.27 (m, 1H), 4.67–4.54 (q, J = 7.3 Hz, 1H), 4.41–4.30 (q, J = 6.9 Hz, 1H), 2.19–2.06 (m, 2H), 2.05–1.89 (m, 2H), 1.70–1.49 (m, 2H).

Example A22

Synthesis of 6'-(((1S,3S)-3-((5-(difluoromethoxy)pyrimidin-2-yl)amino)cyclopentyl)amino)-2-oxo-2H-[1,3'-bipyridine]-3-carboxylic acid



Step A: Synthesis of ethyl 6'-(((1S,3S)-3-((5-(difluoromethoxy)pyrimidin-2-yl)amino)cyclopentyl)amino)-2-oxo-2H-[1,3'-bipyridine]-3-carboxylate

Under nitrogen protection at room temperature, (1S,3S)-N^1-(5-(difluoromethoxy)pyrimidin-2-yl)-N^3-(5-iodopyridin-2-yl)cyclopentane-1,3-diamine (0.642 g, 1.5 mmol, 1.0 eq), ethyl 2-oxo-1,2-dihydropyridine-3-carboxylate (0.502 g, 3 mmol, 2 eq), copper(I) iodide (0.114 g, 0.6 mmol, 0.4 eq), N^1,N^2-dimethylcyclohexane-1,2-diamine (0.043 g, 0.3 mmol, 0.2 eq), and potassium phosphate (0.320 g, 1.5 mmol, 3.0 eq) were dissolved in dimethyl sulfoxide (6 mL), and the mixture was heated to 140 ℃ and reacted overnight.

After completion of the reaction, cold water (25 mL) was added to quench the reaction, followed by extraction with ethyl acetate (50 mL × 3). The organic phases were combined, dried over anhydrous sodium sulfate, filtered, and concentrated. The resulting residue was purified by silica gel column chromatography (eluent: ethyl acetate) to obtain 0.19 g of a yellow solid, ethyl 6'-(((1S,3S)-3-((5-(difluoromethoxy)pyrimidin-2-yl)amino)cyclopentyl)amino)-2-oxo-2H-[1,3'-b

ipyridine]-3-carboxylate (yield: 26%). LC-MS: $[M+H]^+$ = 487.

Step B: Synthesis of 6'-(((1S,3S)-3-((5-(difluoromethoxy)pyrimidin-2-yl)amino)cyclopentyl)amino)-2-oxo-2H-[1,3'-bipyridine]-3-carboxylic acid

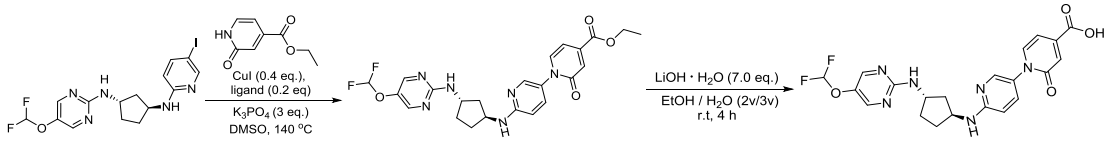
At room temperature, ethyl 6'-(((1S,3S)-3-((5-(difluoromethoxy)pyrimidin-2-yl)amino)cyclopentyl)amino)-2-oxo-2H-[1,3'-bipyridine]-3-carboxylate (0.140 g, 0.288 mmol, 1.0 eq) and lithium hydroxide monohydrate (0.085 g, 2.01 mmol, 7.0 eq) were dissolved in a mixed solvent of ethanol (2 mL) and water (3 mL). The mixture was stirred at room temperature for 4 hours.

After completion of the reaction, the pH of the reaction mixture was adjusted to approximately 6 using 1M dilute hydrochloric acid solution, resulting in the precipitation of a large amount of light yellow solid. The resultant was filtrated to obtain 6'-(((1S,3S)-3-((5-(difluoromethoxy)pyrimidin-2-yl)amino)cyclopentyl)amino)-2-oxo-2H-[1,3'-bipyridine]-3-carboxylic acid. LC-MS: $[M+H]^+$ = 459.

NMR data: ^{1}H NMR (400 MHz, DMSO-d_6) δ 14.36 (s, 1H), 8.44 (dd, J = 7.3, 2.1 Hz, 1H), 8.40–8.12 (m, 3H), 8.04 (d, J = 2.7 Hz, 1H), 7.66–7.42 (m, 2H), 7.22–6.84 (m, 2H), 6.76 (t, J = 7.0 Hz, 1H), 6.56 (d, J = 8.9 Hz, 1H), 4.46–4.24 (m, 2H), 2.27–2.04 (m, 2H), 2.03–1.78 (m, 2H), 1.52 (tt, J = 13.9, 7.4 Hz, 2H).

Example A23

Synthesis of 6'-(((1S,3S)-3-((5-(difluoromethoxy)pyrimidin-2-yl)amino)cyclopentyl)amino)-2-oxo-2H-[1,3'-bipyridine]-4-carboxylic acid



Step A: Synthesis of ethyl 6'-(((1S,3S)-3-((5-(difluoromethoxy)pyrimidin-2-yl)amino)cyclopentyl)amino)-2-oxo-2H-[1,3'-bipyridine]-4-carboxylate

Under nitrogen protection at room temperature, (1S,3S)-N^1-(5-(difluoromethoxy)pyrimidin-2-yl)-N^3-(5-iodopyridin-2-yl)cyclopentane-1,3-diamine (0.642 g, 1.5 mmol, 1.0 eq), ethyl 2-oxo-1,2-dihydropyridine-4-carboxylate (0.502 g, 3 mmol, 2 eq), copper(I) iodide (0.114 g, 0.6 mmol, 0.4 eq), N^1,N^2-dimethylcyclohexane-1,2-diamine (0.043 g, 0.3 mmol, 0.2 eq), and potassium phosphate (0.320 g, 1.5 mmol, 3.0 eq) were dissolved in dimethyl sulfoxide (6 mL), and the mixture was heated to 140 ℃ and reacted overnight.

After completion of the reaction, cold water (25 mL) was added to quench the reaction, followed by extraction with ethyl acetate (50 mL × 3). The organic phases were combined, dried over anhydrous sodium sulfate, filtered, and concentrated. The resulting residue was purified by silica gel column chromatography (eluent: ethyl acetate) to obtain 0.146 g of a yellow solid, ethyl 6'-(((1S,3S)-3-((5-(difluoromethoxy)pyrimidin-2-yl)amino)cyclopentyl)amino)-2-oxo-2H-[1,3'-bipyridine]-4-carboxylate (yield: 22%). LC-MS: $[M+H]^+$ = 487.

Step B: Synthesis of 6'-(((1S,3S)-3-((5-(difluoromethoxy)pyrimidin-2-yl)amino)cyclopentyl)amino)-2-oxo-2H-[1,3'-bipyridine]-4-carboxylic acid

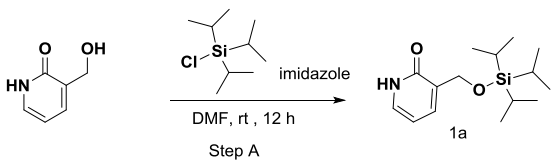
At room temperature, ethyl 6'-(((1S,3S)-3-((5-(difluoromethoxy)pyrimidin-2-yl)amino)cyclopentyl)amino)-2-oxo-2H-[1,3'-bipyridine]-4-carboxylate (0.103 g, 0.211 mmol, 1.0 eq) and lithium hydroxide monohydrate (0.085 g, 2.01 mmol, 7.0 eq) were dissolved in a mixed solvent of ethanol (2 mL) and water (3 mL). The mixture was stirred at room temperature for 4 hours.

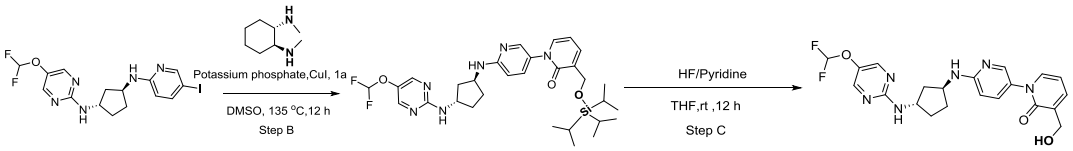
After completion of the reaction, the pH of the reaction mixture was adjusted to approximately 6 using 1M dilute hydrochloric acid solution, resulting in the precipitation of a large amount of light yellow solid. The resultant was filtrated to obtain 6'-(((1S,3S)-3-((5-(difluoromethoxy)pyrimidin-2-yl)amino)cyclopentyl)amino)-2-oxo-2H-[1,3'-bipyridine]-4-carboxylic acid. LC-MS: $[M+H]^+$ = 459.

NMR data: ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.68 (s, 1H), 8.23 (s, 2H), 7.98 (d, J = 2.7 Hz, 1H), 7.73 (d, J = 7.0 Hz, 1H), 7.49 (d, J = 7.1 Hz, 2H), 7.37–6.78 (m, 3H), 6.60 (dt, J = 7.0, 3.1 Hz, 2H), 4.31 (h, J = 6.7 Hz, 2H), 2.13 (dq, J = 20.4, 7.3, 6.4 Hz, 2H), 1.90 (dq, J = 17.5, 6.6 Hz, 2H), 1.53 (qd, J = 14.7, 13.2, 8.0 Hz, 2H).

Example A24

Synthesis of 6'-(((1S,3S)-3-((5-(difluoromethoxy)pyrimidin-2-yl)amino)cyclopentyl)amino)-3-(hydroxymethyl)-2H-[1,3'-bipyridin]-2-one





Step A: Synthesis of 3-(((triisopropylsilyl)oxy)methyl)pyridin-2(1H)-one

At room temperature, 3-(hydroxymethyl)pyridin-2(1H)-one (0.5 g, 4.0 mmol) was added to anhydrous DMF (10 mL). Subsequently, imidazole (0.54 g, 4.0 mmol) and triisopropylsilyl chloride (2.0 g, 5.2 mmol) were added to the system. After purging with nitrogen twice, the mixture was reacted at room temperature for 12 hours.

After completion of the reaction, water (40 mL) was added to the system, and the mixture was extracted with ethyl acetate (20 mL × 3). The organic phases were combined, washed twice with saturated brine (30 mL) and twice with 1M aqueous hydrochloric acid solution, dried, and dried by rotary evaporation. Without further purification, 1.05 g of a pale yellow liquid, 3-(((triisopropylsilyl)oxy)methyl)pyridin-2(1H)-one, was obtained (yield: 93%). LC-MS: $[M+H]^+$ = 282.

Step B: Synthesis of 6'-(((1S,3S)-3-((5-(Difluoromethoxy)pyrimidin-2-yl)amino)cyclopentyl)amino)-3-(((triisopropylsilyl)oxy)methyl)-2H-[1,3'-bipyridin]-2-one

At room temperature, (1S,3S)-N^1-(5-(difluoromethoxy)pyrimidin-2-yl)-N^3-(5-iodopyridin-2-yl)cyclopentane-1,3-diamine (300 mg, 0.67 mmol), 3-(((triisopropylsilyl)oxy)methyl)pyridin-2(1H)-one (378 mg, 1.34 mmol), (1S,2S)-N^1,N^2-dimethylcyclohexane-1,2-diamine (19.0 mg, 0.13 mmol), and potassium phosphate (284.5 mg, 1.34 mmol) were added to DMSO (8 mL). Subsequently, copper(I) iodide (38.2 mg, 0.20 mmol) was added. After completion of addition, the system was purged with nitrogen, and heated to 140 ℃ and reacted for 12 hours.

After completion of the reaction, the mixture was cooled to room temperature, and water (40 mL) was added to the system. The mixture was extracted with ethyl acetate (20 mL × 3). The organic phases were combined, washed with saturated brine (30 mL), dried, filtered, and concentrated under reduced pressure to dryness to obtain a residue. The resulting residue was purified by normal-phase column chromatography (dichloromethane/methanol = 10:1) to obtain 130 mg of a white product, 6'-(((1S,3S)-3-((5-(difluoromethoxy)pyrimidin-2-yl)amino)cyclopentyl)amino)-3-(((triisopropylsilyl)oxy)methyl)-2H-[1,3'-bipyridin]-2-one (yield: 32%). LC-MS: $[M+Na]^+$ = 623.

Step C: Synthesis of 6'-(((1S,3S)-3-((5-(difluoromethoxy)pyrimidin-2-yl)amino)cyclopentyl)amino)-3-(hydroxymeth

yl)-2H-[1,3'-bipyridin]-2-one

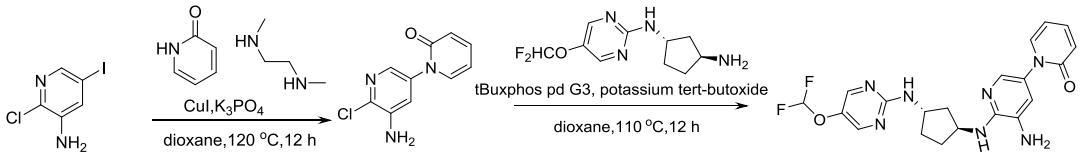
At room temperature, 6'-(((1S,3S)-3-((5-(difluoromethoxy)pyrimidin-2-yl)amino)cyclopentyl)amino)-3-(((triisopropylsilyl)oxy)methyl)-2H-[1,3'-bipyridin]-2-one (130 mg) was dissolved in tetrahydrofuran (5 mL). Subsequently, pyridinium hydrofluoride solution (2.5 mL) was added, and the mixture was reacted at room temperature for 12 hours.

After completion of the reaction, the mixture was first diluted with 20 mL of water, then 2M aqueous potassium carbonate solution was slowly added to adjust the pH to approximately 6. The mixture was then extracted with ethyl acetate (20 mL × 3), dried, and dried by rotary evaporation. The resulting residue was purified by normal-phase column chromatography (dichloromethane/methanol = 10:1) to obtain 6'-(((1S,3S)-3-((5-(difluoromethoxy)pyrimidin-2-yl)amino)cyclopentyl)amino)-3-(hydroxymethyl)-2H-[1,3'-bipyridin]-2-one. LC-MS: $[M+H]^+$ = 445.

NMR data: ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.43–7.37 (s, 2H), 7.10–7.07 (d, J = 2.7 Hz, 1H), 6.70–6.62 (t, J = 7.4 Hz, 3H), 6.58–6.53 (dd, J = 8.9, 2.7 Hz, 1H), 6.40–6.00 (m, 2H), 5.72–5.65 (d, J = 8.9 Hz, 1H), 5.52–5.45 (t, J = 6.8 Hz, 1H), 4.30–4.25 (t, J = 5.5 Hz, 1H), 3.53–3.42 (d, J = 5.8 Hz, 4H), 1.37–1.24 (m, 2H), 1.12–0.98 (m, 2H), 0.76–0.62 (m, 2H).

Example A25

Synthesis of 5'-amino-6'-(((1S,3S)-3-((5-(difluoromethoxy)pyrimidin-2-yl)amino)cyclopentyl)amino)-2H-[1,3'-bipyridin]-2-one



Step A: Synthesis of 5'-amino-6'-chloro-2H-[1,3'-bipyridin]-2-one

At room temperature, pyridin-2(1H)-one (0.82 g, 8.65 mmol, 1.1 eq), 2-chloro-5-iodopyridin-3-amine (2.0 g, 7.87 mmol, 1.0 eq), copper(I) iodide (0.30 g, 1.57 mmol, 0.2 eq), N^1,N^2-dimethylethane-1,2-diamine (0.27 g, 3.14 mmol, 0.4 eq), and potassium phosphate (5.0 g, 23.61 mmol, 3.0 eq) were added to 1,4-dioxane (20 mL). The solution was purged with nitrogen three times, then reacted at 120 ℃ for 12 hours.

After completion of the reaction, cold water (100 mL) was added to quench the reaction, followed by extraction with ethyl acetate (100 mL × 3). The organic phases were combined, dried over anhydrous sodium sulfate, filtered, and concentrated. The resulting residue was

purified by silica gel column chromatography (eluent: dichloromethane/methanol = 20/1) to obtain 0.6 g of a gray solid, 5'-amino-6'-chloro-2H-[1,3'-bipyridin]-2-one (yield: 34%). LC-MS: $[M+H]^+$ = 222.

Step B: Synthesis of 5'-amino-6'-(((1S,3S)-3-((5-(difluoromethoxy)pyrimidin-2-yl)amino)cyclopentyl)amino)-2H-[1,3'-bipyridin]-2-one

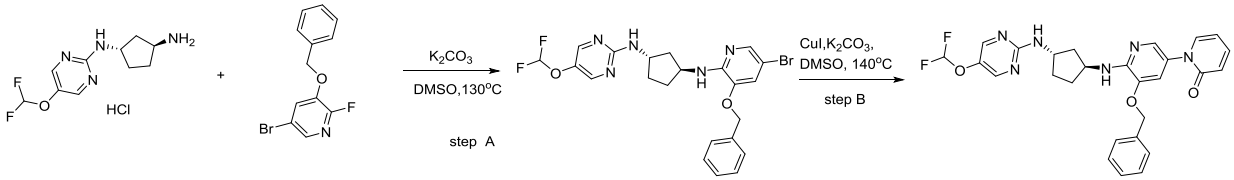
At room temperature, 5'-amino-6'-chloro-2H-[1,3'-bipyridin]-2-one (0.6 g, 2.7 mmol, 1.0 eq), (1S,3S)-N^1-(5-(difluoromethoxy)pyrimidin-2-yl)cyclopentane-1,3-diamine (0.66 g, 2.7 mmol, 1.0 eq), methanesulfonato(2-di-tert-butylphosphino-2',4',6'-triisopropyl-1,1'-biphenyl)(2'-amino-1,1'-biphenyl-2-yl)palladium(II) (0.43 g, 0.54 mmol, 0.2 eq), and potassium tert-butoxide (0.60 g, 5.4 mmol, 2.0 eq) were added to 1,4-dioxane (12 mL). The solution was purged with nitrogen three times, then reacted at 110 ℃ for 12 hours.

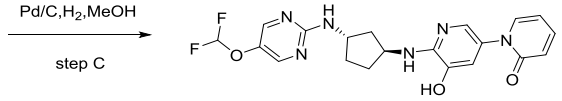
After completion of the reaction, cold water (50 mL) was added to quench the reaction, followed by extraction with ethyl acetate (50 mL × 3). The organic phases were combined, dried over anhydrous sodium sulfate, filtered, and concentrated. The resulting residue was purified by silica gel column chromatography (eluent: dichloromethane/methanol = 10/1) to obtain 0.25 g of a gray solid, 5'-amino-6'-(((1S,3S)-3-((5-(difluoromethoxy)pyrimidin-2-yl)amino)cyclopentyl)amino)-2H-[1,3'-bipyridin]-2-one (yield: 21.5%).

LC-MS: $[M+H]^+$ = 430. NMR data: ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.25–8.22 (s, 2H), 7.56–7.52 (m, 1H), 7.50–7.42 (m, 2H), 7.30–7.27 (d, J = 2.3 Hz, 1H), 7.23–6.84 (t, J = 74.0 Hz, 1H), 6.68–6.64 (d, J = 2.4 Hz, 1H), 6.44–6.39 (m, 1H), 6.26–6.21 (m, 1H), 5.79–5.74 (d, J = 6.5 Hz, 1H), 5.07–5.01 (s, 2H), 4.50–4.41 (q, J = 6.5 Hz, 1H), 4.37–4.29 (p, J = 6.9 Hz, 1H), 2.25–2.06 (m, 2H), 1.97–1.86 (m, 2H), 1.60–1.48 (m, 2H).

Example A26

Synthesis of 6'-(((1S,3S)-3-((5-(difluoromethoxy)pyrimidin-2-yl)amino)cyclopentyl)amino)-5'-hydroxy-2H-[1,3'-bipyridin]-2-one





Step A: Synthesis of (1S,3S)-N^1-(3-(benzyloxy)-5-bromopyridin-2-yl)-N^3-(5-(difluoromethoxy)pyrimidin-2-yl)cyclopentane-1,3-diamine

(1S,3S)-N^1-(5-(difluoromethoxy)pyrimidin-2-yl)cyclopentane-1,3-diamine hydrochloride (200 mg, 0.712 mmol) was dissolved in DMSO (5 mL). 3-(benzyloxy)-5-bromo-2-fluoropyridine (201 mg, 0.712 mmol) and potassium carbonate (412 mg, 3.56 mmol) were added. Under nitrogen protection, the reaction system was slowly heated to 130 ℃ and reacted overnight.

After completion of the reaction, water (50 mL) was added, and the mixture was extracted with ethyl acetate (25 mL × 3). The organic phases were combined and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (dichloromethane → dichloromethane/methanol (10/1)) to obtain 0.2 g of a yellow oil, (1S,3S)-N^1-(3-(benzyloxy)-5-bromopyridin-2-yl)-N^3-(5-(difluoromethoxy)pyrimidin-2-yl)cyclopentane-1,3-diamine. LC-MS: $[M+H]^+$ = 506.

Step B: Synthesis of 5'-(benzyloxy)-6'-((1S,3S)-3-((5-(difluoromethoxy)pyrimidin-2-yl)amino)cyclopentyl)amino)-2H-[1,3'-bipyridin]-2-one

At room temperature, (1S,3S)-N^1-(3-(benzyloxy)-5-bromopyridin-2-yl)-N^3-(5-(difluoromethoxy)pyrimidin-2-yl)cyclopentane-1,3-diamine (0.2 g, 0.395 mmol) was dissolved in DMSO (5 mL). 2-Pyridone (56 mg, 0.592 mmol), (1R,2R)-N^1,N^2-dimethylcyclohexane-1,2-diamine (11 mg, 0.079 mmol), copper(I) iodide (30 mg, 0.158 mmol), and potassium carbonate (109 mg, 0.79 mmol) were added. Under nitrogen protection, the reaction system was heated to 140 ℃ and reacted overnight.

After completion of the reaction, water (50 mL) was added, and the mixture was extracted with ethyl acetate (25 mL × 3). The organic phases were combined and concentrated under reduced pressure. The residue was purified by reverse-phase C18 column chromatography (water → acetonitrile) to obtain 120 mg of a yellow solid, 5'-(benzyloxy)-6'-((1S,3S)-3-((5-(difluoromethoxy)pyrimidin-2-yl)amino)cyclopentyl)amino)-2H-[1,3'-bipyridin]-2-one. LC-MS: $[M+H]^+$ = 521.

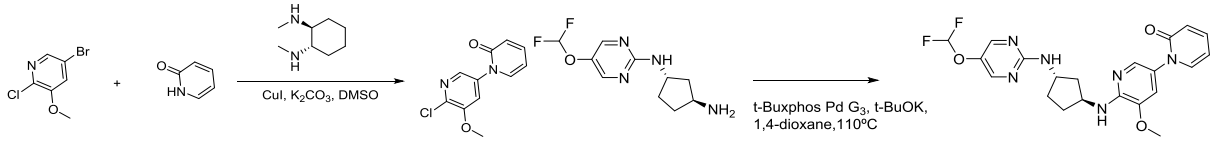
Step C: Synthesis of 6'-(((1S,3S)-3-((5-(difluoromethoxy)pyrimidin-2-yl)amino)cyclopentyl)amino)-5'-hydroxy-2H-[1,3'-bipyridin]-2-one

5'-(benzyloxy)-6'-((1S,3S)-3-((5-(difluoromethoxy)pyrimidin-2-yl)amino)cyclopentyl)amino)-2H-[1,3'-bipyridin]-2-one (100 mg, 0.192 mmol) was dissolved in methanol (5 mL). 10% palladium on carbon (20 mg) was added. Under hydrogen protection, the mixture was reacted at room temperature.

After completion of the reaction, the solid was filtered off, and the filtrate was concentrated under reduced pressure. The residue was purified by reverse-phase C18 column chromatography (water → acetonitrile) to obtain 27 mg of a yellow solid, 6'-(((1S,3S)-3-((5-(difluoromethoxy)pyrimidin-2-yl)amino)cyclopentyl)amino)-5'-hydroxy-2H-[1,3'-bipyridin]-2-one. LC-MS: $[M+H]^+$ = 431. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.19 (s, 1H), 8.22 (s, 2H), 7.58 (dd, J = 6.8, 2.1 Hz, 1H), 7.47 (ddd, J = 10.4, 5.4, 2.2 Hz, 3H), 7.22–6.79 (m, 2H), 6.47–6.39 (m, 1H), 6.26 (td, J = 6.7, 1.4 Hz, 1H), 5.88 (d, J = 7.3 Hz, 1H), 4.46 (q, J = 6.9 Hz, 1H), 4.30 (q, J = 6.8 Hz, 1H), 2.19–2.04 (m, 2H), 1.91 (t, J = 6.9 Hz, 2H), 1.54 (tdd, J = 13.1, 9.0, 5.9 Hz, 2H).

Example A27

Synthesis of 6'-(((1S,3S)-3-((5-(difluoromethoxy)pyrimidin-2-yl)amino)cyclopentyl)amino)-5'-methoxy-2H-[1,3'-bipyridin]-2-one



Step A: Synthesis of 6'-chloro-5'-methoxy-2H-[1,3'-bipyridin]-2-one

At room temperature, pyridin-2(1H)-one (0.94 g, 9.89 mmol, 1.1 eq), 5-bromo-2-chloro-3-methoxypyridine (2.0 g, 8.99 mmol, 1.0 eq), copper(I) iodide (0.34 g, 1.8 mmol, 0.2 eq), (1S,2S)-N^1,N^2-dimethylcyclohexane-1,2-diamine (0.38 g, 2.7 mmol, 0.3 eq), and potassium carbonate (2.48 g, 17.98 mmol, 2.0 eq) were added to dimethyl sulfoxide (20 mL). The solution was purged with nitrogen three times, then reacted at 140 ℃ for 12 hours.

After completion of the reaction, cold water (100 mL) was added to quench the reaction, followed by extraction with ethyl acetate (100 mL × 3). The organic phases were combined, dried over anhydrous sodium sulfate, filtered, and concentrated. The resulting residue was purified by silica gel column chromatography (eluent: dichloromethane/methanol = 20/1) to obtain 0.6 g of a yellow solid, 6'-chloro-5'-methoxy-2H-[1,3'-bipyridin]-2-one (yield: 28%). LC-MS: $[M+H]^+$ = 237.

Step B: Synthesis of 6'-(((1S,3S)-3-((5-(difluoromethoxy)pyrimidin-2-yl)amino)cyclopentyl)amino)-5'-methoxy-2H-[

1,3'-bipyridin]-2-one

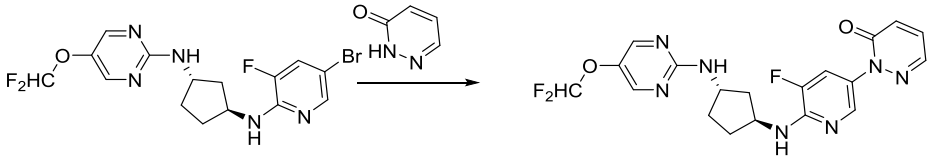
At room temperature, 6'-chloro-5'-methoxy-2H-[1,3'-bipyridin]-2-one (0.6 g, 2.54 mmol, 1 eq), (1S,3S)-N^1-(5-(difluoromethoxy)pyrimidin-2-yl)cyclopentane-1,3-diamine (0.62 g, 2.54 mmol, 1.0 eq), methanesulfonato(2-di-tert-butylphosphino-2',4',6'-triisopropyl-1,1'-biphenyl)(2'-amino-1,1'-biphenyl-2-yl)palladium(II) (0.4 g, 0.51 mmol, 0.2 eq), and potassium tert-butoxide (0.57 g, 5.08 mmol, 2.0 eq) were added to 1,4-dioxane (10 mL). The solution was purged with nitrogen three times, then reacted at 110 ℃ for 12 hours.

After completion of the reaction, the mixture was diluted with ethyl acetate (50 mL) and filtered through diatomaceous earth. The solid was washed three times with ethyl acetate, and the filtrate was concentrated. The resulting residue was purified by C18 reverse-phase column chromatography (eluent: acetonitrile/water, 45% acetonitrile) to obtain 0.5919 g of a yellow solid, 6'-(((1S,3S)-3-((5-(difluoromethoxy)pyrimidin-2-yl)amino)cyclopentyl)amino)-5'-methoxy-2H-[1,3'-bipyridin]-2-one (yield: 52%). LC-MS: $[M+H]^+$ = 445.

NMR data: ^{1}H NMR (400 MHz, DMSO) δ 8.24 (s, 2H), 7.62 (dd, J = 6.8, 2.1 Hz, 1H), 7.56 (d, J = 2.1 Hz, 1H), 7.53–7.44 (m, 2H), 7.25–6.83 (m, 2H), 6.45 (dt, J = 9.2, 1.0 Hz, 1H), 6.28 (td, J = 6.7, 1.4 Hz, 1H), 6.15 (d, J = 7.3 Hz, 1H), 4.51 (p, J = 6.8 Hz, 1H), 4.31 (h, J = 6.7 Hz, 1H), 3.80 (s, 3H), 2.11 (dq, J = 17.6, 7.1, 5.9 Hz, 2H), 1.92 (td, J = 6.8, 1.7 Hz, 2H), 1.68–1.44 (m, 2H).

Example A28

Synthesis of 2-(6-(((1S,3S)-3-((5-(difluoromethoxy)pyrimidin-2-yl)amino)cyclopentyl)amino)-5-fluoropyridin-3-yl)pyridazin-3(2H)-one



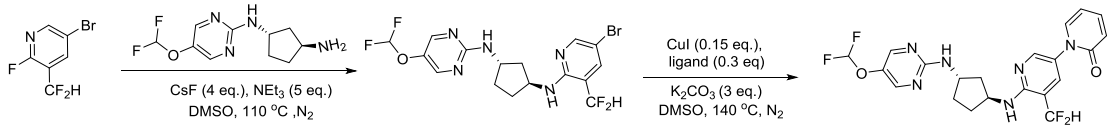
At 20 ℃, (1S,3S)-N^1-(5-(difluoromethoxy)pyrimidin-2-yl)-N^3-(5-iodopyridin-2-yl)cyclopentane-1,3-diamine (0.4 g, 0.9558 mmol), pyridazin-3(2H)-one (275 mg, 2.867 mmol), and potassium phosphate (608.5 mg, 2.867 mmol) were dissolved in DMSO (20 mL). CuI (72.8 mg, 0.3823 mmol) and (1R,2R)-(-)-N,N'-dimethyl-1,2-cyclohexanediamine (27.19 mg, 0.191 mmol) were added. The mixture was purged with N_2 three times, then heated to 130 ℃ and stirred overnight under a N_2 atmosphere.

The reaction mixture was filtered, washed with 50 mL of EA, and then 50 mL of water was added. The mixture was extracted with EA (30 mL × 4). The organic phases were combined, washed with saturated brine (50 mL) and concentrated to obtain the crude product. The crude product was purified by column chromatography (DCM:MeOH = 20:1) to obtain a brown solid, which was further purified by reverse-phase column chromatography to obtain a yellow solid, 2-(6-(((1S,3S)-3-((5-(difluoromethoxy)pyrimidin-2-yl)amino)cyclopentyl)amino)-5-fluoropyridin-3-yl)pyridazin-3(2H)-one (213 mg, 51.4% yield).

LC-MS: $[M+H]^+$ = 434. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.24 (s, 2H), 8.07–8.00 (m, 2H), 7.63 (dd, J = 12.0, 2.1 Hz, 1H), 7.56–7.45 (m, 2H), 7.24–6.83 (m, 3H), 4.51 (p, J = 7.0 Hz, 1H), 4.33 (p, J = 6.9 Hz, 1H), 2.12 (ddt, J = 15.7, 12.0, 6.0 Hz, 2H), 1.94 (dq, J = 10.7, 6.5 Hz, 2H), 1.69–1.42 (m, 2H).

Example A29

Synthesis of 6'-(((1S,3S)-3-((5-(difluoromethoxy)pyrimidin-2-yl)amino)cyclopentyl)amino)-5'-(difluoromethyl)-2H-[1,3'-bipyridin]-2-one



Step A: Synthesis of (1S,3S)-N^1-(5-bromo-3-(difluoromethyl)pyridin-2-yl)-N^3-(5-(difluoromethoxy)pyrimidin-2-yl)cyclopentane-1,3-diamine

Under nitrogen protection at room temperature, (1S,3S)-N^1-(5-(difluoromethoxy)pyrimidin-2-yl)cyclopentane-1,3-diamine (1.16 g, 4.77 mmol, 1.0 eq), 5-bromo-3-(difluoromethyl)-2-fluoropyridine (1.287 g, 5.72 mmol, 1.2 eq), cesium fluoride (2.90 g, 19.08 mmol, 4.0 eq), and triethylamine (2.41 g, 23.85 mmol, 5.0 eq) were dissolved in dimethyl sulfoxide (19 mL). The mixture was heated in an oil bath to 110 ℃ and reacted overnight.

After completion of the reaction, the mixture was cooled to room temperature, diluted with ethyl acetate (100 mL), and filtered to remove solid impurities. Saturated brine (75 mL) was added for extraction. The separated aqueous phase was further extracted with ethyl acetate (75 mL). The organic phases were combined and concentrated under reduced pressure to dryness. The resulting residue was purified by silica gel column chromatography (eluent: ethyl acetate/n-hexane = 3/1) to obtain 1.89 g of a yellow solid, (1S,3S)-N^1-(5-bromo-3-(difluoromethyl)pyridin-2-yl)-N^3-(5-(difluoromethoxy)pyrimidin-2-yl)cy

clopentane-1,3-diamine (yield: 88%). LC-MS: $[M+H]^+$ = 450.

Step B: Synthesis of 6'-(((1S,3S)-3-((5-(difluoromethoxy)pyrimidin-2-yl)amino)cyclopentyl)amino)-5'-(difluoromethyl)-2H-[1,3'-bipyridin]-2-one

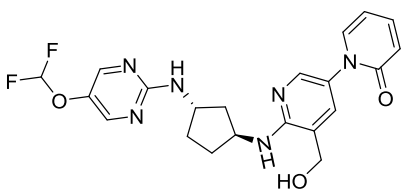
Under nitrogen protection at room temperature, (1S,3S)-N^1-(5-bromo-3-(difluoromethyl)pyridin-2-yl)-N^3-(5-(difluoromethoxy)pyrimidin-2-yl)cyclopentane-1,3-diamine (1.0 g, 2.23 mmol, 1.0 eq), 2-hydroxypyridine (0.424 g, 4.46 mmol, 2.0 eq), copper(I) iodide (0.064 g, 0.335 mmol, 0.15 eq), N^1,N^2-bis(2-thienylmethyl)ethanediamide (0.188 g, 0.669 mmol, 0.3 eq), and potassium carbonate (0.923 g, 6.69 mmol, 3.0 eq) were dissolved in dimethyl sulfoxide (9 mL). The mixture was heated in an oil bath to 140 ℃ and reacted overnight.

After completion of the reaction, the mixture was cooled to room temperature, diluted with ethyl acetate (75 mL), and filtered to remove solid impurities. Saturated brine (50 mL) was added for extraction. The separated aqueous phase was further extracted with ethyl acetate (50 mL). The organic phases were combined and concentrated under reduced pressure to dryness. The resulting residue was purified by silica gel column chromatography (eluent: ethyl acetate) to obtain 0.148 g of a light yellow solid, 6'-(((1S,3S)-3-((5-(difluoromethoxy)pyrimidin-2-yl)amino)cyclopentyl)amino)-5'-(difluoromethyl)-2H-[1,3'-bipyridin]-2-one (yield: 14.3%). LC-MS: $[M+H]^+$ = 465.

Proton NMR: ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.24 (s, 2H), 8.16 (dd, J = 2.6, 1.4 Hz, 1H), 7.71–7.62 (m, 2H), 7.50 (ddd, J = 8.9, 6.5, 2.0 Hz, 2H), 7.31–6.85 (m, 2H), 6.54–6.43 (m, 2H), 6.29 (td, J = 6.7, 1.3 Hz, 1H), 4.58 (h, J = 7.0 Hz, 1H), 4.33 (h, J = 7.0 Hz, 1H), 2.21–2.07 (m, 2H), 1.94 (t, J = 7.1 Hz, 2H), 1.62–1.49 (m, 2H).

Example A30

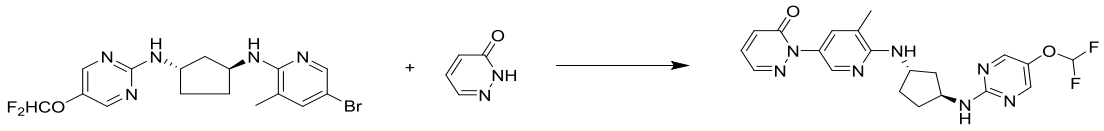
Following the method of the preceding Preparation Example, Compound A30 was prepared:

No.	Structural formula	LC-MS: $[M+H]^+$	NMR
A30		445	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.28–8.20 (s, 2H), 7.92–7.87 (d, J = 2.5 Hz, 1H), 7.64–7.37 (m, 4H), 7.24–6.83 (t, J = 74.0 Hz, 1H), 6.49–6.41 (d, J = 9.2 Hz, 1H), 6.31–6.24 (t, J = 6.6 Hz, 1H), 6.03–5.97 (d, J = 6.8 Hz, 1H), 5.45–5.38 (t, J = 5.3 Hz, 1H), 4.57–4.46 (m, 1H), 4.44–4.37 (d, J = 5.4 Hz, 2H), 4.36–4.26 (m, 1H), 2.24–2.04 (m, 2H), 2.01–1.85 (m, 2H), 1.61–1.46 (m,

			2H).

Example A31

Synthesis of 2-(6-(((1S,3S)-3-((5-(difluoromethoxy)pyrimidin-2-yl)amino)cyclopentyl)amino)-5-methylpyridin-3-yl)pyridazin-3(2H)-one



At 25 ℃, (1S,3S)-N^1-(5-bromo-3-methylpyridin-2-yl)-N^3-(5-(difluoromethoxy)pyrimidin-2-yl)cyclopentane-1,3-diamine (300 mg, 0.729 mmol), pyridazin-3(2H)-one (76.6 mg, 0.797 mmol), potassium phosphate (446 mg, 1.46 mmol), copper(I) iodide (30 mg, 0.146 mmol), and (1R,2R)-(-)-N,N'-dimethyl-1,2-cyclohexanediamine (42 mg, 0.292 mmol) were dissolved in DMSO (10 mL). After addition, the mixture was heated to 140 ℃ and reacted for 16 hours.

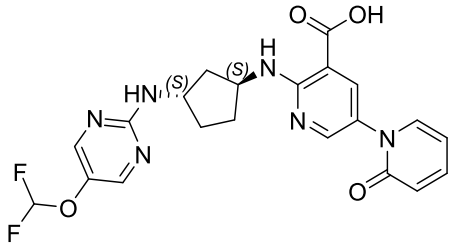
Water (50 mL) was added, followed by extraction with EA (50 mL × 4). The organic phases were combined, washed with saturated brine (50 mL), and concentrated to obtain the crude product. The resulting residue was purified by reverse-phase column chromatography (acetonitrile:water = 5:95 to 60:40) to obtain 130 mg of a white solid, 2-(6-(((1S,3S)-3-((5-(difluoromethoxy)pyrimidin-2-yl)amino)cyclopentyl)amino)-5-methylpyridin-3-yl)pyridazin-3(2H)-one (0.123 g, 41.8% yield). LC-MS: $[M+H]^+$ = 430.

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.24 (s, 2H), 8.04–7.98 (m, 2H), 7.51–7.42 (m, 2H), 7.42–7.37 (m, 1H), 7.07–6.99 (m, 1H), 5.98 (d, J = 7.0 Hz, 1H), 4.54 (h, J = 6.9 Hz, 1H), 4.33 (h, J = 6.9 Hz, 1H), 2.23–2.07 (m, 4H), 1.95 (t, J = 7.1 Hz, 2H), 1.56 (tdd, J = 16.0, 9.3, 4.6 Hz, 2H).

Following the aforementioned method, Compound A31D was prepared: ^{1}H NMR (400 MHz, DMSO) δ 8.24 (s, 2H), 8.01 (dd, J = 3.9, 1.6 Hz, 1H), 7.52 – 7.43 (m, 2H), 7.39 (s, 1H), 7.26 – 6.81 (m, 2H), 5.97 (d, J = 7.0 Hz, 1H), 4.55 (q, J = 7.0 Hz, 1H), 4.34 (q, J = 6.9 Hz, 1H), 2.22 – 2.06 (m, 5H), 1.95 (t, J = 7.1 Hz, 2H), 1.66 – 1.48 (m, 2H).

Example A32

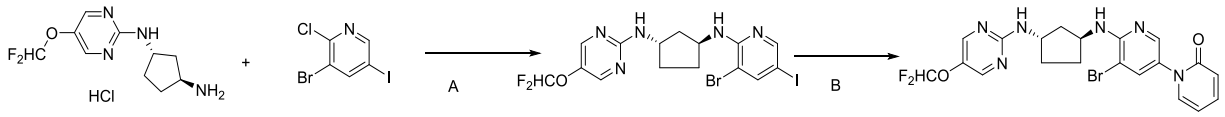
Following the method of the preceding preparation example, Compound A32 was prepared:

A32		LC-MS: $[M+H]^+$ =459	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.66–8.50 (s, 1H), 8.27–8.19 (d, J = 11.1 Hz, 3H), 8.05–7.99 (d, J = 2.8 Hz, 1H), 7.69–7.63 (m, 1H), 7.57–7.46 (m, 2H), 7.23–6.83 (t, J = 74.0 Hz, 1H), 6.49–6.43 (d, J = 9.2 Hz, 1H), 6.33–6.26 (m, 1H), 4.62–4.51

			(m, 1H), 4.39–4.27 (m ,1H), 2.28–2.08 (m, 2H), 2.06–1.84 (m, 2H), 1.65–1.44 (m, 2H).

Example A33

Synthesis of 5'-bromo-6'-(((1S,3S)-3-((5-(difluoromethoxy)pyrimidin-2-yl)amino)cyclopentyl)amino)-2H-[1, 3'-bipyridin]-2-one



Step A: Synthesis of (1S,3S)-N^1-(3-bromo-5-iodopyridin-2-yl)-N^3-(5-(difluoromethoxy)pyrimidin-2-yl)cyclopentane-1,3-diamine

At 20 ℃, (1S,3S)-N^1-(5-(difluoromethoxy)pyrimidin-2-yl)cyclopentane-1,3-diamine hydrochloride (590 mg, 2.10 mmol), 3-bromo-2-chloro-5-iodopyridine (1.00 g, 3.15 mmol), potassium carbonate (0.87 g, 6.30 mmol), and DMSO (20 mL) were added to a 50 mL single-necked flask. The mixture was heated to 100 ℃ and reacted overnight.

Water (50 mL) was added, followed by extraction with EA (30 mL × 4). The organic phases were combined, washed with saturated brine (50 mL), and concentrated to obtain the crude product. The crude product was purified by column chromatography (DCM:MeOH = 100:3) to obtain a yellow solid, (1S,3S)-N^1-(3-bromo-5-iodopyridin-2-yl)-N^3-(5-(difluoromethoxy)pyrimidin-2-yl)cyclopentane-1,3-diamine (460 mg, 41.6% yield). LC-MS: $[M+H]^+$ = 526.

Step B: Synthesis of 5'-bromo-6'-(((1S,3S)-3-((5-(difluoromethoxy)pyrimidin-2-yl)amino)cyclopentyl)amino)-2H-[1, 3'-bipyridin]-2-one

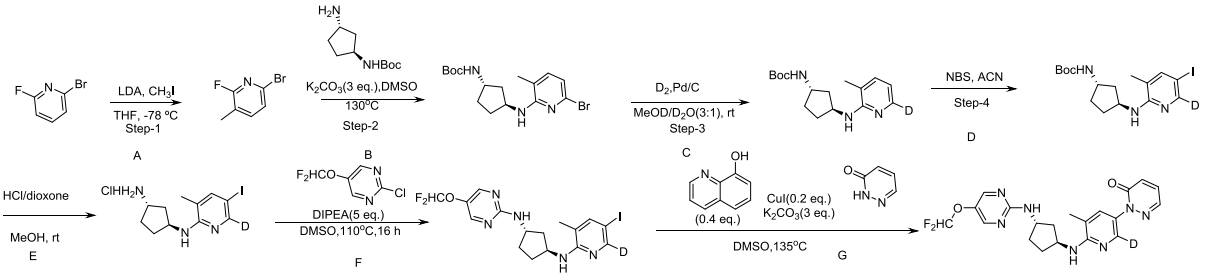
(1S,3S)-N^1-(3-bromo-5-iodopyridin-2-yl)-N^3-(5-(difluoromethoxy)pyrimidin-2-yl)cyclopentane-1,3-diamine (360 mg, 0.68 mmol), 1,2-dihydropyridin-2-one (0.19 g, 2.04 mmol), potassium phosphate (0.14 g, 0.68 mmol), trans-N,N'-dimethyl-1,2-cyclohexanediamine (0.039 g, 0.27 mmol), CuI (0.052 g, 0.27 mmol), and DMSO (10 mL) were added to a reaction flask. The mixture was heated to 130 ℃ and reacted overnight.

Water (50 mL) was added, and the mixture was extracted with EA (30 mL × 5). The organic phases were combined, concentrated, and the solvent was removed. The residue was purified by column chromatography (DCM/MeOH = 10/1) to obtain 130 mg of crude product, which was further purified by preparative chromatography to obtain the product,

5'-bromo-6'-(((1S,3S)-3-((5-(difluoromethoxy)pyrimidin-2-yl)amino)cyclopentyl)amino)-2H-[1,3'-bipyridin]-2-one (25 mg, Yield 7.41%) as a white solid. LC-MS: $[M+H]^+$ = 493.

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.24 (s, 2H), 8.04 (d, J = 2.3 Hz, 1H), 7.90 (d, J = 2.3 Hz, 1H), 7.65 (dd, J = 6.9, 2.0 Hz, 1H), 7.53–7.47 (m, 2H), 7.03 (s, 1H), 6.49–6.44 (m, 1H), 6.29 (ddd, J = 8.9, 5.1, 1.8 Hz, 2H), 4.54 (q, J = 7.2 Hz, 1H), 4.39–4.30 (m, 1H), 2.21–2.06 (m, 2H), 2.03–1.92 (m, 2H), 1.69–1.50 (m, 2H).

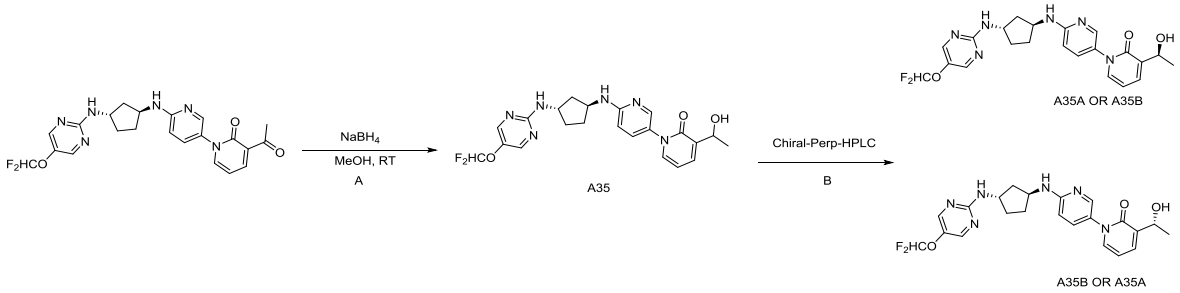
Example A34 (Compound A31D)



NMR Data: ^{1}H NMR (400 MHz, DMSO) δ 8.24 (s, 2H), 8.01 (dd, J = 3.9, 1.6 Hz, 1H), 7.52–7.43 (m, 2H), 7.39 (s, 1H), 7.26–6.81 (m, 2H), 5.97 (d, J = 7.0 Hz, 1H), 4.55 (q, J = 7.0 Hz, 1H), 4.34 (q, J = 6.9 Hz, 1H), 2.22–2.06 (m, 5H), 1.95 (t, J = 7.1 Hz, 2H), 1.66–1.48 (m, 2H).

Example A35

Synthesis of 6'-(((1S,3S)-3-((5-(difluoromethoxy)pyrimidin-2-yl)amino)cyclopentyl)amino)-3-(1-hydroxyethyl)-2H-[1,3'-bipyridin]-2-one (Compound A35)



Step A: Synthesis of 6'-(((1S,3S)-3-((5-(difluoromethoxy)pyrimidin-2-yl)amino)cyclopentyl)amino)-3-(1-hydroxyethyl)-2H-[1,3'-bipyridin]-2-one

At room temperature, 3-acetyl-1-(6-{[(1S,3S)-3-[(5-(difluoromethoxy)pyrimidin-2-yl)amino]cyclopentyl]amino}pyridin-3-yl)-1,2-dihydropyridin-2-one (800 mg, 1.75 mmol) was dissolved in methanol (10 mL). Sodium borohydride (86.06 mg, 2.27 mmol) was added, and the mixture was maintained at room temperature and reacted for 1 hour.

After completion of the reaction, saturated aqueous ammonium chloride solution (2 mL)

was added to quench the reaction. The mixture was then concentrated by rotary evaporation to a residue. The resulting residue was purified by C18 reverse-phase column chromatography (ACN/H_2O, 40% ACN) to obtain a light yellow mixture of 6'-(((1S,3S)-3-((5-(difluoromethoxy)pyrimidin-2-yl)amino)cyclopentyl)amino)-3-(1-hydroxyeth yl)-2H-[1,3'-bipyridin]-2-one (570 mg, yield 70%).

Step B: Synthesis of 6'-(((1S,3S)-3-((5-(difluoromethoxy)pyrimidin-2-yl)amino)cyclopentyl)amino)-3-((S)-1-hydroxy ethyl)-2H-[1,3'-bipyridin]-2-one and 6'-(((1S,3S)-3-((5-(difluoromethoxy)pyrimidin-2-yl)amino)cyclopentyl)amino)-3-((R)-1-hydrox yethyl)-2H-[1,3'-bipyridin]-2-one

The mixture obtained from Step A was subjected to chiral separation (column model: CHIRALCEL OD-H 5 um 10 mm*250 mm; mobile phase: n-hexane/ethanol = 70:30; flow rate: 5 mL/min; column temperature: 30 ℃) to obtain a white solid front peak (RT=12.69 min) and a rear peak of 213 mg (RT=16.03 min). LC-MS: $[M+H]^+$ = 459.

