KINESIN KIF18A INHIBITOR AND METHOD FOR USING SAME

CROSS-REFERENCE TO RELATED APPLICATIONS

The present application claims the benefits of and priorities to the following five Chinese patent applications for invention, the contents of which are hereby incorporated herein by reference in their entireties:

Chinese Patent Application No. 202410362057.X filed with the China National Intellectual Property Administration on March 27, 2024,

Chinese Patent Application No. 202410799138.6 filed with the China National Intellectual Property Administration on June 19, 2024,

Chinese Patent Application No. 202510032448.X filed with the China National Intellectual Property Administration on January 08, 2025, and

Chinese Patent Application No. 202510338448.2.X filed with the China National Intellectual Property Administration on March 20, 2025.

TECHNICAL FIELD

The present disclosure belongs to the field of medicinal chemistry, and specifically relates to a compound as a KIF18A inhibitor, a pharmaceutical composition comprising the compound, and a method for treating and preventing cell proliferative diseases such as cancers using the compound and the pharmaceutical composition.

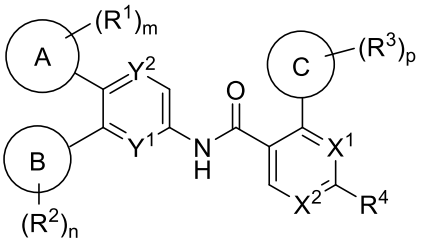
BACKGROUND

KIF18A is a mitotic kinesin, which regulates chromosome arrangement during cell mitosis, prevents errors arising in mitosis, and ensures normal progression of mitosis.

The vast majority of human cells are diploid, and possess multiple cell cycle checkpoints to maintain genomic stability during successive cell divisions. Inactivation of key proteins associated with certain cell cycle checkpoints can lead to mitotic abnormalities and whole-genome doubling, thereby converting naturally diploid cells into chromosomally unstable tetraploid cells. Whole-genome doubling (WGD) events (occurrence of at least one WGD) are widely observed in clinical tumor samples and constitute an important hallmark of chromosomally unstable tumors. Research results demonstrated that the expression level of KIF18A was elevated in WGD^+ cells compared with diploid cells. Upon KIF18A knockout in all ten cell lines, it was found that the viability of WGD^+ cells was markedly reduced, compared with WGD^- cell lines. Live-cell imaging revealed that following KIF18A depletion, WGD^+ breast cancer cells exhibited increased spindle length and chromosome hyperoscillation, compared with WGD^- cells, triggering abnormal events including chromosome missegregation and mitotic delay. The above data indicate that the depletion of KIF18A can result in abnormal mitosis in WGD^+ tumor cells, and inhibit the proliferation of WGD^+ tumor cells. Therefore, KIF18A represents an attractive therapeutic target, and inhibition thereof may help to specifically target tumors having WGD^+ features, without affecting normal diploid cells in human tissues.

SUMMARY

The present disclosure provides a compound represented by formula (I), or a stereoisomer or pharmaceutically acceptable salt thereof:



(I)

wherein

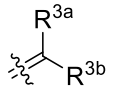
ring A is 5- to 6-membered heteroaryl, and the 5- to 6-membered heteroaryl contains at least 3 heteroatoms selected from the group consisting of N, O, and S;

ring B is 4- to 6-membered heterocyclyl, and the 4- to 6-membered heterocyclyl contains at least one heteroatom selected from the group consisting of N, O, and S;

ring C is 6- to 8-membered heterocyclyl, and the 6- to 8-membered heterocyclyl contains at least one heteroatom selected from the group consisting of N, O, and S;

X^1, X^2, Y^1, and Y^2 are each independently selected from the group consisting of N and CR^x; and R^x is selected from the group consisting of H, halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, and C_{1-6} alkoxy;

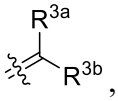
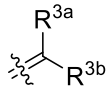
R^1 and R^2 are each independently selected from the group consisting of halogen, C_{1-6} alkyl, and C_{3-6} cycloalkyl, and the C_{1-6} alkyl or C_{3-6} cycloalkyl is optionally substituted with one or more substituents selected from the group consisting of OH, halogen, $-NH_2$, and C_{1-4} alkoxy;