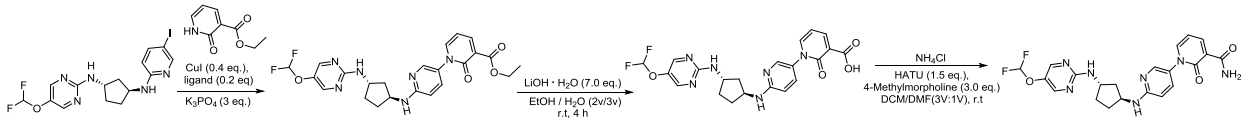
NMR Data:

Compound with RT=12.69 min: ^{1}H NMR (400 MHz, DMSO) δ 8.24 (s, 2H), 7.91 (d, J = 2.6 Hz, 1H), 7.58–7.45 (m, 3H), 7.39 (dd, J = 8.9, 2.6 Hz, 1H), 7.26–6.82 (m, 2H), 6.52 (d, J = 8.9 Hz, 1H), 6.32 (t, J = 6.9 Hz, 1H), 5.11 (d, J = 4.5 Hz, 1H), 4.71 (p, J = 6.0 Hz, 1H), 4.31 (q, J = 7.0 Hz, 2H), 2.13 (p, J = 8.1, 7.5 Hz, 2H), 1.90 (hept, J = 6.9 Hz, 2H), 1.53 (d, J = 21.6 Hz, 2H), 1.26 (d, J = 6.4 Hz, 3H).

Compound with RT=16.03 min: ^{1}H NMR (400 MHz, DMSO) δ 8.24 (s, 2H), 7.91 (d, J = 2.7 Hz, 1H), 7.52 (td, J = 7.8, 7.2, 2.2 Hz, 3H), 7.39 (dd, J = 8.9, 2.7 Hz, 1H), 7.25–6.82 (m, 2H), 6.52 (d, J = 8.9 Hz, 1H), 6.32 (t, J = 6.8 Hz, 1H), 5.08 (d, J = 4.6 Hz, 1H), 4.71 (p, J = 6.0 Hz, 1H), 4.30 (p, J = 6.9 Hz, 2H), 2.21–2.04 (m, 2H), 1.98–1.80 (m, 2H), 1.52 (td, J = 13.1, 11.9, 6.9 Hz, 2H), 1.26 (d, J = 6.3 Hz, 3H).

Example A36

Synthesis of 6'-(((1S,3S)-3-((5-(difluoromethoxy)pyrimidin-2-yl)amino)cyclopentyl)amino)-2-oxo-2H-[1,3'-b ipyridine]-3-carboxamide



Step A: Synthesis of ethyl 6'-(((1S,3S)-3-((5-(difluoromethoxy)pyrimidin-2-yl)amino)cyclopentyl)amino)-2-oxo-2H-[1,3'-b

ipyridine]-3-carboxylate

Under nitrogen protection at room temperature, (1S,3S)-N^1-(5-(difluoromethoxy)pyrimidin-2-yl)-N^3-(5-iodopyridin-2-yl)cyclopentane-1,3-diamine (6.71 g, 15 mmol, 1.0 eq), ethyl 2-oxo-1,2-dihydropyridine-3-carboxylate (5.01 g, 30 mmol, 2 eq), copper(I) iodide (1.14 g, 6.0 mmol, 0.4 eq), N^1,N^2-dimethylcyclohexane-1,2-diamine (0.43 g, 3.0 mmol, 0.2 eq), and potassium phosphate (9.55 g, 45 mmol, 3.0 eq) were dissolved in dimethyl sulfoxide (60 mL), and the mixture was heated to 140 ℃ and reacted overnight.

After completion of the reaction, cold water (150 mL) was added to quench the reaction, followed by extraction with ethyl acetate (250 mL × 3). The organic phases were combined, dried over anhydrous sodium sulfate, filtered, and concentrated. The resulting residue was purified by silica gel column chromatography (eluent: ethyl acetate) to obtain 2.92 g of a yellow solid, ethyl 6'-(((1S,3S)-3-((5-(difluoromethoxy)pyrimidin-2-yl)amino)cyclopentyl)amino)-2-oxo-2H-[1,3'-bipyridine]-3-carboxylate. LC-MS: $[M+H]^+$ = 487.

Step B: Synthesis of 6'-(((1S,3S)-3-((5-(difluoromethoxy)pyrimidin-2-yl)amino)cyclopentyl)amino)-2-oxo-2H-[1,3'-bipyridine]-3-carboxylic acid

At room temperature, ethyl 6'-(((1S,3S)-3-((5-(difluoromethoxy)pyrimidin-2-yl)amino)cyclopentyl)amino)-2-oxo-2H-[1,3'-bipyridine]-3-carboxylate (2.92 g, 6.37 mmol, 1.0 eq) and lithium hydroxide monohydrate (1.90 g, 44.6 mmol, 7.0 eq) were dissolved in a mixed solvent of ethanol (6 mL) and water (9 mL). The mixture was stirred at room temperature for 4 hours.

After completion of the reaction, the pH of the reaction mixture was adjusted to approximately 6 using 1M dilute hydrochloric acid solution, resulting in the precipitation of a large amount of light yellow solid. The resultant was filtrated to obtain 2.63 g of 6'-(((1S,3S)-3-((5-(difluoromethoxy)pyrimidin-2-yl)amino)cyclopentyl)amino)-2-oxo-2H-[1,3'-bipyridine]-3-carboxylic acid. LC-MS: $[M+H]^+$ = 459.

Step C: Synthesis of 6'-(((1S,3S)-3-((5-(difluoromethoxy)pyrimidin-2-yl)amino)cyclopentyl)amino)-2-oxo-2H-[1,3'-bipyridine]-3-carboxamide

At room temperature, 6'-(((1S,3S)-3-((5-(difluoromethoxy)pyrimidin-2-yl)amino)cyclopentyl)amino)-2-oxo-2H-[1,3'-bipyridine]-3-carboxylic acid (0.25 g, 0.44 mmol, 1.0 eq), O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (HATU, 0.251 g,

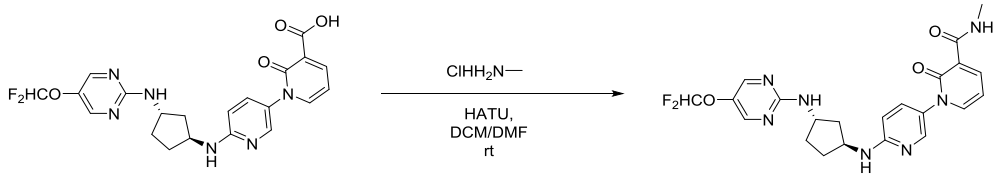
0.66 mmol, 1.5 eq), and N-methylmorpholine (0.135 g, 1.32 mmol, 3.0 eq) were dissolved in a mixed solvent of dichloromethane (3 mL) and N,N-dimethylformamide (1 mL). The mixture was stirred vigorously for 15 minutes. Subsequently, ammonium chloride (0.036 g, 0.66 mmol, 1.5 eq) was added, and the mixture was stirred at room temperature for 4 hours.

After completion of the reaction, the solvent was removed under reduced pressure by rotary evaporation. The resulting crude product was dissolved in an appropriate amount of dimethyl sulfoxide and purified by C18 reverse-phase column (120 g specification, mobile phase: acetonitrile/water) to obtain 140 mg of a red solid, 6'-(((1S,3S)-3-((5-(difluoromethoxy)pyrimidin-2-yl)amino)cyclopentyl)amino)-2-oxo-2H-[1,3'-bipyridine]-3-carboxamide (70% yield). LC-MS: $[M+H]^+$ = 458.

NMR data: ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.91 (d, J = 4.4 Hz, 1H), 8.39 (dd, J = 7.3, 2.2 Hz, 1H), 8.23 (s, 2H), 8.05 – 7.92 (m, 2H), 7.61 (d, J = 4.4 Hz, 1H), 7.54 – 7.42 (m, 2H), 7.22 – 6.85 (m, 2H), 6.62 – 6.49 (m, 2H), 4.32 (p, J = 6.7 Hz, 2H), 2.13 (tt, J = 11.9, 7.0 Hz, 2H), 1.97 – 1.83 (m, 2H), 1.52 (ddt, J = 18.9, 14.1, 6.3 Hz, 2H).

Example A37

Synthesis of 6'-(((1S,3S)-3-((5-(difluoromethoxy)pyrimidin-2-yl)amino)cyclopentyl)amino)-N-methyl-2-oxo-2H-[1,3'-bipyridine]-3-carboxamide



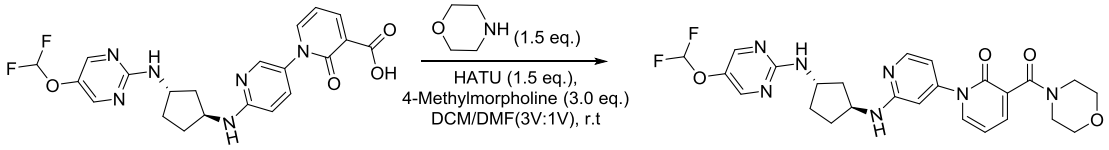
At room temperature, 6'-(((1S,3S)-3-((5-(difluoromethoxy)pyrimidin-2-yl)amino)cyclopentyl)amino)-2-oxo-2H-[1,3'-bipyridine]-3-carboxylic acid (200 mg, 0.42 mmol) was dissolved in DCM/DMF (6/2 mL). HATU (150 mg, 0.42 mmol) and N-methylmorpholine (200 μL, 2.9 mmol) were added, and the mixture was stirred at room temperature for 10 minutes. Methylamine hydrochloride (30 mg, 0.48 mmol) was then added, and the mixture was stirred at room temperature for 2 hours.

After completion of the reaction, water (20 mL) was added, and the mixture was extracted with DCM (20 mL × 4). The organic phases were combined and purified by reverse-phase column chromatography (CAN/H_2O = 40%) to obtain a yellow solid, 6'-(((1S,3S)-3-((5-(difluoromethoxy)pyrimidin-2-yl)amino)cyclopentyl)amino)-N-methyl-2-oxo-2H-[1,3'-bipyridine]-3-carboxamide, yield 81.27%. LC-MS: $[M+H]^+$ = 472. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.47 (q, J = 4.8 Hz, 1H), 8.40 (dd, J = 7.3, 2.2 Hz, 1H), 8.24 (s, 2H), 7.97 (dd, J =

7.8, 2.5 Hz, 2H), 7.51 (d, J = 7.2 Hz, 1H), 7.47 – 7.38 (m, 1H), 7.25 – 6.70 (m, 2H), 6.61 – 6.51 (m, 2H), 4.33 (p, J = 7.0 Hz, 2H), 2.81 (d, J = 4.8 Hz, 3H), 2.19 – 2.08 (m, 2H), 1.98 – 1.81 (m, 2H), 1.53 (td, J = 13.7, 11.9, 7.0 Hz, 2H).

Example A38

Synthesis of 2'-(((1S,3S)-3-((5-(difluoromethoxy)pyrimidin-2-yl)amino)cyclopentyl)amino)-3-(morpholine-4-carbonyl)-2H-[1,4'-bipyridin]-2-one



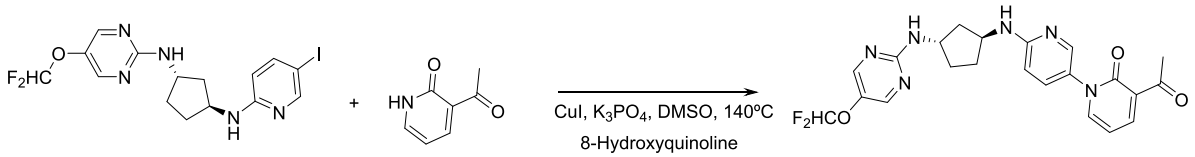
At room temperature, 6'-(((1S,3S)-3-((5-(difluoromethoxy)pyrimidin-2-yl)amino)cyclopentyl)amino)-2-oxo-2H-[1,3'-bipyridine]-3-carboxylic acid (0.25 g, 0.44 mmol, 1.0 eq), O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (HATU, 0.251 g, 0.66 mmol, 1.5 eq), and N-methylmorpholine (0.135 g, 1.32 mmol, 3.0 eq) were dissolved in a mixed solvent of dichloromethane (3 mL) and N,N-dimethylformamide (1 mL). The mixture was stirred vigorously for 15 minutes. Subsequently, morpholine (0.058 g, 0.66 mmol, 1.5 eq) was added, and the mixture was stirred at room temperature for 4 hours.

After completion of the reaction, the solvent was removed under reduced pressure by rotary evaporation. The resulting crude product was dissolved in an appropriate amount of dimethyl sulfoxide and purified by C18 reverse-phase column (120 g specification, mobile phase: acetonitrile/water) to obtain 164 mg of a light yellow solid, 2'-(((1S,3S)-3-((5-(difluoromethoxy)pyrimidin-2-yl)amino)cyclopentyl)amino)-3-(morpholine-4-carbonyl)-2H-[1,4'-bipyridin]-2-one (71% yield). LC-MS: $[M+H]^+$ = 528.

NMR data: ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.23 (s, 2H), 7.95 (d, J = 2.7 Hz, 1H), 7.74 (dd, J = 6.8, 2.1 Hz, 1H), 7.63 – 7.37 (m, 3H), 7.23 – 6.85 (m, 2H), 6.53 (d, J = 8.9 Hz, 1H), 6.36 (t, J = 6.8 Hz, 1H), 4.30 (p, J = 6.8 Hz, 2H), 3.56 (ddt, J = 12.6, 9.0, 5.0 Hz, 6H), 3.25 (t, J = 4.7 Hz, 2H), 2.20 – 2.04 (m, 2H), 1.88 (tdd, J = 13.2, 10.4, 6.3 Hz, 2H), 1.60 – 1.43 (m, 2H).

Example A39

Synthesis of 3-acetyl-6'-(((1S,3S)-3-((5-(difluoromethoxy)pyrimidin-2-yl)amino)cyclopentyl)amino)-2H-[1,3'-bipyridin]-2-one



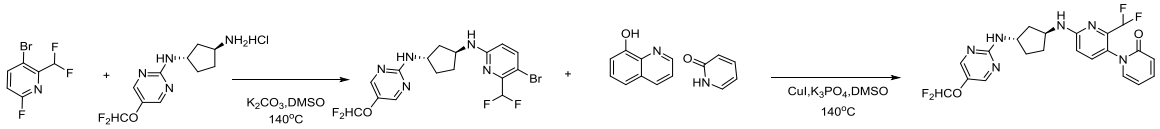
At room temperature, (1S,3S)-N^1-(5-(difluoromethoxy)pyrimidin-2-yl)-N^3-(5-iodopyridin-2-yl)cyclopentane-1,3-diamine (2.75 g, 6.15 mmol), 3-acetyl-1,2-dihydropyridin-2-one (1.69 g, 12.3 mmol), copper(I) iodide (0.23 g, 1.23 mmol), 8-hydroxyquinoline (0.36 g, 2.46 mmol), and potassium phosphate (3.92 g, 18.45 mmol) were added to dimethyl sulfoxide (20 mL). The mixture was purged with nitrogen three times, and then heated in an oil bath at 140 ℃ and reacted for 8 hours.

After completion of the reaction, the reaction mixture was filtered through diatomaceous earth, and the solid was washed with ethyl acetate (3 × 50 mL). Water (150 mL) was added to the filtrate, and the mixture was extracted with ethyl acetate (3 × 80 mL). The organic phases were combined, washed with saturated brine (3 × 50 mL), dried over anhydrous sodium sulfate, filtered, and concentrated by rotary evaporation to a residue. The residue was purified by silica gel column chromatography (eluent: n-hexane/ethyl acetate = 0/100%, V/V) to obtain a yellow-green solid, 3-acetyl-6'-(((1S,3S)-3-((5-(difluoromethoxy)pyrimidin-2-yl)amino)cyclopentyl)amino)-2H-[1,3'-bipyridin]-2-one (1.51 g, Yield 51.11%, Purity 95%). LC-MS: $[M+H]^+$ = 457.

NMR data: ^{1}H NMR (400 MHz, DMSO) δ 8.24 (s, 2H), 8.07 (dd, J = 7.3, 2.2 Hz, 1H), 8.00 (dd, J = 6.6, 2.3 Hz, 1H), 7.97 (d, J = 2.7 Hz, 1H), 7.51 (d, J = 7.2 Hz, 1H), 7.45 (dd, J = 8.9, 2.7 Hz, 1H), 7.26 – 6.82 (m, 2H), 6.55 (d, J = 8.9 Hz, 1H), 6.44 (t, J = 6.9 Hz, 1H), 4.32 (h, J = 6.7 Hz, 2H), 2.53 (s, 3H), 2.23 – 2.06 (m, 2H), 1.89 (tdd, J = 13.2, 10.5, 6.3 Hz, 2H), 1.52 (ddt, J = 16.4, 14.0, 9.2 Hz, 2H).

Example A40

Synthesis of 6'-(((1S,3S)-3-((5-(difluoromethoxy)pyrimidin-2-yl)amino)cyclopentyl)amino)-2'-(difluoromethyl)-2H-[1,3'-bipyridin]-2-one



Step A: Synthesis of (1S,3S)-N^1-(5-bromo-6-(difluoromethyl)pyridin-2-yl)-N^3-(5-(difluoromethoxy)pyrimidin-2-yl)cyclopentane-1,3-diamine

At room temperature,

(1S,3S)-N^1-(5-(difluoromethoxy)pyrimidin-2-yl)cyclopentane-1,3-diamine hydrochloride (500 mg, 1.5 mmol) was dissolved in DMSO (10 mL). 3-Bromo-2-(difluoromethyl)-6-fluoropyridine (382 mg, 1.7 mmol) and potassium carbonate (1.2 g, 8.6 mmol) were added. Under nitrogen protection, the reaction system was heated to 140 ℃ and stirred overnight.

After completion of the reaction, water (100 mL) was added, and the mixture was extracted with DCM (50 mL × 4). The organic phases were combined and purified by silica gel column chromatography (EA/Hex = 1:1, 50%) to obtain 635 mg of a yellow solid, (1S,3S)-N^1-(5-bromo-6-(difluoromethyl)pyridin-2-yl)-N^3-(5-(difluoromethoxy)pyrimidin-2-yl)cyclopentane-1,3-diamine (yield: 94.3%). LC-MS: $[M+H]^+$ = 450.

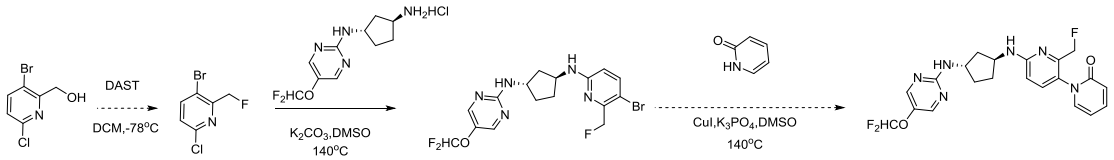
Step B: Synthesis of 6'-(((1S,3S)-3-((5-(difluoromethoxy)pyrimidin-2-yl)amino)cyclopentyl)amino)-2'-(difluoromethyl)-2H-[1,3'-bipyridin]-2-one

At room temperature, (1S,3S)-N^1-(5-bromo-6-(difluoromethyl)pyridin-2-yl)-N^3-(5-(difluoromethoxy)pyrimidin-2-yl)cyclopentane-1,3-diamine (615 mg, 1.23 mmol) was dissolved in DMSO (10 mL). Pyridin-2(1H)-one (351 mg, 3.7 mmol), 8-hydroxyquinoline (53 mg, 0.369 mmol), copper(I) iodide (70 mg, 0.37 mmol), and potassium carbonate (389 mg, 2.46 mmol) were added. Under nitrogen protection, the reaction system was slowly heated to 140 ℃ and reacted overnight.

After completion of the reaction, water (100 mL) was added, and the mixture was extracted with ethyl acetate (80 mL × 3). The organic phases were combined, concentrated under reduced pressure, and the residue was purified by reverse-phase column chromatography (ACN/H_2O = 50%). Lyophilization to obtain 24 mg of a yellow solid product, 6'-(((1S,3S)-3-((5-(difluoromethoxy)pyrimidin-2-yl)amino)cyclopentyl)amino)-2'-(difluoromethyl)-2H-[1,3'-bipyridin]-2-one (yield: 44%). LC-MS: $[M+H]^+$ = 465. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.24 (s, 2H), 7.52 (d, J = 8.1 Hz, 3H), 7.39 (d, J = 8.8 Hz, 1H), 7.31 (d, J = 6.7 Hz, 1H), 7.04 (t, J = 74.0 Hz, 1H), 6.70 (d, J = 8.8 Hz, 1H), 6.62 – 6.33 (m, 2H), 6.29 (t, J = 6.9 Hz, 1H), 4.34 – 4.29 (m, 2H), 2.26 – 2.05 (m, 2H), 1.93 (t, J = 7.0 Hz, 2H), 1.53 (s, 2H).

Example A41

Synthesis of 6'-(((1S,3S)-3-((5-(difluoromethoxy)pyrimidin-2-yl)amino)cyclopentyl)amino)-2'-(fluoromethyl)-2H-[1,3'-bipyridin]-2-one



Step A: Synthesis of 3-bromo-6-chloro-2-(fluoromethyl)pyridine

At room temperature, (3-bromo-6-chloropyridin-2-yl)methanol (500 mg, 2.45 mmol) was dissolved in DCM (20 mL). Under ice bath conditions, DAST (789 μL, 4.90 mmol) was added, and the mixture was stirred at 0 ℃ for 3 hours.

After completion of the reaction, water (100 mL) was added, and the mixture was extracted with DCM (50 mL × 4). The organic phases were combined and purified by silica gel column chromatography (EA/Hex = 1:9, 10%) to obtain 420 mg of a yellow oily liquid, 3-bromo-6-chloro-2-(fluoromethyl)pyridine (yield: 82.8%). LC-MS: $[M+H]^+$ = 207.

Step B: Synthesis of (1S,3S)-N^1-(5-bromo-6-(fluoromethyl)pyridin-2-yl)-N^3-(5-(difluoromethoxy)pyrimidin-2-yl)cyclopentane-1,3-diamine

At room temperature, (1S,3S)-N^1-(5-(difluoromethoxy)pyrimidin-2-yl)cyclopentane-1,3-diamine hydrochloride (380 mg, 1.55 mmol) was dissolved in DMSO (10 mL). 3-Bromo-6-chloro-2-(fluoromethyl)pyridine (420 mg, 1.87 mmol) and potassium carbonate (1.29 g, 9.4 mmol) were added. Under nitrogen protection, the reaction system was heated to 140 ℃ and stirred overnight.

After completion of the reaction, water (100 mL) was added, and the mixture was extracted with DCM (50 mL × 4). The organic phases were combined and purified by silica gel column chromatography (EA/Hex = 1:1, 50%) to obtain 206 mg of a yellow oily liquid, (1S,3S)-N^1-(5-bromo-6-(fluoromethyl)pyridin-2-yl)-N^3-(5-(difluoromethoxy)pyrimidin-2-yl)cyclopentane-1,3-diamine (yield: 30.6%). LC-MS: $[M+H]^+$ = 433.

Step C: Synthesis of 6'-(((1S,3S)-3-((5-(difluoromethoxy)pyrimidin-2-yl)amino)cyclopentyl)amino)-2'-(fluoromethyl)-2H-[1,3'-bipyridin]-2-one

At room temperature, (1S,3S)-N^1-(5-bromo-6-(fluoromethyl)pyridin-2-yl)-N^3-(5-(difluoromethoxy)pyrimidin-2-yl)cyclopentane-1,3-diamine (189 mg, 0.44 mmol) was dissolved in DMSO (10 mL). Pyridin-2(1H)-one (130 mg, 1.3 mmol), 8-hydroxyquinoline (53 mg, 0.369 mmol), copper(I) iodide (25 mg, 0.13 mmol), and potassium carbonate (120 mg, 0.88 mmol) were added. Under nitrogen protection, the reaction system was slowly heated to 140 ℃ and reacted overnight.

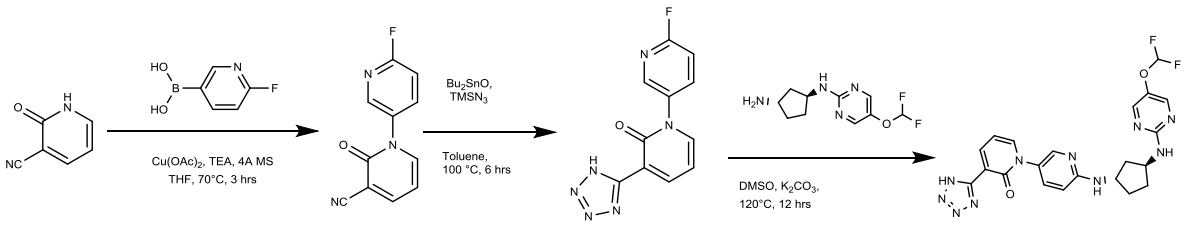
After completion of the reaction, water (100 mL) was added, and the mixture was extracted with ethyl acetate (80 mL × 3). The organic phases were combined, concentrated under reduced pressure, and the residue was purified by reverse-phase column chromatography (ACN/H_2O = 50%). Lyophilization to obtain 20 mg of a yellow solid product, 6'-(((1S,3S)-3-((5-(difluoromethoxy)pyrimidin-2-yl)amino)cyclopentyl)amino)-2'-(fluoromethyl)-2H-[1,3'-bipyridin]-2-one (yield: 10%).

LC-MS: $[M+H]^+$ = 447. ^1H NMR (400 MHz, DMSO-d_6) δ 8.24 (s, 2H), 8.09 (dd, J = 5.0, 2.0 Hz, 1H), 7.83 (ddd, J = 8.7, 7.1, 2.0 Hz, 1H), 7.49 (d, J = 7.2 Hz, 1H), 7.27 (d, J = 8.9 Hz, 1H), 7.09 (dd, J = 7.2, 5.0 Hz, 1H), 7.04 (s, 1H), 7.02 (t, 1H), 6.74 (d, J = 6.8 Hz, 1H), 6.57 (dd, J = 8.9, 2.3 Hz, 1H), 5.14 (d, J = 47.9 Hz, 2H), 4.29 (dq, J = 18.4, 6.8 Hz, 2H), 2.14 (ddd, J = 21.9, 10.6, 4.8 Hz, 2H), 1.90 (td, J = 6.8, 3.0 Hz, 2H), 1.52 (ddt, J = 18.8, 12.8, 8.1 Hz, 2H).

Example A42

Synthesis of 6'-(((1S,3S)-3-((5-(difluoromethoxy)pyrimidin-2-yl)amino)cyclopentyl)amino)-3-(1H-tetrazol-5-yl)-2H-[1,3'-bipyridin]-2-one

Synthetic Route



Step A: Synthesis of 6'-fluoro-2-oxo-2H-[1,3'-bipyridine]-3-carbonitrile

2-Oxo-1,2-dihydropyridine-3-carbonitrile (6.50 g, 54.1 mmol, 1 eq), (6-fluoropyridin-3-yl)boronic acid (15.3 g, 108 mmol, 2 eq), copper(II) acetate (19.7 g, 108 mmol, 2 eq), and triethylamine (27.4 g, 271 mmol, 5 eq) were dissolved in tetrahydrofuran (150 mL), and then 4A molecular sieves (1.00 g) were added. After the addition, the mixture was stirred at 70 ℃ for 3 hours. LCMS detected the MS value of the product (RT = 0.323 min). The reaction mixture was filtered through diatomaceous earth, and the filter cake was washed with dichloromethane several times. The filtrate was concentrated under reduced pressure to obtain a crude product. The crude product was purified by silica gel column chromatography to obtain 6'-fluoro-2-oxo-2H-[1,3'-bipyridine]-3-carbonitrile (450 mg, 2.09 mmol, yield 3.86%). MS (ESI) m/z $[M+1]^+$= 216.1.

Step B: Synthesis of 6'-fluoro-3-(1H-tetrazol-5-yl)-2H-[1,3'-bipyridin]-2-one

6'-Fluoro-2-oxo-2H-[1,3'-bipyridine]-3-carbonitrile (350 mg, 1.63 mmol, 1 eq),

trimethylsilyl azide (562 mg, 4.88 mmol, 3 eq), and dibutyltin oxide (203 mg, 813 μmol, 2.5 eq) were dissolved in toluene (10 mL), and then the mixture was stirred at 100 ℃ for 6 hours. LCMS detected the MS value of the product (RT = 0.342 min). The reaction mixture was concentrated under reduced pressure to obtain a crude product. The crude product was purified by reverse-phase preparative chromatography (Column: Phenomenex luna C18 150*25 mm* 10 um; Mobile phase: [water (TFA)-ACN]; Gradient: 5% to 38% B over min) to obtain 6'-fluoro-3-(1H-tetrazol-5-yl)-2H-[1,3'-bipyridin]-2-one (180 mg, 697 μmol, yield 42.9%). MS (ESI) m/z $[M+1]^+$= 259.1.

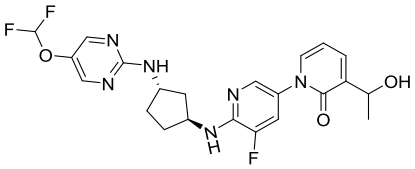
Step C: Synthesis of 6'-(((1S,3S)-3-((5-(difluoromethoxy)pyrimidin-2-yl)amino)cyclopentyl)amino)-3-(1H-tetrazol-5-yl)-2H-[1,3'-bipyridin]-2-one

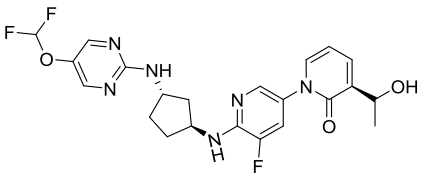
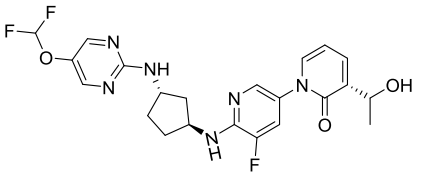
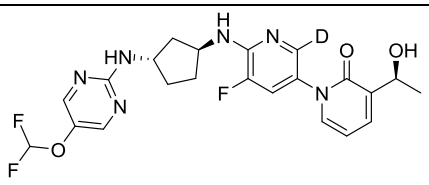
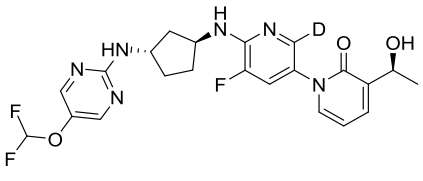
6'-Fluoro-3-(1H-tetrazol-5-yl)-2H-[1,3'-bipyridin]-2-one (180 mg, 697 μmol, 1 eq), (1S,3S)-N^3-[5-(difluoromethoxy)pyrimidin-2-yl]cyclopentane-1,3-diamine hydrochloride (235 mg, 837 μmol, 1.2 eq, hydrochloride salt), and potassium carbonate (289 mg, 2.09 mmol, 3 eq) were dissolved in dimethyl sulfoxide (10 mL), and then the mixture was stirred at 120 ℃ for 12 hours. LCMS detected the MS value of the product (RT = 0.396 min). The reaction mixture was cooled to room temperature, and then filtered. The filtrate was concentrated under reduced pressure to obtain a crude product. The crude product was purified by reverse-phase preparative chromatography (Column: Waters Xbridge 150*25mm* 5um; Mobile phase: [water (ammonium hydroxide v/v)-ACN]; Gradient: 0% to 25% B over 10 min) to obtain 6'-(((1S,3S)-3-((5-(difluoromethoxy)pyrimidin-2-yl)amino)cyclopentyl)amino)-3-(1H-tetrazol-5-yl)-2H-[1,3'-bipyridin]-2-one (68.0 mg, 134 μmol, 19.3% yield, 95.4% purity).

RT = 0.396 min, MS (ESI) m/z $[M+1]^+$ = 483.2, ^{1}H NMR: (400 MHz, DMSO-d_6): δ 8.46 - 8.39 (m, 1H), 8.23 (s, 2H), 8.04 (d, J = 2.6 Hz, 1H), 7.95 (dd, J = 2.0, 6.6 Hz, 1H), 7.55 - 7.45 (m, 2H), 7.24 - 6.82 (m, 2H), 6.61 - 6.52 (m, 2H), 4.38 - 4.26 (m, 2H), 2.21 - 2.08 (m, 2H), 1.98 - 1.82 (m, 2H), 1.61 - 1.44 (m, 2H).

Example A43

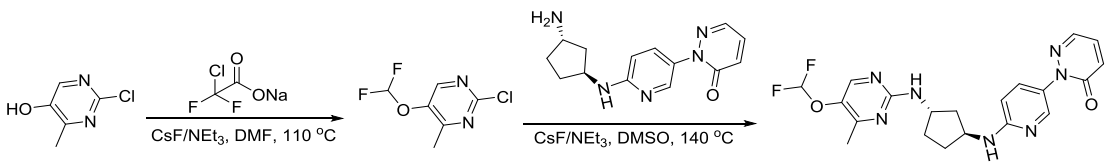
Referring to the aforementioned preparation method, Compound A43 and its isomers A43A, A43B, A43A-D, and A43B-D were prepared:

	Structural formula	NMR data
A43		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.24 – 8.21 (s, 2H), 7.84 – 7.82 (d, *J* = 2.2 Hz, 1H), 7.56 – 7.50 (m, 3H), 7.49 – 7.44 (d, *J* = 7.2 Hz, 1H), 7.22 – 7.01 (d, *J* = 73.9 Hz, 1H), 6.93 – 6.83 (m, 1H), 6.36 – 6.30 (t, *J* = 6.8 Hz, 1H), 5.11 – 5.07 (d, *J* =

		4.6 Hz, 1H), 4.76 – 4.68 (m, 1H), 4.55 – 4.46 (m, 1H), 4.38 – 4.28 (m, 1H), 2.18 – 2.06 (m, 2H), 2.00 – 1.90 (m, 2H), 1.65 – 1.50 (m, 2H), 1.29 – 1.24 (d, *J* = 6.3 Hz, 3H).
A43A or A43B		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.25 – 8.20 (s, 2H), 7.85 – 7.81 (d, *J* = 2.2 Hz, 1H), 7.56 – 7.50 (m, 2H), 7.48 – 7.43 (d, *J* = 7.3 Hz, 1H), 7.23 – 6.82 (m, 2H), 6.36 – 6.29 (t, *J* = 6.8 Hz, 1H), 5.12 – 5.07 (d, *J* = 4.6 Hz, 1H), 4.76 – 4.67 (p, *J* = 6.0 Hz, 1H), 4.55 – 4.45 (q, *J* = 6.9 Hz, 1H), 4.38 – 4.27 (q, *J* = 6.9 Hz, 1H), 2.19 – 2.06 (tt, *J* = 11.3, 6.1 Hz, 2H), 1.99 – 1.88 (dq, *J* = 10.7, 6.6 Hz, 2H), 1.66 – 1.49 (m, 2H), 1.31 – 1.24 (d, *J* = 6.4 Hz, 3H).
4A3B or A43A		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.26 – 8.21 (s, 2H), 7.85 – 7.82 (d, *J* = 2.1 Hz, 1H), 7.58 – 7.50 (m, 3H), 7.49 – 7.44 (d, *J* = 7.2 Hz, 1H), 7.23 – 6.84 (m, 2H), 6.37 – 6.31 (t, *J* = 6.8 Hz, 1H), 5.12 – 5.07 (d, *J* = 4.6 Hz, 1H), 4.76 – 4.68 (p, *J* = 5.9 Hz, 1H), 4.56 – 4.46 (p, *J* = 7.1 Hz, 1H), 4.38 – 4.28 (q, *J* = 6.9 Hz, 1H), 2.21 – 2.07 (tt, *J* = 11.2, 5.6 Hz, 2H), 1.99 – 1.89 (td, *J* = 6.9, 3.0 Hz, 2H), 1.67 – 1.49 (m, 2H), 1.29 – 1.25 (d, *J* = 6.3 Hz, 3H).
A43A-D or A43B-D		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.23 (s, 2H), 7.68 – 7.37 (m, 4H), 7.24 – 6.82 (m, 2H), 6.33 (t, *J* = 6.8 Hz, 1H), 5.08 (d, *J* = 4.4 Hz, 1H), 4.76 – 4.64 (m, 1H), 4.50 (q, *J* = 7.0 Hz, 1H), 4.32 (q, *J* = 6.9 Hz, 1H), 2.22 – 2.06 (m, 2H), 1.93 (td, *J* = 6.8, 3.2 Hz, 2H), 1.64 – 1.48 (m, 2H), 1.26 (d, *J* = 6.4 Hz, 3H).
A43A-D or A43B-D		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.23 (s, 2H), 7.68 – 7.37 (m, 4H), 7.24 – 6.82 (m, 2H), 6.33 (t, *J* = 6.8 Hz, 1H), 5.08 (d, *J* = 4.4 Hz, 1H), 4.76 – 4.64 (m, 1H), 4.50 (q, *J* = 7.0 Hz, 1H), 4.32 (q, *J* = 6.9 Hz, 1H), 2.22 – 2.06 (m, 2H), 1.93 (td, *J* = 6.8, 3.2 Hz, 2H), 1.64 – 1.48 (m, 2H), 1.26 (d, *J* = 6.4 Hz, 3H).

Example A44

Synthesis of 2-(6-(((1S,3S)-3-((5-(difluoromethoxy)-4-methylpyrimidin-2-yl)amino)cyclopentyl)amino)pyridin-3-yl)pyridazin-3(2H)-one



Step A: Synthesis of 2-chloro-5-(difluoromethoxy)-4-methylpyrimidine

Under a nitrogen atmosphere at room temperature, 2-chloro-4-methyl-5-hydroxypyrimidine (2.0 g, 13.84 mmol, 1.0 eq) was dissolved in N,N-dimethylformamide (20 mL). Subsequently, cesium fluoride (4.20 g, 27.68 mmol, 2.0 eq), triethylamine (4.20 g, 41.52 mmol, 3.0 eq), and sodium chlorodifluoroacetate (6.43 g, 41.52 mmol, 3.0 eq) were added. After the mixture was stirred uniformly, the reaction was transferred to an oil bath, and heated to 110 ℃ and reacted overnight.

After completion of the reaction, ethyl acetate (50 mL) was added to dilute the reaction mixture. Insoluble impurities were removed by filtration. Water (150 mL) was added, and the mixture was extracted with ethyl acetate (80 mL × 3). The organic phases were combined, dried over anhydrous sodium sulfate, filtered, and concentrated. The resulting residue was purified by silica gel column chromatography (eluent: ethyl acetate/n-hexane = 3/10) to obtain 1.52 g of 2-chloro-5-(difluoromethoxy)-4-methylpyrimidine as a yellow oil (yield 53%). LC-MS: $[M+H]^+$ = 195.

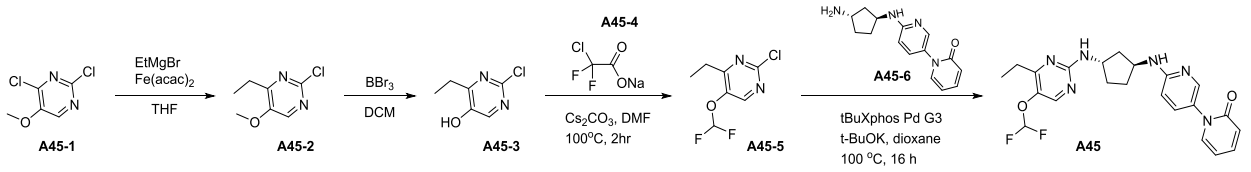
Step B: Synthesis of 2-(6-(((1S,3S)-3-((5-(difluoromethoxy)-4-methylpyrimidin-2-yl)amino)cyclopentyl)amino)pyridin-3-yl)pyridazin-3(2H)-one

Under a nitrogen atmosphere at room temperature, 2-chloro-5-(difluoromethoxy)-4-methylpyrimidine (0.195 g, 1 mmol, 1.0 eq) was dissolved in dimethyl sulfoxide (4 mL). Subsequently, cesium fluoride (0.304 g, 2.0 mmol, 2.0 eq), triethylamine (0.303 g, 3 mmol, 3.0 eq), and 2-(6-(((1S,3S)-3-aminocyclopentyl)amino)pyridin-3-yl)pyridazin-3(2H)-one (0.271 g, 1.0 mmol, 1.0 eq) were added. After the mixture was stirred uniformly, the reaction was transferred to an oil bath, and heated to 140 ℃ and reacted overnight.

After completion of the reaction, water (50 mL) was added, and the mixture was extracted with ethyl acetate (50 mL × 3). The organic phases were combined, dried over anhydrous sodium sulfate, filtered, and concentrated. The resulting residue was purified by C18 column chromatography (120 g specification, eluent: acetonitrile/water) to obtain 0.050 g of 2-(6-(((1S,3S)-3-((5-(difluoromethoxy)-4-methylpyrimidin-2-yl)amino)cyclopentyl)amino)pyridin-3-yl)pyridazin-3(2H)-one as a pale yellow solid (yield 12%). LC-MS: $[M+H]^+$ = 430.

NMR data: ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.21 – 8.03 (m, 2H), 8.01 (dd, J = 3.8, 1.6 Hz, 1H), 7.48 (ddd, J = 19.9, 9.2, 3.3 Hz, 2H), 7.36 (d, J = 7.3 Hz, 1H), 7.19 – 6.81 (m, 3H), 6.52 (d, J = 9.0 Hz, 1H), 4.31 (p, J = 6.6 Hz, 2H), 2.24 (s, 3H), 2.12 (tt, J = 12.8, 6.2 Hz, 2H), 1.87 (ddp, J = 18.7, 13.3, 6.8 Hz, 2H), 1.51 (td, J = 16.3, 8.0 Hz, 2H).

Example A45



Step A: Synthesis of Compound A45-2

Compound A45-1 (5.0 g, 28 mmol) was dissolved in tetrahydrofuran (50 mL). The atmosphere was purged with nitrogen three times. At 0 ℃, iron(III) acetylacetonate (988 mg, 2.8 mmol) and ethylmagnesium bromide (14.5 mL, 29 mmol) were added. The mixture was warmed to room temperature and reacted for 16 hours. The reaction mixture was poured into a saturated ammonium chloride solution and extracted with ethyl acetate (50 mL × 3). The organic phases were combined and dried by rotary evaporation. The resulting material was purified by Flash silica gel column chromatography (0 to 20% ethyl acetate/petroleum ether) to obtain 3.2 g of Compound A45-2 as a colorless oil mixture. LCMS: $[M+H]^+$ = 173.

Step B: Synthesis of Compound A45-3

Compound A45-2 (3.2 g, 18.6 mmol) was dissolved in dichloromethane (30 mL). Boron tribromide (8.9 mL, 93 mmol) was added, and the mixture was stirred at room temperature for 16 hours. The reaction mixture was poured into ice water (50 mL) to quench. The pH was adjusted to 3 with saturated sodium carbonate. The mixture was extracted with ethyl acetate (50 mL × 3). The organic phases were combined and dried by rotary evaporation. The resulting material was purified by Flash silica gel column chromatography (0 to 40% ethyl acetate/petroleum ether) to obtain 500 mg of Compound A45-3 as a white solid (34% yield). LCMS: $[M+H]^+$ = 159.

Step C: Synthesis of Compound A45-5

Compound A45-3 (420 mg, 2.66 mmol) was added to N,N-dimethylformamide (5 mL). Cesium carbonate (1 g, 3.2 mmol) was added, and the mixture was reacted at room temperature for 0.5 hours. Compound A45-4 (1.2 g, 7.98 mmol) was added, and the mixture was reacted at 100 ℃ for 16 hours. The reaction mixture was poured into saturated ammonium chloride (20 mL) and extracted with ethyl acetate (10 mL × 3). The organic phases were combined and dried by rotary evaporation. The resulting material was purified by Flash silica gel column chromatography (0 to 20% ethyl acetate/petroleum ether) to obtain 380 mg of Compound A45-5 as a yellow solid (68.7% yield). LCMS: $[M+H]^+$ = 209.

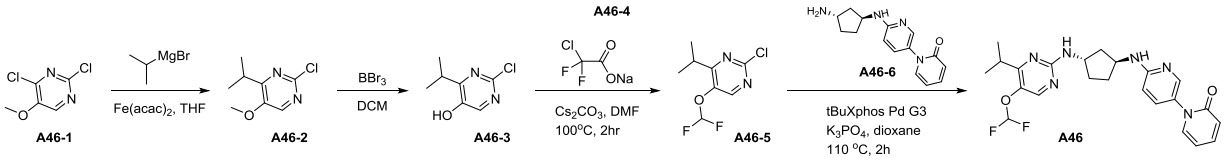
Step D: Synthesis of the Target Compound

Compound A45-5 (320 mg, 1.54 mmol) and Compound A45-6 (346 mg, 1.28 mmol) were added to anhydrous 1,4-dioxane (5 mL). Potassium tert-butoxide (287 mg, 2.56 mmol) and (2-dicyclohexylphosphino-2',4',6'-triisopropyl-1,1'-biphenyl)[2-(2'-amino-1,1'-biphenyl)]palladiu

m(II) methanesulfonate (203 mg, 0.26 mmol) were added. Under nitrogen protection, the mixture was heated to 80 ℃ and reacted for 16 hours. The reaction mixture was poured into saturated ammonium chloride (20 mL) and extracted with ethyl acetate (10 mL × 3). The organic phases were combined and dried by rotary evaporation. The resulting material was purified by Flash silica gel column chromatography (0 to 10% methanol/dichloromethane) and further purified by preparative TLC plate to obtain 36 mg of the target compound (5.3% yield). LCMS: $[M+H]^+$ = 443.

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.11 (s, 1H), 7.94 (d, J = 2.7 Hz, 1H), 7.62 (dd, J = 6.7, 2.1 Hz, 1H), 7.50 (ddd, J = 9.0, 6.6, 2.1 Hz, 1H), 7.42 (dd, J = 8.9, 2.7 Hz, 1H), 7.36 (d, J = 7.1 Hz, 1H), 6.93 (d, J = 6.9 Hz, 1H), 6.55 (d, J = 8.9 Hz, 1H), 6.46 (dt, J = 9.1, 1.1 Hz, 1H), 6.29 (td, J = 6.7, 1.4 Hz, 1H), 4.34 (dd, J = 11.8, 6.0 Hz, 2H), 2.61 (q, J = 7.5 Hz, 2H), 2.15 (dq, J = 14.3, 7.1 Hz, 2H), 2.01 – 1.82 (m, 2H), 1.54 (tt, J = 13.7, 8.5 Hz, 2H), 1.18 (t, J = 7.5 Hz, 3H).

Example A46



Step A: Synthesis of Compound A46-2

Compound A46-1 (5 g, 27.9 mmol) was dissolved in tetrahydrofuran (30 mL). At 0 ℃, iron(III) acetylacetonate (985.4 mg, 2.79 mmol) was added, followed by dropwise addition of a tetrahydrofuran solution of isopropylmagnesium bromide (34 mL, 34 mmol). The reaction was stirred under a nitrogen atmosphere for 12 hours. The reaction mixture was quenched with saturated aqueous ammonium chloride and extracted with dichloromethane (50 mL × 3). The organic phases were combined, dried over anhydrous sodium sulfate and concentrated. The resulting material was purified by Flash silica gel column chromatography (5 to 20% ethyl acetate/petroleum ether) to obtain 2.5 g of Compound A46-2 as a yellow oily liquid mixture (yield: 48.0%). LCMS: $[M+H]^+$ = 187.

Step B: Synthesis of Compound A46-3

The mixture A46-2 (2.5 g, 13.4 mmol) was dissolved in a 1 M solution of boron tribromide in dichloromethane (24.1 mL, 24.1 mmol). Boron tribromide (3.4 mL, 42.9 mmol) was added, and the mixture was reacted at room temperature for 8 hours. The reaction mixture was quenched by adding it to 20 mL of ice water. The pH was adjusted to 5-6 with saturated aqueous sodium carbonate. The mixture was extracted with dichloromethane (30 mL × 3). The organic phases were combined, dried over anhydrous sodium sulfate, filtered, and the filtrate was dried by rotary

evaporation. The resulting material was purified by Flash silica gel column chromatography (0 to 100% ethyl acetate/petroleum ether), followed by purification via reverse-phase column chromatography to obtain 1.2 g of Compound A46-3 as a yellow solid (yield: 52.1%). LCMS: $[M+H]^+$ = 173.

Step C: Synthesis of Compound A46-5

Compound A46-3 (1 g, 5.8 mmol) was dissolved in N,N-dimethylformamide (15 mL). Cesium carbonate (2.28 g, 6.96 mmol) was added, and the mixture was stirred at room temperature for 1 hour. Compound A46-4 (2.65 g, 17.4 mmol) was added, and under a nitrogen atmosphere, the mixture was heated to 100 ℃ and reacted for 3 hours. The reaction mixture was quenched with aqueous ammonium chloride and extracted with dichloromethane (20 mL × 3). The organic phases were combined, dried, concentrated. The resulting material was purified by Flash silica gel column chromatography (10 to 50% ethyl acetate/petroleum ether) to obtain 700 mg of Compound A46-5 as a yellow oily liquid (yield: 54.2%). LCMS: $[M+H]^+$ =223.

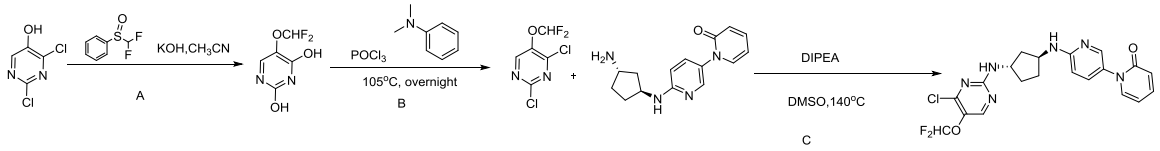
Step D: Synthesis of the Target Compound

Compound A46-5 (222 mg, 1 mmol) and Compound A46-6 (270 mg, 1 mmol) were dissolved in anhydrous dimethyl sulfoxide (8 mL). Potassium phosphate (424 mg, 2 mmol) and methanesulfonato(2-di-tert-butylphosphino-2’,4’,6’-triisopropyl-1,1’-biphenyl)(2’-amino-1,1’-biphenyl-2-yl)palladium(II) (159 mg, 0.2 mmol) were added. Under nitrogen protection, the mixture was heated to 110 ℃ and reacted for 2 hours. The reaction mixture was quenched with aqueous ammonium chloride and extracted with dichloromethane (20 mL × 3). The organic phases were combined, dried, concentrated. The resulting material was purified by preparative reverse-phase column chromatography to obtain 30 mg of the target compound as a yellow solid (yield: 6.5%).