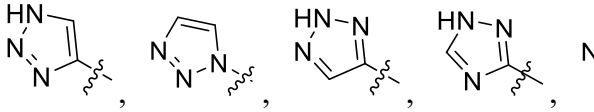
R^3 is halogen, OH, C_{1-6} alkyl, C_{3-6} cycloalkyl, or ;

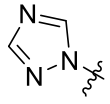
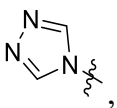
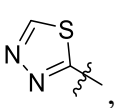
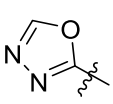
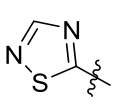
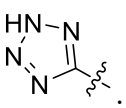
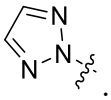
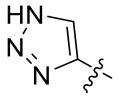
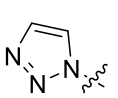
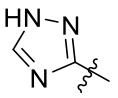
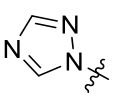
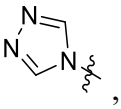
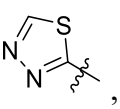
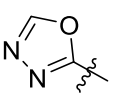
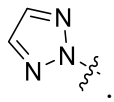
R^{3a} and R^{3b} are each independently selected from the group consisting of H, halogen, and C_{1-6} alkyl, and the C_{1-6} alkyl is optionally substituted with one or more substituents selected from the group consisting of halogen, hydroxy, amino, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxy, C_{3-6} cycloalkyl, 3- to 8-membered heterocyclyl, phenyl, and 5- to 6-membered heteroaryl;

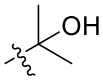
R^4 is selected from $-NHSO_2-C_{1-4}$ alkyl, and the C_{1-4} alkyl is optionally substituted with OH or halogen; and

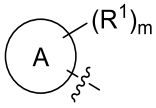
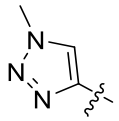
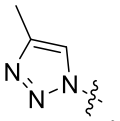
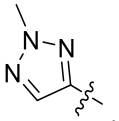
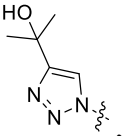
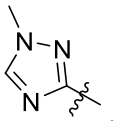
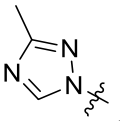
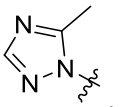
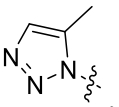
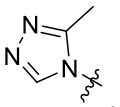
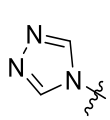
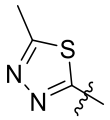
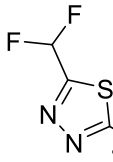
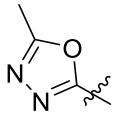
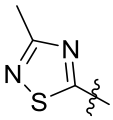
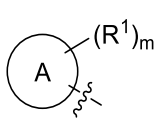
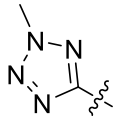
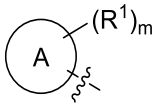
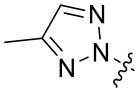
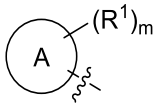
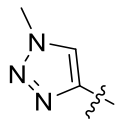
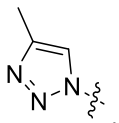
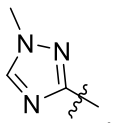
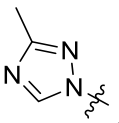
m, n and p are each independently selected from 0, 1, 2, and 3.

In the compound represented by formula (I), the stereoisomer or pharmaceutically acceptable salt thereof of the present disclosure, R^3 is , which means that two R^3 groups on the same ring atom together form .

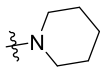
In some embodiments, ring A is 5-membered heteroaryl containing at least 3 heteroatoms selected from the group consisting of N, O, and S. In some embodiments, ring A is 5-membered heteroaryl, which contains 3 heteroatoms selected from N, or 2 heteroatoms selected from N and 1 heteroatom selected from O and S, or 4 heteroatoms selected from N. In some embodiments, ring A is 5-membered heteroaryl, which contains 3 heteroatoms selected from N. In some embodiments, ring A is selected from the group consisting of ,

, , , , and . In some embodiments, ring A is . In some embodiments, ring A is . In some embodiments, ring A is selected from the group consisting of , , , , , , , and .