LCMS: $[M+H]^+$ = 457. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.10 (s, 1H), 7.92 (d, J = 2.7 Hz, 1H), 7.60 (dd, J = 6.8, 2.1 Hz, 1H), 7.48 (ddd, J = 9.0, 6.6, 2.1 Hz, 1H), 7.40 (dd, J = 8.9, 2.7 Hz, 1H), 7.31 (d, J = 7.0 Hz, 1H), 7.02 (s, 1H), 6.91 (d, J = 6.7 Hz, 1H), 6.53 (d, J = 8.9 Hz, 1H), 6.44 (d, J = 8.9 Hz, 1H), 6.27 (td, J = 6.7, 1.4 Hz, 1H), 4.30 (q, J = 7.1 Hz, 2H), 3.21 – 3.14 (m, 1H), 2.14 (dt, J = 13.4, 5.6 Hz, 2H), 1.90 (dq, J = 28.1, 6.5 Hz, 2H), 1.59 – 1.45 (m, 2H), 1.15 (dd, J = 6.8, 2.7 Hz, 6H).

Example A47

Synthesis of 6'-(((1S,3S)-3-((4-chloro-5-(difluoromethoxy)pyrimidin-2-yl)amino)cyclopentyl)amino)-2H-[1,3'-bipyridin]-2-one



Step A: Synthesis of 5-(difluoromethoxy)pyrimidine-2,4-diol

At room temperature, 2,4-dichloropyrimidin-5-ol (0.5 g, 3.03 mmol) and (difluoromethanesulfonyl)benzene (1.34 g, 6.97 mmol) were dissolved in acetonitrile (20 mL). Potassium hydroxide (1.87 g, 33.33 mmol) and water (6 mL) were added. The reaction system was heated to 50 ℃ and stirred overnight.

The mixture was concentrated under reduced pressure. Water (20 mL) was added, and the mixture was extracted with EA (30 mL × 3). The aqueous phase was collected, acidified to an acidic pH with 1 M HCl, and extracted with ethyl acetate (20 mL × 3). The organic phases were combined, purified by column chromatography (EA/Hex = 6:4, 60%) to obtain 184 mg of 5-(difluoromethoxy)pyrimidine-2,4-diol as a white solid (yield 34%). LC-MS: $[M+H]^+$ =197.1.

Step B: Synthesis of 2,4-dichloro-5-(difluoromethoxy)pyrimidine

At room temperature, 5-(difluoromethoxy)pyrimidine-2,4-diol (184 mg, 1.03 mmol) was dissolved in phosphorus oxychloride (4 mL). Under nitrogen protection, the mixture was heated to 105 ℃ and stirred overnight. After completion of the reaction, the mixture was concentrated under reduced pressure and purified by silica gel column chromatography (EA/Hex = 1:4, 20%) to obtain 115 mg of 2,4-dichloro-5-(difluoromethoxy)pyrimidine as a brown liquid (yield 51.8%).

Step C: Synthesis of 6'-(((1S,3S)-3-((4-chloro-5-(difluoromethoxy)pyrimidin-2-yl)amino)cyclopentyl)amino)-2H-[1,3'-bipyridin]-2-one

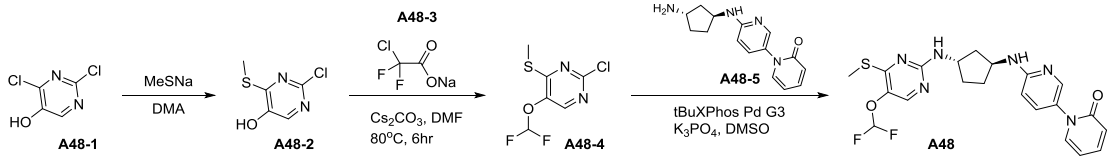
At room temperature, 1-(6-{[(1S,3S)-3-aminocyclopentyl]amino}pyridin-3-yl)-1,2-dihydropyridin-2-one (100.02 mg, 0.367 mmol), 2,4-dichloro-5-(difluoromethoxy)pyrimidine (95.45 mg, 0.44 mmol), and DIPEA (0.24 g, 1.85 mmol) were placed in a 100 mL round-bottom flask. Dimethyl sulfoxide (10 mL) was added. Under nitrogen protection, the reaction system was heated to 140 ℃ and reacted overnight.

After completion of the reaction, water (40 mL) was added, and the mixture was extracted with EA (40 mL × 3). The organic phases were combined, purified by reverse-phase column chromatography (ACN/H_2O = 40%), concentrated under reduced pressure, and lyophilized to obtain 115 mg of 6'-(((1S,3S)-3-((4-chloro-5-(difluoromethoxy)pyrimidin-2-yl)amino)cyclopentyl)amino)-2H-[1,3

'-bipyridin]-2-one as a white solid (yield 65.8%).

LC-MS: $[M+H]^+$=449.3. ^1H NMR (400 MHz, DMSO-d_6) δ 7.96 (d, J = 7.8 Hz, 1H), 7.93 (d, J = 2.7 Hz, 1H), 7.92 (s, 1H), 7.61 (dd, J = 6.8, 2.1 Hz, 1H), 7.48 (ddd, J = 9.0, 6.6, 2.1 Hz, 1H), 7.41 (dd, J = 8.9, 2.7 Hz, 1H), 7.23 (t, J = 72.8 Hz, 1H), 6.97 (d, 1H), 6.53 (d, J = 8.9 Hz, 1H), 6.45 (d, J = 8.9 Hz, 1H), 6.28 (td, J = 6.7, 1.4 Hz, 1H), 4.45 (dq, J = 69.1, 7.0 Hz, 2H), 2.14 (tdd, J = 11.6, 7.1, 3.4 Hz, 2H), 2.08 – 1.85 (m, 2H), 1.69 – 1.45 (m, 2H).

Example A48



Step A: Synthesis of Compound A48-2

Compound A48-1 (1.2 g, 7.3 mmol) was added to N,N-dimethylacetamide (10 mL). Sodium methanethiolate (0.76 g, 10.9 mmol) was added. The atmosphere was purged with nitrogen, and the reaction was stirred at room temperature for 6 hours. The reaction mixture was added to a saturated aqueous ammonium chloride solution (40 mL). The pH was adjusted to 4 with a 1 M aqueous hydrochloric acid solution. The mixture was extracted with ethyl acetate (25 mL × 3). The organic phases were combined, dried and concentrated. The resulting material was purified by Flash silica gel column chromatography (28 to 32% ethyl acetate/petroleum ether) to obtain 540 mg of Compound A48-2 as a pale yellow solid (42.5% yield). LCMS: $[M+H]^+$ = 177.

Step B: Synthesis of Compound A48-4

Compound A48-2 (540 mg, 3.1 mmol) was added to anhydrous N,N-dimethylformamide (10 mL). Cesium carbonate (1.2 g, 3.7 mmol) and Compound A48-3 (1.4 g, 3.1 mmol) were added. The atmosphere was purged with nitrogen, and the mixture was heated to 80℃ and reacted for 6 hours. The reaction mixture was added to a saturated aqueous ammonium chloride solution (40 mL) and extracted with ethyl acetate (25 mL × 3). The organic phases were combined, dried and concentrated. The resulting material was purified by Flash silica gel column chromatography (1 to 3% ethyl acetate/petroleum ether) to obtain 400 mg of Compound A48-4 as a pale yellow solid (56.9% yield). LCMS: $[M+H]^+$ = 227.

Step C: Synthesis of the Target Compound

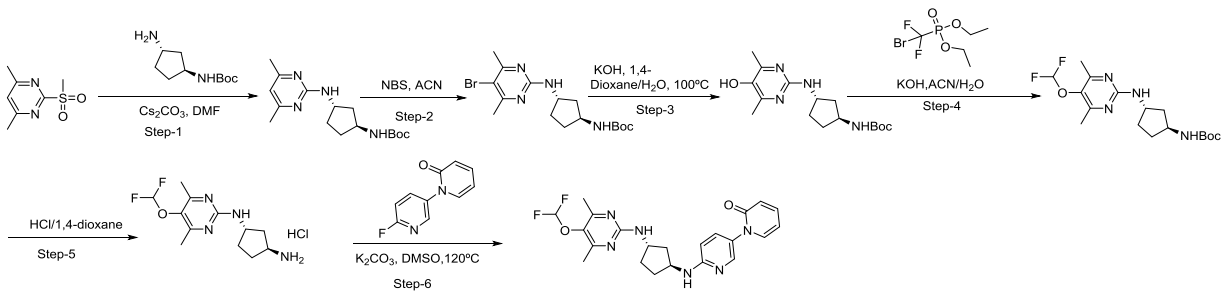
Compound A48-4 (360 mg, 1.6 mmol) and Compound A48-5 (519 mg, 1.9 mmol) were dissolved in anhydrous dimethyl sulfoxide (5 mL). Potassium phosphate (679 mg, 3.2 mmol) and methanesulfonato(2-di-tert-butylphosphino-2',4',6'-triisopropyl-1,1'-biphenyl)(2'-amino-1,1'-bi phenyl-2-yl)palladium(II) (254 mg, 0.3 mmol) were added. The atmosphere was purged with

nitrogen, and the mixture was heated to 110 ℃ and reacted for 16 hours. The reaction mixture was added to a saturated aqueous ammonium chloride solution (20 mL) and extracted with dichloromethane (10 mL × 3). The organic phases were combined, dried and concentrated. The resulting material was purified by Flash silica gel column chromatography (2 to 3% methanol/dichloromethane), followed by reverse-phase column chromatography (18 to 23% acetonitrile/water) to obtain 30.7 mg of the target compound as a white solid (4.2% yield).

LCMS: $[M+H]^+$ = 461. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.92 (d, J = 3.7 Hz, 2H), 7.60 (d, J = 6.9 Hz, 1H), 7.48 (td, J = 6.9, 3.5 Hz, 2H), 7.39 (dd, J = 8.9, 2.6 Hz, 1H), 6.93 (d, J = 6.9 Hz, 1H), 6.52 (d, J = 8.9 Hz, 1H), 6.44 (d, J = 9.2 Hz, 1H), 6.27 (t, J = 6.7 Hz, 1H), 4.39 – 4.23 (m, 2H), 2.45 (s, 3H), 2.14 (d, J = 8.8 Hz, 2H), 1.91 (t, J = 7.0 Hz, 2H), 1.62 – 1.44 (m, 2H).

Example A49

Synthesis of 6'-(((1S,3S)-3-((5-(difluoromethoxy)-4,6-dimethylpyrimidin-2-yl)amino)cyclopentyl)amino)-2H-[1,3'-bipyridin]-2-one



Step A: Synthesis of tert-butyl ((1S,3S)-3-((4,6-dimethylpyrimidin-2-yl)amino)cyclopentyl)carbamate

At room temperature, 4,6-dimethyl-2-(methylsulfonyl)pyrimidine (5 g, 26.8 mmol), tert-butyl ((1S,3S)-3-aminocyclopentyl)carbamate (5.55 g, 28.2 mmol), and cesium carbonate (17.5 g, 53.7 mmol) were added to acetonitrile (100 mL). The mixture was heated to 90 ℃ and reacted overnight.

After completion of the reaction, the reaction mixture was filtered. The filter cake was washed with ethyl acetate (3 × 50 mL). The filtrate was dried by rotary evaporation to a residue. The resulting residue was purified by silica gel column chromatography (ethyl acetate/n-hexane = 2/3, V/V) to obtain tert-butyl ((1S,3S)-3-((4,6-dimethylpyrimidin-2-yl)amino)cyclopentyl)carbamate as a pale yellow solid (5.05 g, yield 61%). LC-MS: $[M+H]^+$ = 307.

Step B: Synthesis of tert-butyl ((1S,3S)-3-((5-bromo-4,6-dimethylpyrimidin-2-yl)amino)cyclopentyl)carbamate

At room temperature, tert-butyl ((1S,3S)-3-((4,6-dimethylpyrimidin-2-yl)amino)cyclopentyl)carbamate (5.05 g, 16.5 mmol) was dissolved in acetonitrile (50 mL). NBS (4.36 g, 24.5 mmol) was added, and the mixture was stirred at room temperature for 2 hours.

After completion of the reaction, the reaction mixture was quenched with a saturated aqueous sodium bicarbonate solution (150 mL) and extracted with ethyl acetate (3 × 50 mL). The organic phases were combined, washed with brine, dried over anhydrous sodium sulfate, filtered, and dried by rotary evaporation to a residue. The resulting residue was purified by silica gel column chromatography (ethyl acetate/n-hexane = 1/4, V/V) to obtain tert-butyl ((1S,3S)-3-((5-bromo-4,6-dimethylpyrimidin-2-yl)amino)cyclopentyl)carbamate as a pale yellow solid (5.5 g, yield 86%). LC-MS: $[M+H]^+$ = 385.

Step C: Synthesis of tert-butyl ((1S,3S)-3-((5-hydroxy-4,6-dimethylpyrimidin-2-yl)amino)cyclopentyl)carbamate

At room temperature, tert-butyl ((1S,3S)-3-((5-bromo-4,6-dimethylpyrimidin-2-yl)amino)cyclopentyl)carbamate (5.5 g, 14.3 mmol), $Pd_2(dba)_3$ (1.3 g, 1.4 mmol), and potassium hydroxide (2.4 g, 42.9 mmol) were added to a mixed solution of 1,4-dioxane (50 mL) and water (50 mL). The atmosphere was purged with nitrogen three times, and the mixture was heated to 100 ℃ in an oil bath to react for 3 hours.

After completion of the reaction, water (50 mL) was added. The mixture was extracted with methyl tert-butyl ether (2 × 50 mL). The aqueous phase was collected, adjusted to pH approximately 5-6 with 1 M HCl(aq), and then extracted with ethyl acetate (3 × 50 mL). The organic phases were combined, dried over anhydrous Na_2SO_4, filtered, and dried by rotary evaporation to a residue. The resulting residue was purified by silica gel column chromatography (eluent: n-hexane/ethyl acetate = 1/1, V/V) to obtain tert-butyl ((1S,3S)-3-((5-hydroxy-4,6-dimethylpyrimidin-2-yl)amino)cyclopentyl)carbamate as a white solid (1.5 g, yield 32%). LC-MS: $[M+H]^+$ = 323.

Step D: Synthesis of tert-butyl ((1S,3S)-3-((5-(difluoromethoxy)-4,6-dimethylpyrimidin-2-yl)amino)cyclopentyl)carbamate

At room temperature, tert-butyl ((1S,3S)-3-((5-hydroxy-4,6-dimethylpyrimidin-2-yl)amino)cyclopentyl)carbamate (0.3 g, 0.93 mmol) was added to acetonitrile (10 mL). In an ice-water bath, sodium hydroxide (0.52 g, 9.3 mmol) dissolved in water (mL) was added to the above solution, followed by dropwise addition of diethyl (bromodifluoromethyl)phosphonate (0.74 g, 2.79 mmol). After the addition, the mixture was warmed to room temperature and reacted for 2 hours.

After completion of the reaction, water (30 mL) was added. The mixture was extracted with ethyl acetate (3 × 20 mL). The organic phases were combined, dried over anhydrous Na_2SO_4, filtered, and dried by rotary evaporation to a residue. The resulting residue was purified by C18 reverse-phase column chromatography (ACN/H_2O, 55% ACN) to obtain tert-butyl ((1S,3S)-3-((5-(difluoromethoxy)-4,6-dimethylpyrimidin-2-yl)amino)cyclopentyl)carbamate as a white solid (0.1 g, yield 28.86%). LC-MS: $[M+H]^+$ = 373.

Step E: Synthesis of (1S,3S)-N^1-(5-(difluoromethoxy)-4,6-dimethylpyrimidin-2-yl)cyclopentane-1,3-diamine hydrochloride

tert-Butyl ((1S,3S)-3-((5-(difluoromethoxy)-4,6-dimethylpyrimidin-2-yl)amino)cyclopentyl)carbamate (0.1 g, 0.27 mmol) was dissolved in dichloromethane (5 mL). Then, 4 M HCl/1,4-dioxane (2 mL) was added. The mixture was reacted at room temperature for 1 hour. After completion of the reaction, the mixture was directly dried by rotary evaporation and used in the next step. LC-MS: $[M+H]^+$ = 273.

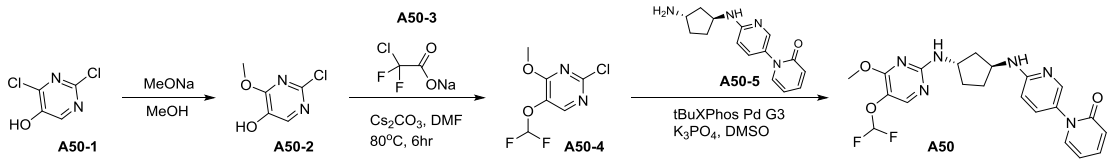
Step F: Synthesis of 6'-(((1S,3S)-3-((5-(difluoromethoxy)-4,6-dimethylpyrimidin-2-yl)amino)cyclopentyl)amino)-2H-[1,3'-bipyridin]-2-one

(1S,3S)-N^1-(5-(difluoromethoxy)-4,6-dimethylpyrimidin-2-yl)cyclopentane-1,3-diamine hydrochloride (70 mg, 0.26 mmol), 1-(6-fluoropyridin-3-yl)-1,2-dihydropyridin-2-one (74.17 mg, 0.39 mmol), and potassium carbonate (179.67 mg, 1.3 mmol) were added to DMSO (3 mL). The mixture was reacted at 120 ℃ for 16 hours.

After completion of the reaction, the mixture was filtered. The filtrate was directly purified by C18 column chromatography (eluent: acetonitrile/water = 45/55, V/V) to obtain 6'-(((1S,3S)-3-((5-(difluoromethoxy)-4,6-dimethylpyrimidin-2-yl)amino)cyclopentyl)amino)-2H-[1,3'-bipyridin]-2-one as a white solid (54.7 mg, yield 47.61%, purity 99%). LC-MS: $[M+H]^+$ = 443.

NMR data: ^{1}H NMR (400 MHz, DMSO) δ 7.92 (d, J = 2.6 Hz, 1H), 7.67 – 7.55 (m, 1H), 7.48 (ddd, J = 8.9, 6.6, 2.1 Hz, 1H), 7.40 (dd, J = 8.9, 2.7 Hz, 1H), 7.24 (d, J = 7.4 Hz, 1H), 7.16 – 6.69 (m, 2H), 6.52 (d, J = 8.9 Hz, 1H), 6.45 (d, J = 9.2 Hz, 1H), 6.27 (t, J = 6.7 Hz, 1H), 4.32 (dp, J = 13.2, 6.7 Hz, 2H), 2.23 (s, 6H), 2.11 (ddd, J = 18.0, 8.6, 4.9 Hz, 2H), 1.87 (dh, J = 26.8, 6.8 Hz, 2H), 1.49 (dq, J = 11.2, 7.1 Hz, 2H).

Example A50



Step A: Synthesis of Compound A50-2

Compound A50-1 (2.0 g, 12.1 mmol) was dissolved in methanol (20 mL). A sodium methoxide methanol solution (3.6 mL, 18.1 mmol) was added. The mixture was reacted at 40 ℃ for 2 days. The reaction mixture was concentrated under reduced pressure. The resulting material was purified by Flash silica gel column chromatography (0 to 10% methanol/dichloromethane) to obtain 820 mg of Compound A50-2 as a yellow oil (42.4% yield). LCMS: $[M+H]^+$ = 161.

Step B: Synthesis of Compound A50-4

Compound A50-2 (820 mg, 5.13 mmol) was dissolved in N,N-dimethylformamide (10 mL). Cesium carbonate (2 g, 6.16 mmol) was added, and the mixture was stirred at room temperature for 0.5 hours. Compound A50-3 (2.34 g, 15.4 mmol) was added, and the mixture was heated to 100 ℃ and reacted for 2 hours. Water (20 mL) was added to the reaction mixture, which was then extracted with ethyl acetate (50 mL × 3). The organic phases were combined and dried by rotary evaporation. The resulting material was purified by Flash silica gel column chromatography (0% to 20% ethyl acetate/petroleum ether) to obtain 230 mg of Compound A50-4 as a yellow oil (21.4% yield). LCMS: $[M+H]^+$ = 211.

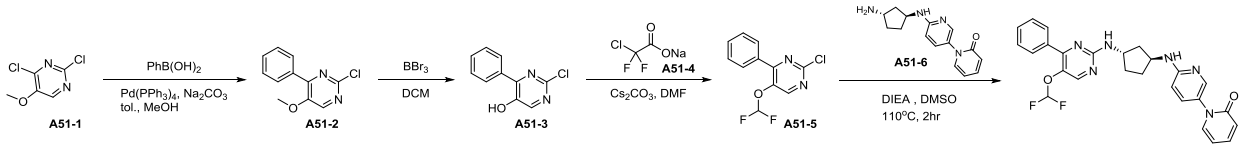
Step C: Synthesis of the Target Compound

Compound A50-4 (230 mg, 1.1 mmol) and Compound A50-5 (355 mg, 1.3 mmol) were added to anhydrous dimethyl sulfoxide (5 mL). Potassium phosphate (466 mg, 2.2 mmol) and methanesulfonato(2-di-tert-butylphosphino-2’,4’,6’-triisopropyl-1,1’-biphenyl)(2’-amino-1,1’-biphenyl-2-yl)palladium(II) (177 mg, 0.22 mmol) were added. The atmosphere was purged with nitrogen, and the mixture was heated to 100 ℃ and reacted for 2 hours. The reaction mixture was added to a saturated aqueous ammonium chloride solution and extracted with ethyl acetate (20 mL × 3). The organic phases were combined and dried by rotary evaporation. The resulting material was purified by Flash silica gel column chromatography (0% to 10% methanol/dichloromethane) and further purified by preparative TLC plate to obtain 11 mg of the target compound as a white solid (5.3% yield). LCMS: $[M+H]^+$ = 445.

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.96 (s, 1H), 7.92 (d, J = 2.4 Hz, 1H), 7.60 (dd, J = 6.8, 2.1 Hz, 1H), 7.48 (ddd, J = 9.2, 6.7, 2.1 Hz, 1H), 7.39 (dd, J = 8.8, 2.6 Hz, 2H), 6.93 (d, J = 6.8 Hz, 1H), 6.88 (s, 1H), 6.52 (d, J = 8.8 Hz, 1H), 6.44 (d, J = 9.2 Hz, 1H), 6.27 (t, J = 6.8 Hz, 1H), 4.30 (d, J = 8.0 Hz, 2H), 3.88 (s, 3H), 2.19 – 2.09 (m, 2H), 1.97 – 1.84 (m, 2H), 1.51 (dq, J =

19.2, 7.2 Hz, 2H).

Example A51



Step A: Synthesis of Compound A51-2

Compound A51-1 (3 g, 16.7 mmol) and phenylboronic acid (3.05 g, 25 mmol) were dissolved in toluene (60 mL) and methanol (12 mL). A 2 M aqueous sodium carbonate solution (16.7 mL, 33.4 mmol) and tetrakis(triphenylphosphine)palladium (1.93 g, 1.67 mmol) were added. Under a nitrogen atmosphere, the mixture was heated to 110 ℃ and reacted for 3 hours. The reaction mixture was filtered. The filtrate was extracted with ethyl acetate (20 mL × 3). The organic phase was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The resulting material was purified by Flash column chromatography (0 to 20% ethyl acetate/petroleum ether) to obtain 3.3 g of Compound A51-2 as a yellow oily liquid (yield: 88.2%). LCMS: $[M+H]^+$ = 221.

Step B: Synthesis of Compound A51-3

Compound A51-2 (3.3 g, 15.4 mmol) was dissolved in dichloromethane (30 mL). Boron tribromide (7.4 mL, 77 mmol) was added, and the mixture was stirred at room temperature for 16 hours. The reaction mixture was quenched by adding it to 30 mL of ice water. The pH was adjusted to 5-6 with saturated aqueous sodium carbonate. The mixture was extracted with ethyl acetate (30 mL × 3). The organic phases were combined, dried over anhydrous sodium sulfate, filtered, and dried by rotary evaporation. The resulting material was purified by Flash column chromatography (0 to 100% ethyl acetate/petroleum ether) to obtain 2.6 g of Compound A51-3 as a yellow solid (yield: 82.0%). LCMS: $[M+H]^+$ = 207.

Step C: Synthesis of Compound A51-5

Compound A51-3 (2.6 g, 12.6 mmol) was dissolved in N,N-dimethylformamide (25 mL). Cesium carbonate (4.9 g, 15.1 mmol) was added, and the mixture was stirred at room temperature for 1 hour. Compound A51-4 (5.7 g, 37.8 mmol) was added. Under a nitrogen atmosphere, the mixture was heated to 100 ℃ and reacted for 3 hours. The reaction mixture was cooled to room temperature, quenched with saturated aqueous ammonium chloride, and extracted with dichloromethane (30 mL × 3). The organic phases were combined, dried over anhydrous sodium sulfate, filtered, and dried by rotary evaporation. The resulting material was purified by Flash column chromatography (0 to 30% ethyl acetate/petroleum ether) to obtain 1.2 g of Compound A51-5 as a yellow oily liquid (yield: 37.2%). LCMS: $[M+H]^+$ = 257.

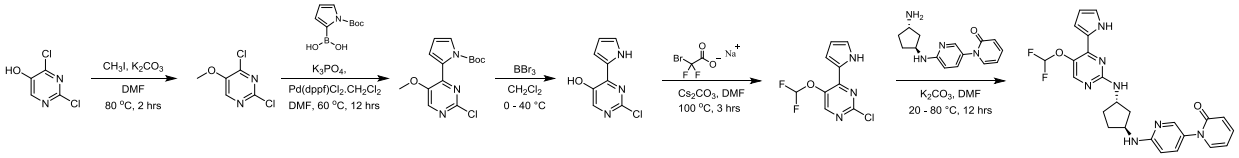
Step D: Synthesis of the Target Compound

Compound A51-5 (80 mg, 0.3 mmol) and Compound A51-6 (81 mg, 0.3 mmol) were dissolved in dimethyl sulfoxide (3 mL). N,N-Diisopropylethylamine (0.16 mL, 0.93 mmol) was added. The mixture was reacted at 110 ℃ under microwave irradiation for 1 hour. The reaction mixture was quenched with saturated aqueous ammonium chloride and extracted with dichloromethane (10 mL × 3). The organic phases were combined, dried over anhydrous sodium sulfate, filtered, and dried by rotary evaporation. The resulting material was purified by preparative reverse-phase HPLC to obtain 65 mg of the target compound as an off-white solid (yield: 44.2%). LCMS: $[M+H]^+$ = 491.

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.30 (s, 1H), 7.90 (dd, J = 16.7, 4.1 Hz, 3H), 7.64 – 7.55 (m, 2H), 7.53 – 7.45 (m, 4H), 7.40 (dd, J = 8.9, 2.7 Hz, 1H), 7.17 – 6.74 (m, 2H), 6.53 (d, J = 8.9 Hz, 1H), 6.44 (d, J = 9.1 Hz, 1H), 6.27 (td, J = 6.7, 1.3 Hz, 1H), 4.35 (dq, J = 20.8, 6.7 Hz, 2H), 2.17 (dd, J = 9.1, 4.4 Hz, 2H), 2.02 – 1.88 (m, 2H), 1.63 – 1.45 (m, 2H).

Example A52

Synthesis of 6'-(((1S,3S)-3-((5-(difluoromethoxy)-4-(1H-pyrrol-2-yl)pyrimidin-2-yl)amino)cyclopentyl)amino)-2H-[1,3'-bipyridin]-2-one



Step 1: Synthesis of 2,4-dichloro-5-methoxypyrimidine

2,4-Dichloropyrimidin-5-ol (5.00 g, 30.3 mmol, 1.00 eq) and potassium carbonate (10.5 g, 75.8 mmol, 2.50 eq) were dissolved in N,N-dimethylformamide (50 mL). Iodomethane (6.45 g, 45.5 mmol, 2.83 mL, 1.50 eq) was added. The mixture was heated to 80 ℃ and reacted for 2 hours.

TLC (petroleum ether: ethyl acetate = 3:1) showed the formation of a new spot (R_f = 0.60).

Water (200 mL) was slowly added to the reaction mixture to quench the reaction, followed by extraction with ethyl acetate (50 mL * 3). The organic phases were combined, washed with saturated brine (50 mL), dried, and concentrated to obtain 2,4-dichloro-5-methoxypyrimidine (2.50 g, 46.1% yield).

Step 2: Synthesis of tert-butyl 2-(2-chloro-5-methoxypyrimidin-4-yl)pyrrole-1-carboxylate

2,4-Dichloro-5-methoxypyrimidine (2.50 g, 14.0 mmol, 1.00 eq), (1-(tert-butoxycarbonyl)-1H-pyrrol-2-yl)boronic acid (2.95 g, 14.0 mmol, 1.00 eq),

[1,1'-bis(diphenylphosphino)ferrocene]palladium(II) dichloride dichloromethane complex (1.14 g, 1.40 mmol, 0.10 eq), and potassium phosphate (17.8 g, 83.8 mmol, 6.00 eq) were dissolved in N,N-dimethylformamide (30 mL). The atmosphere was purged with nitrogen three times. The mixture was heated to 60 ℃ and reacted for 12 hours. LCMS detected the MS value of the product.

The reaction mixture was diluted with water (200 mL) and then extracted with ethyl acetate (40 mL * 4). The organic phases were combined, washed with saturated brine (30 mL * 3), dried over anhydrous sodium sulfate, filtered, and concentrated to obtain a crude product. The crude product was purified by reverse-phase preparative chromatography (hydrochloric acid system) to obtain tert-butyl 2-(2-chloro-5-methoxypyrimidin-4-yl)pyrrole-1-carboxylate (1.50 g, 34.7% yield). LCMS: MS (ESI) m/z = 480.1 $[M-100+1]^+$.

Step 3: Synthesis of 2-chloro-4-(1H-pyrrol-2-yl)pyrimidin-5-ol

tert-Butyl 2-(2-chloro-5-methoxypyrimidin-4-yl)pyrrole-1-carboxylate (1.50 g, 4.84 mmol, 1.00 eq) was dissolved in dichloromethane (10 mL). The temperature was lowered to 0 ℃. Boron tribromide (7.28 g, 29.1 mmol, 6.00 eq) was added dropwise. The mixture was then heated to 40 ℃ and reacted for 4 hours. TLC (petroleum ether: ethyl acetate = 1:1) showed the formation of a new major spot. Methanol was slowly added dropwise at low temperature to quench the reaction, and the mixture was concentrated to obtain a crude product. The crude product was purified by column chromatography (petroleum ether: ethyl acetate = 10:1 to 1:1) to obtain 2-chloro-4-(1H-pyrrol-2-yl)pyrimidin-5-ol (0.50 g, 52.8% yield).

Step 4: Synthesis of 2-chloro-5-(difluoromethoxy)-4-(1H-pyrrol-2-yl)pyrimidine

At 20 ℃, 2-chloro-4-(1H-pyrrol-2-yl)pyrimidin-5-ol (331 mg, 1.69 mmol, 1.00 eq) and cesium carbonate (551 mg, 1.69 mmol, 1.00 eq) were dissolved in N,N-dimethylformamide (5 mL). The mixture was stirred for one hour, then sodium 2-chloro-2,2-difluoroacetate (284 mg, 1.86 mmol, 1.10 eq) was added in batches. After the addition, the mixture was heated to 100 ℃ and stirred for 2 hours.

TLC (petroleum ether: ethyl acetate = 2:1) showed that the starting material (R_f = 0.1) was completely consumed, and a new major spot (R_f = 0.6) was formed.

The reaction mixture was diluted with 50 mL of water and extracted with ethyl acetate (20 mL * 3). The organic phases were combined, washed with saturated brine (30 mL), dried over anhydrous sodium sulfate, filtered, and concentrated to obtain a crude product. The crude product was purified by column chromatography (petroleum ether: ethyl acetate = 50:1 to 1:1) to obtain 2-chloro-5-(difluoromethoxy)-4-(1H-pyrrol-2-yl)pyrimidine (250 mg, 60.2% yield).

Step 5: Synthesis of

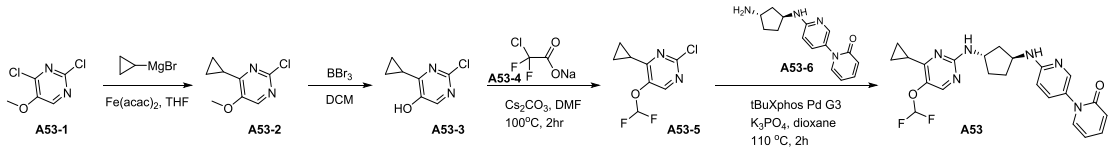
6'-(((1S,3S)-3-((5-(difluoromethoxy)-4-(1H-pyrrol-2-yl)pyrimidin-2-yl)amino)cyclopentyl)amino)-2H-[1,3'-bipyridin]-2-one

At 20 ℃, 2-chloro-5-(difluoromethoxy)-4-(1H-pyrrol-2-yl)pyrimidine (180 mg, 733 μmol, 1.00 eq), 1-[6-[[(1S,3S)-3-aminocyclopentyl]amino]pyridin-3-yl]pyridin-2-one (237.74 mg, 879.43 μmol, 1.2 eq), and potassium carbonate (203 mg, 1.47 mmol, 2.00 eq) were dissolved in N,N-dimethylformamide (1 mL). The mixture was then heated to 80 ℃ and stirred for 12 hours. LCMS detected the MS value.

The reaction mixture was diluted with water (50 mL) and then extracted with ethyl acetate (20 mL * 3). The organic phases were combined, washed with saturated brine (30 mL * 2), dried over anhydrous sodium sulfate, filtered, and concentrated to obtain a crude product. The crude product was purified by preparative chromatography (Column: Waters Xbridge Prep OBD C18 150*40 mm*10 um; Mobile phase: [water (NH_4HCO_3)-ACN]; Gradient: 25% to 55% B over 20 min) to obtain 6'-(((1S,3S)-3-((5-(difluoromethoxy)-4-(1H-pyrrol-2-yl)pyrimidin-2-yl)amino)cyclopentyl)amino)-2H-[1,3'-bipyridin]-2-one (187 mg, 53.1% yield).

LCMS: MS (ESI) m/z = 480.1 $[M+1]^+$. ^1H NMR: (400 MHz, $CDCl_3$): δ 9.95 - 9.46 (m, 1H), 8.13 (s, 1H), 8.04 (d, J = 2.4 Hz, 1H), 7.55 (dd, J = 2.4, 8.8 Hz, 1H), 7.40 (ddd, J = 2.0, 6.8, 9.2 Hz, 1H), 7.30 (dd, J = 2.0, 6.8 Hz, 1H), 7.10 (br s, 1H), 7.04 (br s, 1H), 6.66 (d, J = 9.2 Hz, 1H), 6.59 - 6.18 (m, 3H), 6.18 - 6.18 (m, 1H), 5.22 - 5.01 (m, 2H), 4.59 - 4.43 (m, 1H), 4.34 - 4.18 (m, 1H), 2.44 - 2.26 (m, 2H), 2.09 (t, J = 6.8 Hz, 2H), 1.66 - 1.57 (m, 2H).

Example A53



Step A: Synthesis of Compound A53-2

Compound A53-1 (5 g, 27.9 mmol) was dissolved in tetrahydrofuran (30 mL). At 0 ℃, iron(III) acetylacetonate (985 mg, 2.79 mmol) was added. Under a nitrogen atmosphere, a tetrahydrofuran solution of cyclopropylmagnesium bromide (34 mL, 1 M, 34 mmol) was added dropwise. The reaction was stirred at room temperature overnight. The reaction mixture was quenched with saturated aqueous ammonium chloride and extracted with dichloromethane (50 mL × 3). The organic phases were combined, dried over anhydrous sodium sulfate and concentrated. The resulting material was purified by Flash column chromatography (5 to 30% ethyl acetate/petroleum ether) to obtain 720 mg of Compound A53-2 as a pale yellow solid (yield: 14%). LCMS: $[M+H]^+$ = 185.

Step B: Synthesis of Compound A53-3

Compound A53-2 (750 mg, 3.9 mmol) was dissolved in a 1 M solution of boron tribromide in dichloromethane (7 mL, 7 mmol). Boron tribromide (1.2 mL, 12.5 mmol) was added. The mixture was stirred at room temperature for 4 hours. The reaction mixture was quenched by adding it to 10 mL of ice water. The pH was adjusted to 5-6 with saturated aqueous sodium carbonate. The mixture was then extracted with ethyl acetate (20 mL × 3). The organic phases were combined, dried over anhydrous sodium sulfate, filtered, and dried by rotary evaporation. The resulting material was purified by Flash column chromatography (0 to 50% ethyl acetate/petroleum ether) to obtain 300 mg of Compound A53-3 as a pale yellow solid (yield: 45%). LCMS: $[M+H]^+$ = 171.

Step C: Synthesis of Compound A53-5

Compound A53-3 (300 mg, 1.76 mmol) was dissolved in N,N-dimethylformamide (10 mL). Cesium carbonate (687 mg, 2.11 mmol) was added, and the mixture was stirred at room temperature for 1 hour. Compound A53-4 (805 mg, 5.28 mmol) was added. Under a nitrogen atmosphere, the mixture was heated to 100 ℃ and reacted for 3 hours. The reaction mixture was quenched with saturated aqueous ammonium chloride and extracted with dichloromethane (10 mL × 3). The organic phases were combined, dried, concentrated. The resulting material was purified by Flash column chromatography (0 to 20% ethyl acetate/petroleum ether) to obtain 80 mg of Compound A53-5 as a yellow oil (yield: 20%). LCMS: $[M+H]^+$ = 221.

Step D: Synthesis of the Target Compound

Compound A53-5 (80 mg, 0.36 mmol) and Compound A53-6 (97 mg, 0.36 mmol) were dissolved in anhydrous dimethyl sulfoxide (5 mL). Potassium phosphate (153 mg, 0.72 mmol) and

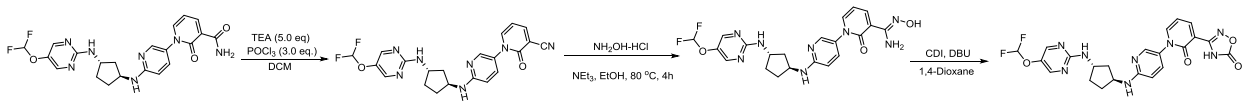
methanesulfonato(2-di-tert-butylphosphino-2’,4’,6’-triisopropyl-1,1’-biphenyl)(2’-amino-1,1’-biphenyl-2-yl)palladium(II) (57 mg, 0.072 mmol) were added. Under a nitrogen atmosphere, the mixture was heated to 110 ℃ and reacted for 2 hours. The reaction mixture was quenched with saturated aqueous ammonium chloride and extracted with dichloromethane (10 mL × 3). The organic phases were combined, dried, concentrated. The resulting material was purified by preparative TLC plate (developing solvent: dichloromethane/methanol = 12:1) to obtain 4 mg of the target compound as an off-white solid (yield: 2.5%). LCMS: $[M+H]^+$ = 455.

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.04 (s, 1H), 7.91 (d, J = 2.7 Hz, 1H), 7.60 (dd, J = 6.8, 2.0 Hz, 1H), 7.48 (ddd, J = 8.9, 6.5, 2.1 Hz, 1H), 7.39 (dd, J = 8.9, 2.7 Hz, 1H), 7.22 (d, J = 7.4 Hz, 1H), 6.91 (d, J = 6.9 Hz, 1H), 6.52 (d, J = 8.9 Hz, 1H), 6.44 (d, J = 9.1 Hz, 1H), 6.27 (t, J = 6.7 Hz, 1H), 4.25 (dq, J = 20.1, 6.8 Hz, 2H), 2.19 – 2.04 (m, 3H), 1.86 (dt, J = 20.3, 6.7 Hz, 2H),

1.55 – 1.44 (m, 2H), 1.23 (s, 2H), 1.01 (s, 2H).

Example A54

Synthesis of 3-(6'-(((1S,3S)-3-((5-(difluoromethoxy)pyrimidin-2-yl)amino)cyclopentyl)amino)-2-oxo-2H-[1,3'-bipyridin]-3-yl)-1,2,4-oxadiazol-5(4H)-one



Step A: Synthesis of 6'-(((1S,3S)-3-((5-(difluoromethoxy)pyrimidin-2-yl)amino)cyclopentyl)amino)-2-oxo-2H-[1,3'-bipyridine]-3-carbonitrile

At room temperature, 6'-(((1S,3S)-3-((5-(difluoromethoxy)pyrimidin-2-yl)amino)cyclopentyl)amino)-2-oxo-2H-[1,3'-bipyridine]-3-carboxamide (2.2 g, 4.82 mmol, 1.0 eq), triethylamine (2.43 g, 24.1 mmol, 5.0 eq), and phosphorus oxychloride (1.2 g, 14.5 mmol, 3.0 eq) were dissolved in dichloromethane (20 mL). The mixture was stirred at room temperature for 3 hours.

After completion of the reaction, the pH of the reaction mixture was adjusted to 7-8 with a 2 M hydrochloric acid solution. Cold water (30 mL) was added to dilute the mixture, followed by extraction with ethyl acetate (75 mL × 3). The organic phases were combined, dried over anhydrous sodium sulfate, filtered, and concentrated to obtain 1.83 g of 6'-(((1S,3S)-3-((5-(difluoromethoxy)pyrimidin-2-yl)amino)cyclopentyl)amino)-2-oxo-2H-[1,3'-bipyridine]-3-carbonitrile as a brown foamy solid powder (yield 87%). LC-MS: $[M+H]^+$ = 439.

Step B: Synthesis of (Z)-6'-(((1S,3S)-3-((5-(difluoromethoxy)pyrimidin-2-yl)amino)cyclopentyl)amino)-N'-hydroxy-2-oxo-2H-[1,3'-bipyridine]-3-carboximidamide

At room temperature, 6'-(((1S,3S)-3-((5-(difluoromethoxy)pyrimidin-2-yl)amino)cyclopentyl)amino)-2-oxo-2H-[1,3'-bipyridine]-3-carbonitrile (0.63 g, 1.44 mmol, 1.0 eq), hydroxylamine hydrochloride (0.8 g, 11.52 mmol, 8.0 eq), and triethylamine (1.16 g, 11.52 mmol, 8.0 eq) were dissolved in ethanol (6 mL). The mixture was heated to 80 ℃ and stirred for 4 hours.

After completion of the reaction, the organic solvent was removed by concentration under reduced pressure. The crude product was purified by C18 column chromatography (eluent: acetonitrile/water) to obtain 0.493 g of (Z)-6'-(((1S,3S)-3-((5-(difluoromethoxy)pyrimidin-2-yl)amino)cyclopentyl)amino)-N'-hydroxy-

2-oxo-2H-[1,3'-bipyridine]-3-carboximidamide as a brown solid powder (yield 73%). LC-MS: $[M+H]^+$ = 473.

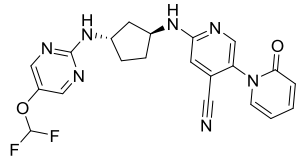
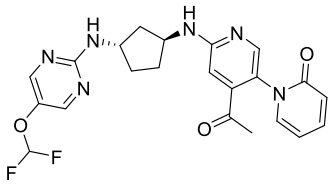
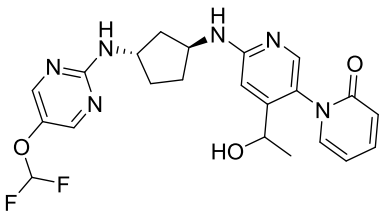
Step C: Synthesis of 3-(6'-(((1S,3S)-3-((5-(difluoromethoxy)pyrimidin-2-yl)amino)cyclopentyl)amino)-2-oxo-2H-[1,3'-bipyridin]-3-yl)-1,2,4-oxadiazol-5(4H)-one

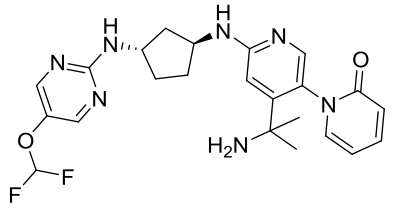
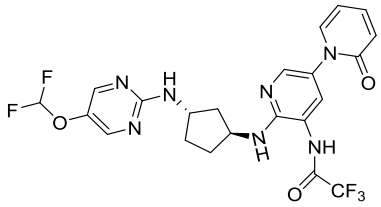
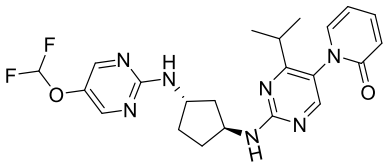
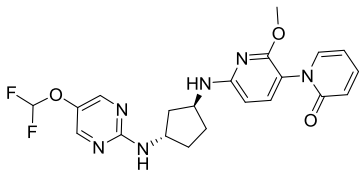
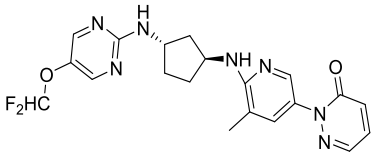
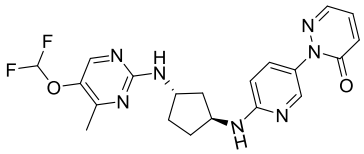
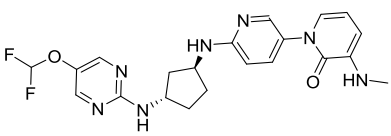
At room temperature, (Z)-6'-(((1S,3S)-3-((5-(difluoromethoxy)pyrimidin-2-yl)amino)cyclopentyl)amino)-N'-hydroxy-2-oxo-2H-[1,3'-bipyridine]-3-carboximidamide (0.4 g, 0.85 mmol, 1.0 eq), N,N'-carbonyldiimidazole (0.152 g, 0.94 mmol, 1.1 eq), and DBU (0.194 g, 1.28 mmol, 1.5 eq) were dissolved in 1,4-dioxane (6 mL). The mixture was stirred vigorously for 6 hours.

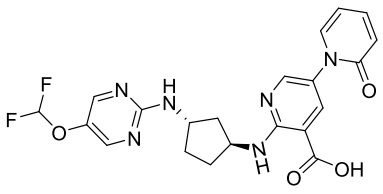
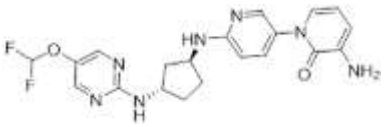
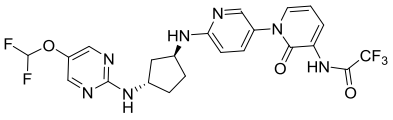
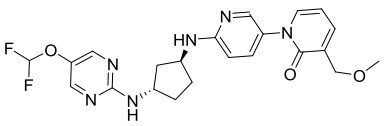
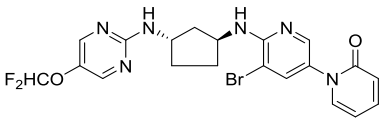
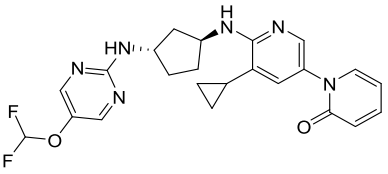
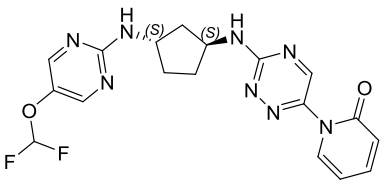
After completion of the reaction, the organic solvent was removed by concentration under reduced pressure. The crude product was purified by C18 column chromatography (eluent: acetonitrile/water) to obtain 0.175 g of 3-(6'-(((1S,3S)-3-((5-(difluoromethoxy)pyrimidin-2-yl)amino)cyclopentyl)amino)-2-oxo-2H-[1,3'-bipyridin]-3-yl)-1,2,4-oxadiazol-5(4H)-one as a yellow solid powder (yield 41%). LC-MS: $[M+H]^+$ = 499.

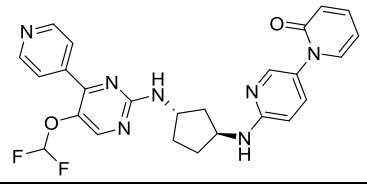
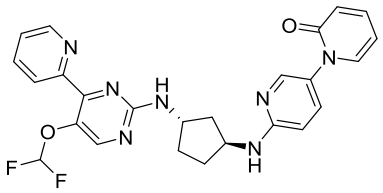
Proton NMR: ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.23 (s, 2H), 8.14 – 7.82 (m, 3H), 7.56 – 7.38 (m, 2H), 7.22 – 6.84 (m, 2H), 6.64 – 6.43 (m, 2H), 4.31 (q, J = 7.0 Hz, 2H), 2.13 (tt, J = 13.0, 6.8 Hz, 2H), 1.89 (qt, J = 12.9, 6.7 Hz, 2H), 1.51 (ddd, J = 19.0, 14.1, 7.1 Hz, 2H).

Examples A55 to A73

A55		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.24 (s, 2H), 8.17 – 8.04 (m, 2H), 7.94 – 7.83 (m, 1H), 7.51 (d, *J* = 7.2 Hz, 1H), 7.25 – 6.80 (m, 5H), 4.28 (dq, *J* = 21.3, 6.6 Hz, 2H), 2.22 – 2.02 (m, 2H), 1.89 (dq, *J* = 22.5, 6.5 Hz, 2H), 1.60 – 1.41 (m, 2H).
A56		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.25 (s, 2H), 8.11 – 8.04 (m, 1H), 7.92 (s, 1H), 7.85 (ddd, *J* = 9.0, 7.2, 2.0 Hz, 1H), 7.51 (d, *J* = 7.2 Hz, 1H), 7.25 – 6.85 (m, 4H), 6.73 (s, 1H), 4.31 (dq, *J* = 13.5, 6.8 Hz, 2H), 2.35 (s, 4H), 2.14 (dq, *J* = 14.2, 7.3 Hz, 2H), 1.90 (h, *J* = 6.7 Hz, 2H), 1.51 (dq, *J* = 22.2, 9.3, 8.1 Hz, 2H).
A57		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.25 (s, 2H), 8.11 (dd, *J* = 5.2, 2.0 Hz, 1H), 7.83 (ddd, *J* = 8.7, 7.2, 2.0 Hz, 1H), 7.67 (s, 1H), 7.49 (d, *J* = 7.3 Hz, 1H), 7.27 – 6.82 (m, 3H), 6.69 (s, 1H), 6.56 (dd, *J* = 6.9, 2.4 Hz, 1H), 5.21 (d, *J* = 4.0 Hz, 1H), 4.57 (t, *J* = 5.4 Hz, 1H), 4.29 (dt, *J* = 12.3, 6.5 Hz, 2H), 2.12 (dt, *J* = 11.4, 5.8 Hz, 2H), 1.88 (t, *J* = 6.9 Hz, 2H), 1.51 (t, *J* = 12.7 Hz, 2H), 1.18 (d, *J* = 6.5 Hz, 3H).