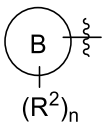
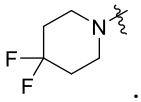
In some embodiments, R^1 is selected from C_{1-6} alkyl, and the C_{1-6} alkyl is optionally substituted with one or more substituents selected from the group consisting of OH and halogen; and/or m is selected from 0 and 1. In some embodiments, R^1 is selected from the group consisting of methyl, CHF_2, and ; and m is selected from 0 and 1. In some embodiments, R^1 is methyl.

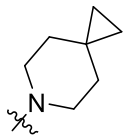
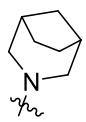
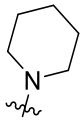
In some embodiments, the structural unit  is selected from the group consisting of , , , , , , , , , , , , , and . In some embodiments, the structural unit  is . In some embodiments, the structural unit  is . In some embodiments, the structural unit  is selected from the group consisting of , , , , , , , , , and . In some embodiments, the structural unit is selected from the group consisting of , , and .

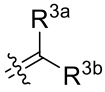
In some embodiments, ring B is 6-membered heterocyclyl containing one heteroatom

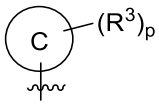
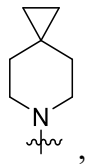
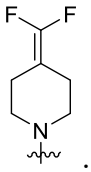
selected from N. In some embodiments, ring B is .

In some embodiments, R^2 is halogen; and/or n is selected from 0, 1, and 2, or n is 2. In some embodiments, R^2 is selected from the group consisting of F, Cl, and Br; and n is selected from 0, 1, and 2.

In some embodiments, the structural unit  is selected from .

In some embodiments, ring C is 6-, 7-, or 8-membered heterocyclyl containing one heteroatom selected from N. In some embodiments, ring C is selected from the group consisting of , , and .

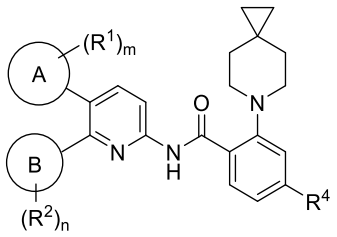
In some embodiments, R^3 is ; and/or R^{3a} and R^{3b} are each independently selected from the group consisting of H and halogen; and/or p is selected from 0, 1, and 2; or p is selected from 0 and 1. In some embodiments, R^3 is ; and p is selected from 0, 1, and 2.

In some embodiments, the structural unit  is selected from the group consisting of , , and .

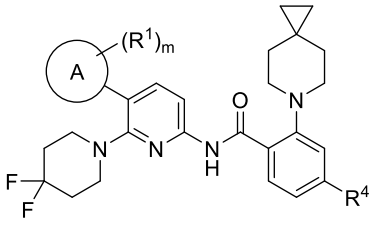
In some embodiments, X^1 and X^2 are each independently selected from CR^x; and/or R^x is selected from the group consisting of H and halogen. In some embodiments, X^1 and X^2 are each independently selected from the group consisting of CH and N; or X^1 and X^2 are each CH. In some embodiments, X^1 and X^2 are each independently selected from the group consisting of CH, -CF, and N; or X^1 is CH, and X^2 is CH or -CF. In some embodiments, Y^1 and Y^2 are each independently selected from the group consisting of CH and N; or Y^1 is N, and Y^2 is CH; or Y^1 is N, and Y^2 is N.

In some embodiments, R^4 is selected from $-NHSO_2-C_{1-4}$ alkyl, and the C_{1-4} alkyl is optionally substituted with one or more OH. In some embodiments, R^4 is selected from the group consisting of $-NHSO_2-CH_2CH_2OH$ and $-NHSO_2-CH_3$.

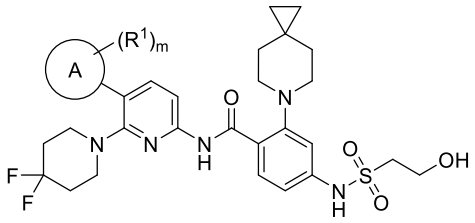
In some embodiments, the compound represented by formula (I), or the stereoisomer or pharmaceutically acceptable salt thereof of the present disclosure is selected from the group consisting of compounds represented by formulae (IIa), (IIb), (IIc), (IId), (IIe), (IIf), and (IIg), and stereoisomers or pharmaceutically acceptable salts thereof:



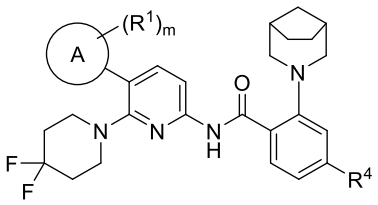
(IIa)



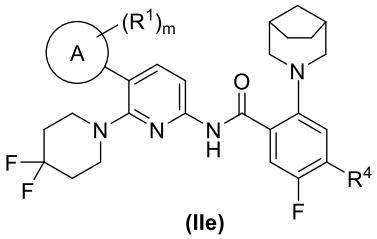
(IIb)



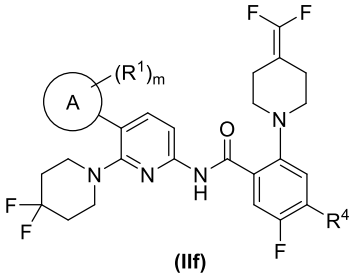
(IIc)



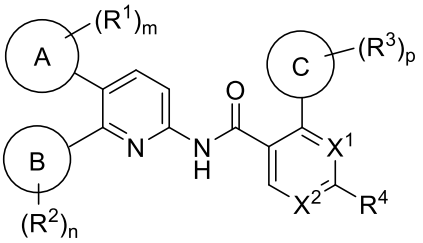
(IId)



(IIe)



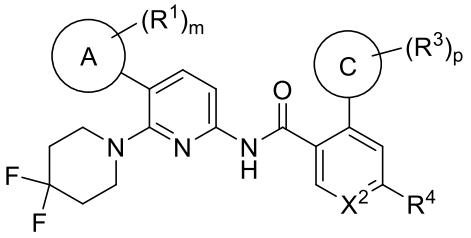
(IIf)



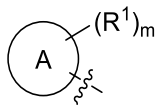
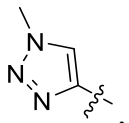
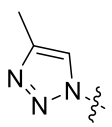
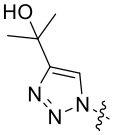
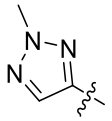
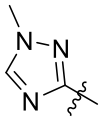
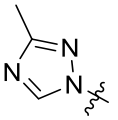
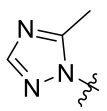
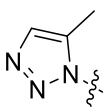
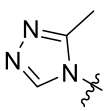
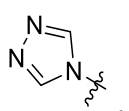
(IIg)

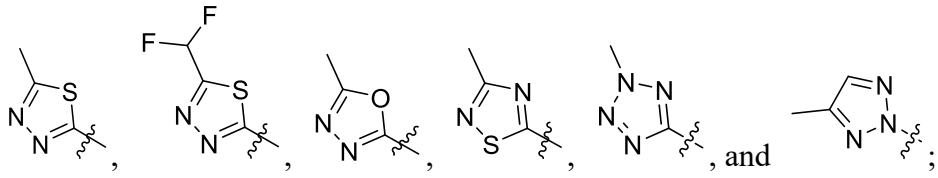
wherein ring A, ring B, ring C, R^1, R^2, R^3, R^4, X^1, X^2, m, p, and n are as defined in the above formula (I).

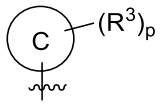
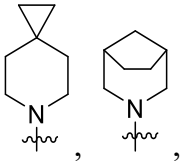
In some embodiments, the compound represented by formula (I), or the stereoisomer or pharmaceutically acceptable salt thereof of the present disclosure is a compound represented by formula (III), or a stereoisomer or pharmaceutically acceptable salt thereof:



(III)