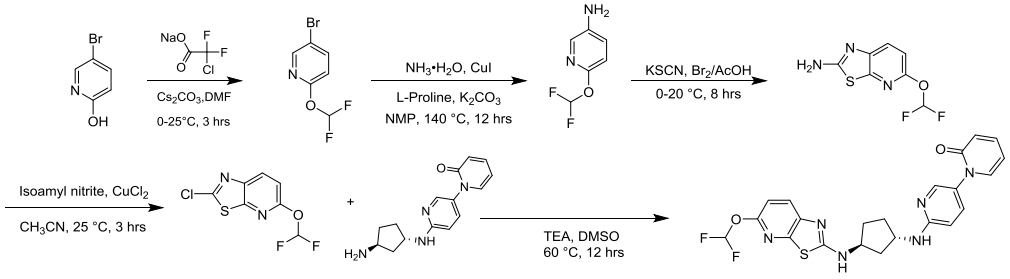
A58		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.63 (s, 1H), 8.24 (s, 2H), 7.86 (dd, *J* = 5.3, 1.8 Hz, 1H), 7.49 – 7.39 (m, 2H), 7.34 (ddd, *J* = 8.8, 7.0, 2.0 Hz, 1H), 7.05 (t, *J* = 74.0 Hz, 1H), 6.54 – 6.43 (m, 3H), 6.38 (s, 1H), 5.80 (d, *J* = 6.7 Hz, 1H), 4.25 (q, *J* = 7.0 Hz, 1H), 4.07 (q, *J* = 6.4 Hz, 1H), 2.10 – 1.99 (m, 2H), 1.77 (t, *J* = 7.1 Hz, 2H), 1.68 (s, 6H), 1.54 – 1.33 (m, 2H).
A59		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.26 – 8.20 (s, 2H), 7.95 – 7.86 (s, 1H), 7.67 – 7.58 (dd, J = 6.9, 2.1 Hz, 2H), 7.55 – 7.45 (m, 2H), 7.24 – 6.84 (t, J = 74.0 Hz, 1H), 6.50 – 6.41 (t, J = 7.2 Hz, 2H), 6.34 – 6.25 (m, 1H), 4.54 – 4.44 (m, 1H), 4.36 – 4.25 (m, 1H), 2.24 – 2.03 (m, 2H), 2.02 – 1.85 (m, 2H), 1.60 – 1.47 (m, 2H).
A60		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.23 (s, 2H), 8.13 – 8.06 (m, 1H), 8.02 (s, 1H), 7.84 (ddd, *J* = 8.3, 7.3, 2.0 Hz, 1H), 7.46 (d, *J* = 7.2 Hz, 1H), 7.21 – 6.84 (m, 4H), 4.30 (h, *J* = 6.8 Hz, 2H), 2.87 (p, *J* = 6.8 Hz, 1H), 2.16 – 2.05 (m, 2H), 1.95 – 1.86 (m, 2H), 1.59 – 1.49 (m, 2H), 1.05 (dd, *J* = 6.8, 3.3 Hz, 6H).
A61		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.26 – 8.23 (s, 2H), 7.53 – 7.48 (d, J = 7.2 Hz, 1H), 7.47 – 7.40 (m, 2H), 7.27 – 7.22 (m, 1H), 7.06 – 6.85 (m, 2H), 6.44 – 6.39 (m, 1H), 6.23 – 6.18 (m, 1H), 6.13 – 6.07 (d, J = 8.4 Hz, 1H), 4.38 – 4.22 (m, 2H), 3.79 – 3.73 (s, 3H), 2.24 – 2.06 (m, 2H), 2.03 – 1.83 (m, 2H), 1.60 – 1.48 (m, 2H).
A62		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.24 (s, 2H), 8.04 – 7.98 (m, 2H), 7.51 – 7.42 (m, 2H), 7.42 – 7.37 (m, 1H), 7.07 – 6.99 (m, 1H), 5.98 (d, J = 7.0 Hz, 1H), 4.54 (h, J = 6.9 Hz, 1H), 4.33 (h, J = 6.9 Hz, 1H), 2.23 – 2.07 (m, 4H), 1.95 (t, J = 7.1 Hz, 2H), 1.56 (tdd, J = 16.0, 9.3, 4.6 Hz, 2H).
A63		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.21 – 8.03 (m, 2H), 8.01 (dd, *J* = 3.8, 1.6 Hz, 1H), 7.48 (ddd, *J* = 19.9, 9.2, 3.3 Hz, 2H), 7.36 (d, *J* = 7.3 Hz, 1H), 7.19 – 6.81 (m, 3H), 6.52 (d, *J* = 9.0 Hz, 1H), 4.31 (p, *J* = 6.6 Hz, 2H), 2.24 (s, 3H), 2.12 (tt, *J* = 12.8, 6.2 Hz, 2H), 1.87 (ddp, *J* = 18.7, 13.3, 6.8 Hz, 2H), 1.51 (td, *J* = 16.3, 8.0 Hz, 2H).
A64		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.25 – 8.21 (s, 2H), 7.93 – 7.90 (d, J = 2.6 Hz, 1H), 7.50 – 7.47 (d, J = 7.2 Hz, 1H), 7.40 – 7.36 (m, 1H), 7.23 – 7.02 (d, J = 74.0 Hz, 1H), 6.91 – 6.76 (m, 2H), 6.55 – 6.51 (d, J = 8.9 Hz, 1H), 6.22 – 6.12 (m, 2H), 5.64 – 5.58 (m 1H), 4.38 – 4.26 (m, 2H), 2.73 – 2.68 (d, J = 5.2 Hz, 3H), 2.19 – 2.07 (m, 2H), 1.95 – 1.81 (m, 2H), 1.59 – 1.45 (m, 2H).

A65		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.69 – 8.49 (s, 1H), 8.28 – 8.19 (d, J = 11.1 Hz, 3H), 8.05 – 7.99 (d, J = 2.8 Hz, 1H), 7.70 – 7.64 (dd, J = 6.8, 2.1 Hz, 1H), 7.57 – 7.46 (m, 2H), 7.24 – 6.83 (s, 1H), 6.51 – 6.43 (d, J = 9.2 Hz, 1H), 6.33 – 6.26 (m, 1H), 4.62 – 4.51 (q, J = 6.7 Hz, 1H), 4.39 – 4.27 (m, 1H), 2.28 – 2.19 (m, 1H), 2.18 – 2.08 (m, 4.6 Hz, 1H), 2.06 – 1.96 (m, 1H), 1.94 – 1.83 (m, 1H), 1.65 – 1.45 (m, 2H).
A66		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.25 – 8.22 (s, 2H), 7.93 – 7.90 (d, J = 2.7 Hz, 1H), 7.51 – 7.47 (d, J = 7.2 Hz, 1H), 7.40 – 7.36 (m, 1H), 7.23 – 7.02 (d, J = 74.0 Hz, 1H), 6.91 – 6.78 (m, 2H), 6.55 – 6.46 (m, 2H), 6.12 – 6.07 (t, J = 7.0 Hz, 1H), 5.21 – 5.15 (s, 2H), 4.36 – 4.26 (m, 2H), 2.20 – 2.06 (m, 2H), 1.95 – 1.82 (m, 2H), 1.59 – 1.43 (m, 2H).
A67		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.25 – 8.21 (s, 2H), 8.03 – 7.95 (m, 2H), 7.60 – 7.55 (d, J = 6.8 Hz, 1H), 7.51 – 7.40 (m, 2H), 7.23 – 6.83 (m, 3H), 6.57 – 6.51 (d, J = 9.0 Hz, 1H), 6.43 – 6.37 (t, J = 7.1 Hz, 1H), 4.37 – 4.26 (m, 2H), 2.20 – 2.07 (m, 2H), 1.95 – 1.81 (m, 2H), 1.58 – 1.45 (m, 2H).
A68		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.25 – 8.21 (s, 2H), 7.93 – 7.90 (d, J = 2.7 Hz, 1H), 7.57 – 7.53 (dd, J = 6.8, 2.1 Hz, 1H), 7.50 – 7.43 (m, 2H), 7.42 – 7.37 (dd, J = 8.9, 2.7 Hz, 1H), 7.23 – 7.02 (d, J = 73.9 Hz, 1H), 6.94 – 6.83 (m, 1H), 6.54 – 6.50 (d, J = 8.9 Hz, 1H), 6.33 – 6.28 (t, J = 6.8 Hz, 1H), 4.36 – 4.26 (m, 2H), 4.25 – 4.22 (s, 2H), 2.18 – 2.07 m, 2H), 1.94 – 1.81 (m, 2H), 1.59 – 1.42 (m, 2H).
A69		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.24 (s, 2H), 8.04 (d, J = 2.3 Hz, 1H), 7.90 (d, J = 2.3 Hz, 1H), 7.65 (dd, J = 6.9, 2.0 Hz, 1H), 7.53 – 7.47 (m, 2H), 7.03 (s, 1H), 6.49 – 6.44 (m, 1H), 6.29 (ddd, J = 8.9, 5.1, 1.8 Hz, 2H), 4.54 (q, J = 7.2 Hz, 1H), 4.39 – 4.30 (m, 1H), 2.21 – 2.06 (m, 2H), 2.03 – 1.92 (m, 2H), 1.69 – 1.50 (m, 2H).
A70		^{1}H NMR: (400 MHz, $CDCl_3$) *δ* 8.19 (s, 2H), 7.97 (d, *J* = 2.4 Hz, 1H), 7.39 (ddd, *J* = 2.1, 6.8, 9.1 Hz, 1H), 7.35 (d, *J* = 1.6 Hz, 1H), 7.29 (br d, *J* = 2.0 Hz, 1H), 6.65 (d, *J* = 9.3 Hz, 1H), 6.61 - 6.18 (m, 2H), 5.53 - 5.30 (m, 1H), 5.11 (br d, *J* = 4.1 Hz, 1H), 4.73 - 4.58 (m, 1H), 4.52 - 4.36 (m, 1H), 2.50 - 2.28 (m, 2H), 2.20 - 2.02 (m, 2H), 1.62 - 1.55 (m, 3H), 1.00 - 0.93 (m, 2H), 0.67 - 0.59 (m, 2H)
A71		^{1}H NMR: (DMSO-d_6, 400 MHz) 8.60 (s, 1H), 8.24 (s, 2H), 7.83 (dd, J = 1.5, 7.0 Hz, 1H), 7.58 (ddd, J = 2.1, 6.8, 9.1 Hz, 1H), 7.51 (d, J = 7.1 Hz, 1H), 7.03 (t, J = 74.0 Hz, 1H), 6.52 (d, J = 9.1 Hz, 1H), 6.41 (dt, J = 1.1, 6.8 Hz, 1H), 4.54 - 4.27 (m, 2H), 2.20 - 2.08 (m, 2H), 1.96 (br t, J = 6.8 Hz, 2H),

		1.67 - 1.51 (m, 2H)
A72		^{1}H NMR: (400 MHz, MeOD) δ 8.81 - 8.54 (m, 2H), 8.39 - 8.24 (m, 1H), 8.10 - 7.86 (m, 3H), 7.64 - 7.55 (m, 2H), 7.50 - 7.37 (m, 1H), 6.89 - 6.42 (m, 4H), 4.59 - 4.28 (m, 2H), 2.41 - 2.21 (m, 2H), 2.17 - 1.95 (m, 2H), 1.79 - 1.53 (m, 2H).
A73		^{1}H NMR: (400 MHz, DMSO-d_6)δ8.68 (d, *J* = 4.8 Hz, 1H), 8.32 (s, 1H), 8.03 - 7.83 (m, 3H), 7.68 (br d, *J* = 7.0 Hz, 1H), 7.60 (dd, *J* = 1.6, 6.8 Hz, 1H), 7.55 - 7.44 (m, 2H), 7.40 (dd, *J* = 2.6, 8.9 Hz, 1H), 7.26 - 6.80 (m, 2H), 6.53 (d, *J* = 8.9 Hz, 1H), 6.44 (d, *J* = 8.9 Hz, 1H), 6.27 (dt, *J* = 1.3, 6.7 Hz, 1H), 4.45 - 4.26 (m, 2H), 2.22 - 2.10 (m, 2H), 2.03 - 1.85 (m, 2H), 1.66 - 1.44 (m, 2H).

Example C1

Synthesis of 6'-(((1S,3S)-3-((5-(difluoromethoxy)thiazolo[5,4-b]pyridin-2-yl)amino)cyclopentyl)amino)-2H-[1,3'-bipyridin]-2-one



Step 1: Synthesis of 5-bromo-2-(difluoromethoxy)pyridine

At room temperature, 5-bromopyridin-2-ol (10.0 g, 57.5 mmol, 1.00 eq) was dissolved in DMF (200 mL). Cesium carbonate (22.5 g, 69.0 mmol, 1.20 eq) was added. Under nitrogen protection, the mixture was stirred at 25℃ for 1.5 hours. Sodium 2-chloro-2,2-difluoroacetate (26.3 g, 172 mmol, 3.00 eq) was then added. The mixture was heated to 100℃ and stirred for 1.5 hours.

LCMS showed the MS of the target product (RT = 0.537 min, m/z = 223.9 $[M+H]^+$). The mixture was cooled to room temperature. 600 mL water was added, and the mixture was extracted with ethyl acetate (600 mL × 5). The organic phases were combined, washed with saturated sodium chloride solution, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The resultant was mixed with silica gel and purified by column chromatography, eluting with petroleum ether to obtain 5-bromo-2-(difluoromethoxy)pyridine as a colorless oily liquid (3.01 g, 13.4 mmol, 23.38% yield). LCMS (ESI) m/z = 223.9 $[M+H]^+$.

Step 2: Synthesis of 6-(difluoromethoxy)pyridin-3-amine

At room temperature, 5-bromo-2-(difluoromethoxy)pyridine (3.00 g, 13.4 mmol, 1.00 eq),

ammonia water (2.35 g, 20.1 mmol, 2.58 mL, 30% purity, 1.50 eq), copper(I) iodide (510 mg, 2.68 mmol, 0.2 eq), potassium carbonate (2.78 g, 20.09 mmol, 1.50 eq), and L-proline (616.76 mg, 5.36 mmol, 0.40 eq) were added to N-methylpyrrolidone (30 mL). The mixture was heated to 140 ℃ in a sealed vessel and stirred for 12 hours.

TLC (petroleum ether/ethyl acetate = 5/1) indicated the reaction of the starting material was complete. 20 mL water was added, and the mixture was extracted with ethyl acetate (30 mL × 4). The organic phases were combined, washed with saturated sodium chloride solution, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The resultant was mixed with silica gel and purified by column chromatography (petroleum ether/ethyl acetate = 5/1) to obtain 6-(difluoromethoxy)pyridin-3-amine as a yellow oily product (1.3 g, 8.12 mmol, 60.62% yield).

Step 3: Synthesis of 5-(difluoromethoxy)thiazolo[5,4-b]pyridin-2-amine

In an ice bath at 0 ℃, 6-(difluoromethoxy)pyridin-3-amine (1.00 g, 6.25 mmol, 1.00 eq) and potassium thiocyanate (4.86 g, 50.0 mmol, 4.84 mL, 8.00 eq) were dissolved in glacial acetic acid (3.00 mL). A solution of bromine (2.99 g, 18.8 mmol, 965 μL, 3.00 eq) in glacial acetic acid (1.00 mL) was slowly added dropwise, keeping the reaction temperature below 0 ℃. After the addition, the mixture was allowed to warm naturally to 20 ℃ and stirred at 20 ℃ for 8 hours.

TLC (petroleum ether/ethyl acetate = 2/1) indicated the reaction of the starting material was complete. 5 mL water was added, and the mixture was heated to 85 ℃. The mixture was filtered while hot. The filter cake was added to acetic acid (1.5 mL), heated to 85 ℃, and filtered while hot. The two filtrates were combined, and the pH was adjusted to 8 with ammonia water in an ice-water bath, resulting in the precipitation of a large amount of yellow solid. The mixture was filtered under reduced pressure, and the filter cake was dried to obtain 5-(difluoromethoxy)thiazolo[5,4-b]pyridin-2-amine as a yellow solid (0.9 g, 4.14 mmol, 66.35% yield).

Step 4: Synthesis of 2-chloro-5-(difluoromethoxy)thiazolo[5,4-b]pyridine

At room temperature, 5-(difluoromethoxy)thiazolo[5,4-b]pyridin-2-amine (0.90 g, 4.14 mmol, 1.00 eq) was dissolved in acetonitrile (15 mL). Under nitrogen protection, isoamyl nitrite (728 mg, 6.22 mmol, 837 μL, 1.50 eq) and copper(II) chloride (669 mg, 4.97 mmol, 161 μL, 1.20 eq) were added. The mixture was stirred at 25 ℃ for 3 hours.

TLC (petroleum ether/ethyl acetate = 2/1) indicated the reaction of the starting material was complete. 8 mL saturated ammonium chloride solution was added, and the mixture was stirred for 10 minutes. 25 mL water was added to dilute the mixture, followed by extraction with ethyl acetate (80 mL × 4). The organic phases were combined, washed with saturated sodium chloride

solution, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The resultant was mixed with silica gel and purified by column chromatography (petroleum ether/ethyl acetate = 1/0 to 0/1) to obtain 2-chloro-5-(difluoromethoxy)thiazolo[5,4-b]pyridine as a white solid (0.7 g, 2.96 mmol, 71.39% yield). LCMS (ESI) m/z = 236.9 $[M+H]^+$.

Step 5: Synthesis of 6'-(((1S,3S)-3-((5-(difluoromethoxy)thiazolo[5,4-b]pyridin-2-yl)amino)cyclopentyl)amino)-2H-[1,3'-bipyridin]-2-one

At room temperature, 2-chloro-5-(difluoromethoxy)thiazolo[5,4-b]pyridine (200 mg, 845 μmol, 1 eq), 6'-(((1S,3S)-3-aminocyclopentyl)amino)-2H-[1,3'-bipyridin]-2-one hydrochloride (259 mg, 845 μmol, 1.00 eq, HCl), and triethylamine (257 mg, 2.54 mmol, 352 μL, 3.00 eq) were added to DMSO (10.0 mL). Under nitrogen protection, the mixture was heated to 60 ℃ and reacted for 12 hours.

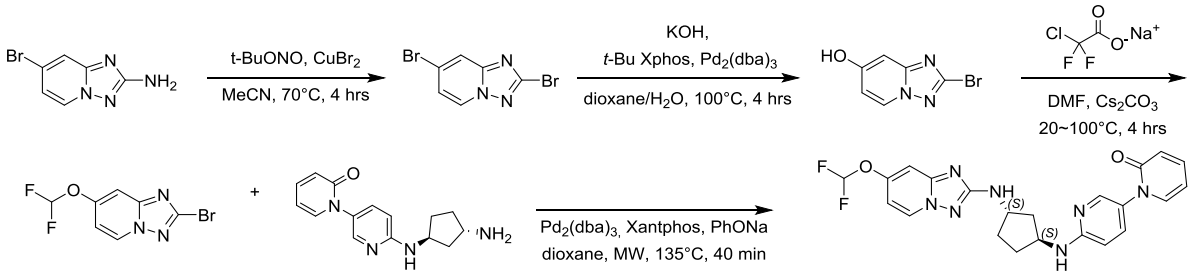
LCMS showed the MS of the target product (RT = 0.423 min, m/z = 471.1 $[M+H]^+$). 30 mL water was added to the reaction mixture to quench the reaction. The mixture was extracted with ethyl acetate (60 mL × 4). The organic phases were combined, washed with saturated sodium chloride solution, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The resultant was mixed with silica gel and purified by column chromatography (petroleum ether/ethyl acetate = 1/0 to 1/1) to obtain 6'-(((1S,3S)-3-((5-(difluoromethoxy)thiazolo[5,4-b]pyridin-2-yl)amino)cyclopentyl)amino)-2H-[1,3'-bipyridin]-2-one as a yellow solid (124 mg, 264 μmol, 31.18% yield).

LCMS (ESI) m/z = 471.1 $[M+H]^+$.

^{1}H NMR (400 MHz, CDCl3): δ 8.41 (d, J = 6.6 Hz, 1H), 7.93 (d, J = 2.6 Hz, 1H), 7.84 - 7.77 (m, 1H), 7.64 - 7.56 (m, 1H), 7.47 (ddd, J = 2.1, 6.8, 9.1 Hz, 1H), 7.44 - 7.37 (m, 1H), 7.02 - 6.88 (m, 2H), 6.53 (d, J = 9.0 Hz, 1H), 6.44 (d, J = 9.1 Hz, 1H), 6.27 (dt, J = 1.2, 6.7 Hz, 1H), 4.47 - 4.26 (m, 2H), 2.26 - 2.11 (m, 2H), 1.96 (tq, J = 6.6, 13.7 Hz, 2H), 1.65 - 1.49 (m, 2H).

Example C2

Synthesis of 6'-(((1S,3S)-3-((7-(difluoromethoxy)-[1,2,4]triazolo[1,5-a]pyridin-2-yl)amino)cyclopentyl)amino)-2H-[1,3'-bipyridin]-2-one



Step 1: Synthesis of 2,7-dibromo-[1,2,4]triazolo[1,5-a]pyridine

7-Bromo-[1,2,4]triazolo[1,5-a]pyridin-2-amine (2.00 g, 9.39 mmol, 1 eq), copper(II) bromide (3.15 g, 14.1 mmol, 1.5 eq), and tert-butyl nitrite (1.45 g, 14.1 mmol, 1.5 eq) were dissolved in acetonitrile (120 mL). The mixture was stirred at 80 ℃ for 3 hours. LCMS detected the MS value of the product (RT = 0.452 min). The reaction mixture was cooled to room temperature, diluted with water (200 mL), and extracted with ethyl acetate (80 mL × 2). The organic phases were combined, washed with saturated brine (200 mL × 2), dried over anhydrous sodium sulfate, filtered, and concentrated to obtain 2,7-dibromo-[1,2,4]triazolo[1,5-a]pyridine (2.00 g, 7.22 mmol, 76.9% yield). This was used directly in the next step without purification. LCMS (ESI) m/z = 277.9 $[M+1]^+$.

Step 2: Synthesis of 2-bromo-[1,2,4]triazolo[1,5-a]pyridin-7-ol

2,7-dibromo-[1,2,4]triazolo[1,5-a]pyridine (2.00 g, 7.22 mmol, 1 eq), potassium hydroxide (1.2 g, 21.7 mmol, 3 eq), t-Bu XPhos (675 mg, 1.59 mmol, 0.22 eq), and $Pd_2(dba)_3$ (728 mg, 794 μmol, 0.11 eq) were dissolved in 1,4-dioxane (20 mL) and water (5 mL). The mixture was stirred at 100 ℃ for 4 hours. LCMS detected the MS value of the product (RT = 0.358 min). The reaction mixture was cooled to room temperature. Water (60 mL) and ethyl acetate (40 mL) were added to dilute the mixture. The organic phase was separated and discarded. The aqueous phase was adjusted to pH = 5 with dilute hydrochloric acid and then extracted with ethyl acetate (60 mL × 2). The organic phases were combined, washed with saturated brine (100 mL × 2), dried over anhydrous sodium sulfate, filtered, and concentrated to obtain 2-bromo-[1,2,4]triazolo[1,5-a]pyridin-7-ol (860 mg, 3.97 mmol, 54.9% yield, 98.7% purity). This was used directly in the next step without purification. LCMS (ESI) m/z = 215.9 $[M+1]^+$.

Step 3: Synthesis of 2-bromo-7-(difluoromethoxy)-[1,2,4]triazolo[1,5-a]pyridine

2-Bromo-[1,2,4]triazolo[1,5-a]pyridin-7-ol (400 mg, 1.84 mmol, 1 eq) and cesium carbonate (721 mg, 2.21 mmol, 1.2 eq) were dissolved in N,N-dimethylformamide (10 mL). The mixture was stirred at 20 ℃ for 1 hour. Sodium chlorodifluoroacetate (844 mg, 5.53 mmol, 3 eq) was then added to the reaction mixture. The mixture was stirred at 100 ℃ for 3 hours. TLC (petroleum ether/ethyl acetate = 3/1) indicated the completion of the reaction.The reaction

mixture was cooled to room temperature, diluted with water (100 mL), and extracted with ethyl acetate (20 mL × 2). The organic phases were combined, washed with saturated brine (50 mL × 2), dried over anhydrous sodium sulfate, filtered, and concentrated to obtain a crude product. The crude product was purified by reverse-phase preparative chromatography (Column: C18 150×30mm; Mobile phase: [water (FA)-ACN]; Gradient: 30% to 60% B over 7 min) to obtain 2-bromo-7-(difluoromethoxy)-[1,2,4]triazolo[1,5-a]pyridine (230 mg, 871 μmol, 47.2% yield, 100% purity). LCMS (ESI) m/z = 263.9 $[M+1]^+$.

Step 4: Synthesis of 6'-(((1S,3S)-3-((7-(difluoromethoxy)-[1,2,4]triazolo[1,5-a]pyridin-2-yl)amino)cyclopentyl)amino)-2H-[1,3'-bipyridin]-2-one

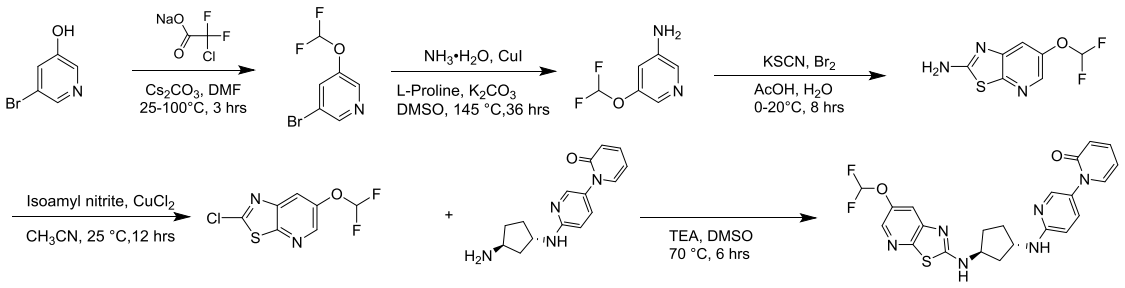
2-Bromo-7-(difluoromethoxy)-[1,2,4]triazolo[1,5-a]pyridine (100 mg, 379 μmol, 1 eq), 6'-(((1S,3S)-3-aminocyclopentyl)amino)-2H-[1,3'-bipyridin]-2-one (123 mg, 455 μmol, 1.2 eq), XantPhos (17.5 mg, 30.3 μmol, 0.08 eq), sodium phenoxide (66.0 mg, 568 μmol, 1.5 eq), and Pd2(dba)3 (13.9 mg, 15.2 μmol, 0.04 eq) were dissolved in 1,4-dioxane (4 mL). The mixture was stirred at 135 ℃ under microwave irradiation for 40 minutes. LCMS detected the MS value of the product (RT = 0.391 min). The reaction mixture was filtered. The filtrate was concentrated to obtain a crude product. The crude product was purified by reverse-phase preparative chromatography (Column: C18 150×30mm; Mobile phase: [water (FA)-ACN]; Gradient: 12% to 42% B over 7 min) to obtain 6'-(((1S,3S)-3-((7-(difluoromethoxy)-[1,2,4]triazolo[1,5-a]pyridin-2-yl)amino)cyclopentyl)amino)-2H-[1,3'-bipyridin]-2-one (49.0 mg, 103 μmol, 27.1% yield, 95.1% purity).

LCMS (ESI) m/z = 454.2 $[M+1]^+$.

^{1}H NMR: (400 MHz, DMSO-d_6): δ 8.63 (d, J = 7.3 Hz, 1H), 7.92 (d, J = 2.5 Hz, 1H), 7.63 - 7.22 (m, 4H), 7.14 (d, J = 2.6 Hz, 1H), 6.91 (d, J = 6.9 Hz, 1H), 6.78 - 6.70 (m, 2H), 6.52 (d, J = 9.0 Hz, 1H), 6.44 (d, J = 8.9 Hz, 1H), 6.26 (dt, J = 1.3, 6.7 Hz, 1H), 4.38 - 4.26 (m, 1H), 4.15 (qd, J = 6.8, 13.4 Hz, 1H), 2.22 - 2.09 (m, 2H), 2.02 - 1.82 (m, 2H), 1.64 - 1.43 (m, 2H).

Example C3

Synthesis of 6'-(((1S,3S)-3-((6-(difluoromethoxy)thiazolo[5,4-b]pyridin-2-yl)amino)cyclopentyl)amino)-2H-[1,3'-bipyridin]-2-one



Step 1: Synthesis of 3-bromo-5-(difluoromethoxy)pyridine

At room temperature, 3-bromo-5-hydroxypyridine (40.0 g, 230 mmol, 1.00 eq) was dissolved in DMF (800 mL). Cs_2CO_3 (89.9 g, 276 mmol, 1.20 eq) was added. Under nitrogen protection, the mixture was stirred at 25 ℃ for 1.5 hours. Sodium 2-chloro-2,2-difluoroacetate (105 g, 690 mmol, 3.00 eq) was then added. The mixture was heated to 100 ℃ and stirred for 1.5 hours.

TLC (petroleum ether/ethyl acetate = 5/1) indicated the reaction of the starting material was complete and the target product formed. 60 mL water was added. The mixture was extracted with ethyl acetate (50 mL × 3). The organic phases were combined, washed with saturated sodium chloride solution, dried over anhydrous sodium sulfate, and concentrated under reduced pressure to obtain a crude product. The resultant was mixed with silica gel and purified by column chromatography, eluting with pure petroleum ether to obtain 3-bromo-5-(difluoromethoxy)pyridine as a yellow oily product (6.3 g, 28.1 mmol, 12.23% yield).

Step 2: Synthesis of 5-(difluoromethoxy)pyridin-3-amine

At room temperature, 3-bromo-5-(difluoromethoxy)pyridine (5.00 g, 22.3 mmol, 1.00 eq), ammonia water (3.91 g, 33.5 mmol, 4.30 mL, 30% purity, 1.50 eq), copper(I) iodide (850 mg, 4.46 mmol, 0.20 eq), K_2CO_3 (4.63 g, 33.48 mmol, 1.5 eq), and N,N'-bis(2-furylmethyl)oxalamide (2.22 g, 8.93 mmol, 0.4 eq) were added to NMP (10 mL). The mixture was reacted in a sealed vessel. The mixture was heated to 145 ℃ and stirred for 36 hours.

TLC (petroleum ether/ethyl acetate = 1/1) indicated the reaction of the starting material was complete and a new main spot formed. 100 mL water was added to the reaction mixture to quench the reaction. The mixture was extracted with ethyl acetate (100 mL × 4). The organic phases were combined, washed with saturated sodium chloride solution, dried over anhydrous sodium sulfate, and concentrated under reduced pressure to obtain a crude product. The crude product was purified by column chromatography (petroleum ether/ethyl acetate = 1/1) to obtain the target product 5-(difluoromethoxy)pyridin-3-amine (3 g, 18.7 mmol, 83.94% yield).

Step 3: Synthesis of 6-(difluoromethoxy)thiazolo[5,4-b]pyridin-2-amine

In an ice bath at 0 ℃, 5-(difluoromethoxy)pyridin-3-amine (2.00 g, 12.5 mmol, 1.00 eq) and KSCN (9.71 g, 100 mmol, 9.68 mL, 8.00 eq) were dissolved in AcOH (6 mL). A solution of Br_2 (5.99 g, 37.5 mmol, 1.93 mL, 3.00 eq) in AcOH (2 mL) was slowly added dropwise, keeping the reaction temperature below 0 ℃. After the addition, the mixture was allowed to warm naturally to 20 ℃ and stirred for 8 hours.

TLC (petroleum ether/ethyl acetate = 2/1) indicated the reaction of the starting material was incomplete and a new spot for the target product formed. 5 mL water was added, and the mixture was heated to 85 ℃. The mixture was filtered while hot. The filter cake was added to 1.5 mL acetic acid, heated to 85 ℃, and filtered while hot. The two filtrates were combined, and the pH was adjusted to 8 with ammonia water in an ice-water bath, resulting in the precipitation of a large amount of yellow solid. The mixture was filtered under reduced pressure, and the filter cake was dried. The resultant was mixed with silica gel and purified by column chromatography (petroleum ether/ethyl acetate = 2/1) to obtain the target solid product 6-(difluoromethoxy)thiazolo[5,4-b]pyridin-2-amine as a yellow solid (460 mg, 2.12 mmol, 16.96% yield). LCMS (ESI) m/z = 218.0 $[M+H]^+$.

Step 4: Synthesis of 2-chloro-6-(difluoromethoxy)thiazolo[5,4-b]pyridine

At room temperature, 6-(difluoromethoxy)thiazolo[5,4-b]pyridin-2-amine (450 mg, 2.07 mmol, 1.00 eq) was dissolved in acetonitrile (10 mL). Under nitrogen protection, isoamyl nitrite (364 mg, 3.11 mmol, 418 μL, 1.50 eq) and $CuCl_2$ (334 mg, 2.49 mmol, 1.20 eq) were added. The mixture was stirred at 25 ℃ for 12 hours.

LCMS showed the MS of the target product (RT = 0.524 min, m/z = 236.9 $[M+H]^+$). 20 mL saturated ammonium chloride solution was added, and the mixture was stirred for 10 minutes. 100 mL water was added to dilute the mixture, followed by extraction with ethyl acetate (150 mL × 4). The organic phases were combined, washed with saturated sodium chloride solution, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The resultant was purified by column chromatography (petroleum ether/ethyl acetate = 5/1) to obtain the target product 2-chloro-6-(difluoromethoxy)thiazolo[5,4-b]pyridine as a white solid (275 mg, 1.16 mmol, 56.09% yield). LCMS (ESI) m/z = 236.9 $[M+H]^+$.

Step 5: Synthesis of 6'-(((1S,3S)-3-((6-(difluoromethoxy)thiazolo[5,4-b]pyridin-2-yl)amino)cyclopentyl)amino)-2H-[1,3'-bipyridin]-2-one

At room temperature, 2-chloro-6-(difluoromethoxy)thiazolo[5,4-b]pyridine (100 mg, 423 μmol, 1.00 eq), 6'-(((1S,3S)-3-aminocyclopentyl)amino)-2H-[1,3'-bipyridin]-2-one (114 mg, 423

μmol, 1 eq), and TEA (128 mg, 1.27 mmol, 176 μL, 3.00 eq) were added to DMSO (2.00 mL). The mixture was stirred at 70 ℃ for 6 hours.

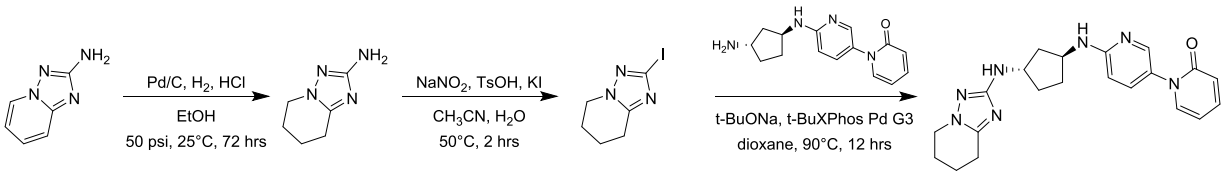
LCMS showed the MS of the target product (RT = 0.417 min, m/z = 471.2 $[M+H]^+$). The mixture was cooled to room temperature. 10 mL water was added to dilute the mixture, followed by extraction with ethyl acetate (60 mL × 4). The organic phases were combined, washed with saturated sodium chloride solution, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The resultant was purified by column chromatography (petroleum ether/ethyl acetate = 0/1) to obtain the target product 6'-(((1S,3S)-3-((6-(difluoromethoxy)thiazolo[5,4-b]pyridin-2-yl)amino)cyclopentyl)amino)-2H-[1,3'-bipyridin]-2-one as a pale yellow solid (198 mg, 421 μmol, 99.58% yield).

LCMS (ESI) m/z = 471.2 $[M+H]^+$.

^{1}H NMR (400 MHz, DMSO-d_6): δ 8.67 (d, J = 6.8 Hz, 1H), 8.01 (d, J = 2.4 Hz, 1H), 7.93 (d, J = 2.6 Hz, 1H), 7.60 (dd, J = 1.6, 6.8 Hz, 1H), 7.56 (d, J = 2.5 Hz, 1H), 7.51 - 7.07 (m, 3H), 6.97 (d, J = 6.9 Hz, 1H), 6.53 (d, J = 8.9 Hz, 1H), 6.44 (d, J = 8.9 Hz, 1H), 6.27 (dt, J = 1.2, 6.7 Hz, 1H), 4.46 - 4.28 (m, 2H), 2.28 - 2.11 (m, 2H), 2.06 - 1.87 (m, 2H), 1.69 - 1.45 (m, 2H).

Example C4

Synthesis of 6'-(((1S,3S)-3-((5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyridin-2-yl)amino)cyclopentyl)amino)-2H-[1,3'-bipyridin]-2-one



Step 1: Synthesis of 5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyridin-2-amine

At 25 ℃, [1,2,4]triazolo[1,5-a]pyridin-2-amine (2.50 g, 18.6 mmol, 1.00 eq), wet palladium on carbon (0.40 g, 10% purity), and HCl (3.65 mL, 36.5% purity, 2.00 eq) were dissolved in ethanol (30 mL). The atmosphere was then replaced with hydrogen three times. The mixture was reacted under a hydrogen atmosphere (50 psi) for 72 hours.

LCMS detected the MS value of the product. After completion of the reaction, the mixture was filtered and concentrated to obtain 5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyridin-2-amine (2.50 g, 97.1% yield). MS (ESI) m/z = 139.1 $[M+1]^+$.

Step 2: Synthesis of 2-iodo-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyridine

5,6,7,8-Tetrahydro-[1,2,4]triazolo[1,5-a]pyridin-2-amine (0.20 g, 1.45 mmol, 1.00 eq), potassium iodide (601 mg, 3.62 mmol, 2.50 eq), p-toluenesulfonic acid (997 mg, 5.79 mmol,

4.00 eq), and sodium nitrite (200 mg, 2.89 mmol, 2.00 eq) were dissolved in acetonitrile (2 mL) and water (0.40 mL). The mixture was then heated to 50 ℃ and reacted for 2 hours.

TLC (dichloromethane:methanol = 20:1) indicated the starting material was completely consumed (R_f = 0.24).

The reaction mixture was concentrated, then diluted with ethyl acetate (50 mL) and water (70 mL). The phases were separated. The aqueous phase was extracted with ethyl acetate (20 mL × 3). The organic phases were combined, washed with saturated brine (30 mL × 2), dried over anhydrous sodium sulfate, filtered, and concentrated to obtain a crude product. The crude product was purified by column chromatography (petroleum ether:ethyl acetate = 50:1 to 1:1) to obtain 2-iodo-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyridine (250 mg, 69.4% yield).

Step 3: Synthesis of 6'-(((1S,3S)-3-((5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyridin-2-yl)amino)cyclopentyl)amino)-2H-[1,3'-bipyridin]-2-one

2-Iodo-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyridine (200 mg, 1.00 eq), 6'-(((1S,3S)-3-aminocyclopentyl)amino)-2H-[1,3'-bipyridin]-2-one (217 mg, 1.00 eq), sodium tert-butoxide (232 mg, 2.41 mmol, 3.00 eq), and t-BuXPhos Pd G3 (63.8 mg, 0.10 eq) were dissolved in 1,4-dioxane (15 mL). The atmosphere was purged with nitrogen three times. The mixture was then heated to 90 ℃ and reacted for 12 hours.

LCMS detected the MS value of the product.

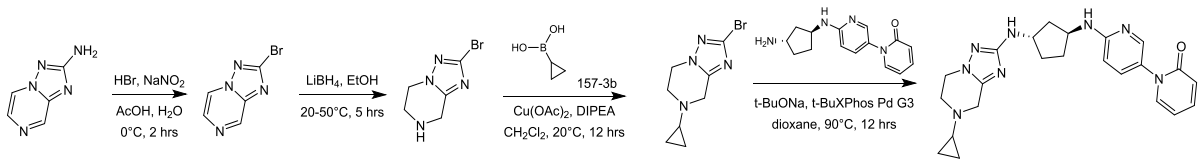
The reaction mixture was concentrated to obtain a crude product. The crude product was purified by reverse-phase preparative chromatography (Column: C18 150×30mm; Mobile phase: [water (FA)-ACN]; Gradient: 2% to 32% B over 7 min) to obtain 6'-(((1S,3S)-3-((5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyridin-2-yl)amino)cyclopentyl)amino)-2H-[1,3'-bipyridin]-2-one (45 mg, 13.80% yield, 96.4% purity).

LCMS (ESI) m/z = 392.2 $[M+1]^+$.

^{1}H NMR (400 MHz, CD3OD): δ 7.98 - 7.89 (m, 1H), 7.66 - 7.54 (m, 2H), 7.49 - 7.36 (m, 1H), 6.61 (dd, J = 5.2, 8.8 Hz, 2H), 6.47 (dt, J = 1.2, 6.8 Hz, 1H), 4.40 - 4.27 (m, 1H), 4.06 (quintet, J = 6.4 Hz, 1H), 3.94 (t, J = 6.0 Hz, 2H), 2.74 (t, J = 6.4 Hz, 2H), 2.66 (s, 1H), 2.35 - 2.16 (m, 2H), 2.09 - 1.87 (m, 5H), 1.66 - 1.51 (m, 2H).

Example C5

Synthesis of 6'-(((1S,3S)-3-((7-cyclopropyl-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyrazin-2-yl)amino)cyclopentyl)amino)-2H-[1,3'-bipyridin]-2-one



Step 1: Synthesis of 2-bromo-[1,2,4]triazolo[1,5-a]pyrazine

At 0 ℃, [1,2,4]triazolo[1,5-a]pyrazin-2-amine (7.00 g, 51.8 mmol, 1.00 eq) and hydrobromic acid (29.3 mL, 48% purity, 5.00 eq) were dissolved in acetic acid (40 mL). A solution of sodium nitrite (7.15 g, 2.00 eq) in water (40 mL) was then added dropwise to the reaction mixture. After the addition, the reaction was maintained for 2 hours.

LCMS detected the MS value of the product.

The reaction mixture was concentrated, then diluted with water (100 mL) and ethyl acetate (60 mL). The aqueous phase was extracted with ethyl acetate (20 mL × 3). The organic phases were combined, washed with saturated brine (30 mL × 3), dried over anhydrous sodium sulfate, filtered, and concentrated to obtain a crude product. The crude product was purified by column chromatography (petroleum ether:ethyl acetate = 20:1 to 1:1) to obtain 2-bromo-[1,2,4]triazolo[1,5-a]pyrazine (3.50 g, 33.9% yield). LCMS (ESI) m/z = 200.9 $[M+1]^+$.

Step 2: Synthesis of 2-bromo-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyrazine

At 20 ℃, 2-bromo-[1,2,4]triazolo[1,5-a]pyrazine (3.00 g, 1.00 eq) was dissolved in ethanol (20 mL). Lithium borohydride (2.00 M, 30.2 mL, 4.00 eq) was then added to the solution. After the addition, the reaction mixture was heated to 50 ℃ and reacted for 5 hours.

LCMS detected the MS value of the product.

After completion of the reaction, the mixture was quenched with 1 M hydrochloric acid (800 mL). The mixture was then washed with ethyl acetate (30 mL × 2), and the organic phases were discarded. The aqueous phase was adjusted to pH = 9 with saturated sodium carbonate solution and then extracted with dichloromethane (40 mL × 5). The organic phases from the second extraction were washed with saturated brine (30 mL × 2), dried over anhydrous sodium sulfate, filtered, and concentrated to obtain a crude product. The crude product was purified by reverse-phase preparative chromatography (Column: Waters Xbridge 150*25mm 5um; Mobile phase: [water (NH_4HCO_3)-ACN]; Gradient: 1% to 30% B over 9 min) to obtain 2-bromo-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyrazine (1.60 g, 52.3% yield). MS (ESI) m/z = 203.0 $[M+1]^+$.

Step 3: Synthesis of 2-bromo-7-cyclopropyl-6,8-dihydro-5H-[1,2,4]triazolo[1,5-a]pyrazine

2-Bromo-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyrazine (0.70 g, 3.45 mmol, 1.00 eq), cyclopropylboronic acid (4441 mg, 5.17 mmol, 1.50 eq), copper(II) acetate (1.25 g, 6.90 mmol,

2.00 eq), and N,N-diisopropylethylamine (891 mg, 1.20 mL, 2.00 eq) were dissolved in dichloromethane (2 mL). The mixture was then stirred at 20 ℃ for 12 hours.

LCMS detected the MS value of the product.

The reaction mixture was diluted with dichloromethane (50 mL) and water (30 mL). The aqueous phase was then extracted with dichloromethane (10 mL × 4). The organic phases were combined, washed with saturated brine (20 mL), dried over anhydrous sodium sulfate, filtered, and concentrated to obtain a crude product. The crude product was purified by column chromatography (petroleum ether:ethyl acetate = 20:1 to 1:1) to obtain 2-bromo-7-cyclopropyl-6,8-dihydro-5H-[1,2,4]triazolo[1,5-a]pyrazine (160 mg, 19.09% yield). MS (ESI) m/z = 243.0 $[M+1]^+$.

Step 4: Synthesis of 6'-(((1S,3S)-3-((7-cyclopropyl-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyrazin-2-yl)amino)cyclopentyl)amino)-2H-[1,3'-bipyridin]-2-one

2-Bromo-7-cyclopropyl-6,8-dihydro-5H-[1,2,4]triazolo[1,5-a]pyrazine (140 mg, 1.00 eq), 6'-(((1S,3S)-3-aminocyclopentyl)amino)-2H-[1,3'-bipyridin]-2-one (156 mg, 1.00 eq), sodium tert-butoxide (166 mg, 3.00 eq), and t-BuXPhos Pd G3 (45.7 mg, 0.10 eq) were dissolved in 1,4-dioxane (12 mL). The atmosphere was purged with nitrogen three times. The mixture was then heated to 90 ℃ and reacted for 12 hours.

LCMS detected the MS value of the product.

The reaction mixture was concentrated to obtain a crude product. The crude product was purified by reverse-phase preparative chromatography (Column: C18 150×30mm; Mobile phase: [water (FA)-ACN]; Gradient: 5% to 35% B over 7 min and Column: C18 150×30mm; Mobile phase: [water (FA)-ACN]; Gradient: 5% to 35% B over 7 min) to obtain 6'-(((1S,3S)-3-((7-cyclopropyl-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyrazin-2-yl)amino)cyclopentyl)amino)-2H-[1,3'-bipyridin]-2-one (20 mg, 8.03% yield).

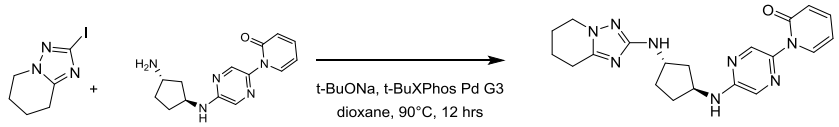
LCMS (ESI) m/z = 433.2 $[M+1]^+$.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.03 (d, J = 2.4 Hz, 1H), 7.52 (dd, J = 2.4, 8.8 Hz, 1H), 7.39 (ddd, J = 2.4, 6.8, 9.2 Hz, 1H), 7.30 (dd, J = 2.0, 7.2 Hz, 1H), 6.65 (d, J = 9.2 Hz, 1H), 6.44 (d, J = 8.8 Hz, 1H), 6.23 (dt, J = 1.2, 6.8 Hz, 1H), 4.77 (br dd, J = 1.2, 5.6 Hz, 1H), 4.28 - 4.12 (m, 2H), 4.07 - 3.95 (m, 3H), 3.79 (s, 2H), 3.12 (t, J = 5.6 Hz, 2H), 2.39 - 2.23 (m, 2H), 2.11 - 1.97 (m, 2H), 1.95 - 1.86 (m, 1H), 0.62 - 0.55 (m, 2H), 0.54 - 0.48 (m, 2H).

Example C6

Synthesis of 1-(5-(((1S,3S)-3-((5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyridin-2-yl)amino)cyclopentyl)amino

)pyrazin-2-yl)pyridin-2(1H)-one



Step 1: Synthesis of 1-(5-(((1S,3S)-3-((5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyridin-2-yl)amino)cyclopentyl)amino)pyrazin-2-yl)pyridin-2(1H)-one

2-Iodo-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyridine (300 mg, 1.00 eq), 1-(5-(((1S,3S)-3-aminocyclopentyl)amino)pyrazin-2-yl)pyridin-2(1H)-one (327 mg, 1.00 eq), sodium tert-butoxide (347 mg, 3.61 mmol, 3.00 eq), and t-BuXPhos Pd G3 (95.7 mg, 0.10 eq) were dissolved in 1,4-dioxane (10 mL). The atmosphere was purged with nitrogen three times. The mixture was then heated to 90 ℃ and reacted for 12 hours.

LCMS detected the MS value of the product.

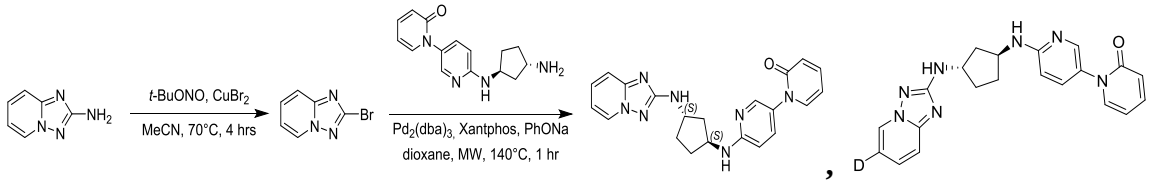
The reaction mixture was concentrated to obtain a crude product. The crude product was purified by reverse-phase preparative chromatography (Column: Waters Xbridge 150*25mm* 5um; Mobile phase: [water (ammonium hydroxide v/v)-ACN]; Gradient: 0% to 25% B over 10 min) to obtain 1-(5-(((1S,3S)-3-((5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyridin-2-yl)amino)cyclopentyl)amino)pyrazin-2-yl)pyridin-2(1H)-one (30 mg, 6.35% yield).

LCMS (ESI) m/z = 391.1 [M-1]+.

^{1}H NMR: (400 MHz, CDCl3): δ 7.76 (d, J = 1.2 Hz, 1H), 7.63 (dd, J = 2.0, 6.8 Hz, 1H), 7.38 (ddd, J = 2.0, 6.8, 9.2 Hz, 1H), 6.64 (d, J = 9.2 Hz, 1H), 6.32 - 6.22 (m, 1H), 4.93 (br d, J = 6.8 Hz, 1H), 4.41 - 4.29 (m, 1H), 4.24 - 4.12 (m, 1H), 4.04 (br d, J = 6.8 Hz, 1H), 3.97 (t, J = 6.0 Hz, 2H), 2.78 (t, J = 6.4 Hz, 2H), 2.42 - 2.25 (m, 2H), 2.12 - 1.99 (m, 4H), 1.96 - 1.87 (m, 2H), 1.60 - 1.51 (m, 2H).

Example C7

Synthesis of 6'-(((1S,3S)-3-([1,2,4]triazolo[1,5-a]pyridin-2-ylamino)cyclopentyl)amino)-2H-[1,3'-bipyridin]-2 -one



Step 1: Synthesis of 2-bromo-[1,2,4]triazolo[1,5-a]pyridine

[1,2,4]Triazolo[1,5-a]pyridin-2-amine (1.90 g, 14.2 mmol, 1.0 eq), copper(II) bromide (4.75 g, 21.3 mmol, 1.5 eq), and tert-butyl nitrite (2.19 g, 21.3 mmol, 1.50 eq) were dissolved in acetonitrile (30 mL). The mixture was stirred at 70 ℃ for 4 hours. TLC (petroleum ether/ethyl acetate = 1/1) indicated the completion of the reaction. The reaction mixture was cooled to room temperature, diluted with water (50 mL), and extracted with ethyl acetate (30 mL × 2). The organic phases were combined, washed with saturated brine (100 mL × 2), dried over anhydrous sodium sulfate, filtered, and concentrated to obtain 2-bromo-[1,2,4]triazolo[1,5-a]pyridine (2.17 g, 11.0 mmol, 77.4% yield). This was used directly in the next step without purification. LCMS MS (ESI) m/z = 200.0 $[M+1]^+$.

Step 2: Synthesis of 6'-(((1S,3S)-3-([1,2,4]triazolo[1,5-a]pyridin-2-ylamino)cyclopentyl)amino)-2H-[1,3'-bipyridin]-2-one

2-Bromo-[1,2,4]triazolo[1,5-a]pyridine (100 mg, 505 μmol, 1.0 eq), 6'-(((1S,3S)-3-aminocyclopentyl)amino)-2H-[1,3'-bipyridin]-2-one (150 mg, 556 μmol, 1.1 eq), XantPhos (23.4 mg, 40.4 μmol, 0.08 eq), sodium phenoxide (87.9 mg, 758 μmol, 1.5 eq), and $Pd_2(dba)_3$ (18.5 mg, 20.2 μmol, 0.04 eq) were dissolved in 1,4-dioxane (4 mL). The mixture was stirred at 140 ℃ under microwave irradiation for 1 hour. LCMS detected the MS value of the product (RT = 0.347 min). The reaction mixture was filtered. The filtrate was concentrated to obtain a crude product. The crude product was first purified by reverse-phase preparative chromatography (Column: Waters Xbridge 150*25mm* 5um; Mobile phase: [water (NH_4HCO_3)-ACN]; Gradient: 12% to 42% B over 9 min) to obtain 6'-(((1S,3S)-3-([1,2,4]triazolo[1,5-a]pyridin-2-ylamino)cyclopentyl)amino)-2H-[1,3'-bipyridin]-2-one (a total of 4 parallel batches under microwave irradiation, 83.1 mg, 211 μmol, 10.5% yield, 98.4% purity).

LCMS MS (ESI) m/z = 388.2 $[M+1]^+$.

^{1}H NMR, (400 MHz, DMSO-d_6): δ 8.61 - 8.55 (m, 1H), 7.92 (d, J = 2.8 Hz, 1H), 7.60 (dd, J = 1.6, 6.8 Hz, 1H), 7.47 (ddd, J = 2.1, 6.7, 9.1 Hz, 1H), 7.44 - 7.34 (m, 2H), 6.92 (d, J = 6.9 Hz, 1H), 6.85 (dt, J = 1.6, 6.8 Hz, 1H), 6.64 (d, J = 7.3 Hz, 1H), 6.53 (d, J = 8.8 Hz, 1H), 6.44 (d, J = 8.8 Hz, 1H), 6.26 (dt, J = 1.3, 6.7 Hz, 1H), 4.40 - 4.26 (m, 1H), 4.18 (sext, J = 6.7 Hz, 1H), 2.21 - 2.09 (m, 2H), 2.00 - 1.84 (m, 2H), 1.63 - 1.43 (m, 2H).

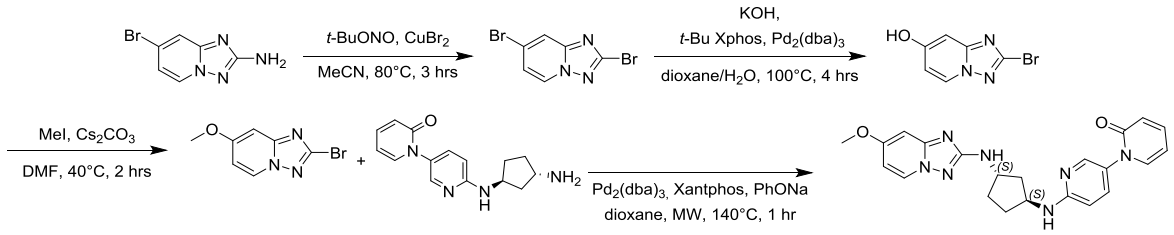
Wherein, using this preparation method combined with a deuteration preparation method, the deuterated Compound C7A of Compound C7 was prepared, with the structure as follows:

Identification data: ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.59 (s, 1H), 7.92 (d, J = 2.7 Hz, 1H), 7.61 (dd, J = 6.8, 2.1 Hz, 1H), 7.53 – 7.46 (m, 1H), 7.46 – 7.33 (m, 3H), 6.94 (d, J = 6.9 Hz, 1H),

6.66 (d, J = 7.3 Hz, 1H), 6.53 (d, J = 8.9 Hz, 1H), 6.49 – 6.40 (m, 1H), 6.27 (td, J = 6.7, 1.4 Hz, 1H), 4.33 (q, J = 6.6 Hz, 1H), 4.19 (q, J = 6.7 Hz, 1H), 2.15 (ddt, J = 12.1, 7.0, 4.5 Hz, 2H), 1.97 (dt, J = 13.4, 6.8 Hz, 1H), 1.93 – 1.83 (m, 1H), 1.65 – 1.40 (m, 2H).

Example C8

Synthesis of 6'-(((1S,3S)-3-((7-methoxy-[1,2,4]triazolo[1,5-a]pyridin-2-yl)amino)cyclopentyl)amino)-2H-[1,3'-bipyridin]-2-one



Step 1: Synthesis of 2,7-dibromo-[1,2,4]triazolo[1,5-a]pyridine

7-Bromo-[1,2,4]triazolo[1,5-a]pyridin-2-amine (2.00 g, 9.39 mmol, 1.0 eq), copper(II) bromide (3.15 g, 14.1 mmol, 1.5 eq), and tert-butyl nitrite (1.45 g, 14.1 mmol, 1.5 eq) were dissolved in acetonitrile (120 mL). The mixture was stirred at 80 ℃ for 3 hours. LCMS detected the MS value of the product (RT = 0.452 min). The reaction mixture was cooled to room temperature, diluted with water (200 mL), and extracted with ethyl acetate (80 mL × 2). The organic phases were combined, washed with saturated brine (200 mL × 2), dried over anhydrous sodium sulfate, filtered, and concentrated to obtain 2,7-dibromo-[1,2,4]triazolo[1,5-a]pyridine (2.00 g, 7.22 mmol, 76.9% yield). This was used directly in the next step without purification. LCMS MS (ESI) m/z = 277.9 $[M+1]^+$.

Step 2: Synthesis of 2-bromo-[1,2,4]triazolo[1,5-a]pyridin-7-ol

2,7-Dibromo-[1,2,4]triazolo[1,5-a]pyridine (2.00 g, 7.22 mmol, 1.0 eq), potassium hydroxide (1.20 g, 21.7 mmol, 3.0 eq), t-Bu XPhos (675 mg, 1.59 mmol, 0.22 eq), and Pd2(dba)3 (728 mg, 794 μmol, 0.11 eq) were dissolved in 1,4-dioxane (20 mL) and water (5 mL). The mixture was stirred at 100 ℃ for 4 hours. LCMS detected the MS value of the product (RT = 0.358 min). The reaction mixture was cooled to room temperature. Water (60 mL) and ethyl acetate (40 mL) were added to dilute the mixture. The organic phase was separated and discarded. The aqueous phase was adjusted to pH = 5 with dilute hydrochloric acid and then extracted with ethyl acetate (60 mL × 2). The organic phases were combined, washed with saturated brine (100 mL × 2), dried over anhydrous sodium sulfate, filtered, and concentrated to obtain 2-bromo-[1,2,4]triazolo[1,5-a]pyridin-7-ol (860 mg, 3.97 mmol, 54.9% yield, 98.7% purity). This was used directly in the next step without purification. LCMS MS (ESI) m/z = 215.9

$[M+1]^+$.

Step 3: Synthesis of 2-bromo-7-methoxy-[1,2,4]triazolo[1,5-a]pyridine

2-Bromo-[1,2,4]triazolo[1,5-a]pyridin-7-ol (1.30 g, 6.07 mmol, 1.0 eq) and cesium carbonate (4.95 g, 15.2 mmol, 2.5 eq) were dissolved in N,N-dimethylformamide (20 mL). Iodomethane (1.72 g, 12.2 mmol, 2.0 eq) was then added to the reaction mixture. After the addition, the mixture was stirred at 40 ℃ for 2 hours. TLC (petroleum ether/ethyl acetate = 3/1) indicated the completion of the reaction. The reaction mixture was cooled to room temperature, diluted with water (100 mL), and extracted with ethyl acetate (30 mL × 2). The organic phases were combined, washed with saturated brine (50 mL × 2), dried over anhydrous sodium sulfate, filtered, and concentrated to obtain a crude product. The crude product was purified by silica gel column chromatography to obtain 2-bromo-7-methoxy-[1,2,4]triazolo[1,5-a]pyridine (1.00 g, 4.39 mmol, 72.2% yield).

Step 4: Synthesis of 6'-(((1S,3S)-3-((7-methoxy-[1,2,4]triazolo[1,5-a]pyridin-2-yl)amino)cyclopentyl)amino)-2H-[1,3'-bipyridin]-2-one

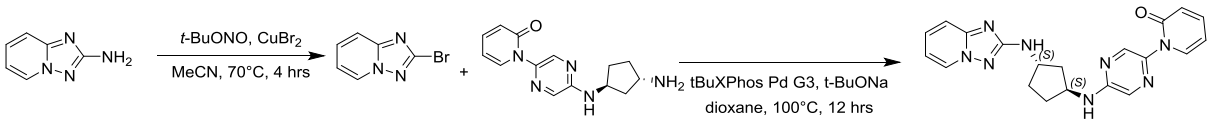
2-Bromo-7-methoxy-[1,2,4]triazolo[1,5-a]pyridine (100 mg, 439 μmol, 1 eq), 6'-(((1S,3S)-3-aminocyclopentyl)amino)-2H-[1,3'-bipyridin]-2-one (130 mg, 482 μmol, 1.1 eq), XantPhos (20.3 mg, 35.1 μmol, 0.08 eq), sodium phenoxide (76.4 mg, 658 μmol, 1.5 eq), and Pd2(dba)3 (16.1 mg, 17.5 μmol, 0.04 eq) were dissolved in 1,4-dioxane (5 mL). The mixture was stirred at 140 ℃ under microwave irradiation for 1 hour. LCMS detected the MS value of the product (RT = 0.366 min). The reaction mixture was filtered. The filtrate was concentrated to obtain a crude product. The crude product was first purified by reverse-phase preparative chromatography under acidic conditions (Column: Phenomenex luna C18 150*40mm* 15um; Mobile phase: [water (FA)-ACN]; Gradient: 20% to 50% B over 15 min), and then further purified by reverse-phase preparative chromatography under basic conditions (Column: Waters Xbridge 150*25mm* 5um; Mobile phase: [water (ammonium hydroxide v/v)-ACN]; Gradient: 0% to 30% B over 10 min) to obtain 6'-(((1S,3S)-3-((7-methoxy-[1,2,4]triazolo[1,5-a]pyridin-2-yl)amino)cyclopentyl)amino)-2H-[1,3'-bipyridin]-2-one (a total of 8 parallel batches under microwave irradiation, 69.9 mg, 166 μmol, 4.72% yield, 98.9% purity).

LCMS MS (ESI) m/z = 418.2 $[M+1]^+$. ^{1}H NMR, (400 MHz, DMSO-d_6): δ 8.39 (d, J = 7.4 Hz, 1H), 7.91 (d, J = 2.6 Hz, 1H), 7.59 (dd, J = 1.7, 6.8 Hz, 1H), 7.47 (ddd, J = 2.0, 6.7, 9.1 Hz, 1H), 7.39 (dd, J = 2.6, 8.9 Hz, 1H), 6.89 (d, J = 6.9 Hz, 1H), 6.81 (d, J = 2.6 Hz, 1H), 6.58 - 6.38 (m, 4H), 6.26 (dt, J = 1.3, 6.7 Hz, 1H), 4.31 (sext, J = 6.4 Hz, 1H), 4.13 (sext, J = 6.7 Hz, 1H),

3.82 (s, 3H), 2.19 - 2.08 (m, 2H), 1.99 - 1.82 (m, 2H), 1.62 - 1.44 (m, 2H).

Example C9

Synthesis of 1-(5-(((1S,3S)-3-([1,2,4]triazolo[1,5-a]pyridin-2-ylamino)cyclopentyl)amino)pyrazin-2-yl)pyridin-2(1H)-one



Step 1: Synthesis of 2-bromo-[1,2,4]triazolo[1,5-a]pyridine

[1,2,4]Triazolo[1,5-a]pyridin-2-amine (1.90 g, 14.2 mmol, 1.0 eq), copper(II) bromide (4.75 g, 21.3 mmol, 1.5 eq), and tert-butyl nitrite (2.19 g, 21.3 mmol, 1.50 eq) were dissolved in acetonitrile (30 mL). The mixture was stirred at 70 ℃ for 4 hours. TLC (petroleum ether/ethyl acetate = 1/1) indicated the completion of the reaction. The reaction mixture was cooled to room temperature, diluted with water (50 mL), and extracted with ethyl acetate (30 mL × 2). The organic phases were combined, washed with saturated brine (100 mL × 2), dried over anhydrous sodium sulfate, filtered, and concentrated to obtain 2-bromo-[1,2,4]triazolo[1,5-a]pyridine (2.17 g, 11.0 mmol, 77.4% yield). This was used directly in the next step without purification. LCMS MS (ESI) m/z = 200.0 $[M+1]^+$.

Step 2: Synthesis of 1-(5-(((1S,3S)-3-([1,2,4]triazolo[1,5-a]pyridin-2-ylamino)cyclopentyl)amino)pyrazin-2-yl)pyridin-2(1H)-one

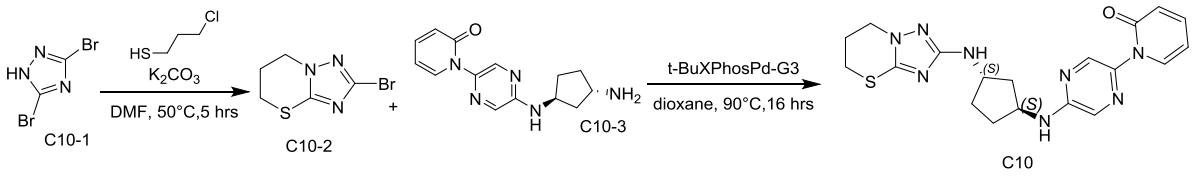
2-Bromo-[1,2,4]triazolo[1,5-a]pyridine (300 mg, 1.51 mmol, 1.0 eq), 1-(5-((((1S,3S)-3-aminocyclopentyl)amino)pyrazin-2-yl)pyridin-2(1H)-one (411 mg, 1.51 mmol, 1.0 eq), sodium tert-butoxide (437 mg, 4.54 mmol, 3.0 eq), and tBuXPhos Pd G3 (120 mg, 152 μmol, 0.10 eq) were dissolved in 1,4-dioxane (10 mL). The mixture was stirred at 100 ℃ for 12 hours. LCMS detected the MS value of the product (RT = 0.394 min). The reaction mixture was filtered. The filtrate was concentrated to obtain a crude product. The crude product was purified by reverse-phase preparative chromatography (Column: Phenomenex luna C18 150*40mm* 15um; Mobile phase: [water (FA)-ACN]; Gradient: 10% to 40% B over 15 min) to obtain 1-(5-(((1S,3S)-3-([1,2,4]triazolo[1,5-a]pyridin-2-ylamino)cyclopentyl)amino)pyrazin-2-yl)pyridin-2(1H)-one (79.6 mg, 201 μmol, 13.2% yield, 97.9% purity).

LCMS MS (ESI) m/z = 389.2 $[M+1]^+$. ^{1}H NMR, (400 MHz, DMSO-d_6): δ 8.62 - 8.54 (m, 1H), 8.25 (d, J = 1.4 Hz, 1H), 7.87 (d, J = 1.3 Hz, 1H), 7.72 (dd, J = 1.5, 6.9 Hz, 1H), 7.56 - 7.32 (m, 4H), 6.87 (dt, J = 1.5, 6.8 Hz, 1H), 6.66 (d, J = 7.3 Hz, 1H), 6.47 (d, J = 9.0 Hz, 1H), 6.32 (dt,

J = 1.3, 6.7 Hz, 1H), 4.41 - 4.15 (m, 2H), 2.25 - 2.11 (m, 2H), 2.06 - 1.86 (m, 2H), 1.67 - 1.47 (m, 2H).

Example C10

Synthesis of 1-(5-(((1S,3S)-3-((6,7-dihydro-5H-[1,2,4]triazolo[5,1-b][1,3]thiazin-2-yl)amino)cyclopentyl)amino)pyrazin-2-yl)pyridin-2(1H)-one



Step 1: Synthesis of 2-bromo-6,7-dihydro-5H-[1,2,4]triazolo[5,1-b][1,3]thiazine

Compound C10-1 (3.00 g, 13.2 mmol, 1.00 eq), 3-chloropropane-1-thiol (1.76 g, 15.8 mmol, 1.55 mL, 1.20 eq), and K_2CO_3 (3.60 g, 26.5 mmol, 2.00 eq) were dissolved in DMF (20 mL). The reaction mixture was stirred at 50 ℃ for 5 hours.

LCMS detected the formation of the target product. 200 mL water was added to quench the reaction. The mixture was extracted with ethyl acetate (100 mL × 3). The organic phases were combined, washed with saturated brine (100 mL × 2), dried over anhydrous sodium sulfate, filtered, and concentrated. The solid of organic phases reaction mixture was purified by normal-phase silica gel column chromatography (petroleum ether:ethyl acetate = 1:1) to obtain Compound C10-2 (800 mg, 3.63 mmol, yield: 27.5%) as a white solid.

Step 2: Synthesis of 1-(5-(((1S,3S)-3-((6,7-dihydro-5H-[1,2,4]triazolo[5,1-b][1,3]thiazin-2-yl)amino)cyclopentyl)amino)pyrazin-2-yl)pyridin-2(1H)-one

Under nitrogen protection, Compound C10-3 (300 mg, 1.11 mmol, 1.00 eq), Compound C10-2 (4988 mg, 2.27 mmol, 2.05 eq), t-BuONa (318 mg, 3.32 mmol, 3.00 eq), and [2-(2-aminophenyl)phenyl]methylsulfonyloxy-palladium; ditert-butyl-[2-(2,4,6-triisopropylphenyl)phenyl]phosphine (175 mg, 221 μmol, 0.20 eq) were dissolved in 1,4-dioxane (20 mL). The reaction mixture was stirred at 90 ℃ for 16 hours.

LCMS and HPLC detected the formation of the target product. 200 mL water was added to quench the reaction. The mixture was extracted with ethyl acetate (100 mL × 3). The organic phases were combined, washed with saturated brine (100 mL × 2), dried over anhydrous sodium sulfate, filtered, and concentrated. The organic phase was purified by reverse-phase preparative chromatography (Column: Phenomenex Luna C18 150*25mm*10um; Mobile phase: [water (TFA)-ACN]; Gradient: 12% to 42% B over 11 min) to obtain the target Compound (60.0 mg,

146 μmol, yield: 13.2%) as a pale yellow gummy compound. LC-MS: $[M+H]^+$ = 411.

^{1}H NMR (400 MHz, Chloroform-d) δ 8.52 (s, 1H), 7.73 (d, J = 1.6 Hz, 1H), 7.62 (dd, J = 7.2, 2.1 Hz, 1H), 7.41 – 7.33 (m, 1H), 6.62 (d, J = 9.3 Hz, 1H), 6.33 – 6.21 (m, 1H), 5.01 (d, J = 6.8 Hz, 1H), 4.31 (q, J = 6.6 Hz, 1H), 4.22 – 4.04 (m, 4H), 3.23 – 3.06 (m, 2H), 2.43 – 2.22 (m, 4H), 2.07 – 1.99 (m, 2H), 1.63 – 1.49 (m, 3H).

Example C11

Synthesis of 1-(5-(((1S,3S)-3-((4-oxido-6,7-dihydro-5H-[1,2,4]triazolo[5,1-b][1,3]thiazin-2-yl)amino)cyclopentyl)amino)pyrazin-2-yl)pyridin-2(1H)-one



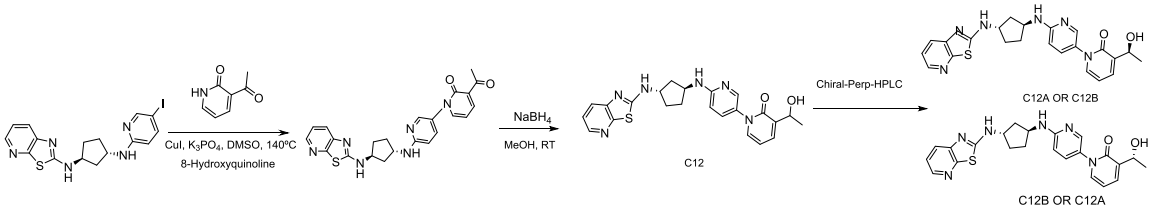
Compound C10 (20.0 mg, 48.7 μmol, 1.00 eq) was dissolved in THF (8.00 mL). $NaIO_4$ (10.4 mg, 48.7 μmol, 2.70 μL, 1.00 eq) dissolved in H_2O (3 mL) was added. The reaction mixture was stirred at 70 ℃ for 12 hours.

LCMS and HPLC detected the formation of the target product. The reaction mixture was directly concentrated under reduced pressure. The compound was purified by reverse-phase preparative chromatography (Column: Phenomenex Luna C18 150*25mm*10um; Mobile phase: [water (TFA)-ACN]; Gradient: 10% to 40% B over 11 min) to obtain the target Compound (18.0 mg, 42.2 μmol, yield: 86.6%) as a white solid. LC-MS: $[M-H]^-$ = 427.1.

^{1}H NMR, (CHLOROFORM-d, 400 MHz): δ 8.54 (dd, 1H, J =1.0, 4.3 Hz), 8.04 (d, 1H, J =5.6 Hz), 7.7-7.8 (m, 1H), 7.52 (ddd, 1H, J =1.9, 6.9, 9.0 Hz), 6.81 (d, 1H, J =9.1 Hz), 6.46 (dt, 1H, J =0.9, 6.8 Hz), 4.3-4.4 (m, 2H), 4.1-4.2 (m, 2H), 3.42 (dd, 1H, J=5.9, 12.6 Hz), 2.9-3.2 (m, 2H), 2.3-2.5 (m, 3H), 2.0-2.2 (m, 2H), 1.6-1.8 (m, 2H).

Example C12

Referring to the preparation methods of the above Examples C1 and C3, Compounds C12, C12A, and C12B were prepared. The synthetic route is as follows:



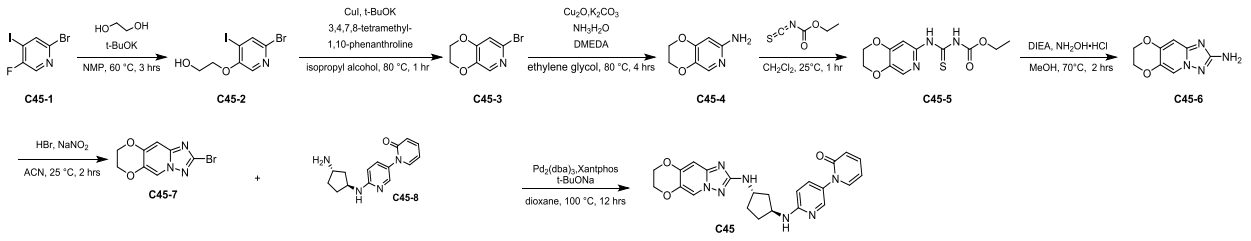
Compound C12 was subjected to chiral separation (Column: CHIRALCEL OD-H 5um 10mm*250mm; Mobile phase: n-hexane/ethanol = 70:30; Flow rate: 5 mL/min; Column temperature: 30 ℃) to obtain white solids C12A and C12B:

Compound C12A, ^{1}H NMR: (400 MHz, DMSO-d_6): δ 8.59 - 8.33 (m, 1H), 8.08 (dd, J = 1.6, 4.8 Hz, 1H), 7.92 (d, J = 2.4 Hz, 1H), 7.66 (dd, J = 1.4, 8.0 Hz, 1H), 7.55 - 7.48 (m, 2H), 7.40 (dd, J = 2.8, 8.9 Hz, 1H), 7.24 (dd, J = 4.8, 8.0 Hz, 1H), 6.96 (d, J = 6.9 Hz, 1H), 6.53 (d, J = 8.9 Hz, 1H), 6.31 (t, J = 6.8 Hz, 1H), 5.06 (br s, 1H), 4.79 - 4.62 (m, 1H), 4.37 (dt, J = 6.4, 13.8 Hz, 2H), 2.27 - 2.12 (m, 2H), 2.04 - 1.90 (m, 2H), 1.65 - 1.48 (m, 2H), 1.26 (d, J = 6.4 Hz, 3H).

Compound C12B, ^{1}H NMR: (400 MHz, DMSO-d_6): δ 8.54 - 8.37 (m, 1H), 8.08 (dd, J = 1.4, 4.8 Hz, 1H), 7.92 (d, J = 2.6 Hz, 1H), 7.66 (dd, J = 1.4, 8.1 Hz, 1H), 7.55 - 7.48 (m, 2H), 7.40 (dd, J = 2.6, 8.9 Hz, 1H), 7.24 (dd, J = 4.8, 8.0 Hz, 1H), 6.96 (d, J = 6.9 Hz, 1H), 6.53 (d, J = 8.9 Hz, 1H), 6.31 (t, J = 6.8 Hz, 1H), 5.06 (d, J = 4.6 Hz, 1H), 4.75 - 4.67 (m, 1H), 4.44 - 4.29 (m, 2H), 2.27 - 2.13 (m, 2H), 2.03 - 1.91 (m, 2H), 1.66 - 1.49 (m, 2H), 1.25 (d, J = 6.4 Hz, 3H).

Example C45

Synthesis of 6'-(((1S,3S)-3-((7,8-dihydro-[1,4]dioxino[2,3-d][1,2,4]triazolo[1,5-a]pyridin-2-yl)amino)cyclopentyl)amino)-2H-[1,3'-bipyridin]-2-one



Step 1: Synthesis of 2-((6-bromo-4-iodopyridin-3-yl)oxy)ethan-1-ol

To a solution of C45-1 (8.00 g, 26.5 mmol, 1.00 eq) and ethylene glycol (55.6 g, 896 mmol, 50 mL, 33.8 eq) in NMP (50 mL) was added t-BuOK (5.95 g, 53.0 mmol, 2.00 eq). The mixture was stirred at 60 ℃ for 3 hours.

LCMS detected the formation of the target product. The reaction mixture was poured into water and extracted with ethyl acetate. The organic phase was washed with saturated sodium chloride solution, dried over anhydrous sodium sulfate, filtered, and concentrated and dried by rotary evaporation. The crude product was purified by reverse-phase HPLC (0.1% FA condition) to obtain Compound C45-2 (3.50 g, 10.1 mmol, 38.4% yield) as a white solid.

Step 2: Synthesis of 7-bromo-2,3-dihydro-[1,4]dioxino[2,3-c]pyridine

To a solution of C45-2 (3.50 g, 10.1 mmol, 1.00 eq) in isopropanol (35 mL) was added CuI (116 mg, 610 μmol, 0.06 eq), t-BuOK (1.60 g, 14.2 mmol, 1.40 eq), and 3,4,7,8-tetramethyl-1,10-phenanthroline (192 mg, 814 μmol, 0.08 eq). Under nitrogen protection, the mixture was stirred at 80 ℃ for 1 hour.

LCMS detected the formation of the target product. The reaction mixture was poured into

water and extracted with ethyl acetate. The organic phase was washed with saturated sodium chloride solution, dried over anhydrous sodium sulfate, filtered, and concentrated and dried by rotary evaporation to obtain Compound C45-3 (2.20 g, 9.12 mmol, 89.6% yield) as a brown solid.

Step 3: Synthesis of 2,3-dihydro-[1,4]dioxino[2,3-c]pyridin-7-amine

Cu_2O (14.5 mg, 101 μmol, 10.4 μL, 0.01 eq), NH_3H_2O (50.9 g, 407 mmol, 56.0 mL, 40.0 eq), K_2CO_3 (281 mg, 2.04 mmol, 0.200 eq), and N',N'-dimethylethane-1,2-diamine (89.7 mg, 1.02 mmol, 111 μL, 0.100 eq) were added to a solution of C45-3 (2.20 g, 10.1 mmol, 1.00 eq) in ethylene glycol (20 mL). The mixture was stirred at 80 ℃ for 4 hours.

LCMS detected the formation of the target product. The reaction mixture was poured into water and extracted with ethyl acetate. The organic phase was washed with saturated sodium chloride solution, dried over anhydrous sodium sulfate, filtered, and concentrated to dryness to obtain Compound C45-4 (1.50 g, crude) as a yellow oily product.

Step 4: Synthesis of ethyl N-((2,3-dihydro-[1,4]dioxino[2,3-c]pyridin-7-yl)carbamothioyl)carbamate

Ethyl N-(thioiminocarbamate) (1.29 g, 9.86 mmol, 1.00 eq) was added to a solution of C45-4 (1.50 g, 9.86 mmol, 1.00 eq) in dichloromethane (15 mL). The mixture was stirred at 25 ℃ for 1 hour.

LCMS detected the formation of the target product. The reaction mixture was poured into water and extracted with dichloromethane. The organic phase was washed with saturated sodium chloride solution, dried over anhydrous sodium sulfate, filtered, and concentrated and dried by rotary evaporation to obtain Compound C45-5 (2.20 g, 7.77 mmol, 78.7% yield) as a yellow solid.

Step 5: Synthesis of 7,8-dihydro-[1,4]dioxino[2,3-d][1,2,4]triazolo[1,5-a]pyridin-2-amine

$NH_2OH.HCl$ (2.43 g, 34.9 mmol, 4.50 eq) and DIEA (3.01 g, 23.30 mmol, 4.06 mL, 3 eq) were added to a solution of C45-5 (2.20 g, 7.77 mmol, 1.00 eq) in methanol (15 mL). The mixture was stirred at 70 ℃ for 2 hours.

LCMS detected the formation of the target product. The reaction mixture was cooled to 25 ℃ and filtered. The filter cake was Compound C45-6 (1.30 g, 6.76 mmol, 87.1% yield) as a white solid.

Step 6: Synthesis of 2-bromo-7,8-dihydro-[1,4]dioxino[2,3-d][1,2,4]triazolo[1,5-a]pyridine

At 0 ℃, $NaNO_2$ (359 mg, 5.20 mmol, 2.00 eq) and HBr (1.21 g, 5.98 mmol, 812 μL, 2.30 eq) were added to a solution of C45-6 (500 mg, 2.60 mmol, 1.00 eq) in acetonitrile (5 mL). The mixture was stirred at 25 ℃ for 2 hours.

LCMS detected the formation of the target product. The reaction mixture was poured into water and extracted with ethyl acetate. The organic phase was washed with saturated sodium chloride solution, dried over anhydrous sodium sulfate, filtered, and concentrated and dried by rotary evaporation to obtain Compound C45-7 (300 mg, 1.17 mmol, 45.0% yield) as a yellow solid.

Step 7: Synthesis of 6'-(((1S,3S)-3-((7,8-dihydro-[1,4]dioxino[2,3-d][1,2,4]triazolo[1,5-a]pyridin-2-yl)amino)cyclopentyl)amino)-2H-[1,3'-bipyridin]-2-one

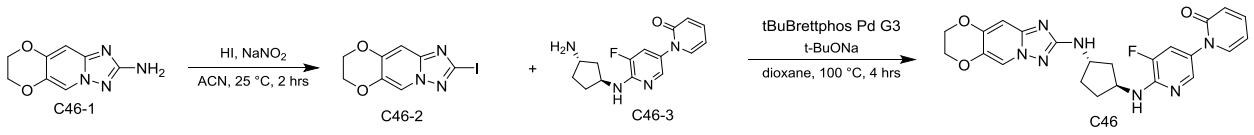
t-BuONa (225 mg, 2.34 mmol, 2.00 eq), $Pd_2(dba)_3$ (107 mg, 117 μmol, 0.100 eq), and XantPhos (135 mg, 234 μmol, 0.200 eq) were added to a solution of C45-7 (300 mg, 1.17 mmol, 1.00 eq) and C45-8 (316 mg, 1.17 mmol, 1.00 eq) in 1,4-dioxane (5 mL). The mixture was stirred under nitrogen protection at 100 ℃ for 12 hours.

LCMS detected the formation of the target product. The reaction mixture was poured into water and extracted with ethyl acetate. The organic phase was washed with saturated sodium chloride solution, dried over anhydrous sodium sulfate, filtered, and concentrated and dried by rotary evaporation. The crude product was purified by reverse-phase preparative chromatography (Column: Waters Xbridge Prep OBD C18 150*40mm*10um; Mobile phase: [water (NH_4HCO_3)-ACN]; Gradient: 10% to 40% B over 52 min) and (Column: Phenomenex luna C18 150*25mm* 10um; Mobile phase: [water (FA)-ACN]; Gradient: 1% to 25% B over 10 min) to obtain the target Compound (36.6 mg).

LC-MS: $[M+H]^+$ = 446.1. ^1H NMR: (DMSO-d_6, 400 MHz): δ (ppm) = 8.38 (s, 1H), 7.91 (d, J = 2.4 Hz, 1H), 7.60 (dd, J = 2.0, 6.8 Hz, 1H), 7.49 - 7.45 (m, 1H), 7.39 (dd, J = 2.8, 8.8 Hz, 1H), 6.90 (d, J = 6.8 Hz, 1H), 6.78 (s, 1H), 6.52 (d, J = 9.2 Hz, 1H), 6.44 (d, J = 9.2 Hz, 1H), 6.36 (d, J = 7.2 Hz, 1H), 6.26 (dt, J = 1.2, 6.8 Hz, 1H), 4.37 - 4.24 (m, 5H), 4.18 - 4.05 (m, 1H), 2.20 - 2.06 (m, 2H), 1.99 - 1.78 (m, 2H), 1.64 - 1.41 (m, 2H).

Example C46

Synthesis of 6'-(((1S,3S)-3-((7,8-dihydro-[1,4]dioxino[2,3-d][1,2,4]triazolo[1,5-a]pyridin-2-yl)amino)cyclopentyl)amino)-5'-fluoro-2H-[1,3'-bipyridin]-2-one



C46-1 C46-2 C46-3 C46

Step 1: Synthesis of 2-iodo-7,8-dihydro-[1,4]dioxino[2,3-d][1,2,4]triazolo[1,5-a]pyridine

At 0 ℃, $NaNO_2$ (215 mg, 3.12 mmol, 2.00 eq) and HI (1.02 g, 3.59 mmol, 600 μL, 2.30 eq)

were added to a solution of C46-1 (300 mg, 1.56 mmol, 1.00 eq) in acetonitrile (5 mL). The mixture was stirred at 25 ℃ for 2 hours.

LCMS detected the formation of the target product. The reaction mixture was poured into water and extracted with ethyl acetate. The organic phase was washed with aqueous sodium bicarbonate, dried over anhydrous sodium sulfate, filtered, and concentrated and dried by rotary evaporation to obtain Compound C46-2 (480 mg, 1.11 mmol, 71.0% yield) as a brown solid.

Step 2: Synthesis of 6'-(((1S,3S)-3-((7,8-dihydro-[1,4]dioxino[2,3-d][1,2,4]triazolo[1,5-a]pyridin-2-yl)amino)cyclopentyl)amino)-5'-fluoro-2H-[1,3'-bipyridin]-2-one

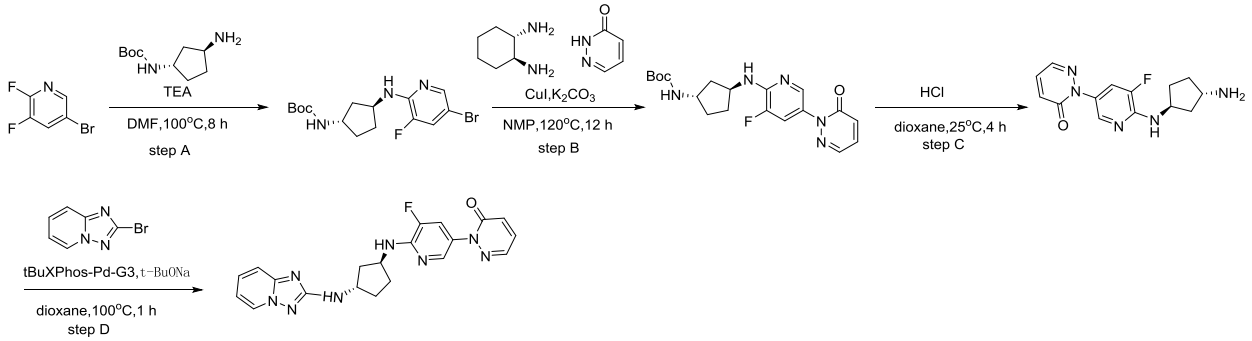
t-BuONa(190.26 mg, 1.98 mmol, 2 eq) and tBuBrettPhos Pd G3 (84.5 mg, 98.9 μmol, 0.100 eq) were added to a solution of C46-2 (300 mg, 989 μmol, 1.00 eq) and C46-3 (285 mg, 989 μmol, 1.00 eq) in 1,4-dioxane (5 mL). Under nitrogen protection, the mixture was stirred at 100 ℃ for 4 hours.

LCMS detected the formation of the target product. The reaction mixture was filtered, and the filtrate was concentrated and dried by rotary evaporation. The crude product was purified by reverse-phase preparative chromatography (Column: Waters Xbridge Prep OBD C18 150*40 mm*10 um; Mobile phase: [water (NH_4HCO_3)-ACN]; Gradient: 16% to 46% B over 15 min) to obtain the target Compound (20.0 mg).

LC-MS: $[M+H]^+$ = 464.1. ^1H NMR: (DMSO-d_6, 400 MHz): δ (ppm) = 8.38 (s, 1H), 7.84 (d, J = 2.0 Hz, 1H), 7.64 (dd, J = 1.6, 6.8 Hz, 1H), 7.57 - 7.45 (m, 2H), 6.90 (br d, J = 7.2 Hz, 1H), 6.78 (s, 1H), 6.46 (d, J = 8.8 Hz, 1H), 6.35 (d, J = 7.2 Hz, 1H), 6.28 (t, J = 6.4 Hz, 1H), 4.57 - 4.47 (m, 1H), 4.35 (br dd, J = 2.0, 5.2 Hz, 2H), 4.31 - 4.24 (m, 2H), 4.17 - 4.07 (m, 1H), 2.18 - 2.06 (m, 2H), 1.99 - 1.90 (m, 2H), 1.63 - 1.50 (m, 2H).

Example C47

Synthesis of 2-(6-(((1S,3S)-3-([1,2,4]triazolo[1,5-a]pyridin-2-ylamino)cyclopentyl)amino)-5-fluoropyridin-3-yl)pyridazin-3(2H)-one



Step A: Synthesis of tert-butyl ((1S,3S)-3-((5-bromo-3-fluoropyridin-2-yl)amino)cyclopentyl)carbamate

At room temperature, 5-bromo-2,3-difluoropyridine (100.0 g, 0.52 mol) and tert-butyl ((1S,3S)-3-aminocyclopentyl)carbamate (114.58 g, 0.57 mol) were added to DMF (800 mL). Triethylamine (156.99 g, 1.55 mol) was then added to the system. The mixture was heated to 100 ℃ and reacted for 8 hours.

After completion of the reaction, the mixture was cooled to room temperature. Water (500 mL) was added to the system, followed by extraction with ethyl acetate (400 mL × 3). The organic phases were combined, washed twice with saturated brine (300 mL), dried, filtered, and concentrated under reduced pressure. The residue was triturated with isopropyl ether (300 mL) to obtain 130 g of tert-butyl ((1S,3S)-3-((5-bromo-3-fluoropyridin-2-yl)amino)cyclopentyl)carbamate as a white solid (yield 67%). LC-MS: [M+H]+ = 374.

Step B: Synthesis of tert-butyl ((1s,3s)-3-((3-fluoro-5-(6-oxopyridazin-1(6h)-yl)pyridin-2-yl)amino)cyclopentyl)carbamate

At room temperature, tert-butyl ((1S,3S)-3-((5-bromo-3-fluoropyridin-2-yl)amino)cyclopentyl)carbamate (120 g, 0.32 mol), pyridazin-3(2H)-one (40 g, 0.41 mol), (1S,2S)-N^1,N^2-dimethylcyclohexane-1,2-diamine (9.1 g, 0.064 mol), and potassium carbonate (133.19 g, 0.96 mol) were added to NMP (960 mL). CuI (12.3 g, 0.064 mol) was then added. After the addition, the system was purged with nitrogen and the mixture was heated to 120 ℃ and reacted for 12 hours.

After completion of the reaction, the mixture was cooled to room temperature. Water (1000 mL) was added to the system, followed by extraction with ethyl acetate (400 mL × 3). The organic phases were combined, washed three times with saturated brine (400 mL), dried, filtered, and concentrated under reduced pressure. The residue was purified by normal-phase column chromatography (dichloromethane/methanol = 50:1) to obtain 70 g of tert-butyl ((1S,3S)-3-((3-fluoro-5-(6-oxopyridazin-1(6H)-yl)pyridin-2-yl)amino)cyclopentyl)carbamate as a black oil (yield 56%). LC-MS: [M+H]+ = 390.

Step C: Synthesis of 2-(6-(((1S,3S)-3-aminocyclopentyl)amino)-5-fluoropyridin-3-yl)pyridazin-3(2H)-one

At room temperature, tert-butyl ((1S,3S)-3-((3-fluoro-5-(6-oxopyridazin-1(6H)-yl)pyridin-2-yl)amino)cyclopentyl)carbamate (70 g, 0.17 mol) was dissolved in a hydrochloric acid/1,4-dioxane solution (2 M, 300 mL), reacted at room temperature for 4 hours.

After completion of the reaction, the mixture was concentrated to dryness to obtain 2-(6-(((1S,3S)-3-aminocyclopentyl)amino)-5-fluoropyridin-3-yl)pyridazin-3(2H)-one hydrochloride. This was dissolved in methanol (200 mL), and the pH of the system was adjusted to approximately 9 using a basic ion exchange resin. The mixture was filtered, and the filter cake was washed three times with methanol (100 mL). The filtrates were combined and concentrated to dryness to obtain 55 g of 2-(6-(((1S,3S)-3-aminocyclopentyl)amino)-5-fluoropyridin-3-yl)pyridazin-3(2H)-one as a brown solid. This was used directly in the next step without further treatment. LC-MS: [M+H]+ = 290.

Step D: Synthesis of 2-(6-(((1S,3S)-3-([1,2,4]triazolo[1,5-a]pyridin-2-ylamino)cyclopentyl)amino)-5-fluoropyridin-3-yl)pyridazin-3(2H)-one

At room temperature, 2-(6-(((1S,3S)-3-aminocyclopentyl)amino)-5-fluoropyridin-3-yl)pyridazin-3(2H)-one (55 g, 0.19 mol) and 2-bromo-[1,2,4]triazolo[1,5-a]pyridine (37.4 g, 0.19 mol) were dissolved in 1,4-dioxane (550 mL). Sodium tert-butoxide (36.5 g, 0.38 mol) and methanesulfonato(2-di-tert-butylphosphino-2’,4’,6’-triisopropyl-1,1’-biphenyl)(2’-amino-1,1’-biphenyl-2-yl)palladium(II) (30 g, 0.037 mol) were then added. After the addition, the system was purged with nitrogen, and the mixture was slowly heated to 100 ℃ and reacted for 1 hour.

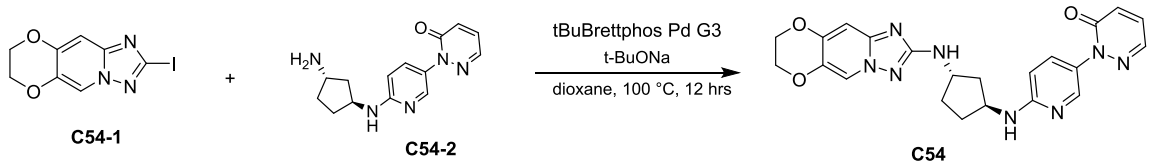
After completion of the reaction, the mixture was cooled to room temperature. Water (400 mL) was added to the system, followed by extraction with ethyl acetate (300 mL × 3). The organic phases were combined, washed with saturated brine (200 mL), dried, filtered, and concentrated under reduced pressure. The residue was purified by normal-phase column chromatography (dichloromethane/methanol = 10:1) to obtain 20.5 g of 2-(6-(((1S,3S)-3-([1,2,4]triazolo[1,5-a]pyridin-2-ylamino)cyclopentyl)amino)-5-fluoropyridin-3-yl)pyridazin-3(2H)-one. LC-MS: $[M+H]^{+}$ = 407.

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.61 – 8.58 (dd, J = 6.7, 1.1 Hz, 1H), 8.06 – 8.04 (q, J = 1.7 Hz, 2H), 7.67 – 7.61 (dd, J = 12.1, 2.2 Hz, 1H), 7.52 – 7.47 (dd, J = 9.5, 3.9 Hz, 1H), 7.46 – 7.41 (m, 1H), 7.40 – 7.37 (dt, J = 8.8, 1.3 Hz, 1H), 7.09 – 7.05 (dd, J = 9.5, 1.6 Hz, 1H), 6.99 – 6.94 (m, 1H), 6.90 – 6.84 (td, J = 6.7, 1.6 Hz, 1H), 6.68 – 6.63 (d, J = 7.2 Hz, 1H), 4.61 – 4.51 (p, J = 7.0 Hz, 1H), 4.26 – 4.17 (p, J = 6.6 Hz, 1H), 2.22 – 2.12 (m, 2H), 2.02 – 1.97 (m, 2H), 1.67 – 1.54 (m, 2H).

Example C54

Synthesis of 2-(6-(((1S,3S)-3-((7,8-dihydro-[1,4]dioxino[2,3-d][1,2,4]triazolo[1,5-a]pyridin-2-yl)amino)cyclo

pentyl)amino)pyridin-3-yl)pyridazin-3(2H)-one



C54-1 C54-2 C54

Step 1: Synthesis of 2-(6-(((1S,3S)-3-((7,8-dihydro-[1,4]dioxino[2,3-d][1,2,4]triazolo[1,5-a]pyridin-2-yl)amino)cyclopentyl)amino)pyridin-3-yl)pyridazin-3(2H)-one

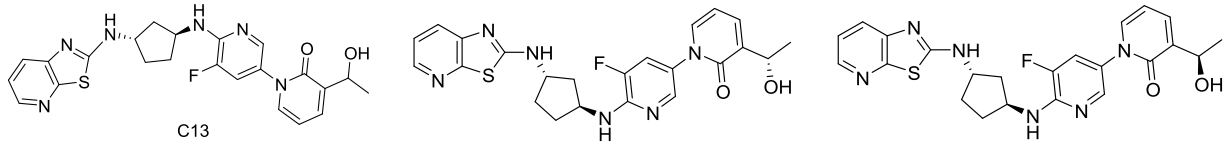
Sodium tert-butoxide (190 mg, 1.98 mmol, 5.00 eq) and tBuBrettPhos Pd G3 (33.8 mg, 39.60 μmol, 0.100 eq) was added to a solution of C54-1 (120 mg, 395 μmol, 1.00 eq) and C54-2 (107 mg, 395 μmol, 1.00 eq) in 1,4-dioxane (4 mL). Under nitrogen protection, the mixture was stirred at 100 ℃ for 12 hours.

LCMS detected the formation of the target product. The reaction mixture was filtered, and the filtrate was concentrated to dryness. The crude product was purified by reverse-phase preparative chromatography (Column: Phenomenex luna C18 150*25 mm* 10um; Mobile phase: [water (FA)-ACN]; Gradient: 1% to 30% B over 10 min) to obtain the target Compound (18.6 mg).

LC-MS: [M+H]+ = 447.1. ^{1}H NMR: (DMSO-d_6, 400 MHz): δ (ppm) = 8.37 (s, 1H), 8.09 (d, J = 2.4 Hz, 1H), 8.01 (dd, J = 1.6, 4.0 Hz, 1H), 7.51 (dd, J = 2.4, 8.8 Hz, 1H), 7.46 (dd, J = 4.0, 9.6 Hz, 1H), 7.02 (dd, J = 1.6, 9.6 Hz, 1H), 6.91 (d, J = 7.2 Hz, 1H), 6.77 (s, 1H), 6.52 (d, J = 8.8 Hz, 1H), 6.35 (d, J = 7.6 Hz, 1H), 4.37 - 4.25 (m, 5H), 4.16 - 4.07 (m, 1H), 2.18 - 2.08 (m, 2H), 1.99 - 1.83 (m, 2H), 1.56 - 1.44 (m, 2H).