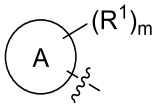
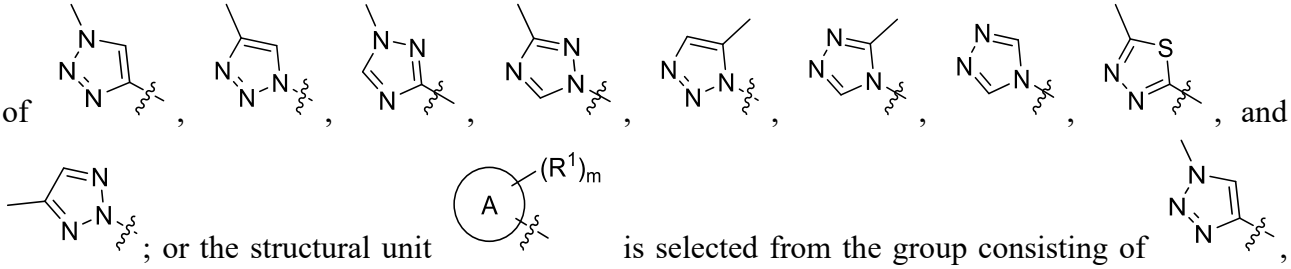
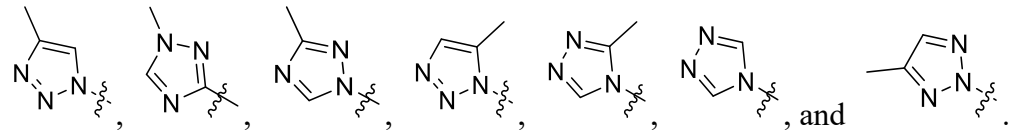
wherein the structural unit  is selected from the group consisting of , , , , , , , , , ,

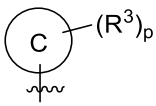
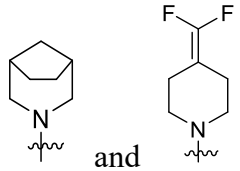
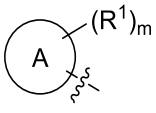
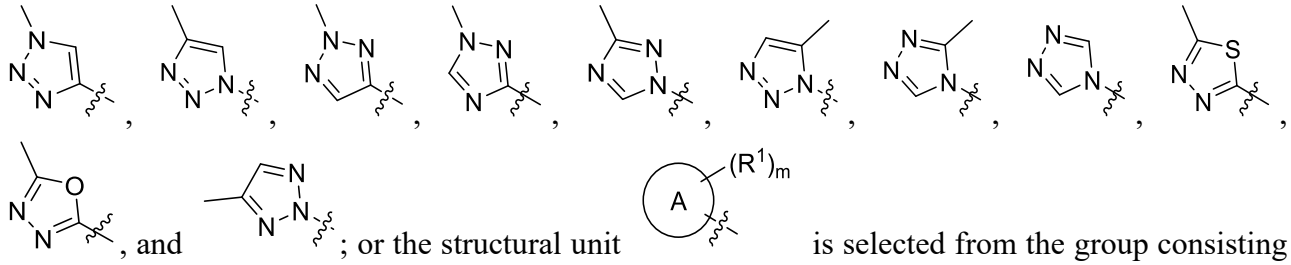
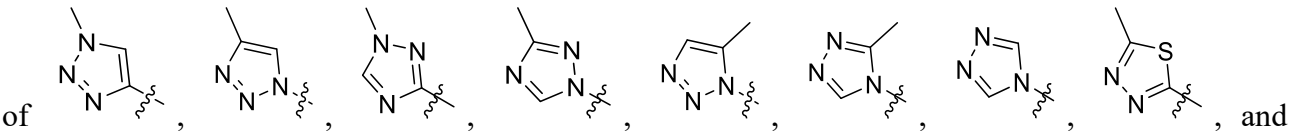


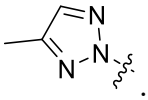
the structural unit  is selected from the group consisting of ;

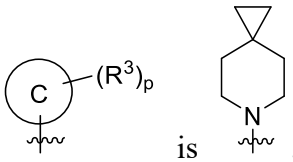
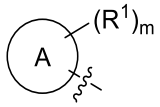
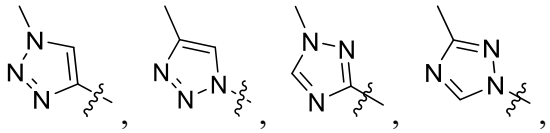
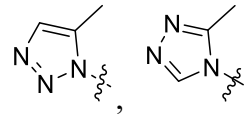
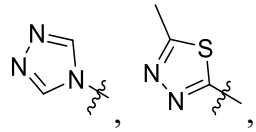
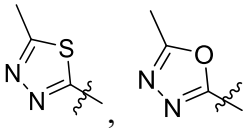
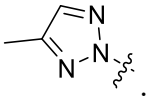
X^2 is selected from the group consisting of CH and -CF; and

R^4 is selected from the group consisting of $-NHSO_2-CH_2CH_2OH$ and $-NHSO_2-CH_3$.