Example C13

Referring to the preparation methods of the aforementioned Examples C1, C3, and C12, Compounds C13, C13A, and C13B were prepared:



C13 C13A or C13B C13B or C13A

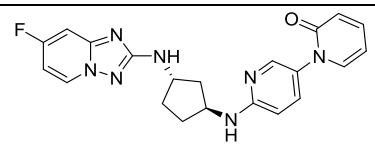
Compound C13A, ^{1}H NMR: (400 MHz, DMSO-d_6): δ 8.49 (br d, J = 6.4 Hz, 1H), 8.16 - 8.08 (m, 1H), 7.89 (d, J = 2.0 Hz, 1H), 7.70 (dd, J = 1.2, 8.0 Hz, 1H), 7.62 - 7.55 (m, 3H), 7.28 (dd, J = 4.8, 8.0 Hz, 1H), 7.03 (br d, J = 7.2 Hz, 1H), 6.37 (t, J = 6.8 Hz, 1H), 5.12 (d, J = 4.4 Hz, 1H), 4.76 (quintet, J = 5.6 Hz, 1H), 4.66 - 4.53 (m, 1H), 4.51 - 4.39 (m, 1H), 2.31 - 2.16 (m, 2H), 2.11 - 2.02 (m, 2H), 1.74 - 1.60 (m, 2H), 1.30 (d, J = 6.4 Hz, 3H).

Compound C13B, ^{1}H NMR: (400 MHz, DMSO-d_6): δ 8.45 (br d, J = 4.4 Hz, 1H), 8.08 (dd,

J = 1.2, 4.8 Hz, 1H), 7.84 (d, J = 2.0 Hz, 1H), 7.66 (dd, J = 1.2, 8.0 Hz, 1H), 7.60 - 7.51 (m, 3H), 7.24 (dd, J = 4.8, 8.0 Hz, 1H), 6.98 (br d, J = 6.8 Hz, 1H), 6.33 (t, J = 6.8 Hz, 1H), 5.08 (d, J = 4.4 Hz, 1H), 4.80 - 4.65 (m, 1H), 4.55 (sextet, J = 7.2 Hz, 1H), 4.46 - 4.35 (m, 1H), 2.27 - 2.15 (m, 2H), 2.02 (t, J = 7.2 Hz, 2H), 1.69 - 1.56 (m, 2H), 1.26 (d, J = 6.4 Hz, 3H).

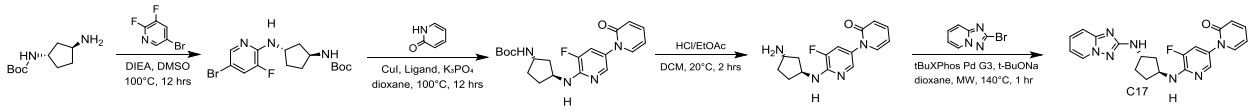
Example C14

Referring to the preparation method of the aforementioned Example C2, Compound C14 was prepared:

 C14	^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.65 (dd, 1H, *J*=5.7, 7.3 Hz), 7.92 (d, 1H, *J*=2.6 Hz), 7.59 (dd, 1H, *J*=1.7, 6.8 Hz), 7.47 (ddd, 1H, *J*=2.1, 6.7, 9.1 Hz), 7.39 (dd, 1H, *J*=2.7, 8.8 Hz), 7.26 (dd, 1H, *J*=2.7, 9.7 Hz), 6.91 (d, 1H, *J*=6.9 Hz), 6.86 (dt, 1H, *J*=2.8, 7.6 Hz), 6.74 (d, 1H, *J*=7.1 Hz), 6.52 (d, 1H, *J*=9.0 Hz), 6.44 (d, 1H, *J*=9.0 Hz), 6.26 (dt, 1H, *J*=1.3, 6.7 Hz), 4.2-4.4 (m, 1H), 4.1-4.2 (m, 1H), 2.1-2.2 (m, 2H), 1.9-2.0 (m, 1H), 1.8-1.9 (m, 1H), 1.4-1.6 (m, 2H).

Example C17

Synthesis of 6'-(((1S,3S)-3-([1,2,4]triazolo[1,5-a]pyridin-2-ylamino)cyclopentyl)amino)-5'-fluoro-2H-[1,3'-bipyridin]-2-one



Step 1: Synthesis of tert-butyl ((1S,3S)-3-((5-bromo-3-fluoropyridin-2-yl)amino)cyclopentyl)carbamate

Tert-butyl ((1S,3S)-3-aminocyclopentyl)carbamate (3.00 g, 15.0 mmol, 1 eq), 5-bromo-2,3-difluoropyridine (2.91 g, 15.0 mmol, 1.0 eq), and N,N-diisopropylethylamine (4.84 g, 37.5 mmol, 2.5 eq) were dissolved in dimethyl sulfoxide (40 mL). The mixture was stirred at 100 ℃ for 12 hours. LCMS showed the MS value of the product (RT = 0.568 min). The reaction solution was cooled to room temperature. Then the reaction mixture was diluted with water (200 mL) and extracted with ethyl acetate (100 mL * 2). The organic phases were combined, washed with saturated brine (500 mL * 2), dried over anhydrous sodium sulfate, filtered, and concentrated to obtain the crude product. The crude product was purified by silica gel column chromatography to obtain tert-butyl ((1S,3S)-3-((5-bromo-3-fluoropyridin-2-yl)amino)cyclopentyl)carbamate (4.00 g). LCMS: RT = 0.568 min, MS (ESI) m/z = 374.0 $[M+1]^+$

Step 2: Synthesis of tert-butyl ((1S,3S)-3-((5'-fluoro-2-oxo-2H-[1,3'-bipyridin]-6'-yl)amino)cyclopentyl)carbamate

Tert-butyl ((1S,3S)-3-((5-bromo-3-fluoropyridin-2-yl)amino)cyclopentyl)carbamate (1.5 g, 4.01 mmol, 1.0 eq), pyridin-2(1H)-one (457 mg, 4.81 mmol, 1.2 eq), Potassium phosphate (2.55 g, 12.0 mmol, 3.0 eq), CuI (153 mg, 802 μmol, 0.20 eq), and (1S,2S)-N^1,N^2-dimethylcyclohexane-1,2-diamine (114 mg, 802 μmol, 0.2 eq) were dissolved in 1,4-dioxane (20 mL). The mixture was stirred at 100 ℃ for 12 hours. TLC (petroleum ether/ethyl acetate = 3/1) showed the reaction was complete. The reaction mixture was cooled to room temperature. Then the reaction mixture was diluted with water (100 mL) and extracted with ethyl acetate (30 mL * 2). The organic phases were combined, washed with saturated brine (100 mL * 2), dried over anhydrous sodium sulfate, filtered, and concentrated to obtain the crude product. The crude product was purified by silica gel column chromatography to obtain tert-butyl ((1S,3S)-3-((5'-fluoro-2-oxo-2H-[1,3'-bipyridin]-6'-yl)amino)cyclopentyl)carbamate (1.00 g).

Step 3: Synthesis of 6'-(((1S,3S)-3-aminocyclopentyl)amino)-5'-fluoro-2H-[1,3'-bipyridin]-2-one

Tert-butyl ((1S,3S)-3-((5'-fluoro-2-oxo-2H-[1,3'-bipyridin]-6'-yl)amino)cyclopentyl)carbamate (1.00 g, 2.57 mmol, 1.0 eq) was dissolved in dichloromethane (10 mL). Then HCl/EtOAc (2 M, 20 mL, 15.5 eq) was added. The mixture was stirred at 20 ℃ for 2 hours. LCMSshowed the MS value of the product (RT = 0.320 min). The reaction mixture was concentrated directly under reduced pressure to dryness to obtain 6'-(((1S,3S)-3-aminocyclopentyl)amino)-5'-fluoro-2H-[1,3'-bipyridin]-2-one (600 mg, 2.08 mmol, 80.8% yield). It was used in the next step without further purification. LCMS: RT = 0.320 min, MS (ESI) m/z = 577.3 $[2M+1]^+$

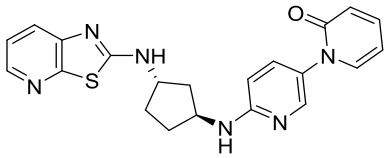
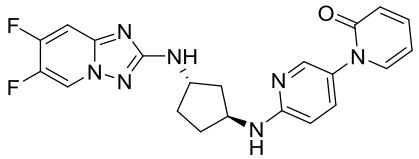
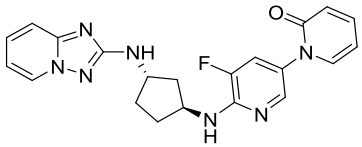
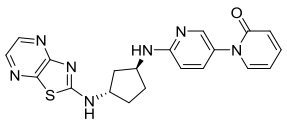
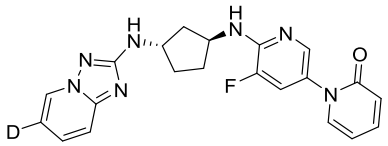
Step 4: Synthesis of 6'-(((1S,3S)-3-([1,2,4]triazolo[1,5-a]pyridin-2-ylamino)cyclopentyl)amino)-5'-fluoro-2H-[1,3'-bi pyridin]-2-one

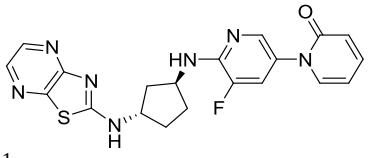
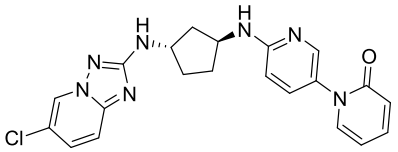
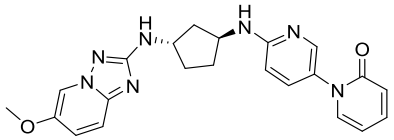
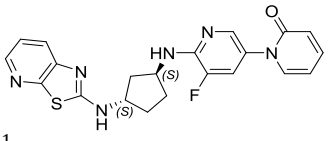
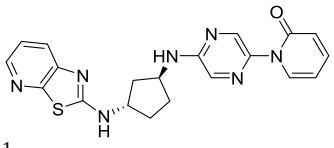
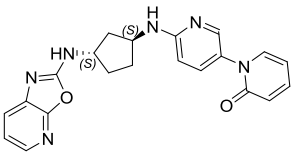
6'-(((1S,3S)-3-aminocyclopentyl)amino)-5'-fluoro-2H-[1,3'-bipyridin]-2-one (120 mg, 416 μmol, 1.0 eq), 2-bromo-[1,2,4]triazolo[1,5-a]pyridine (90.7 mg, 458 μmol, 1.1 eq), sodium tert-butoxide (120 mg, 1.25 mmol, 3.0 eq), and tBuXPhos Pd G3 (33.1 mg, 41.6 μmol, 0.1 eq) were dissolved in 1,4-dioxane (4 mL). The mixture was stirred at 140 ℃ for 1 hour in a microwave reactor. LCMS showed the MS value of the product (RT = 0.399 min). The reaction mixture was filtered. The filtrate was concentrated to obtain the crude product. The crude product was purified by reverse-phase preparative chromatography (column: Phenomenex luna C18 150*40mm*15um; mobile phase: [water(FA)-ACN]; gradient: 15% to 45% B over 15 min) twice to obtain

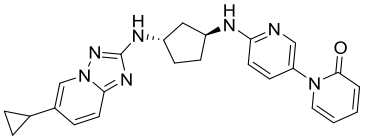
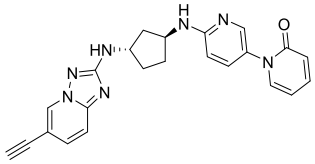
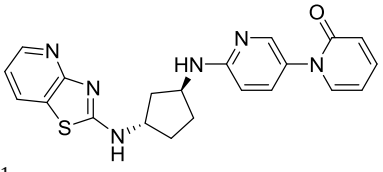
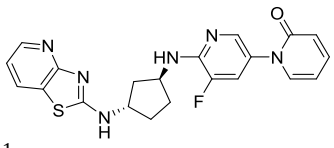
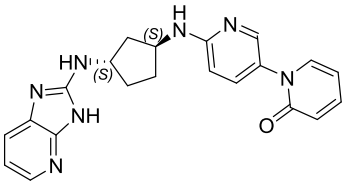
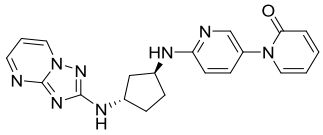
6'-(((1S,3S)-3-([1,2,4]triazolo[1,5-a]pyridin-2-ylamino)cyclopentyl)amino)-5'-fluoro-2H-[1,3'-bi pyridin]-2-one (36.6 mg). LCMS: RT = 0.399 min, MS (ESI) m/z = 406.1 $[M+1]^+$.

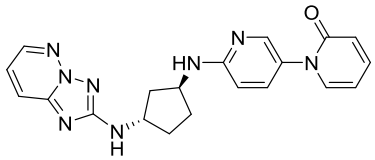
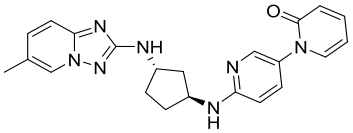
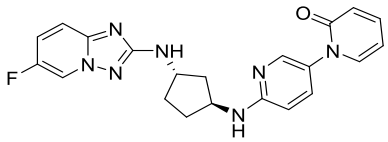
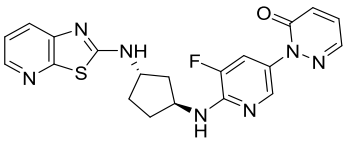
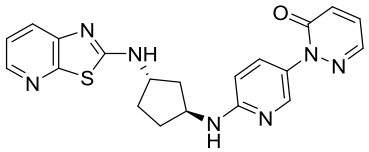
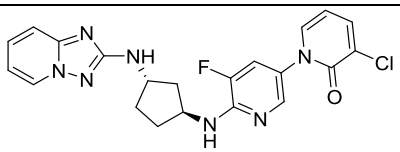
Example C15 to C44, C48 to C53, and C55 to C95

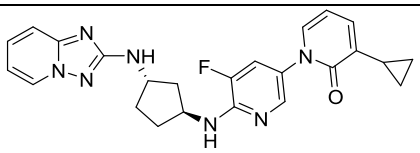
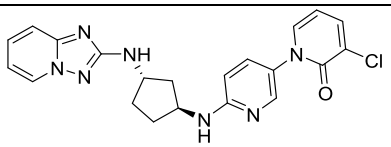
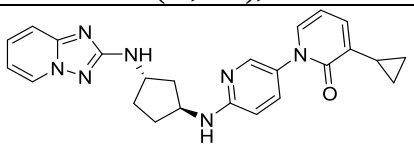
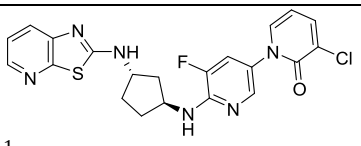
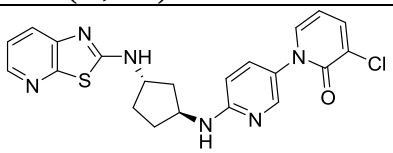
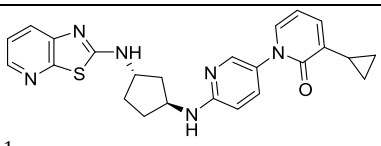
According to the aforementioned preparation methods, Compounds C15 to C44, C48 to C53, and C55to C95 were prepared.

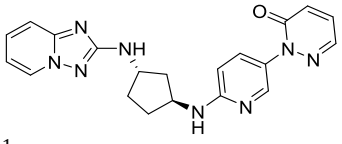
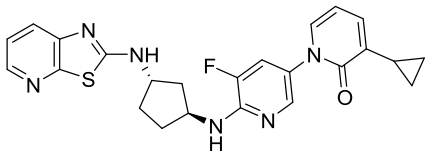
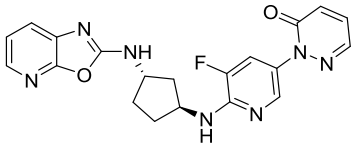
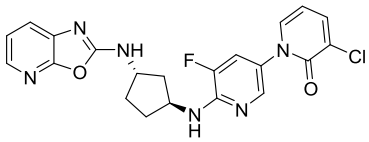
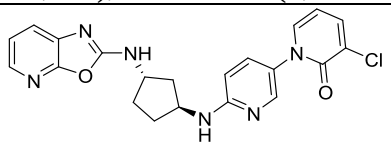
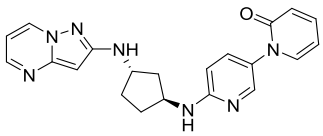
C15	 ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.48 (d, *J* = 6.8 Hz, 1H), 8.09 (dd, *J* = 4.9, 1.5 Hz, 1H), 7.94 (d, *J* = 2.7 Hz, 1H), 7.66 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.60 (dd, *J* = 6.8, 2.1 Hz, 1H), 7.48 (ddd, *J* = 9.0, 6.6, 2.1 Hz, 1H), 7.41 (dd, *J* = 8.9, 2.7 Hz, 1H), 7.24 (dd, *J* = 8.0, 4.8 Hz, 1H), 6.99 (d, *J* = 6.9 Hz, 1H), 6.54 (d, *J* = 8.9 Hz, 1H), 6.45 (d, *J* = 9.1 Hz, 1H), 6.28 (td, *J* = 6.7, 1.4 Hz, 1H), 4.43 – 4.34 (m, 2H), 2.25 – 2.13 (m, 2H), 1.97 (dq, *J* = 20.2, 6.6 Hz, 2H), 1.64 – 1.50 (m, 2H).	C16	 ^{1}H NMR (METHANOL-d_4, 400 MHz) *δ* 8.77 (dd, 1H, *J*=5.2, 6.8 Hz), 7.94 (br d, 1H, *J*=2.3 Hz), 7.5-7.6 (m, 2H), 7.44 (dd, 1H, *J*=2.6, 9.0 Hz), 7.27 (br dd, 1H, *J*=7.4, 10.3 Hz), 6.62 (br d, 2H, *J*=9.0 Hz), 6.46 (dt, 1H, *J*=1.2, 6.7 Hz), 4.35 (td, 1H, *J*=6.5, 13.0 Hz), 4.2-4.3 (m, 1H), 2.2-2.3 (m, 2H), 2.0-2.1 (m, 2H), 1.6-1.7 (m, 2H)
C17	 ^{1}H NMR (400 MHz, DMSO-d_6) δ = 8.58 (d, *J* = 6.9 Hz, 1H), 7.84 (d, *J* = 2.0 Hz, 1H), 7.64 (dd, *J* = 1.7, 6.7 Hz, 1H), 7.54 (dd, *J* = 2.1, 11.9 Hz, 1H), 7.49 (ddd, *J* = 2.1, 6.8, 9.0 Hz, 1H), 7.44 - 7.34 (m, 2H), 6.94 (br d, *J* = 6.9 Hz, 1H), 6.85 (dt, *J* = 1.4, 6.7 Hz, 1H), 6.64 (d, *J* = 7.3 Hz, 1H), 6.46 (d, *J* = 9.0 Hz, 1H), 6.32 - 6.25 (m, 1H), 4.57 - 4.47 (m, 1H), 4.25 - 4.14 (m, 1H), 2.19 - 2.10 (m, 2H), 2.01 - 1.94 (m, 2H), 1.65 - 1.51 (m, 2H).	C18	 ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.10 (s, 1H), 8.24 (d, *J* = 2.8 Hz, 1H), 8.04 (d, *J* = 2.8 Hz, 1H), 7.94 (d, *J* = 2.7 Hz, 1H), 7.61 (dd, *J* = 6.9, 2.1 Hz, 1H), 7.48 (ddd, *J* = 9.0, 6.6, 2.1 Hz, 1H), 7.41 (dd, *J* = 8.9, 2.7 Hz, 1H), 7.02 (d, *J* = 6.9 Hz, 1H), 6.55 (d, *J* = 8.9 Hz, 1H), 6.45 (d, *J* = 9.2 Hz, 1H), 6.30 – 6.26 (m, 1H), 4.50 – 4.31 (m, 2H), 2.29 – 2.16 (m, 2H), 2.01 (dt, *J* = 9.9, 6.5 Hz, 2H), 1.60 (ddt, *J* = 25.7, 12.6, 6.9 Hz, 2H).
C17A:		1H NMR (400 MHz, DMSO-d6) δ 8.59 (s, 1H), 7.85 (d, J = 2.1 Hz, 1H), 7.65 (dd, J = 6.8, 2.0 Hz, 1H), 7.55 (dd, J = 11.9, 2.2 Hz, 1H), 7.50 (ddd, J = 8.9, 6.6, 2.1 Hz, 1H), 7.42 (dd, J = 8.8, 1.3 Hz, 1H), 7.37 (d, J = 8.8 Hz, 1H), 7.00 – 6.88 (m, 1H), 6.65 (d, J = 7.2 Hz, 1H), 6.52 – 6.41 (m, 1H), 6.29 (td, J = 6.7, 1.3 Hz, 1H), 4.53 (q, J = 6.9 Hz, 1H), 4.20 (q, J = 6.6 Hz, 1H), 2.21 – 2.10 (m, 2H), 1.98 (td, J = 6.7, 2.8 Hz, 2H), 1.68 – 1.50 (m, 2H).	

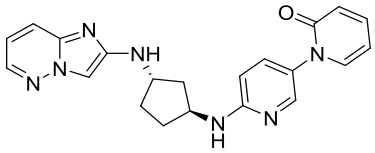
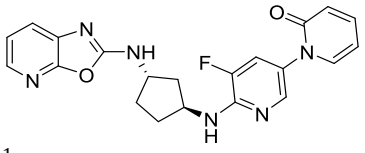
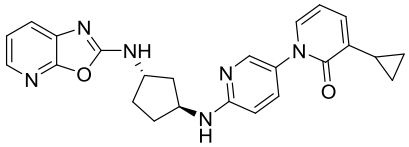
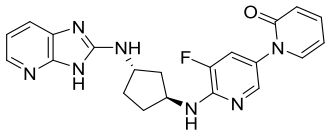
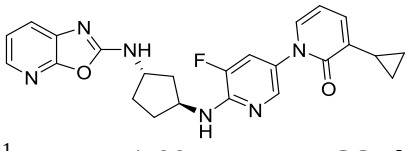
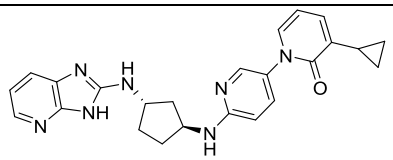
C19	 ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.08 (s, 1H), 8.25 (d, J = 2.8 Hz, 1H), 8.04 (d, J = 2.8 Hz, 1H), 7.87 (d, J = 2.2 Hz, 1H), 7.66 (dd, J = 6.9, 2.1 Hz, 1H), 7.57 (dd, J = 11.9, 2.2 Hz, 1H), 7.50 (ddd, J = 9.0, 6.6, 2.1 Hz, 1H), 7.07 – 6.97 (m, 1H), 6.47 (d, J = 9.2 Hz, 1H), 6.29 (td, J = 6.7, 1.4 Hz, 1H), 4.56 (dt, J = 23.1, 11.6 Hz, 2H), 2.30 – 2.17 (m, 2H), 2.11 – 2.02 (m, 2H), 1.71 – 1.61 (m, 2H).	C20	 ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.93 (d, J = 2.0 Hz, 1H), 7.92 (d, J = 2.7 Hz, 1H), 7.60 (dd, J = 6.9, 2.1 Hz, 1H), 7.54 – 7.45 (m, 2H), 7.40 (dd, J = 9.0, 2.9 Hz, 2H), 6.93 (d, J = 6.9 Hz, 1H), 6.82 (d, J = 7.2 Hz, 1H), 6.53 (d, J = 8.9 Hz, 1H), 6.45 (d, J = 9.1 Hz, 1H), 6.27 (td, J = 6.7, 1.3 Hz, 1H), 4.32 (q, J = 6.5 Hz, 1H), 4.18 (q, J = 6.7 Hz, 1H), 2.22 – 2.09 (m, 2H), 1.97 (dt, J = 13.4, 6.8 Hz, 1H), 1.89 (td, J = 7.3, 3.6 Hz, 1H), 1.63 – 1.43 (m, 2H).
C21	 ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.39 (d, J = 2.4 Hz, 1H), 7.92 (d, J = 2.7 Hz, 1H), 7.61 (dd, J = 6.9, 2.1 Hz, 1H), 7.54 – 7.44 (m, 1H), 7.40 (dd, J = 8.9, 2.7 Hz, 1H), 7.31 (d, J = 9.5 Hz, 1H), 7.21 (dd, J = 9.5, 2.5 Hz, 1H), 6.93 (d, J = 6.8 Hz, 1H), 6.51 (dd, J = 14.2, 8.0 Hz, 2H), 6.45 (d, J = 8.8 Hz, 1H), 6.27 (td, J = 6.7, 1.4 Hz, 1H), 4.32 (q, J = 6.6 Hz, 1H), 4.15 (q, J = 6.7 Hz, 1H), 3.79 (s, 3H), 2.15 (qd, J = 7.6, 2.8 Hz, 2H), 1.96 (dt, J = 13.2, 6.7 Hz, 1H), 1.92 – 1.80 (m, 1H), 1.65 – 1.43 (m, 2H).	C22	 ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.50 (d, J = 6.8 Hz, 1H), 8.26 (d, J = 1.4 Hz, 1H), 8.09 (dd, J = 4.8, 1.5 Hz, 1H), 7.88 (d, J = 1.3 Hz, 1H), 7.72 (dd, J = 7.0, 2.1 Hz, 1H), 7.67 (dd, J = 8.0, 1.5 Hz, 1H), 7.56 (d, J = 6.8 Hz, 1H), 7.50 (ddd, J = 8.9, 6.5, 2.1 Hz, 1H), 7.25 (dd, J = 8.0, 4.8 Hz, 1H), 6.47 (dd, J = 9.2, 1.2 Hz, 1H), 6.33 (td, J = 6.8, 1.4 Hz, 1H), 4.39 (dq, J = 26.9, 6.5 Hz, 2H), 2.27 – 2.16 (m, 2H), 2.01 (tt, J = 13.3, 6.7 Hz, 2H), 1.61 (ddt, J = 21.4, 12.8, 5.7 Hz, 2H).
C23	 ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.50 (d, J = 6.8 Hz, 1H), 8.26 (d, J = 1.4 Hz, 1H), 8.09 (dd, J = 4.8, 1.5 Hz, 1H), 7.88 (d, J = 1.3 Hz, 1H), 7.72 (dd, J = 7.0, 2.1 Hz, 1H), 7.67 (dd, J = 8.0, 1.5 Hz, 1H), 7.56 (d, J = 6.8 Hz, 1H), 7.51 (td, J = 6.7, 3.2 Hz, 1H), 7.25 (dd, J = 8.0, 4.8 Hz, 1H), 6.47 (dd, J = 9.2, 1.2 Hz, 1H), 6.33 (td, J = 6.8, 1.4 Hz, 1H), 4.45 – 4.34 (m, 2H), 2.23 (td, J = 10.7, 10.1, 5.6 Hz, 2H), 2.01 (dt, J = 13.2, 6.6 Hz, 2H), 1.61 (ddd, J = 16.7, 13.9, 7.0 Hz, 2H).	C24	 ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.44 – 8.39 (d, J = 7.0 Hz, 1H), 7.96 – 7.92 (d, J = 2.7 Hz, 1H), 7.86 – 7.81 (dd, J = 5.1, 1.5 Hz, 1H), 7.63 – 7.56 (m, 2H), 7.51 – 7.38 (m, 2H), 7.19 – 7.14 (dd, J = 7.6, 5.1 Hz, 1H), 7.01 – 6.97 (d, J = 6.8 Hz, 1H), 6.57 – 6.51 (d, J = 8.9 Hz, 1H), 6.49 – 6.42 (d, J = 9.2 Hz, 1H), 6.30 – 6.24 (td, J = 6.7, 1.3 Hz, 1H), 4.40 – 4.23 (m, 2H), 2.25 – 2.13 (m, 2H), 2.06 – 1.91 (m, 2H), 1.72 – 1.49 (m, 2H).

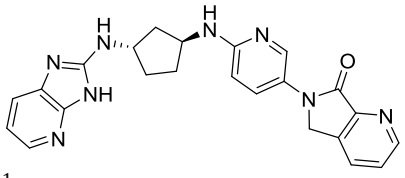
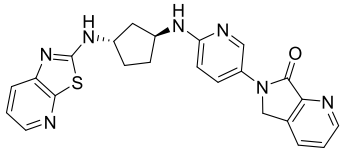
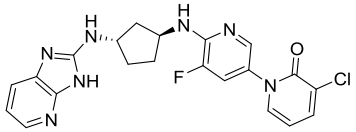
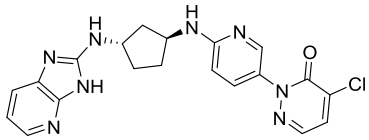
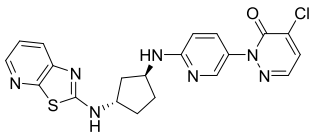
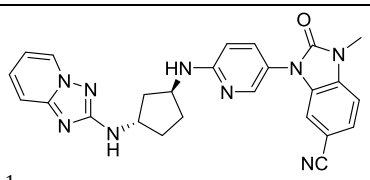
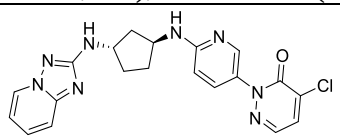
C25	 ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.42 (s, 1H), 7.92 (d, *J* = 2.7 Hz, 1H), 7.61 (dd, *J* = 6.9, 2.1 Hz, 1H), 7.48 (ddd, *J* = 8.9, 6.6, 2.1 Hz, 1H), 7.40 (dd, *J* = 8.9, 2.8 Hz, 1H), 7.27 (d, *J* = 9.0 Hz, 1H), 7.22 – 7.11 (m, 1H), 6.93 (d, *J* = 6.9 Hz, 1H), 6.54 (t, *J* = 9.0 Hz, 2H), 6.45 (d, *J* = 9.2 Hz, 1H), 6.27 (t, *J* = 6.7 Hz, 1H), 4.31 (d, *J* = 6.9 Hz, 1H), 4.23 – 4.10 (m, 1H), 2.15 (dt, *J* = 11.6, 6.4 Hz, 2H), 2.04 – 1.91 (m, 2H), 1.87 (q, *J* = 6.6 Hz, 1H), 1.52 (ddd, *J* = 24.9, 13.0, 6.8 Hz, 2H), 0.91 (dt, *J* = 8.7, 3.2 Hz, 2H), 0.77 – 0.59 (m, 2H).	C26	 ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.88 (t, *J* = 1.2 Hz, 1H), 7.92 (d, *J* = 2.7 Hz, 1H), 7.61 (dd, *J* = 6.9, 2.1 Hz, 1H), 7.53 – 7.44 (m, 2H), 7.44 – 7.32 (m, 2H), 6.95 (d, *J* = 6.9 Hz, 1H), 6.90 (d, *J* = 7.3 Hz, 1H), 6.53 (d, *J* = 8.9 Hz, 1H), 6.49 – 6.40 (m, 1H), 6.27 (td, *J* = 6.6, 1.4 Hz, 1H), 4.33 (q, *J* = 6.6 Hz, 1H), 4.27 (s, 1H), 4.18 (q, *J* = 6.7 Hz, 1H), 2.23 – 2.11 (m, 2H), 1.97 (dt, *J* = 13.3, 6.9 Hz, 1H), 1.88 (ddd, *J* = 13.2, 7.5, 5.8 Hz, 1H), 1.64 – 1.46 (m, 2H).
C27	 ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.58 (d, *J* = 6.8 Hz, 1H), 8.23 (d, *J* = 4.9 Hz, 1H), 8.07 (d, *J* = 7.6 Hz, 1H), 7.94 (d, *J* = 2.6 Hz, 1H), 7.62 (dd, *J* = 6.9, 2.0 Hz, 1H), 7.48 (ddd, *J* = 8.9, 6.6, 2.1 Hz, 1H), 7.41 (dd, *J* = 8.9, 2.7 Hz, 1H), 7.02 (d, *J* = 6.9 Hz, 1H), 6.98 (dd, *J* = 7.7, 4.9 Hz, 1H), 6.54 (d, *J* = 8.9 Hz, 1H), 6.45 (d, *J* = 9.2 Hz, 1H), 6.28 (t, *J* = 6.7 Hz, 1H), 4.37 (dt, *J* = 13.4, 6.7 Hz, 2H), 2.21 (ddt, *J* = 17.8, 12.3, 6.0 Hz, 2H), 1.98 (dt, *J* = 13.9, 6.9 Hz, 2H), 1.65 – 1.53 (m, 2H).	C28	 ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.60 (d, *J* = 6.8 Hz, 1H), 8.23 (dd, *J* = 4.9, 1.6 Hz, 1H), 8.06 (dd, *J* = 7.7, 1.7 Hz, 1H), 7.86 (s, 1H), 7.66 (dd, *J* = 6.9, 2.1 Hz, 1H), 7.57 (dd, *J* = 11.9, 2.2 Hz, 1H), 7.50 (ddd, *J* = 9.0, 6.6, 2.1 Hz, 1H), 7.04 (d, *J* = 7.1 Hz, 1H), 6.97 (dd, *J* = 7.7, 4.9 Hz, 1H), 6.47 (d, *J* = 9.2 Hz, 1H), 6.31 – 6.27 (m, 1H), 4.56 (q, *J* = 7.1 Hz, 1H), 4.41 (q, *J* = 7.1, 6.6 Hz, 1H), 2.21 (ddt, *J* = 19.9, 12.4, 5.0 Hz, 2H), 2.04 (h, *J* = 5.8, 5.1 Hz, 2H), 1.64 (dt, *J* = 11.5, 7.6 Hz, 2H).
C29	 1H NMR (400 MHz, DMSO-d6) δ 9.10 – 8.90 (s, 1H), 8.08 – 8.02 (d, J = 6.0 Hz, 1H), 8.00 – 7.95 (d, J = 2.6 Hz, 1H), 7.84 – 7.79 (d, J = 7.6 Hz, 1H), 7.63 – 7.58 (dd, J = 6.9, 2.1 Hz, 1H), 7.54 – 7.46 (m, 2H), 7.41 – 7.25 (s, 1H), 7.24 – 7.16 (m 1H), 6.65 – 6.60 (d, J = 9.0 Hz, 1H), 6.48 – 6.43 (d, J = 9.2 Hz, 1H), 6.33 – 6.26 (t, J = 6.7 Hz, 1H), 4.41 – 4.25 (t, J = 7.0 Hz, 2H), 2.28 – 2.18 (m, 2H), 2.08 – 2.00	C30	 1H NMR (400 MHz, DMSO-d6) δ 9.01 (dd, J = 6.5, 1.9 Hz, 1H), 8.49 (dd, J = 4.5, 1.9 Hz, 1H), 7.92 (d, J = 2.7 Hz, 1H), 7.61 (dd, J = 7.0, 2.0 Hz, 1H), 7.51 – 7.46 (m, 1H), 7.40 (dd, J = 8.8, 2.7 Hz, 1H), 7.10 (d, J = 7.2 Hz, 1H), 7.01 (dd, J = 6.5, 4.6 Hz, 1H), 6.95 (d, J = 6.9 Hz, 1H), 6.53 (d, J = 8.9 Hz, 1H), 6.46 – 6.43 (m, 1H), 6.27 (td, J = 6.7, 1.4 Hz, 1H), 4.36 – 4.30 (m, 1H), 4.23 – 4.16 (m, 1H), 2.17 (dt, J = 8.4, 5.0 Hz, 2H), 2.00 – 1.91 (m, 2H), 1.56 (ddd, J = 26.4, 12.5, 6.7 Hz,

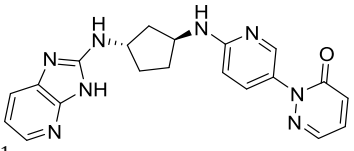
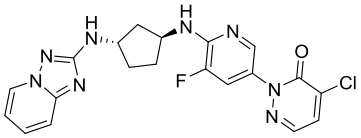
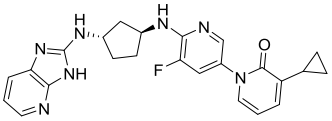
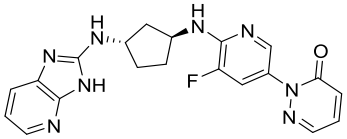
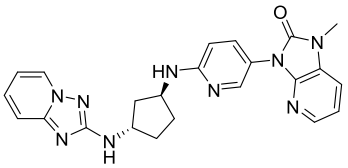
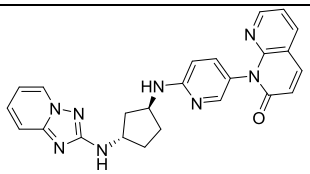
	(m, 2H), 1.72 – 1.56 (m, 2H).		2H).
C31	 ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.34 (dd, *J* = 4.6, 1.7 Hz, 1H), 7.94 (dd, *J* = 8.8, 2.0 Hz, 2H), 7.61 (dd, *J* = 6.8, 2.2 Hz, 1H), 7.50 – 7.46 (m, 1H), 7.40 (dd, *J* = 8.6, 3.3 Hz, 2H), 7.03 (d, *J* = 7.2 Hz, 1H), 6.96 (d, *J* = 6.9 Hz, 1H), 6.54 (d, *J* = 8.9 Hz, 1H), 6.46 – 6.43 (m, 1H), 6.29 – 6.25 (m, 1H), 4.34 (q, *J* = 6.6 Hz, 1H), 4.23 (q, *J* = 6.7 Hz, 1H), 2.17 (ddd, *J* = 10.7, 7.9, 3.5 Hz, 2H), 2.00 – 1.89 (m, 2H), 1.62 – 1.50 (m, 2H).	C32	 ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.44 (s, 1H), 7.92 (d, *J* = 2.7 Hz, 1H), 7.61 (dd, *J* = 6.9, 2.1 Hz, 1H), 7.48 (ddd, *J* = 8.9, 6.5, 2.1 Hz, 1H), 7.40 (dd, *J* = 8.9, 2.7 Hz, 1H), 7.29 (s, 2H), 6.94 (d, *J* = 6.8 Hz, 1H), 6.54 (t, *J* = 8.4 Hz, 2H), 6.44 (d, *J* = 9.2 Hz, 1H), 6.27 (t, *J* = 6.7 Hz, 1H), 4.32 (q, *J* = 6.6 Hz, 1H), 4.16 (q, *J* = 6.7 Hz, 1H), 2.27 (s, 3H), 2.15 (dq, *J* = 10.5, 5.1 Hz, 2H), 1.93 (ddd, *J* = 28.0, 13.6, 7.0 Hz, 2H), 1.62 – 1.39 (m, 2H).
C33	 ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.99 – 8.87 (m, 1H), 7.92 (d, *J* = 2.7 Hz, 1H), 7.60 (ddd, *J* = 6.9, 2.1, 0.7 Hz, 1H), 7.55 – 7.44 (m, 2H), 7.44 – 7.37 (m, 2H), 6.92 (d, *J* = 6.8 Hz, 1H), 6.72 (d, *J* = 7.2 Hz, 1H), 6.53 (d, *J* = 8.9 Hz, 1H), 6.45 (dt, *J* = 9.1, 1.1 Hz, 1H), 6.27 (td, *J* = 6.7, 1.4 Hz, 1H), 4.32 (q, *J* = 6.6 Hz, 1H), 4.17 (q, *J* = 6.7 Hz, 1H), 2.15 (dq, *J* = 11.9, 5.0 Hz, 2H), 1.97 (dt, *J* = 13.4, 6.8 Hz, 1H), 1.93 – 1.83 (m, 1H), 1.64 – 1.43 (m, 2H).	C34	 ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.46 (d, *J* = 6.8 Hz, 1H), 8.10 (dd, *J* = 4.8, 1.5 Hz, 1H), 8.07 – 8.04 (m, 2H), 7.69 – 7.64 (m, 2H), 7.49 (dd, *J* = 9.5, 3.9 Hz, 1H), 7.25 (dd, *J* = 8.1, 4.8 Hz, 1H), 7.07 (dd, *J* = 9.5, 1.6 Hz, 1H), 7.04 – 7.01 (m, 1H), 4.59 – 4.35 (m, 2H), 2.27 – 2.18 (m, 2H), 2.05 (td, *J* = 6.7, 2.1 Hz, 2H), 1.70 – 1.61 (m, 2H).
C35	 ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.47 (d, *J* = 6.8 Hz, 1H), 8.14 (d, *J* = 2.7 Hz, 1H), 8.10 (dd, *J* = 4.8, 1.5 Hz, 1H), 8.03 (dd, *J* = 3.8, 1.7 Hz, 1H), 7.68 (dd, *J* = 8.1, 1.5 Hz, 1H), 7.55 (dd, *J* = 8.9, 2.7 Hz, 1H), 7.48 (dd, *J* = 9.5, 3.8 Hz, 1H), 7.25 (dd, *J* = 8.1, 4.8 Hz, 1H), 7.04 (dd, *J* = 9.5, 1.6 Hz, 1H), 7.00 (d, *J* = 6.9 Hz, 1H), 6.56 (d, *J* = 8.9 Hz, 1H), 4.39 (dt, *J* = 13.7, 7.3 Hz, 2H), 2.22 (ddt, *J* = 18.0, 13.0, 5.8 Hz, 2H), 1.99 (tt, *J* = 13.3, 6.3 Hz, 2H), 1.67 – 1.53 (m, 2H).	C36	 ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.66 – 8.47 (m, 1H), 7.90 (d, *J* = 2.2 Hz, 1H), 7.84 (dd, *J* = 7.4, 1.9 Hz, 1H), 7.72 (dd, *J* = 6.9, 1.9 Hz, 1H), 7.62 (dd, *J* = 11.9, 2.2 Hz, 1H), 7.49 – 7.34 (m, 2H), 7.01 (dd, *J* = 7.2, 1.7 Hz, 1H), 6.87 (td, *J* = 6.7, 1.5 Hz, 1H), 6.66 (d, *J* = 7.2 Hz, 1H), 6.33 (t, *J* = 7.1 Hz, 1H), 4.54 (p, *J* = 6.9 Hz, 1H), 4.22 (p, *J* = 6.5 Hz, 1H), 2.16 (ddt, *J* = 9.5, 6.6, 3.1 Hz, 2H), 2.00 (td, *J* = 6.9, 6.5, 2.6 Hz, 2H), 1.61 (dtd, *J* = 14.4, 8.8, 4.5 Hz, 2H).

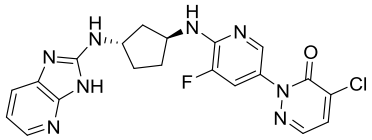
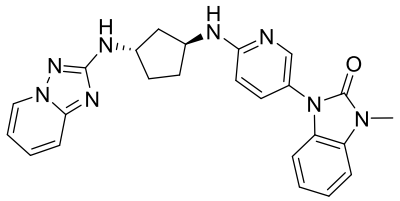
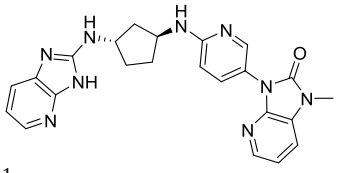
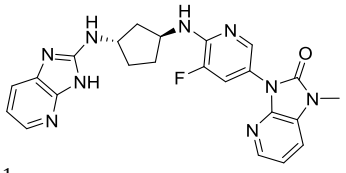
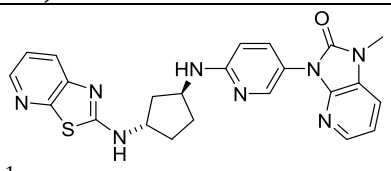
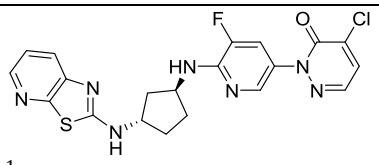
C37	 ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.60 (d, J = 6.6 Hz, 1H), 7.86 (d, J = 2.2 Hz, 1H), 7.57 (dd, J = 12.0, 2.2 Hz, 1H), 7.50 – 7.34 (m, 3H), 7.03 (dd, J = 7.0, 2.0 Hz, 1H), 6.97 – 6.90 (m, 1H), 6.90 – 6.82 (m, 1H), 6.67 (d, J = 7.2 Hz, 1H), 6.20 (t, J = 6.8 Hz, 1H), 4.55 (q, J = 6.9 Hz, 1H), 4.22 (q, J = 6.5 Hz, 1H), 2.17 (q, J = 6.1, 5.6 Hz, 2H), 2.02 (dtd, J = 13.9, 7.1, 6.2, 3.2 Hz, 3H), 1.61 (q, J = 5.3 Hz, 2H), 0.92 – 0.80 (m, 2H), 0.73 – 0.57 (m, 2H).	C38	 ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.62 (d, J = 6.8 Hz, 1H), 7.98 (s, 1H), 7.91 – 7.75 (m, 1H), 7.68 (d, J = 6.7 Hz, 1H), 7.44 (dt, J = 11.4, 5.5 Hz, 3H), 7.01 (d, J = 6.8 Hz, 1H), 6.88 (t, J = 6.5 Hz, 1H), 6.69 (s, 1H), 6.56 (d, J = 8.9 Hz, 1H), 6.32 (t, J = 7.0 Hz, 1H), 4.35 (q, J = 6.8 Hz, 1H), 4.20 (s, 1H), 2.18 (q, J = 7.1 Hz, 2H), 1.95 (dq, J = 30.0, 6.6 Hz, 2H), 1.72 – 1.40 (m, 2H).
C39	 ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.60 (d, J = 6.6 Hz, 1H), 7.94 (d, J = 2.6 Hz, 1H), 7.42 (dq, J = 10.0, 2.7 Hz, 4H), 7.02 (dd, J = 6.9, 2.0 Hz, 1H), 6.92 (d, J = 6.9 Hz, 1H), 6.90 – 6.83 (m, 1H), 6.67 (d, J = 7.1 Hz, 1H), 6.55 (d, J = 8.9 Hz, 1H), 6.19 (t, J = 6.9 Hz, 1H), 4.34 (p, J = 6.7 Hz, 1H), 4.21 (q, J = 6.7 Hz, 1H), 2.25 – 2.12 (m, 2H), 2.08 – 1.94 (m, 2H), 1.90 (ddd, J = 13.2, 7.5, 5.8 Hz, 1H), 1.67 – 1.40 (m, 2H), 0.94 – 0.79 (m, 2H), 0.70 – 0.60 (m, 2H).	C40	 ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.48 (d, J = 6.8 Hz, 1H), 8.11 – 8.09 (m, 1H), 7.91 (d, J = 2.2 Hz, 1H), 7.85 (dd, J = 7.3, 1.9 Hz, 1H), 7.73 – 7.70 (m, 1H), 7.68 (dd, J = 8.0, 1.5 Hz, 1H), 7.64 (dd, J = 11.9, 2.2 Hz, 1H), 7.28 – 7.24 (m, 1H), 7.09 (d, J = 7.2 Hz, 1H), 6.33 (d, J = 7.1 Hz, 1H), 4.51 (dq, J = 56.0, 6.8 Hz, 2H), 2.25 – 2.17 (m, 2H), 2.06 (d, J = 7.1 Hz, 2H), 1.65 (td, J = 12.3, 11.4, 6.8 Hz, 2H).
C41	 ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.48 (d, J = 6.8 Hz, 1H), 8.10 (dd, J = 4.8, 1.5 Hz, 1H), 7.99 (d, J = 2.7 Hz, 1H), 7.83 (dd, J = 7.3, 1.9 Hz, 1H), 7.69 (t, J = 1.4 Hz, 1H), 7.67 (d, J = 1.7 Hz, 1H), 7.46 (dd, J = 8.9, 2.7 Hz, 1H), 7.26 (dd, J = 8.0, 4.8 Hz, 1H), 7.06 (d, J = 6.9 Hz, 1H), 6.56 (d, J = 8.9 Hz, 1H), 6.32 (t, J = 7.1 Hz, 1H), 4.39 (dt, J = 13.8, 7.1 Hz, 2H), 2.22 (ddd, J = 18.8, 9.9, 6.2 Hz, 2H), 2.03 – 1.95 (m, 2H), 1.66 – 1.53 (m, 2H).	C42	 ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.48 (d, J = 6.8 Hz, 1H), 8.11 (d, J = 4.4 Hz, 1H), 7.95 (s, 1H), 7.68 (dd, J = 8.0, 1.4 Hz, 1H), 7.45 – 7.43 (m, 1H), 7.41 (d, J = 2.2 Hz, 1H), 7.27 – 7.24 (m, 1H), 7.04 – 7.02 (m, 1H), 6.98 (d, J = 6.8 Hz, 1H), 6.56 (d, J = 8.9 Hz, 1H), 6.20 (d, J = 6.8 Hz, 1H), 4.44 – 4.37 (m, 2H), 2.22 (ddd, J = 11.3, 8.3, 5.5 Hz, 2H), 2.05 – 2.01 (m, 2H), 1.98 (d, J = 7.6 Hz, 1H), 1.66 – 1.55 (m, 2H), 0.87 (dd, J = 6.1, 2.4 Hz, 2H), 0.68 – 0.64 (m, 2H).

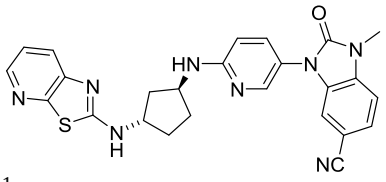
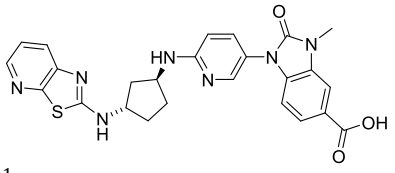
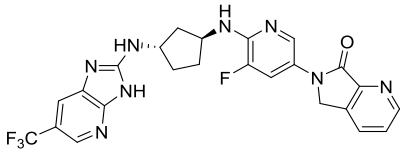
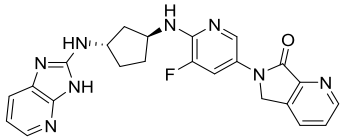
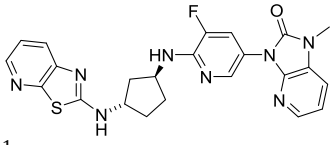
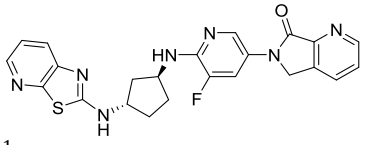
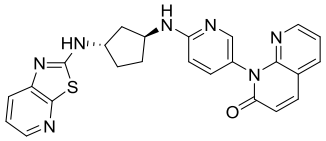
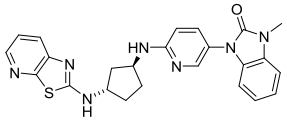
C43	 ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.61 – 8.58 (dt, *J* = 6.6, 1.2 Hz, 1H), 8.13 – 8.11 (m, 1H), 8.04 – 8.02 (dd, *J* = 3.8, 1.6 Hz, 1H), 7.55 – 7.51 (dd, *J* = 8.9, 2.7 Hz, 1H), 7.50 – 7.45 (m, 1H), 7.44 – 7.41 (m, 1H), 7.40 – 7.37 (dt, *J* = 8.7, 1.4 Hz, 1H), 7.06 – 7.02 (dd, *J* = 9.5, 1.6 Hz, 1H), 6.98 – 6.93 (d, *J* = 6.9 Hz, 1H), 6.91 – 6.84 (td, *J* = 6.7, 1.6 Hz, 1H), 6.69 – 6.63 (d, *J* = 7.2 Hz, 1H), 6.58 – 6.52 (dd, *J* = 9.0, 0.7 Hz, 1H), 4.39 – 4.30 (q, *J* = 6.6 Hz, 1H), 4.24 – 4.17 (q, *J* = 6.7 Hz, 1H), 2.23 – 2.11 (td, *J* = 11.4, 10.8, 4.9 Hz, 2H), 1.98 – 1.86 (ddd, *J* = 19.1, 14.1, 6.7 Hz, 2H), 1.66 – 1.45 (ddt, *J* = 25.0, 12.9, 6.7 Hz, 2H).	C44	 ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.48 (d, *J* = 6.8 Hz, 1H), 8.10 (dd, *J* = 4.8, 1.5 Hz, 1H), 7.87 (d, *J* = 2.2 Hz, 1H), 7.68 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.58 (dd, *J* = 11.9, 2.2 Hz, 1H), 7.47 (dd, *J* = 6.8, 2.0 Hz, 1H), 7.26 (dd, *J* = 8.1, 4.8 Hz, 1H), 7.02 (ddd, *J* = 13.1, 7.1, 1.8 Hz, 2H), 6.21 (t, *J* = 6.9 Hz, 1H), 4.58 (q, *J* = 7.0 Hz, 1H), 4.44 (q, *J* = 6.3 Hz, 1H), 2.23 (ddd, *J* = 18.2, 9.7, 5.0 Hz, 2H), 2.08 – 2.04 (m, 2H), 2.03 (d, *J* = 1.9 Hz, 1H), 1.64 (ddd, *J* = 11.8, 7.0, 3.7 Hz, 2H), 0.90 – 0.85 (m, 2H), 0.66 (dd, *J* = 5.4, 2.1 Hz, 2H).
C48	 ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.43 – 8.37 (d, *J* = 7.0 Hz, 1H), 8.07 – 8.01 (t, *J* = 3.4 Hz, 2H), 7.85 – 7.80 (d, *J* = 5.1 Hz, 1H), 7.67 – 7.55 (m, 2H), 7.52 – 7.44 (dd, *J* = 9.5, 3.9 Hz, 1H), 7.19 – 7.12 (dd, *J* = 7.7, 5.1 Hz, 1H), 7.09 – 6.99 (m, 2H), 4.61 – 4.51 (m, 1H), 4.34 – 4.24 (d, *J* = 6.4 Hz, 1H), 2.26 – 2.13 (td, *J* = 11.6, 11.2, 3.8 Hz, 2H), 2.07 – 1.99 (t, *J* = 6.8 Hz, 2H), 1.70 – 1.58 (d, *J* = 11.6 Hz, 2H).	C49	 ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.46 – 8.40 (d, *J* = 7.0 Hz, 1H), 7.94 – 7.82 (m, 3H), 7.76 – 7.58 (m, 3H), 7.22 – 7.07 (m, 2H), 6.38 – 6.29 (t, *J* = 7.0 Hz, 1H), 4.65 – 4.51 (q, *J* = 7.0 Hz, 1H), 4.35 – 4.23 (q, *J* = 6.6 Hz, 1H), 2.27 – 2.11 (dt, *J* = 18.0, 9.0 Hz, 2H), 2.11 – 1.91 (t, *J* = 6.8 Hz, 2H), 1.74 – 1.60 (tt, *J* = 7.4, 3.6 Hz, 2H).
C50	 ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.45 – 8.37 (t, *J* = 5.5 Hz, 1H), 8.01 – 7.94 (s, 1H), 7.87 – 7.78 (d, *J* = 7.5 Hz, 2H), 7.69 – 7.64 (dd, *J* = 6.4, 3.6 Hz, 1H), 7.61 – 7.52 (dd, *J* = 8.0, 3.9 Hz, 1H), 7.48 – 7.41 (dt, *J* = 8.9, 3.2 Hz, 1H), 7.21 – 7.11 (dt, *J* = 8.3, 4.4 Hz, 1H), 7.08 – 6.99 (t, *J* = 5.5 Hz, 1H), 6.59 – 6.50 (dd, *J* = 9.0, 3.9 Hz, 1H), 6.35 – 6.26 (td, *J* = 7.1, 3.7 Hz, 1H), 4.42 – 4.21 (d, *J* = 34.1 Hz, 2H), 2.25 – 2.12 (s, 2H), 2.07 – 1.87 (m, 2H), 1.70 – 1.45 (d, *J* = 42.2 Hz, 2H).	C51	 ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.72 (d, *J* = 6.7 Hz, 1H), 8.22 (dd, *J* = 4.3, 1.8 Hz, 1H), 7.94 (d, *J* = 2.7 Hz, 1H), 7.67 – 7.58 (m, 1H), 7.49 (ddd, *J* = 9.0, 6.6, 2.0 Hz, 1H), 7.42 (dd, *J* = 8.9, 2.9 Hz, 1H), 6.99 – 6.89 (m, 1H), 6.64 (dd, *J* = 6.8, 4.3 Hz, 1H), 6.54 (d, *J* = 9.0 Hz, 1H), 6.46 (d, *J* = 9.2 Hz, 1H), 6.35 (d, *J* = 7.1 Hz, 1H), 6.29 (t, *J* = 6.6 Hz, 1H), 5.75 (s, 1H), 4.34 (q, *J* = 6.5 Hz, 1H), 4.16 – 3.99 (m, 1H), 2.18 (p, *J* = 4.9 Hz, 2H), 1.95 (ddd, *J* = 22.3, 14.0, 6.8 Hz, 2H), 1.54 (dd, *J* =

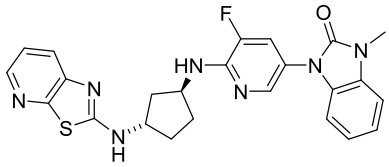
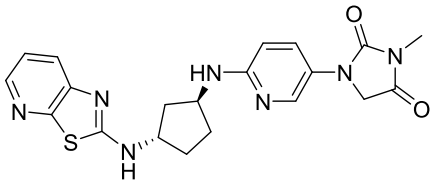
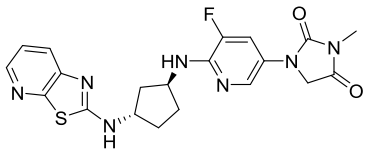
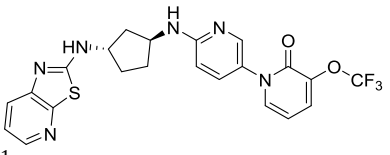
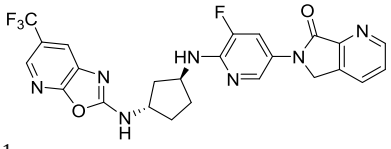
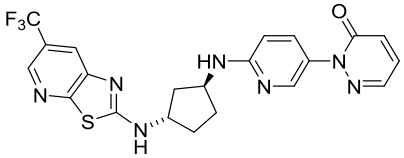
			10.8, 5.6 Hz, 2H).
C52	 ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.20 (dd, *J* = 4.8, 1.6 Hz, 1H), 7.94 (d, *J* = 2.6 Hz, 1H), 7.74 – 7.65 (m, 1H), 7.62 (dd, *J* = 6.9, 2.0 Hz, 1H), 7.49 (ddd, *J* = 9.0, 6.6, 2.1 Hz, 1H), 7.42 (q, *J* = 4.4, 3.6 Hz, 2H), 7.06 – 6.88 (m, 2H), 6.54 (d, *J* = 8.9 Hz, 1H), 6.46 (d, *J* = 9.2 Hz, 1H), 6.28 (t, *J* = 6.7 Hz, 1H), 6.11 (d, *J* = 7.2 Hz, 1H), 4.42 – 4.30 (m, 1H), 4.02 (dt, *J* = 13.2, 6.8 Hz, 1H), 2.17 (tt, *J* = 12.6, 6.2 Hz, 2H), 2.06 – 1.87 (m, 2H), 1.55 (dtd, *J* = 19.8, 13.9, 11.3, 7.2 Hz, 2H).	C53	 ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.43 – 8.38 (d, *J* = 7.1 Hz, 1H), 7.87 – 7.81 (m, 2H), 7.67 – 7.63 (ddd, *J* = 6.8, 2.1, 0.8 Hz, 1H), 7.60 – 7.54 (m, 2H), 7.52 – 7.47 (ddd, *J* = 9.0, 6.6, 2.1 Hz, 1H), 7.19 – 7.13 (dd, *J* = 7.6, 5.1 Hz, 1H), 7.02 – 6.98 (d, *J* = 7.0 Hz, 1H), 6.48 – 6.43 (dt, *J* = 9.0, 1.1 Hz, 1H), 6.32 – 6.26 (td, *J* = 6.7, 1.4 Hz, 1H), 4.60 – 4.51 (q, *J* = 6.9 Hz, 1H), 4.34 – 4.24 (q, *J* = 6.5 Hz, 1H), 2.25 – 2.13 (tt, *J* = 11.3, 5.6 Hz, 2H), 2.08 – 2.00 (t, *J* = 6.8 Hz, 2H), 1.71 – 1.58 (m, 2H).
C55	 ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.43 – 8.39 (d, *J* = 7.0 Hz, 1H), 7.94 – 7.91 (d, *J* = 2.7 Hz, 1H), 7.86 – 7.82 (dd, *J* = 5.1, 1.5 Hz, 1H), 7.61 – 7.56 (dd, *J* = 7.6, 1.5 Hz, 1H), 7.44 – 7.38 (m, 2H), 7.18 – 7.14 (dd, *J* = 7.6, 5.1 Hz, 1H), 7.04 – 6.94 (m, 2H), 6.56 – 6.51 (d, *J* = 8.9 Hz, 1H), 6.20 – 6.16 (t, *J* = 6.9 Hz, 1H), 4.40 – 4.23 (dp, *J* = 33.2, 6.6 Hz, 2H), 2.25 – 2.13 (tt, *J* = 12.4, 6.2 Hz, 2H), 2.07 – 2.01 (dd, *J* = 8.0, 5.3 Hz, 1H), 1.98 – 1.89 (ddd, *J* = 13.3, 7.5, 6.0 Hz, 1H), 1.71 – 1.48 (m, 2H), 0.88 – 0.80 (m, 2H), 0.68 – 0.60 (m, 2H).	C56	 ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.91 (s, 1H), 7.87 (d, *J* = 2.2 Hz, 1H), 7.67 (dd, *J* = 6.9, 2.1 Hz, 1H), 7.58 (dd, *J* = 11.9, 2.2 Hz, 1H), 7.55 – 7.32 (m, 3H), 6.98 (d, *J* = 7.0 Hz, 1H), 6.95 – 6.86 (m, 1H), 6.48 (d, *J* = 9.1 Hz, 1H), 6.31 (td, *J* = 6.7, 1.4 Hz, 1H), 4.57 (q, *J* = 7.0 Hz, 1H), 4.39 – 4.25 (m, 1H), 2.37 – 2.14 (m, 2H), 2.10 – 1.96 (m, 3H), 1.64 (td, *J* = 12.7, 7.1 Hz, 2H).
C57	 ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.44 – 8.41 (d, *J* = 7.0 Hz, 1H), 7.87 – 7.84 (m, 2H), 7.62 – 7.55 (m, 2H), 7.48 – 7.44 (dd, *J* = 6.8, 1.9 Hz, 1H), 7.21 – 7.16 (dd, *J* = 7.7, 5.1 Hz, 1H), 7.06 – 6.97 (ddd, *J* = 19.6, 7.2, 1.7 Hz, 2H), 6.25 – 6.19 (t, *J* = 6.9 Hz, 1H), 4.61 – 4.53 (q, *J* = 6.9 Hz, 1H), 4.36 – 4.26 (q, *J* = 6.6 Hz, 1H), 2.27 – 2.14 (m, 2H), 2.09 – 2.02 (m, 3H), 1.75 – 1.59 (m, 2H), 0.89 – 0.85 (m, 2H), 0.70	C58	 ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.95 (d, *J* = 2.7 Hz, 2H), 7.53 (ddd, *J* = 11.3, 6.9, 2.1 Hz, 3H), 7.43 (dd, *J* = 8.9, 2.7 Hz, 1H), 6.98 (d, *J* = 6.7 Hz, 2H), 6.70 – 6.51 (m, 2H), 6.44 (dd, *J* = 15.8, 1.8 Hz, 1H), 6.30 (t, *J* = 6.9 Hz, 1H), 4.35 (dq, *J* = 24.7, 6.6 Hz, 2H), 2.22 (ddd, *J* = 15.7, 10.5, 6.1 Hz, 2H), 2.07 – 1.94 (m, 2H), 1.84 (dd, *J* = 6.6, 1.6 Hz, 3H), 1.75 – 1.48 (m, 2H).

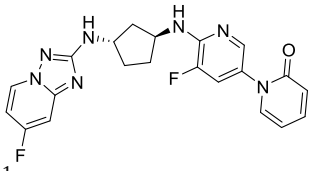
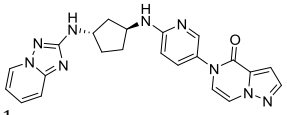
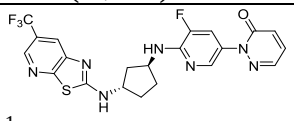
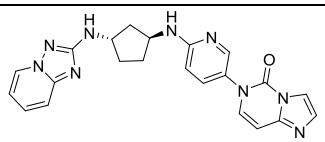
	– 0.61 (m, 2H).		
C59	 ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.76 (dd, J = 4.7, 1.5 Hz, 1H), 8.37 (d, J = 2.7 Hz, 1H), 8.14 (s, 1H), 8.11 (dd, J = 7.8, 1.5 Hz, 1H), 7.94 – 7.82 (m, 2H), 7.62 (dd, J = 7.7, 4.8 Hz, 1H), 7.47 (dd, J = 7.6, 1.4 Hz, 2H), 6.92 (dd, J = 7.7, 5.2 Hz, 1H), 6.73 (d, J = 6.7 Hz, 1H), 6.57 (d, J = 9.0 Hz, 1H), 4.93 (s, 2H), 4.31 (dq, J = 14.1, 6.8 Hz, 2H), 2.20 (tp, J = 12.4, 6.7, 6.0 Hz, 2H), 1.97 (dh, J = 19.9, 6.6 Hz, 2H), 1.75 – 1.40 (m, 2H).	C60	 ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.76 (d, J = 4.7 Hz, 1H), 8.47 (d, J = 6.7 Hz, 1H), 8.37 (d, J = 2.7 Hz, 1H), 8.09 (dd, J = 4.6, 2.9 Hz, 2H), 7.89 (dd, J = 9.0, 2.7 Hz, 1H), 7.66 (d, J = 6.6 Hz, 1H), 7.63 – 7.60 (m, 1H), 7.25 (t, J = 3.0 Hz, 1H), 6.75 (d, J = 6.9 Hz, 1H), 6.57 (d, J = 9.0 Hz, 1H), 4.93 (s, 2H), 4.41 – 4.32 (m, 2H), 2.24 – 2.18 (m, 2H), 1.98 (d, J = 7.5 Hz, 2H), 1.61 – 1.51 (m, 2H).
C61	 ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.15 (s, 1H), 7.92 – 7.80 (m, 3H), 7.70 (dd, J = 6.8, 1.9 Hz, 1H), 7.62 (dd, J = 11.9, 2.2 Hz, 1H), 7.41 – 7.33 (m, 1H), 7.13 (s, 1H), 7.02 (dd, J = 7.0, 1.6 Hz, 1H), 6.84 (t, J = 6.4 Hz, 1H), 6.32 (t, J = 7.1 Hz, 1H), 4.55 (q, J = 7.0 Hz, 1H), 4.30 (q, J = 6.7 Hz, 1H), 2.26 – 2.14 (m, 2H), 2.02 (tq, J = 11.5, 6.5, 5.9 Hz, 2H), 1.61 (td, J = 7.4, 6.9, 4.1 Hz, 2H).	C62	 ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.20 – 8.07 (m, 1H), 7.99 (d, J = 4.5 Hz, 1H), 7.84 (d, J = 4.5 Hz, 2H), 7.54 (dd, J = 9.0, 2.7 Hz, 1H), 7.41 (s, 1H), 7.20 (s, 1H), 7.04 (d, J = 6.7 Hz, 1H), 6.88 (s, 1H), 6.54 (d, J = 8.9 Hz, 1H), 4.33 (d, J = 26.9 Hz, 2H), 2.19 (s, 2H), 1.98 (td, J = 16.8, 16.0, 7.1 Hz, 2H), 1.67 – 1.40 (m, 2H).
C63		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.48 (d, J = 6.8 Hz, 1H), 8.15 – 8.09 (m, 2H), 8.00 (d, J = 4.5 Hz, 1H), 7.85 (d, J = 4.5 Hz, 1H), 7.68 (dd, J = 8.1, 1.5 Hz, 1H), 7.56 (dd, J = 8.9, 2.7 Hz, 1H), 7.28 – 7.24 (m, 1H), 7.07 (d, J = 6.9 Hz, 1H), 6.56 (d, J = 8.9 Hz, 1H), 4.40 (dd, J = 13.9, 7.0 Hz, 2H), 2.22 (ddt, J = 17.8, 12.9, 6.9 Hz, 2H), 1.98 (dd, J = 13.6, 6.7 Hz, 2H), 1.70 – 1.29 (m, -2H).		
C64	 ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.19 (s, 1H), 8.13 (d, J = 2.6 Hz, 1H), 8.01 (d, J = 4.5 Hz, 1H), 7.86 (d, J = 4.5 Hz, 1H), 7.55 (dd, J = 9.0, 2.7 Hz, 2H), 7.04 (d, J = 7.0 Hz, 1H), 6.55 (d, J = 9.0 Hz, 1H), 4.37 (dt, J = 13.2, 6.7 Hz, 2H), 2.40 (s, 3H), 2.17 (dt, J = 9.9, 5.7 Hz, 2H), 1.99 –	C65	 ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.62 (s, 1H), 8.15 (d, J = 6.0 Hz, 1H), 8.01 (d, J = 4.5 Hz, 1H), 7.85 (d, J = 4.5 Hz, 1H), 7.55 (dd, J = 9.0, 2.5 Hz, 1H), 7.43 (d, J = 7.0 Hz, 2H), 7.03 (d, J = 6.9 Hz, 1H), 6.88 (t, J = 6.6 Hz, 1H), 6.68 (s, 1H), 6.56 (d, J = 9.0 Hz, 1H), 4.35 (d, J = 8.1 Hz, 1H), 4.20 (s, 1H), 2.17 (dt, J = 11.5, 6.0

	1.91 (m, 2H), 1.63 – 1.52 (m, 2H).		Hz, 2H), 1.99 (dt, *J* = 13.4, 6.8 Hz, 1H), 1.91 (q, *J* = 6.6 Hz, 1H), 1.55 (ddd, *J* = 25.0, 12.7, 6.6 Hz, 2H).
C66	 ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.13 (d, *J* = 2.6 Hz, 1H), 8.03 (dd, *J* = 3.9, 1.6 Hz, 1H), 7.93 (d, *J* = 5.3 Hz, 1H), 7.63 (s, 1H), 7.55 (dd, *J* = 9.0, 2.7 Hz, 1H), 7.53 – 7.44 (m, 2H), 7.04 (dd, *J* = 9.5, 1.6 Hz, 1H), 6.99 (d, *J* = 6.8 Hz, 1H), 6.95 (dd, *J* = 7.7, 5.3 Hz, 1H), 6.56 (d, *J* = 9.0 Hz, 1H), 4.34 (dq, *J* = 24.0, 6.7 Hz, 2H), 2.21 (dq, *J* = 11.6, 6.1 Hz, 2H), 2.00 (dq, *J* = 23.2, 6.6 Hz, 2H), 1.69 – 1.48 (m, 2H).	C67	 ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.58 (dt, *J* = 6.7, 1.2 Hz, 1H), 8.10 – 7.97 (m, 2H), 7.86 (d, *J* = 4.5 Hz, 1H), 7.64 (dd, *J* = 12.0, 2.1 Hz, 1H), 7.47 – 7.31 (m, 2H), 7.01 (dd, *J* = 7.2, 1.7 Hz, 1H), 6.85 (td, *J* = 6.7, 1.6 Hz, 1H), 6.64 (d, *J* = 7.3 Hz, 1H), 4.54 (q, *J* = 6.9 Hz, 1H), 4.20 (q, *J* = 6.5 Hz, 1H), 2.25 – 2.11 (m, 2H), 1.98 (td, *J* = 7.2, 6.7, 1.8 Hz, 2H), 1.70 – 1.51 (m, 2H).
C68	 ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.97 – 7.81 (m, 2H), 7.63 – 7.49 (m, 3H), 7.45 (d, *J* = 7.8 Hz, 1H), 7.01 – 6.82 (m, 2H), 6.60 (dd, *J* = 15.8, 6.7 Hz, 1H), 6.42 (dd, *J* = 15.8, 1.8 Hz, 1H), 6.29 (t, *J* = 6.9 Hz, 1H), 4.55 (q, *J* = 7.0 Hz, 1H), 4.31 (q, *J* = 6.5 Hz, 1H), 2.19 (ddd, *J* = 11.8, 7.0, 4.1 Hz, 2H), 2.02 (dd, *J* = 14.5, 7.9 Hz, 2H), 1.83 (dd, *J* = 6.7, 1.7 Hz, 3H), 1.63 (dt, *J* = 10.3, 6.2 Hz, 2H).	C69	 ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.11 – 7.98 (m, 2H), 7.92 (d, *J* = 5.3 Hz, 1H), 7.64 (dd, *J* = 12.1, 2.1 Hz, 2H), 7.55 – 7.41 (m, 2H), 7.06 (dd, *J* = 9.5, 1.6 Hz, 1H), 6.97 (ddd, *J* = 13.0, 7.4, 3.5 Hz, 2H), 4.56 (q, *J* = 7.1 Hz, 1H), 4.31 (q, *J* = 6.6 Hz, 1H), 2.19 (ddt, *J* = 12.4, 9.3, 4.5 Hz, 2H), 2.11 – 1.98 (m, 2H), 1.63 (dtt, *J* = 10.9, 7.1, 3.1 Hz, 2H).
C70	 ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.61 – 8.57 (dt, *J* = 6.7, 1.2 Hz, 1H), 8.10 – 8.07 (d, *J* = 2.6 Hz, 1H), 7.95 – 7.91 (dd, *J* = 5.2, 1.4 Hz, 1H), 7.59 – 7.54 (dd, *J* = 7.7, 1.4 Hz, 1H), 7.52 – 7.47 (dd, *J* = 8.9, 2.6 Hz, 1H), 7.44 – 7.34 (m, 2H), 7.16 – 7.09 (dd, *J* = 7.7, 5.2 Hz, 1H), 6.93 – 6.82 (m, 2H), 6.67 – 6.56 (dd, *J* = 21.8, 8.1 Hz, 2H), 4.38 – 4.29 (q, *J* = 6.1 Hz, 1H), 4.24 – 4.14 (p, *J* = 6.7 Hz, 1H), 3.41 – 3.39 (s, 3H), 2.26 – 2.10 (m, 2H), 2.05 – 1.84 (m, 2H), 1.64 – 1.43 (m, 2H).	C71	 ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.63 – 8.56 (d, *J* = 6.7 Hz, 1H), 8.48 – 8.38 (d, *J* = 4.8 Hz, 1H), 8.24 – 8.14 (d, *J* = 7.7 Hz, 1H), 8.07 – 7.94 (d, *J* = 9.5 Hz, 1H), 7.82 – 7.75 (d, *J* = 2.6 Hz, 1H), 7.46 – 7.35 (dt, *J* = 14.9, 8.5 Hz, 2H), 7.32 – 7.21 (ddd, *J* = 16.1, 8.4, 3.8 Hz, 2H), 6.91 – 6.72 (m, 3H), 6.70 – 6.53 (dd, *J* = 29.1, 8.0 Hz, 2H), 4.40 – 4.29 (m, 1H), 4.27 – 4.11 (q, *J* = 6.9 Hz, 1H), 2.26 – 2.09 (m, 2H), 2.05 – 1.83 (qt, *J* = 12.8, 5.7 Hz, 2H), 1.67 – 1.46 (m, 2H).

C72	 ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.15 (s, 1H), 8.05 (d, *J* = 2.2 Hz, 1H), 8.01 (d, *J* = 4.5 Hz, 1H), 7.86 (d, *J* = 4.5 Hz, 2H), 7.65 (dd, *J* = 12.0, 2.2 Hz, 1H), 7.37 (d, *J* = 7.6 Hz, 1H), 7.04 (d, *J* = 7.1 Hz, 2H), 6.84 (s, 1H), 4.56 (h, *J* = 7.0 Hz, 1H), 4.30 (h, *J* = 6.5 Hz, 1H), 2.18 (dt, *J* = 12.6, 6.1 Hz, 2H), 2.01 (td, *J* = 8.0, 7.4, 3.7 Hz, 2H), 1.61 (tt, *J* = 12.0, 7.0 Hz, 2H).	C73	 ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.58 (dt, *J* = 6.7, 1.1 Hz, 1H), 8.04 (d, *J* = 2.7 Hz, 1H), 7.46 (dd, *J* = 8.9, 2.7 Hz, 1H), 7.44 – 7.34 (m, 2H), 7.22 (dd, *J* = 7.8, 1.2 Hz, 1H), 7.12 (td, *J* = 7.6, 1.2 Hz, 1H), 7.03 (td, *J* = 7.6, 1.2 Hz, 1H), 6.96 (d, *J* = 6.9 Hz, 1H), 6.93 – 6.81 (m, 2H), 6.70 – 6.56 (m, 2H), 4.35 (q, *J* = 6.6 Hz, 1H), 4.20 (q, *J* = 6.8 Hz, 1H), 3.38 (s, 3H), 2.23 – 2.12 (m, 2H), 2.03 – 1.87 (m, 2H), 1.66 – 1.44 (m, 2H).
C74	 ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.01 (s, 1H), 8.16 – 8.09 (m, 1H), 8.05 (d, *J* = 6.0 Hz, 1H), 7.94 (dd, *J* = 5.2, 1.4 Hz, 1H), 7.81 (d, *J* = 7.7 Hz, 1H), 7.57 (ddd, *J* = 8.3, 5.5, 2.0 Hz, 2H), 7.20 (dd, *J* = 7.6, 5.9 Hz, 1H), 7.15 (dd, *J* = 7.7, 5.2 Hz, 1H), 7.07 (s, 1H), 6.64 (d, *J* = 8.9 Hz, 1H), 4.45 – 4.24 (m, 2H), 3.41 (s, 3H), 2.35 – 2.13 (m, 2H), 2.05 (dp, *J* = 20.2, 7.0 Hz, 2H), 1.69 (ddd, *J* = 14.6, 9.0, 6.0 Hz, 1H), 1.60 (qd, *J* = 8.7, 8.1, 5.7 Hz, 1H).	C75	 ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.06 (d, *J* = 2.0 Hz, 1H), 7.96 (d, *J* = 5.2 Hz, 1H), 7.89 (s, 1H), 7.64 (dd, *J* = 12.1, 2.1 Hz, 1H), 7.59 (d, *J* = 7.7 Hz, 1H), 7.43 (s, 1H), 7.33 (d, *J* = 12.2 Hz, 1H), 7.16 (dd, *J* = 7.7, 5.2 Hz, 1H), 6.94 (d, *J* = 6.9 Hz, 1H), 6.89 (s, 1H), 4.57 (q, *J* = 7.0 Hz, 1H), 4.31 (q, *J* = 6.6 Hz, 1H), 3.41 (s, 3H), 2.20 (dt, *J* = 12.4, 6.0 Hz, 2H), 2.04 (td, *J* = 15.6, 13.7, 7.3 Hz, 2H), 1.74 – 1.57 (m, 2H).
C76	 ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.47 (d, *J* = 6.8 Hz, 1H), 8.10 (d, *J* = 2.7 Hz, 1H), 8.08 (dd, *J* = 4.8, 1.5 Hz, 1H), 7.93 (dd, *J* = 5.2, 1.4 Hz, 1H), 7.67 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.57 (dd, *J* = 7.7, 1.4 Hz, 1H), 7.52 (dd, *J* = 8.9, 2.6 Hz, 1H), 7.40 (d, *J* = 7.7 Hz, 1H), 7.24 (dd, *J* = 8.0, 4.8 Hz, 1H), 7.14 (dd, *J* = 7.8, 5.2 Hz, 1H), 7.00 – 6.95 (m, 1H), 6.60 (d, *J* = 8.9 Hz, 1H), 4.37 (dd, *J* = 14.8, 8.2 Hz, 2H), 3.40 (s, 3H), 2.22 (dq, *J* = 11.6, 6.7, 5.9 Hz, 2H), 2.02 – 1.97 (m, 2H), 1.66 –	C77	 ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.48 (d, *J* = 6.9 Hz, 1H), 8.10 (s, 1H), 8.07 (s, 1H), 8.03 (s, 1H), 7.87 (s, 1H), 7.69 (s, 1H), 7.67 (d, *J* = 1.5 Hz, 1H), 7.26 (s, 1H), 7.11 (s, 1H), 4.63 – 4.41 (m, 2H), 2.21 (d, *J* = 5.2 Hz, 2H), 2.05 (s, 2H), 1.65 (d, *J* = 10.8 Hz, 2H).

	1.53 (m, 2H).		
C78	 ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.47 (d, J = 6.8 Hz, 1H), 8.10 – 8.07 (m, 2H), 7.69 – 7.65 (m, 1H), 7.62 – 7.59 (m, 1H), 7.50 (d, J = 3.0 Hz, 1H), 7.42 (d, J = 8.2 Hz, 1H), 7.31 (s, 1H), 7.24 (dd, J = 8.1, 4.8 Hz, 1H), 7.08 (d, J = 6.8 Hz, 1H), 6.62 (d, J = 8.9 Hz, 1H), 4.41 (dd, J = 12.8, 6.6 Hz, 2H), 3.43 (s, 3H), 2.21 (q, J = 7.6, 6.2 Hz, 2H), 1.99 (t, J = 8.0 Hz, 2H), 1.65 (d, J = 7.6 Hz, 2H).	C79	 ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.47 (d, J = 6.8 Hz, 1H), 8.08 (s, 2H), 7.77 – 7.70 (m, 2H), 7.67 (d, J = 8.0 Hz, 1H), 7.49 (dd, J = 8.8, 2.4 Hz, 1H), 7.25 (dd, J = 8.0, 4.4 Hz, 1H), 7.07 (s, 1H), 6.96 (d, J = 7.9 Hz, 1H), 6.63 (d, J = 8.9 Hz, 1H), 4.40 (dd, J = 12.9, 6.5 Hz, 2H), 3.44 (s, 3H), 2.21 (dq, J = 12.5, 6.0, 5.1 Hz, 2H), 1.99 (dd, J = 11.7, 6.3 Hz, 2H), 1.59 (ddd, J = 13.7, 10.1, 4.7 Hz, 2H).
C80	 ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.77 (dd, J = 4.8, 1.5 Hz, 1H), 8.26 (d, J = 2.2 Hz, 2H), 8.13 (dd, J = 7.8, 1.4 Hz, 1H), 8.04 (dd, J = 13.0, 2.2 Hz, 1H), 7.75 – 7.38 (m, 3H), 6.72 (s, 1H), 4.97 (s, 2H), 4.53 (q, J = 6.9 Hz, 1H), 4.34 (q, J = 6.8 Hz, 1H), 2.19 (t, J = 6.3 Hz, 2H), 2.02 (d, J = 7.3 Hz, 2H), 1.62 (dt, J = 11.4, 6.2 Hz, 2H).	C81	 ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.77 (dd, J = 4.7, 1.5 Hz, 1H), 8.26 (d, J = 2.2 Hz, 1H), 8.12 (dd, J = 7.9, 1.5 Hz, 1H), 8.04 (dd, J = 13.1, 2.2 Hz, 1H), 7.92 (dd, J = 5.4, 1.4 Hz, 1H), 7.64 (dd, J = 7.7, 4.7 Hz, 2H), 7.50 (dd, J = 7.7, 1.4 Hz, 1H), 6.94 (dd, J = 7.6, 5.3 Hz, 1H), 6.70 (dd, J = 7.1, 1.6 Hz, 1H), 4.97 (s, 2H), 4.53 (q, J = 6.9 Hz, 1H), 4.31 (q, J = 6.6 Hz, 1H), 2.27 – 2.11 (m, 2H), 2.03 (td, J = 6.7, 2.3 Hz, 2H), 1.63 (qd, J = 6.4, 2.2 Hz, 2H).
C82	 ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.47 (d, J = 6.8 Hz, 1H), 8.09 (s, 1H), 8.06 (d, J = 2.1 Hz, 1H), 7.96 (dd, J = 5.2, 1.4 Hz, 1H), 7.68 – 7.66 (m, 1H), 7.66 – 7.62 (m, 1H), 7.59 (dd, J = 7.8, 1.4 Hz, 1H), 7.26 – 7.23 (m, 1H), 7.16 (dd, J = 7.8, 5.2 Hz, 1H), 7.01 – 6.97 (m, 1H), 4.57 (q, J = 7.1 Hz, 1H), 4.43 (q, J = 6.4 Hz, 1H), 3.41 (s, 3H), 2.21 (dt, J = 12.8, 6.5 Hz, 2H), 2.08 – 2.03 (m, 2H), 1.64 (tt, J = 12.7, 8.0 Hz, 2H).	C83	 ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.77 (d, J = 4.7 Hz, 1H), 8.53 (d, J = 4.7 Hz, 1H), 8.26 (d, J = 2.1 Hz, 1H), 8.13 (d, J = 7.8 Hz, 1H), 8.09 (dd, J = 4.8, 1.6 Hz, 1H), 8.05 (dd, J = 13.0, 2.2 Hz, 1H), 7.67 – 7.65 (m, 1H), 7.65 – 7.61 (m, 1H), 7.26 – 7.23 (m, 1H), 6.75 (d, J = 7.1 Hz, 1H), 4.97 (s, 2H), 4.47 (dt, J = 41.5, 6.6 Hz, 2H), 2.21 (dd, J = 13.2, 6.0 Hz, 2H), 2.04 (d, J = 6.8 Hz, 2H), 1.63 (dd, J = 12.4, 6.2 Hz, 2H).
C84	 ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.47	C85	 ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.02

	(d, *J* = 6.8 Hz, 1H), 8.44 (dd, *J* = 4.7, 1.9 Hz, 1H), 8.20 (dd, *J* = 7.8, 1.8 Hz, 1H), 8.09 (dd, *J* = 4.8, 1.5 Hz, 1H), 8.04 (d, *J* = 9.6 Hz, 1H), 7.80 (d, *J* = 2.5 Hz, 1H), 7.68 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.31 – 7.23 (m, 3H), 6.89 (d, *J* = 6.8 Hz, 1H), 6.76 (d, *J* = 9.5 Hz, 1H), 6.59 (d, *J* = 8.8 Hz, 1H), 4.40 (dq, *J* = 19.4, 6.6 Hz, 2H), 2.22 (ddd, *J* = 20.3, 12.5, 5.1 Hz, 2H), 2.03 – 1.97 (m, 2H), 1.67 – 1.55 (m, 2H).		(dd, *J* = 4.8, 1.5 Hz, 1H), 7.99 (d, *J* = 2.6 Hz, 1H), 7.60 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.40 (dd, *J* = 8.9, 2.6 Hz, 1H), 7.20 – 7.16 (m, 1H), 7.16 – 7.14 (m, 1H), 7.05 (td, *J* = 7.7, 1.2 Hz, 1H), 6.99 – 6.94 (m, 2H), 6.81 (dd, *J* = 7.8, 1.1 Hz, 1H), 6.55 (d, *J* = 8.9 Hz, 1H), 4.31 (dd, *J* = 14.0, 7.4 Hz, 2H), 3.32 (s, 3H), 2.14 (tdd, *J* = 12.4, 8.2, 5.2 Hz, 2H), 1.99 – 1.89 (m, 2H), 1.61 – 1.47 (m, 2H).
C86	 ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.40 (d, *J* = 6.8 Hz, 1H), 8.04 (s, 1H), 7.92 (d, *J* = 2.1 Hz, 1H), 7.60 (d, *J* = 8.0 Hz, 1H), 7.53 (dd, *J* = 11.9, 2.1 Hz, 1H), 7.17 (dt, *J* = 7.9, 2.8 Hz, 2H), 7.09 – 7.05 (m, 1H), 7.00 – 6.95 (m, 2H), 6.90 – 6.87 (m, 1H), 4.44 (dq, *J* = 59.6, 6.8 Hz, 2H), 3.32 (s, 3H), 2.14 (dtd, *J* = 14.9, 7.3, 4.0 Hz, 2H), 2.01 – 1.96 (m, 2H), 1.64 – 1.53 (m, 2H).	C87	 ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.44 (d, *J* = 6.8 Hz, 1H), 8.10 (d, *J* = 2.7 Hz, 1H), 8.08 (dd, *J* = 4.8, 1.5 Hz, 1H), 7.65 (ddd, *J* = 9.0, 5.1, 2.1 Hz, 2H), 7.24 (dd, *J* = 8.1, 4.8 Hz, 1H), 6.66 (d, *J* = 6.9 Hz, 1H), 6.50 (d, *J* = 9.0 Hz, 1H), 4.39 (s, 2H), 4.38 (s, 2H), 2.91 (s, 3H), 2.21 – 2.10 (m, 2H), 2.00 – 1.90 (m, 2H), 1.61 – 1.47 (m, 2H).
C88	 ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.44 (d, *J* = 6.9 Hz, 1H), 8.08 (dd, *J* = 4.8, 1.5 Hz, 1H), 8.00 (d, *J* = 2.2 Hz, 1H), 7.75 (dd, *J* = 12.9, 2.2 Hz, 1H), 7.65 (dd, *J* = 8.0, 1.4 Hz, 1H), 7.24 (dd, *J* = 8.0, 4.7 Hz, 1H), 6.64 (dd, *J* = 7.1, 1.5 Hz, 1H), 4.50 – 4.40 (m, 2H), 4.40 (s, 2H), 2.92 (s, 3H), 2.23 – 2.11 (m, 2H), 1.99 (t, *J* = 6.8 Hz, 2H), 1.63 – 1.56 (m, 2H).	C89	 ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.09 – 8.08 (m, 1H), 7.98 (d, *J* = 2.7 Hz, 1H), 7.71 (ddd, *J* = 7.0, 5.1, 1.7 Hz, 2H), 7.67 – 7.65 (m, 1H), 7.45 (dd, *J* = 8.9, 2.7 Hz, 1H), 7.24 (dd, *J* = 4.0, 2.1 Hz, 1H), 7.06 (d, *J* = 6.9 Hz, 1H), 6.57 – 6.54 (m, 1H), 6.46 – 6.41 (m, 1H), 6.33 (t, *J* = 7.2 Hz, 1H), 4.41 – 4.34 (m, 2H), 2.22 – 2.16 (m, 2H), 1.98 (dd, *J* = 14.3, 7.4 Hz, 2H), 1.62 – 1.52 (m, 2H).
C90	 ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.83 – 8.79 (d, *J* = 7.1 Hz, 1H), 8.78 – 8.75 (m, 1H), 8.27 – 8.24 (dd, *J* = 5.2, 2.0 Hz, 2H), 8.15 – 8.11 (m, 1H), 8.07 – 8.02 (dd, *J* = 13.1, 2.2 Hz, 1H), 7.95 – 7.92 (d, *J* = 2.1 Hz, 1H), 7.66 – 7.61 (dd, *J* = 7.7, 4.7 Hz, 1H), 6.78 – 6.74 (d, *J* = 7.2 Hz, 1H), 4.99 – 4.95 (s, 2H), 4.59 – 4.49 (q, *J* =	C91	 ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.84 (d, *J* = 6.8 Hz, 1H), 8.45 – 8.44 (m, 1H), 8.12 (d, *J* = 2.7 Hz, 1H), 8.02 (dd, *J* = 3.8, 1.7 Hz, 1H), 7.98 (d, *J* = 2.0 Hz, 1H), 7.53 (dd, *J* = 8.9, 2.7 Hz, 1H), 7.46 (dd, *J* = 9.5, 3.8 Hz, 1H), 7.03 (dd, *J* = 9.5, 1.7 Hz, 2H), 6.54 (d, *J* = 8.9 Hz, 1H), 4.46 –

	6.7 Hz, 1H), 4.38 – 4.28 (q, *J* = 6.7 Hz, 1H), 2.27 – 2.14 (dt, *J* = 11.4, 5.7 Hz, 2H), 2.09 – 2.00 (t, *J* = 6.9 Hz, 2H), 1.74 – 1.58 (tt, *J* = 13.1, 7.5 Hz, 2H).		4.35 (m, 2H), 2.26 – 2.17 (m, 2H), 2.03 – 1.93 (m, 2H), 1.59 (ddt, *J* = 21.2, 9.8, 4.1 Hz, 2H).
C92	 ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.66 (dd, *J* = 7.4, 5.6 Hz, 1H), 7.84 (d, *J* = 2.1 Hz, 1H), 7.64 (dd, *J* = 6.9, 2.1 Hz, 1H), 7.54 (dd, *J* = 11.9, 2.2 Hz, 1H), 7.49 (ddd, *J* = 8.9, 6.6, 2.1 Hz, 1H), 7.27 (dd, *J* = 9.7, 2.8 Hz, 1H), 6.92 (dd, *J* = 7.2, 1.6 Hz, 1H), 6.86 (td, *J* = 7.6, 2.8 Hz, 1H), 6.74 (d, *J* = 7.2 Hz, 1H), 6.46 (d, *J* = 9.2 Hz, 1H), 6.29 (td, *J* = 6.7, 1.3 Hz, 1H), 4.51 (p, *J* = 6.8 Hz, 1H), 4.17 (h, *J* = 6.4 Hz, 1H), 2.15 (dt, *J* = 9.1, 4.1 Hz, 2H), 1.97 (td, *J* = 7.1, 6.7, 2.7 Hz, 2H), 1.65 – 1.52 (m, 2H).	C93	 ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.58 (d, *J* = 6.6 Hz, 1H), 8.02 (d, *J* = 2.7 Hz, 1H), 7.96 (d, *J* = 2.2 Hz, 1H), 7.82 (d, *J* = 6.0 Hz, 1H), 7.49 – 7.43 (m, 1H), 7.43 – 7.33 (m, 2H), 7.11 (d, *J* = 6.0 Hz, 1H), 7.08 (d, *J* = 2.2 Hz, 1H), 6.96 (d, *J* = 6.9 Hz, 1H), 6.86 (td, *J* = 6.7, 1.5 Hz, 1H), 6.64 (d, *J* = 7.3 Hz, 1H), 6.56 (d, *J* = 8.9 Hz, 1H), 4.33 (q, *J* = 6.6 Hz, 1H), 4.19 (q, *J* = 6.7 Hz, 1H), 2.16 (dq, *J* = 11.7, 6.0 Hz, 2H), 1.98 (dt, *J* = 13.4, 7.0 Hz, 1H), 1.89 (dt, *J* = 13.2, 6.7 Hz, 1H), 1.64 – 1.44 (m, 2H).
C94	 ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.83 (d, *J* = 6.8 Hz, 1H), 8.45 (dd, *J* = 2.1, 1.0 Hz, 1H), 8.06 – 8.03 (m, 2H), 7.98 (d, *J* = 2.0 Hz, 1H), 7.65 (dd, *J* = 12.1, 2.1 Hz, 1H), 7.48 (dd, *J* = 9.5, 3.9 Hz, 1H), 7.08 – 7.03 (m, 2H), 4.60 – 4.43 (m, 2H), 2.26 – 2.17 (m, 2H), 2.06 (ddd, *J* = 6.9, 4.8, 2.6 Hz, 2H), 1.65 (ddd, *J* = 12.1, 8.5, 4.8 Hz, 2H).	C95	 ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.59 (d, *J* = 6.6 Hz, 1H), 8.06 (d, *J* = 2.8 Hz, 1H), 7.86 (s, 1H), 7.56 – 7.32 (m, 5H), 7.00 (d, *J* = 6.8 Hz, 1H), 6.86 (t, *J* = 6.7 Hz, 1H), 6.72 (s, 1H), 6.65 (s, 1H), 6.56 (d, *J* = 8.9 Hz, 1H), 4.34 (q, *J* = 6.6 Hz, 1H), 4.19 (q, *J* = 6.6 Hz, 1H), 2.17 (dt, *J* = 9.7, 5.7 Hz, 2H), 1.98 (dt, *J* = 13.3, 6.8 Hz, 1H), 1.89 (dt, *J* = 13.2, 6.6 Hz, 1H), 1.66 – 1.46 (m, 2H).

Example A74: Related Activity Test

Test Method:

Surface plasmon resonance data were collected on a Biacore™ 8K system (GE Healthcare) at 25 ℃. At 25 ℃, HBS-EP (10 mM HEPES, 0.15 M NaCl, 0.05% Tween-20, pH 7.4) was used as a running buffer, streptavidin was immobilized on an SA (Cytiva) sensor chip using standard amine coupling chemistry. Briefly, the carboxymethyl dextran surface was activated by injecting a 1:1 ratio of 0.4 M 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDC)/0.1 M N-hydroxysuccinimide (NHS) for 12 min at a flow rate of 10 μL/min. To capture streptavidin, the protein was diluted to 0.5 mg/mL in 10 mM sodium acetate (pH 4.5) and 100 μL of the

diluted protein was injected onto the activated chip surface for capture. Excess remaining active groups were blocked by injecting 1 M ethanolamine (pH 8.5) for 7 min. 5 μL protein was diluted to 10 μg/mL in NBS-N, 0.05% Tween, and 0.1 mM $CaCl_2$ at a flow rate of 5 μL/min for 60 s. The Aci-tagged PCSK9 protein was captured on the streptavidin surface. Typical surface densities obtained were 2900-3200 RU. SPR binding data were obtained using an appropriate dilution series of each compound at a flow rate of 30 μL/min, with an association time of 60 s per concentration point and a dissociation time of 3600 s. The running buffer used for compound binding studies was 10 mM HEPES, pH 7.4, 150 mM NaCl, 0.05% Tween-20, 2% DMSO. Data were corrected for DMSO excluding bulk effects. All data were double-referenced against blank injections and the reference surface using standard processing procedures. Data processing and kinetic fitting were performed using Scrubber software version 2.0c (BioLogic Software). Data were fitted using a simple 1:1 binding model to determine KD values.

Test Results:

K_D values are shown in Table 1 below:

Table 1. PCSK9 Kinetics Data

Examples	Kinetics K_D (M)	Examples	Kinetics K_D (M)
A1	8.78E-14	A25	9.77E-10
A2	1.13E-09	A28	2.11E-10
A3	1.96E-09	A29	4.98E-10
A4	6.85E-09	A31	1.48E-13
A5	4.22E-11	A34	1.02E-10
A6A	3.19E-12	A39	7.07E-10
A8	6.18E-11	A42	1.82E-10
A9	3.78E-11	C2	A
A10	3.62E-12	C3	A
A11A	8.73E-11		
A12	1.26E-10		
A13	5.10E-13		
A14	9.01E-10		
A15	3.44E-10		
A17	3.34E-10		
A18	4.14E-10		
A24	2.55E-10		

A<1*E-8.

Example A75: Pharmacokinetic Experiment

1. Reagents and Instruments

Polyethylene glycol 400 (lot number R22040588, Shanghai Shaoyuan Reagent Co., Ltd.), DMSO (lot number 20200319, Guangdong Guanghua Sci-Tech Co., Ltd.), Sodium Chloride Physiological Solution (lot number 2011110727, Chenxin Pharmaceutical Co., Ltd.). LC-MS instrument (Thermo Fisher Ultimate 3000 UPLC, TSQ QUANTUM ULTRA triple quadrupole mass spectrometer, AB SCIEX 5500+ QTARP).

2. Experimental Animals

SD rats: Male, 180-250 g, purchased from Guangdong Vital River Laboratory Animal Technology Co., Ltd.

3. Formulation Preparation

The test compound powder was accurately weighed and completely dissolved in DMSO. PEG-400 was added, vortexed and sonicated to mix, then sodium chloride physiological solution was added, vortexed and sonicated to mix to form a 0.5 mg/mL solution (DMSO:PEG-400:NS = 5:60:35, V/V/V). For oral gavage administration, the dose was 10 mL/kg; for intravenous administration, the dose was 2 mL/kg.

4. Blood Sample Collection

After intravenous or oral gavage administration to rats, venous blood (200 μL) was collected at 5 min (not collected for oral gavage administration), 15 min, 30 min, 1 h, 2 h, 5 h, 7 h, and 24 h into EDTA-K2-anticoagulated EP tubes. The samples were centrifuged at 10000 rpm for 2 min, and the plasma was collected and stored at -80 ℃ until analysis.

5. Bioanalysis

A certain amount of the test compound was accurately weighed and dissolved in DMSO to 2 mg/mL as a stock solution. An appropriate volume of the compound stock solution was accurately transferred and diluted with acetonitrile to prepare a series of standard solutions. 4 μL of each standard solution was accurately transferred, and 36 μL of blank plasma was added, vortexed to mix, to prepare plasma samples equivalent to plasma concentrations of 1, 3, 5, 10, 30, 100, 300, 1000, 3000 ng/mL. Each concentration was analyzed in duplicate to establish a standard curve. 30 μL of plasma was taken, and 200 μL of an acetonitrile solution containing internal standard propranolol (5 ng/mL) was added. After vortex mixing, the samples were centrifuged at 4000 rpm for 10 min, and the supernatant was taken for LC-MS analysis. The LC-MS detection conditions were as follows:

Column: YMC-Triart C18, 50×2.1 mm, S-3μm, 12 nm.

Mobile phase A: water (0.1% formic acid), mobile phase B: acetonitrile, flow rate: 0.5 mL/min, gradient elution as shown in Table 2 below:

Table 2

Time (min)	A(%)	B(%)
0	80%	20%
1.2	20%	80%
2.6	20%	80%
2.61	80%	20%
3.0	80%	20%

6. Data Processing

After detecting plasma concentrations by LC-MS, pharmacokinetic parameters in rats after administration were calculated using a non-compartmental model with WinNonlin 6.1 software. The results are shown in Table 3 below.