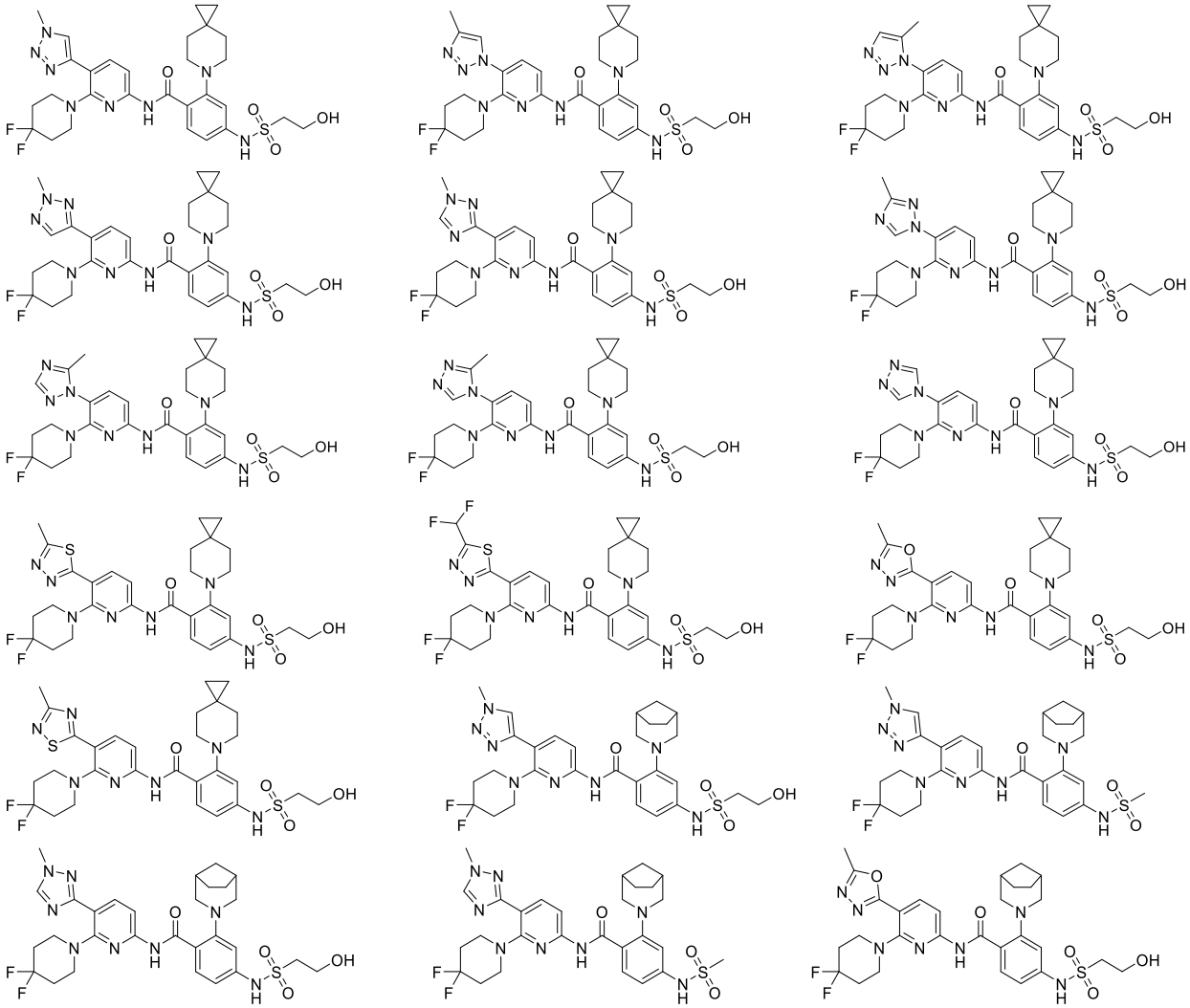
In some embodiments, the structural unit  is selected from the group consisting of ; or the structural unit is selected from the group consisting of .