Table 3: Pharmacokinetic Parameters of the Compound of the Present Disclosure in Rats (iv and PO Administration)

Compound No.	Route of Administration and Dose (mg/kg)	t1/2 (h)	AUC0-24h (h*ng/mL)
A9	PO, 5	/	29400
A13	PO, 5	6.02	42500
A14	PO, 5	4.42	31400
A17	PO, 5	2.97	43800
A27	PO, 5	3.89	32000
A28	PO, 5	/	70100
A35	PO, 5	14.9	60100
C9	5, PO	/	40300
C17	5, PO	/	39800
C22	5, PO	/	37700
C34	5, PO	/	41400
C35	5, PO	/	39700
C47	5, PO	/	53000

The half-life and in vivo exposure of the compound of the present disclosure were improved compared to the control compound, and superior to Compound 458B and 464 of CN113574055A, as well as Compound C14.

Example A76: Effect on hERG Current in hERG-HEK293 Cells

Test Method: Human embryonic kidney cells stably expressing the hERG channel (hERG-HEK293 cells) were used for the experiment. An automated patch-clamp system was

used to clamp hERG-HEK293 cells to establish whole-cell voltage-clamp mode, and corresponding voltages were applied to elicit hERG currents. Cells were perfused with extracellular solution containing 0.3% DMSO (negative control), 30 μM compound, or 1, 10, 100, and 1000 nM Cisapride (positive control). The hERG channel tail currents were recorded, and the peak tail current at each concentration was obtained. Using the peak tail current recorded under the negative control (0.3% DMSO) as 100%, the inhibition rates of hERG current by 30 μM compound and different concentrations of Cisapride were calculated. The concentration-response curve fitting and IC_{50} calculation for Cisapride were performed using GraphPad Prism software. The results are shown in Table 4.

Table 4: Effect on hERG Current in hERG-HEK293 Cells

Compound No.	30 uM-hERG Inhibition
A22	19.56
A27	40.72
A30	33.75
A35	33.81

Compound No.	hERG Inhibition (%)	Compound No.	hERG Inhibition (%)	Compound No.	hERG Inhibition (%)
C7	<50%	C30	<50%	C58	<50%
C8	<50%	C32	<50%	C61	<50%
C12	<50%	C34	<50%	C64	<50%
C13	<50%	C35	<50%	C65	<50%
C15	<50%	C36	<50%	C66	<50%
C17	<50%	C43	<50%	C67	<50%
C19	<50%	C47	<50%	C69	<50%
C21	<50%	C48	<50%	C71	<50%
C22	<50%	C53	<50%	C84	<50%
C26	<50%	C56	<50%		

The hERG risk of the compound of the present disclosure was improved compared to the control compound, and superior to the control compound 458B of CN113574055A.

Example A77: Binding Affinity Test of Compound with PCSK9 Protein

The binding affinity of the compounds of the present disclosure to the PCSK9 protein was determined using a fluorescence polarization assay.

All compounds were dissolved in DMSO to prepare 10 mM stock solutions. Positive control compounds and test compounds were serially diluted from 10 mM with DMSO using 5-fold serial dilutions, resulting in 8 concentration gradients. First, a certain volume of

fluorescent probe solution was prepared using assay buffer (20 mM HEPES, 150 mM NaCl, 1 mM $CaCl_2$, and 0.01% Tween-20) to achieve a concentration of 5 nM. Then, the series of DMSO solutions of the test compounds were diluted 50-fold with the fluorescent probe solution. Finally, a human recombinant PCSK9 protein (ACRO, Cat# PC9-H5223) solution at a concentration of 4.5 μg/mL was prepared using assay buffer. After preparation of the test solutions, 5 μL of PCSK9 protein was added to a black 384-well plate (PerkinElmer, Cat# 6008260), followed by the addition of 5 μL of different concentrations of compound (final DMSO concentration of 1%). Positive control groups (assay buffer + equal volume of target protein + proportional fluorescent probe molecule) and negative control groups (assay buffer + proportional fluorescent probe molecule) were set up simultaneously. The final concentration of the probe molecule in the system was 2.5 nM, and the final concentration of PCSK9 protein was 2.25 μg/mL. After shaking and incubating at room temperature for 15 minutes, the fluorescence polarization (mP) values were read using a microplate reader at an excitation wavelength of 485 nm and an emission wavelength of 520 nm. The inhibition rate of the drug = [1 - ($mP_{(drug\ screening\ group)}$ - $mP_{(negative\ control\ group)}$)] ÷ [$mP_{(positive\ control\ group)}$ - $mP_{(negative\ control\ group)}$)] × 100. Using the logarithm of the compound concentration as the x-axis and the inhibition rate as the y-axis, a 4-parameter nonlinear regression curve was fitted to calculate the IC_{50} value (Y=Bottom + (Top-Bottom)/(1+10^((LogIC_{50}-X)*HillSlope)), where: HillSlope represents the slope of the curve, and IC_{50} represents the half-maximal inhibitory concentration.

Table 5. FP-IC_{50} Data

Example	FP-IC_{50} (nm)	Example
A17-D	B	B4
A43	B	B6
A43A	B	B7
A43B	B	B8
A43A-D	B	B9*
A43B-D	B	B10
A51	B	B11
A52	B	B24

Example	FP-IC_{50} (nm)	Example	FP-IC_{50} (nm)	Example	FP-IC_{50} (nm)
C3	B	C49	B	C80	B
C7	B	C50	B	C81	B
C8	B	C51	B	C82	B
C12A	B	C52	B	C83	B

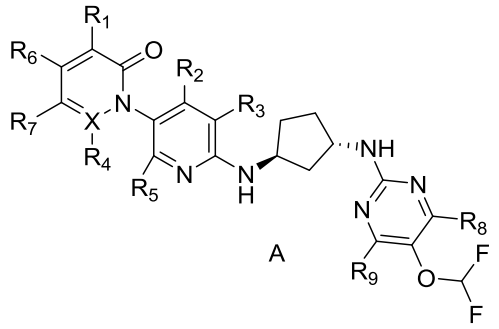
C12B	B	C53	B	C84	B
C13A	B	C55	B	C85	B
C13B	B	C57	B	C86	B
C15	B	C58	B	C87	B
C17	B	C59	B	C88	B
C17A	B	C60	B	C89	B
C19	B	C61	B	C90	B
C20	B	C62	B	C91*	B
C21	B	C63	B	C92*	B
C22	B	C64	B	C93*	B
C24	B	C65	B	C94*	B
C25	B	C66	B	C95*	B
C26	B	C67	B		
C31	B	C68	B		
C32	B	C69	B		
C33	B	C70	B		
C34	B	C71	B		
C35	B	C72	B		
C44	B	C77	B		
C47	B	C78	B		
C48	B	C79	B		

B < 300 nm. * Incubated for 18 h.

The above examples are preferred embodiments of the present disclosure, but the embodiments of the present disclosure are not limited by the above examples. Any other changes, modifications, substitutions, combinations, and simplifications made without departing from the spirit and principle of the present disclosure shall be considered as equivalent substitution methods and are included within the protection scope of the present disclosure.

CLAIMS

1. A compound represented by general formula (A), or an isomer thereof, or a racemate thereof, or a pharmaceutically acceptable salt thereof, wherein



A

X is C or N, and when X is N, R_4 is absent;

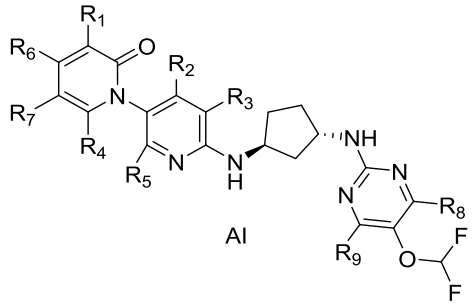
R_1, R_4, R_6, and R_7 are selected from the group consisting of hydrogen, halogen, hydroxyl, substituted or unsubstituted alkyl, cyano, -C(O)-O-alkyl, phenylalkoxy, carboxyl, hydroxymethyl, cycloalkyl, amide, alkyl-substituted amide, Z-C(O)-, and heteroaryl, Z being selected from the group consisting of alkyl and heterocycloalkyl, and a substituent being hydroxyl;

R_2, R_3, and R_5 are each selected from the group consisting of hydrogen, alkyl, alkoxy, cyano, halogen, haloalkyl, amide, hydroxyl, hydroxyl-substituted alkyl, carboxyl, amino, amino-substituted alkyl, alkylcarbonyl, and $-(CH_2)_n-O-(CH_2)_n$-phenyl, and n = 1, 2, or 3;

R_8 and R_9 are each selected from the group consisting of hydrogen, alkyl, halogen, cycloalkyl, alkylthio, alkoxy, aryl, and heteroaryl; and

R_1, R_2, R_3, R_4, R_5, R_6, and R_7 are not all hydrogen simultaneously; or when R_1, R_2, R_3, R_4, R_5, R_6, and R_7 are all hydrogen simultaneously, then R_8 and R_9 are not both hydrogen simultaneously.

2. The compound, or the isomer thereof, or the racemate thereof, or the pharmaceutically acceptable salt thereof according to claim 1, wherein the compound, or the isomer thereof, or the racemate thereof, or the pharmaceutically acceptable salt thereof is a compound represented by general formula (AI), or an isomer thereof, or a racemate thereof, or a pharmaceutically acceptable salt thereof:



AI

R_1, R_4, R_6, and R_7 are selected from the group consisting of hydrogen, halogen, hydroxyl, substituted or unsubstituted alkyl, cyano, -C(O)-O-alkyl, phenylalkoxy, carboxyl, hydroxymethyl, cycloalkyl, amide, alkyl-substituted amide, Z-C(O)-, and heteroaryl, Z being selected from the group consisting of alkyl and heterocycloalkyl, and a substituent being hydroxyl;

R_2, R_3, and R_5 are each selected from the group consisting of hydrogen, alkyl, alkoxy, cyano, halogen, haloalkyl, amide, hydroxyl, hydroxyl-substituted alkyl, carboxyl, amino, amino-substituted alkyl, alkylcarbonyl, and $-(CH_2)_n-O-(CH_2)_n$-phenyl, and n = 1, 2, or 3;

R_8 and R_9 are each selected from the group consisting of hydrogen, alkyl, halogen, cycloalkyl, alkylthio, alkoxy, aryl, and heteroaryl; and

R_1, R_2, R_3, R_4, R_5, R_6, and R_7 are not all hydrogen simultaneously; or when R_1, R_2, R_3, R_4, R_5, R_6, and R_7 are all hydrogen simultaneously, then R_8 and R_9 are not both hydrogen simultaneously.

3. The compound, or the isomer thereof, or the racemate thereof, or the pharmaceutically acceptable salt thereof according to claim 1 or 2, wherein R_1, R_2, R_4, R_5, R_6, and R_7 are all hydrogen simultaneously, and R_3 is selected from the group consisting of alkyl, alkoxy, cyano, halogen, haloalkyl, amide, hydroxyl, hydroxyl-substituted alkyl, carboxyl, amino, amino-substituted alkyl, alkylcarbonyl, and $-(CH_2)_n-O-(CH_2)_n$-phenyl, and n = 1, 2, or 3; or

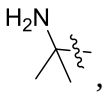
R_1, R_3, R_4, R_5, R_6, and R_7 are all hydrogen simultaneously, and R_2 is selected from the group consisting of alkyl, alkoxy, cyano, halogen, haloalkyl, amide, hydroxyl, hydroxyl-substituted alkyl, carboxyl, amino, amino-substituted alkyl, alkylcarbonyl, and $-(CH_2)_n-O-(CH_2)_n$-phenyl, and n = 1, 2, or 3.

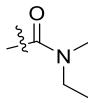
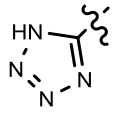
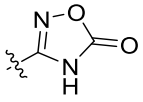
4. The compound, or the isomer thereof, or the racemate thereof, or the pharmaceutically acceptable salt thereof according to claim 1 or 2, wherein

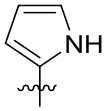
the alkyl is selected from the group consisting of methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, n-pentyl, sec-pentyl, 1-ethylpropyl, 2-methylbutyl, tert-pentyl, 1,2-dimethylpropyl, isopentyl, neopentyl, n-hexyl, isohexyl, sec-hexyl, tert-hexyl, neohexyl, 2-methylpentyl, 1,2-dimethylbutyl, and 1-ethylbutyl; the haloalkyl refers to alkyl in which one or more hydrogens are substituted by halogen; the hydroxyl-substituted alkyl refers to alkyl in which one or more hydrogens are substituted by hydroxyl; the halogen is selected from the group consisting of fluorine, chlorine, bromine, and iodine; and

the cycloalkyl is selected from the group consisting of cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl; the heterocycloalkyl refers to cycloalkyl in which one or more carbon atoms are replaced by heteroatoms, the heteroatoms being selected from the group consisting of N, O, and S; the alkoxy is selected from the group consisting of methoxy, ethoxy, n-propoxy, and

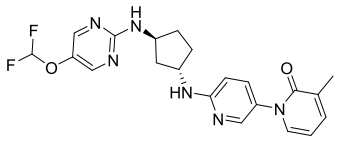
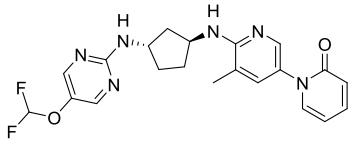
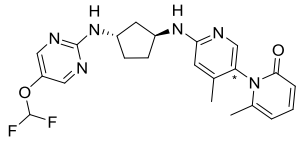
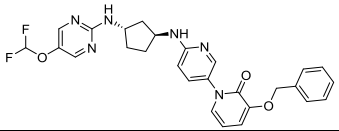
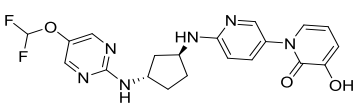
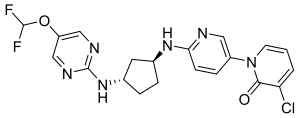
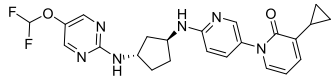
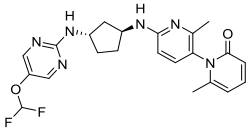
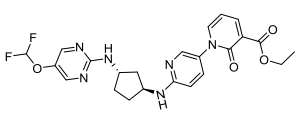
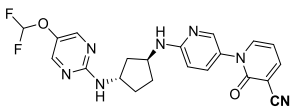
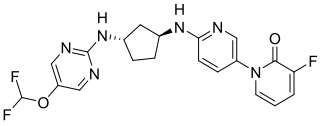
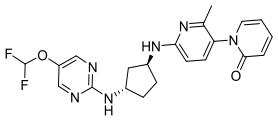
isopropoxy.

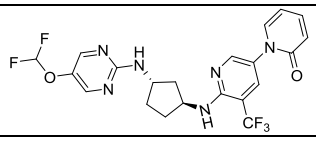
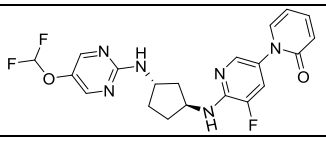
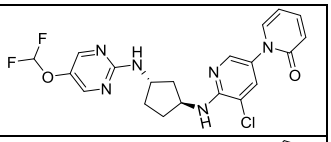
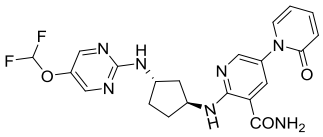
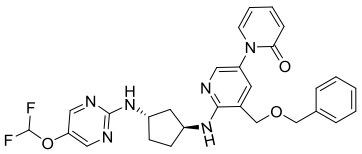
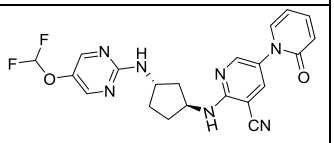
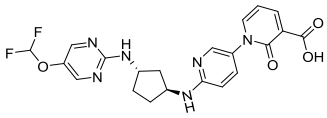
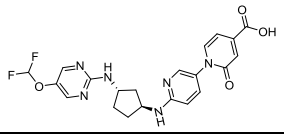
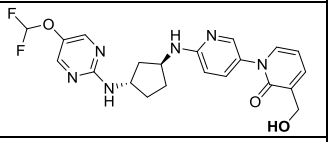
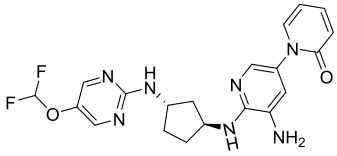
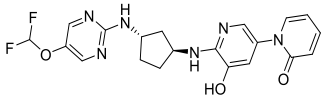
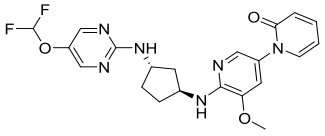
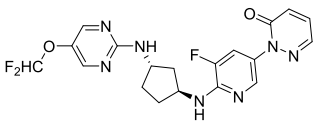
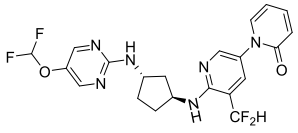
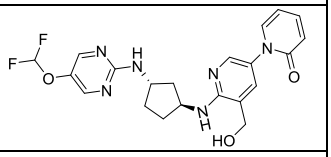
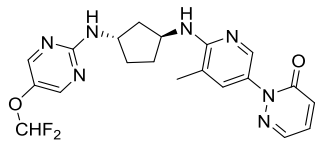
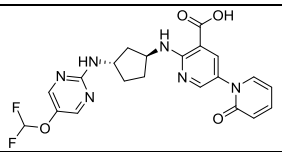
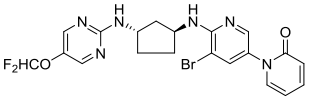
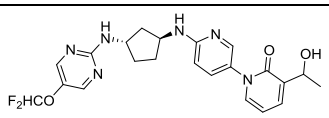
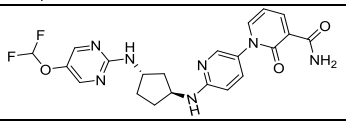
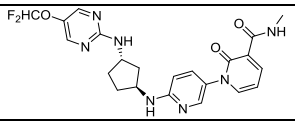
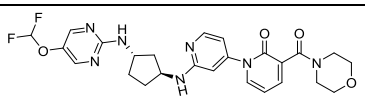
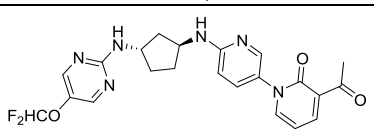
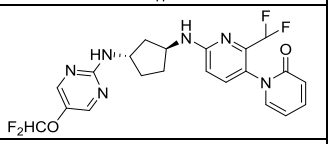
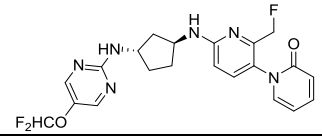
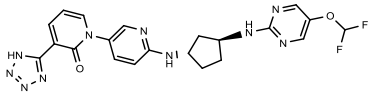
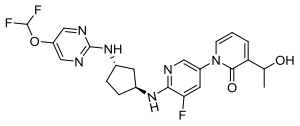
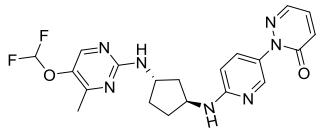
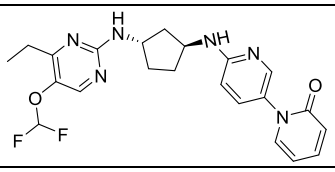
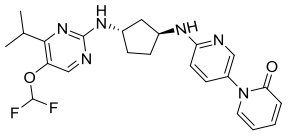
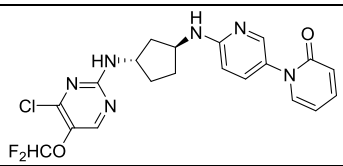
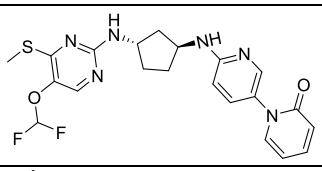
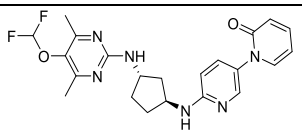
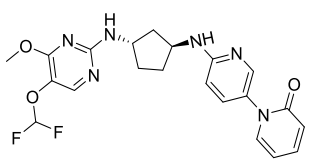
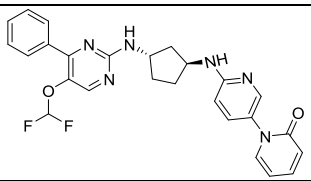
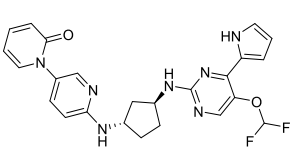
5. The compound, or the isomer thereof, or the racemate thereof, or the pharmaceutically acceptable salt thereof according to claim 1 or 2, wherein R_2 or R_3 is selected from the group consisting of F, Cl, Br, methyl, hydroxyl, hydroxymethyl, trifluoromethyl, $-CF_2H$, $-C(O)NH_2$, $-NH_2$, cyano, -COOH, methoxy, $-CH_2-O-CH_2$-phenyl, , , and ; and/or

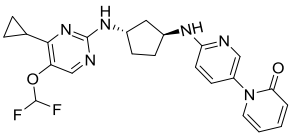
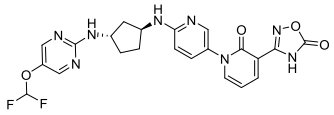
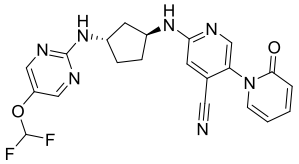
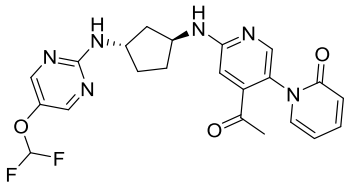
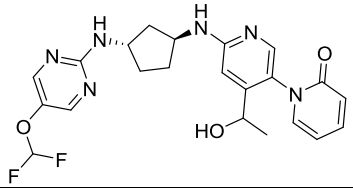
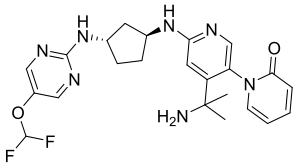
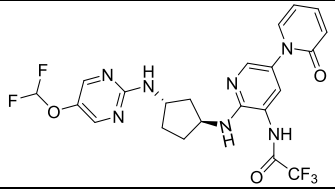
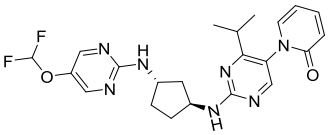
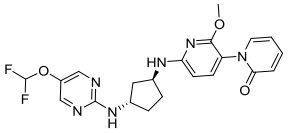
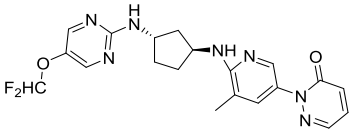
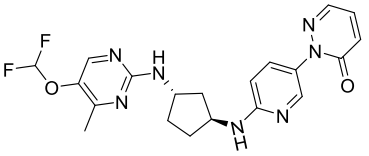
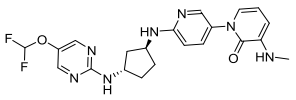
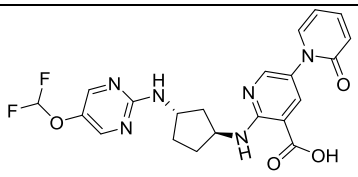
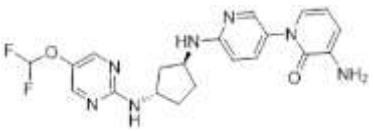
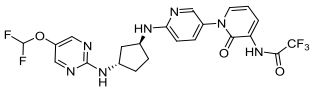
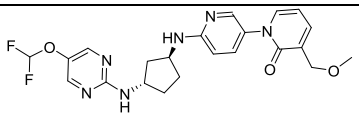
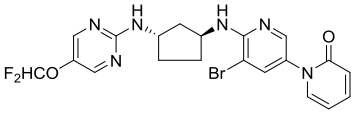
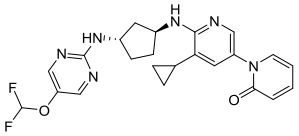
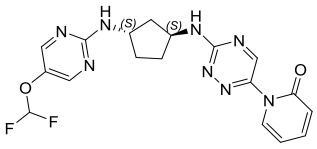
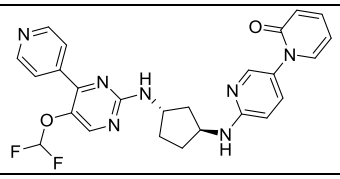
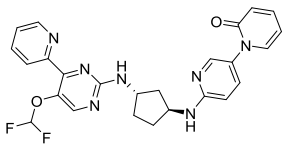
R_1 is selected from the group consisting of methyl, hydroxyl, hydroxymethyl, cyano, F, Cl, Br, $-O-CH_2$-phenyl, -COOH, $-COOCH_2CH_3$, , , amide, formamide, $CH_3-C(O)-$, , , and ; and/or

R_6 and R_7 are independently H or -COOH; and/or R_4, R_6, and R_7 are independently H; and/or R_8 and R_9 are independently selected from the group consisting of hydrogen, chlorine, methyl, methoxy, methylthio, ethyl, isopropyl, phenyl, cyclopropyl, and .

6. The compound, or the isomer thereof, or the racemate thereof, or the pharmaceutically acceptable salt thereof according to claim 1 or 2, wherein the compound, or the isomer thereof, or the racemate thereof, or the pharmaceutically acceptable salt thereof is selected from the group consisting of:

No.	Compound Structure	No.	Compound Structure	No.	Compound Structure
A1		A5		A6	
A7		A8		A9	
A10		A11		A12	
A13		A14		A15	

A16		A17		A18	
A19		A20		A21	
A22		A23		A24	
A25		A26		A27	
A28		A29		A30	
A31		A32		A33	
A35		A36		A37	
A38		A39		A40	
A41		A42		A43	
A44		A45		A46	
A47		A48		A49	
A50		A51		A52	

A53		A54		A55	
A56		A57		A58	
A59		A60		A61	
A62		A63		A64	
A65		A66		A67	
A68		A69		A70	
A71		A72		A73	

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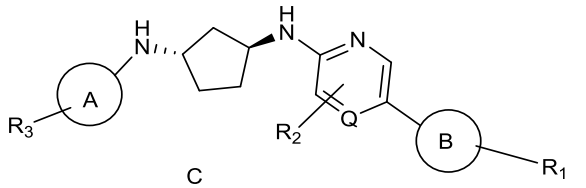
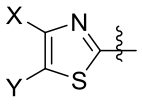
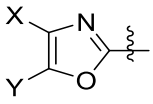
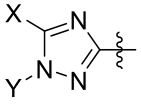
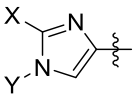
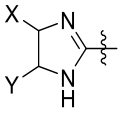
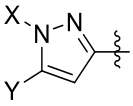
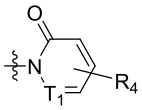
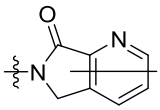
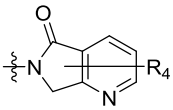
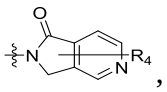
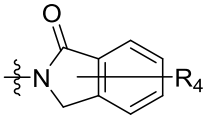
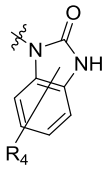
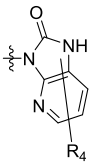
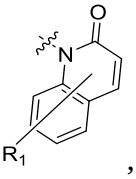
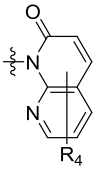
7. A compound represented by general formula (C), or an isomer thereof, or a racemate thereof, or a pharmaceutically acceptable salt thereof, wherein



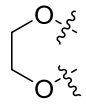
C ,

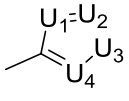
ring A is selected from the group consisting of , , , , , and , and X and Y together form a 5- to 7-membered saturated or unsaturated ring, the 5- to 7-membered saturated or unsaturated ring comprises 0, 1, or 2 heteroatoms, the heteroatoms being selected from the group consisting of O, N, and S; B is selected from the group consisting of , , , , , , , , and ;

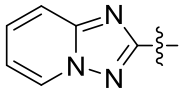
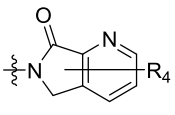
Q is selected from the group consisting of N and CR_{Q1}, R_{Q1} being selected from the group consisting of H and halogen;

T_1 is selected from the group consisting of N and CH;

R_2 is selected from the group consisting of H, alkyl, and halogen, and a number of R_2 is one or more;

R_3 is hydrogen, or R_3 represents that the hydrogen on ring A is further substituted by oxo, alkyl, halogen, alkoxy, alkylthio, haloalkyl, haloalkoxy, cycloalkyl, cycloalkylalkyl, or alkynyl; and a number of R_3 is one or more, or adjacent R_3 together form an alkoxy group ;

R_4 is selected from the group consisting of hydrogen, halogen, hydroxyl, alkoxy, haloalkoxy, substituted or unsubstituted alkyl, cyano, -C(O)-O-alkyl, phenylalkoxy, carboxyl, hydroxymethyl, and cycloalkyl, a substituent being selected from the group consisting of hydroxyl, amide, halogen, and ; U_1, U_2, and U_4 are independently selected from the group consisting of CH and N; U_3 is selected from the group consisting of CH_2 and NH; and a number of R_4 is one or more; and

when ring A is , ring B is not .

8. The compound, or the isomer thereof, or the racemate thereof, or the pharmaceutically acceptable salt thereof according to claim 7, wherein

the alkyl is selected from the group consisting of methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, n-pentyl, sec-pentyl, 1-ethylpropyl, 2-methylbutyl, tert-pentyl, 1,2-dimethylpropyl, isopentyl, neopentyl, n-hexyl, isohexyl, sec-hexyl, tert-hexyl, neohexyl, 2-methylpentyl, 1,2-dimethylbutyl, and 1-ethylbutyl;

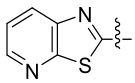
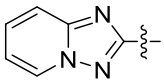
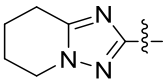
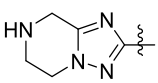
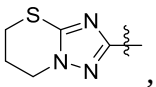
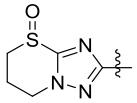
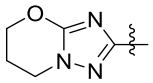
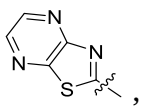
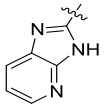
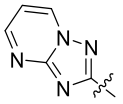
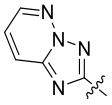
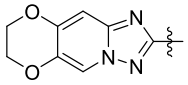
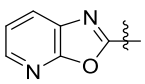
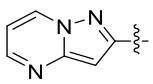
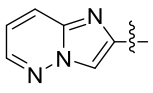
the alkoxy is selected from the group consisting of methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, sec-butoxy, and tert-butoxy;

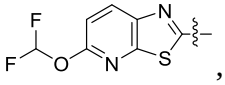
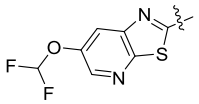
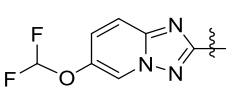
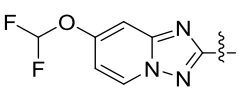
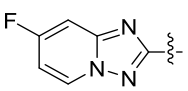
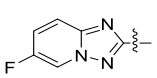
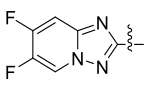
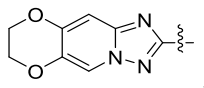
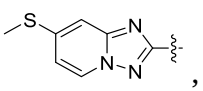
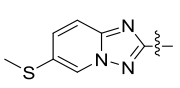
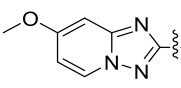
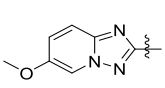
the cycloalkyl is selected from the group consisting of cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl; and

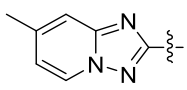
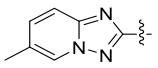
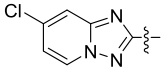
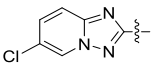
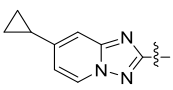
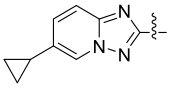
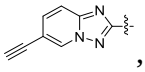
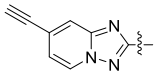
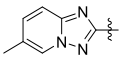
the halogen is selected from the group consisting of fluorine, chlorine, bromine, and iodine.

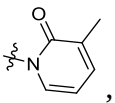
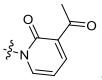
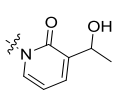
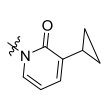
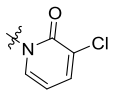
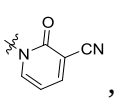
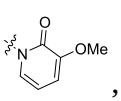
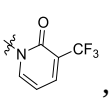
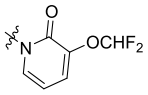
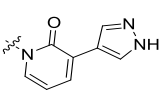
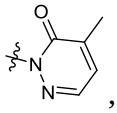
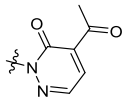
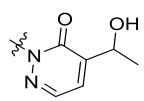
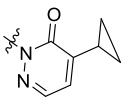
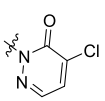
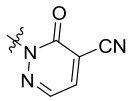
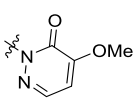
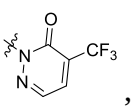
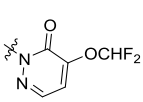
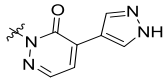
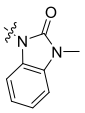
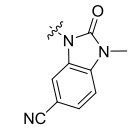
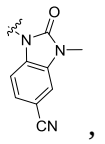
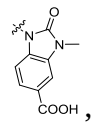
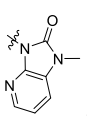
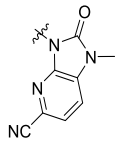
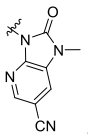
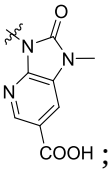
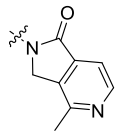
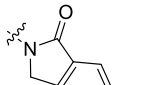
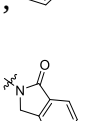
9. The compound, or the isomer thereof, or the racemate thereof, or the pharmaceutically acceptable salt thereof according to claim 7, wherein Q is N; and/or Q is CH, and R_2 is F; and/or T_1 is N; and/or

R_3 is selected from the group consisting of hydrogen, methyl, methoxy, cyclopropyl, cyclopropylmethyl, fluorine, chlorine, oxo, and CHF_2-O-; and R_4 is selected from the group consisting of hydrogen, methyl, hydroxyl, hydroxymethyl, cyano, F, Cl, Br, -O-CH_2-phenyl, -COOH, -$COOCH_2CH_3$, , , amide, formamide, CH_3-C(O)-, ethynyl, trifluoromethyl, difluoromethoxy, and methoxy.

10. The compound, or the isomer thereof, or the racemate thereof, or the pharmaceutically acceptable salt thereof according to claim 7, wherein ring A is selected from the group consisting of , , , , , , , , , , , , , , and ;

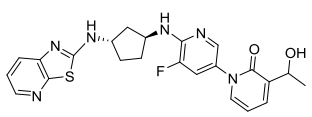
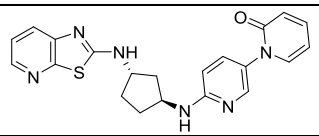
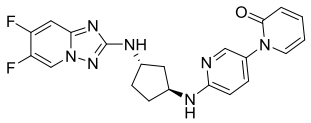
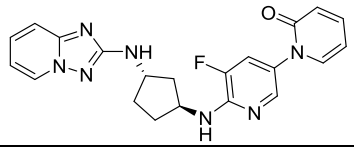
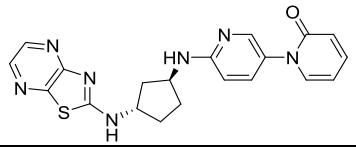
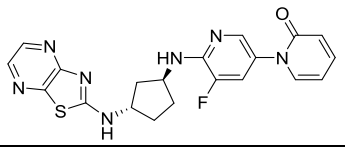
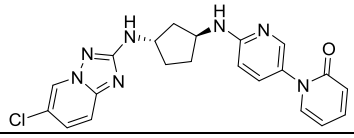
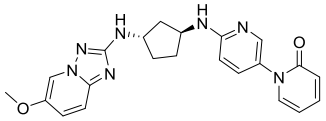
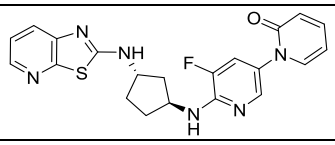
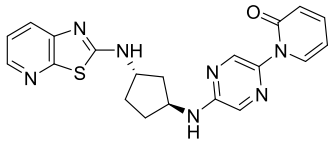
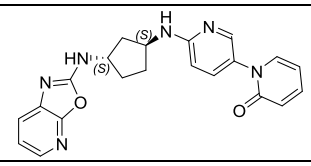
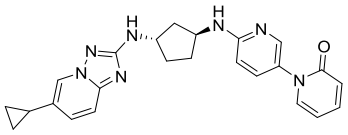
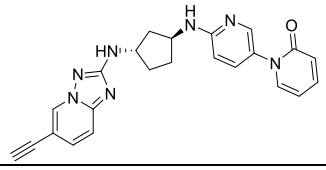
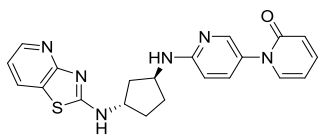
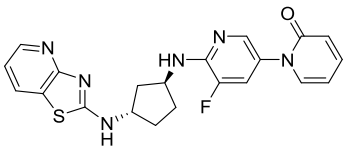
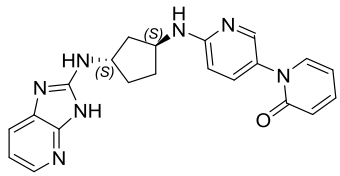
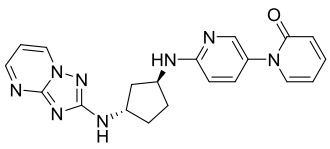
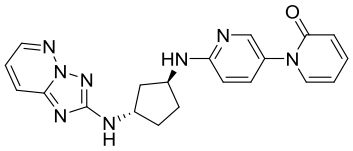
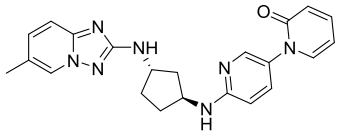
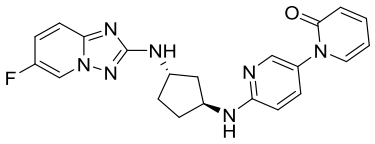
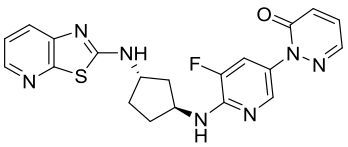
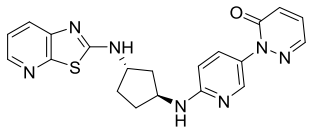
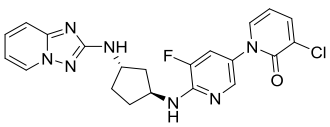
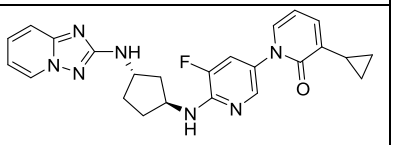
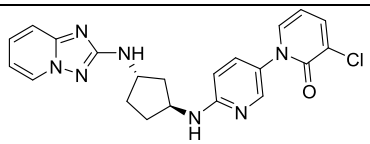
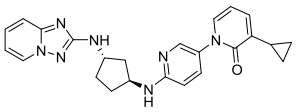
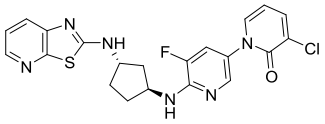
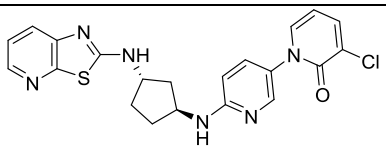
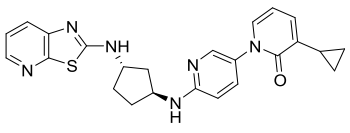
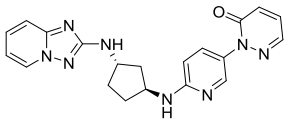
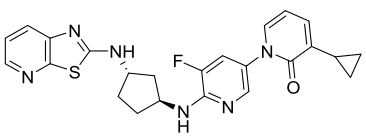
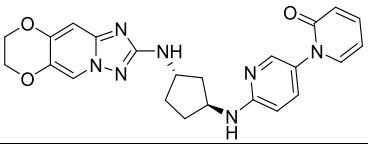
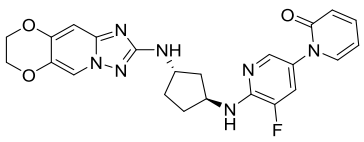
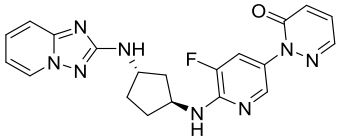
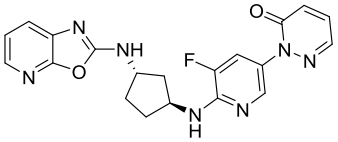
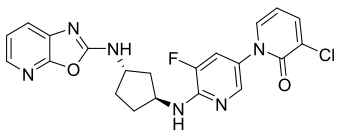
further, R_3-substituted ring A is selected from the group consisting of: , , , , , , , , , , , ,

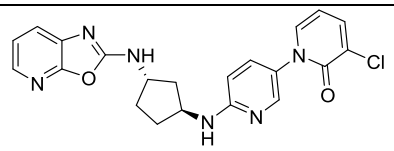
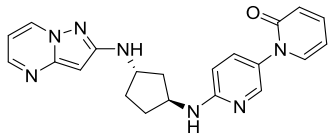
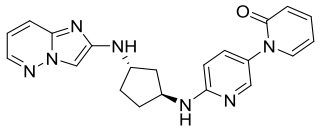
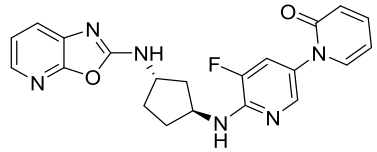
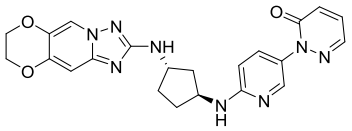
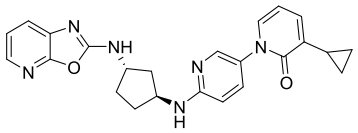
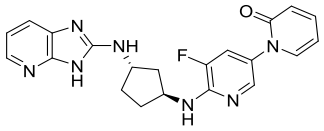
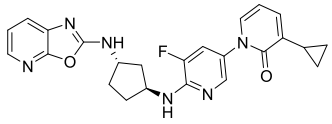
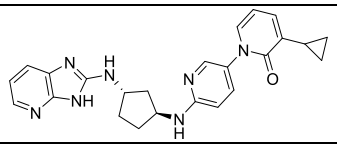
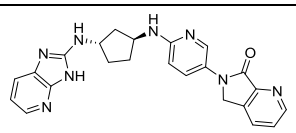
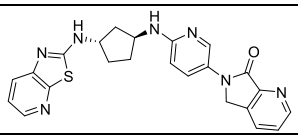
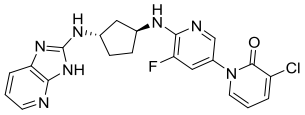
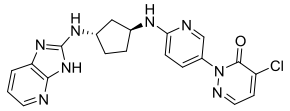
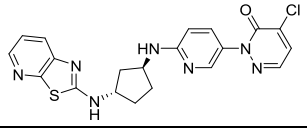
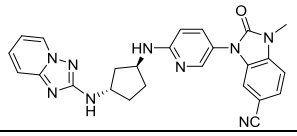
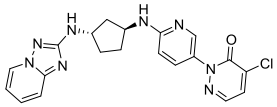
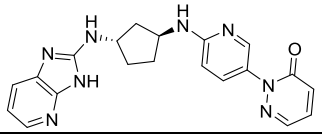
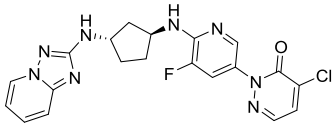
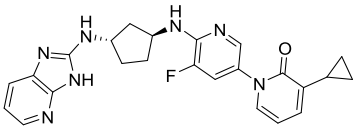
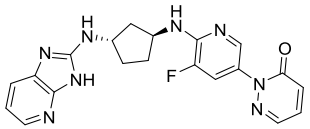
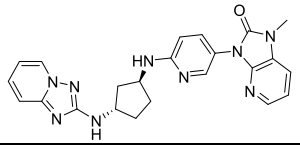
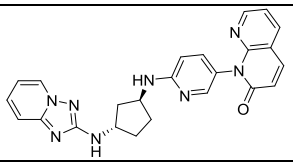
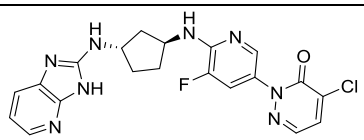
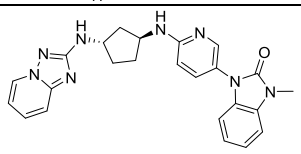
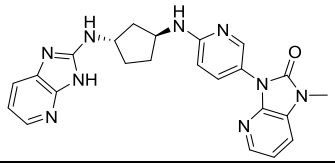
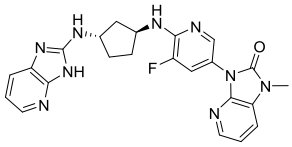
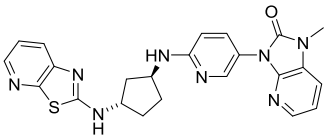
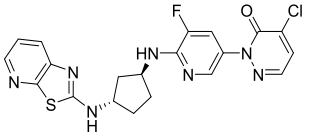
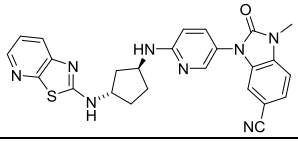
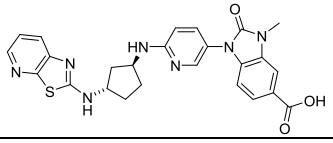
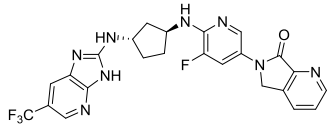
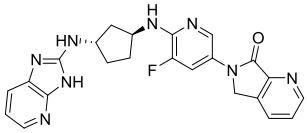
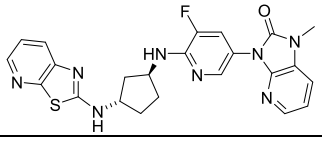
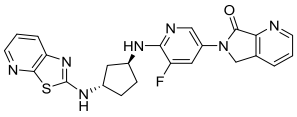
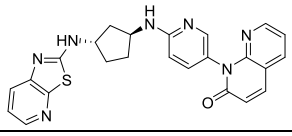
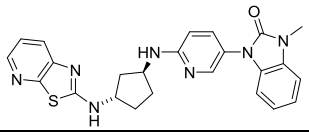
, , , , , , , , and ;

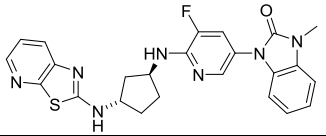
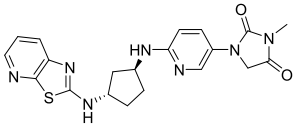
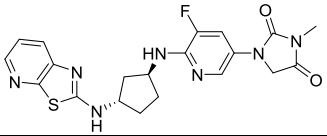
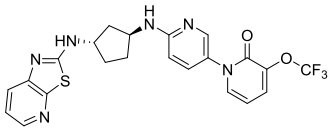
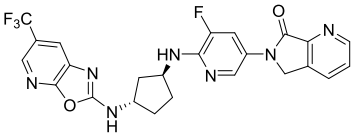
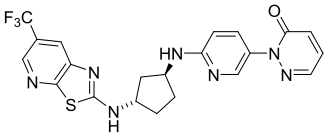
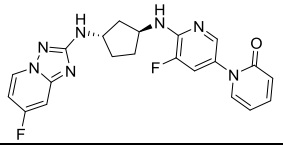
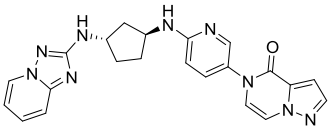
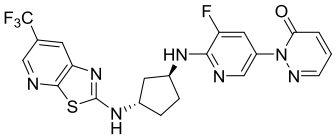
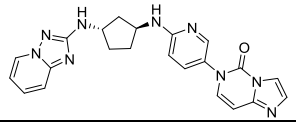
further, R_4-substituted ring B is selected from the group consisting of: , , , , , , , , , , , , , , , , , , , ; , , , , , , , ; , ; , , , , , , , ; , , , , , , , , ; , , , , , , , , , and .

11. The compound, or the isomer thereof, or the racemate thereof, or the pharmaceutically acceptable salt thereof according to claim 7, wherein the compound, or the isomer thereof, or the racemate thereof, or the pharmaceutically acceptable salt thereof is selected from the group consisting of:

No.	Compound	No.	Compound	No.	Compound
C1		C2		C3	
C4		C5		C6	
C7		C8		C9	
C10		C11		C12	

C13		C15		C16	
C17		C18		C19	
C20		C21		C22	
C23		C24		C25	
C26		C27		C28	
C29		C30		C31	
C32		C33		C34	
C35		C36		C37	
C38		C39		C40	
C41		C42		C43	
C44		C45		C46	
C47		C48		C49	

C50		C51		C52	
C53		C54		C55	
C56		C57		C58	
C59		C60		C61	
C62		C63		C64	
C65		C66		C67	
C68		C69		C70	
C71		C72		C73	
C74		C75		C76	
C77		C78		C79	
C80		C81		C82	
C83		C84		C85	

C86		C87		C88	
C89		C90		C91	
C92		C93		C94	
C95					

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12. A pharmaceutical composition, comprising a therapeutically effective amount of the compound, or the isomer thereof, or the racemate thereof, or the pharmaceutically acceptable salt thereof according to any one of claims 1 to 6, and a pharmaceutically acceptable carrier.

13. Use of the compound, or the isomer thereof, or the racemate thereof, or the pharmaceutically acceptable salt thereof according to any one of claims 1 to 6 in the manufacture of a medicament for treating a PCSK9 inhibitor-related disease; optionally, the PCSK9 inhibitor-related disease comprises hypercholesterolemia.

14. A pharmaceutical composition, comprising a therapeutically effective amount of the compound, or the isomer thereof, or the racemate thereof, or the pharmaceutically acceptable salt thereof according to any one of claims 7 to 11, and a pharmaceutically acceptable carrier.

15. Use of the compound, or the isomer thereof, or the racemate thereof, or the pharmaceutically acceptable salt thereof according to any one of claims 7 to 11 in the manufacture of a medicament for treating a PCSK9 inhibitor-related disease; optionally, the PCSK9 inhibitor-related disease comprises hypercholesterolemia.