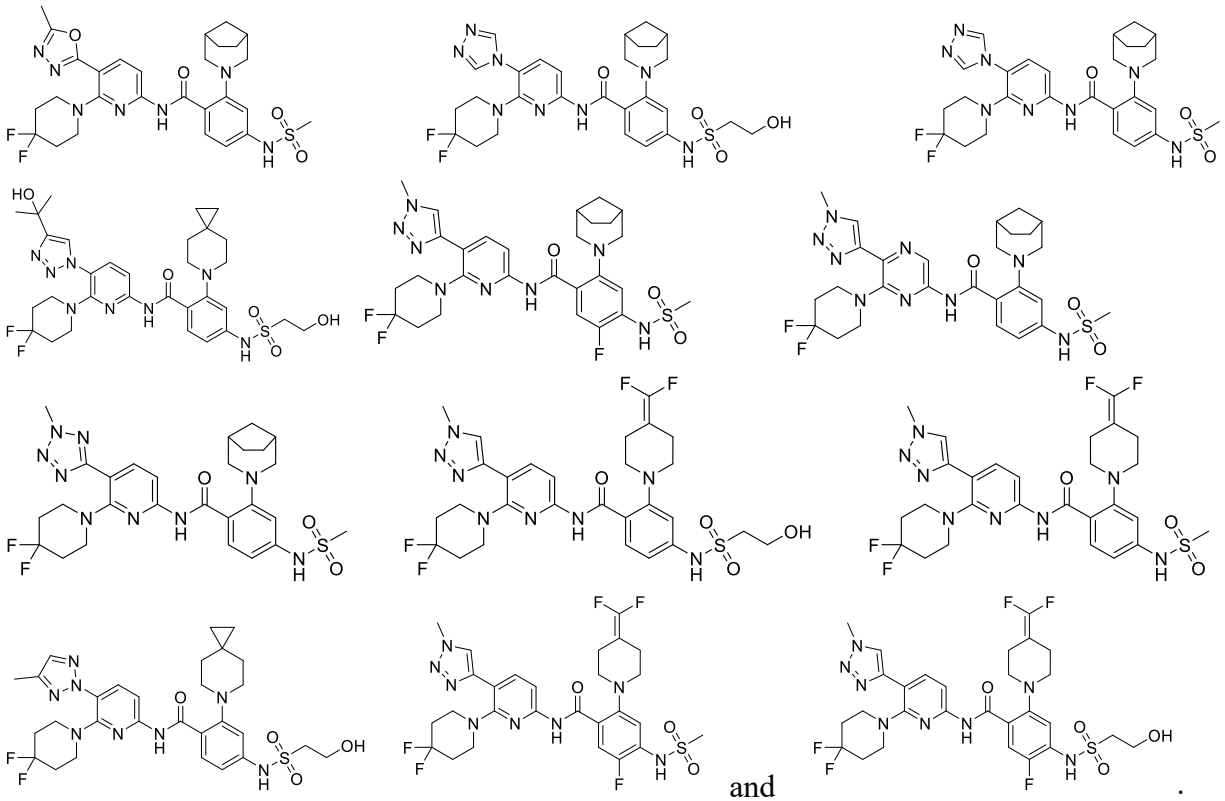
In some embodiments, the structural unit  is selected from the group consisting of , and the structural unit  is selected from the group consisting of ; or the structural unit is selected from the group consisting of .

.

In some embodiments, the structural unit  is , and the structural unit  is selected from the group consisting of , , , , and .

In some embodiments, the compound, or the stereoisomer or pharmaceutically acceptable salt thereof of the present disclosure is selected from the following compounds, and stereoisomers or pharmaceutically acceptable salts thereof:





and .

In another aspect, the present disclosure further relates to a pharmaceutical composition, comprising the compound represented by any one of formulae (I), (IIa) to (IIg), and (III), or the stereoisomer or pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier. In some embodiments, the pharmaceutical composition comprises a therapeutically effective amount of the compound, or the stereoisomer or pharmaceutically acceptable salt thereof of the present disclosure, and the pharmaceutically acceptable carrier.

In some embodiments, in the pharmaceutical composition, the compound, or the stereoisomer or pharmaceutically acceptable salt thereof has a content raning from 0.1 mg to 1,000 mg. In some embodiments, in the pharmaceutical composition, the compound, or the stereoisomer or pharmaceutically acceptable salt thereof has a content ranging from 1% to 95%.

In some embodiments, in the pharmaceutical composition, the pharmaceutically acceptable carrier includes one or more of a filler, a disintegrant, a binder, a glidant, and a lubricant.

In another aspect, the present disclosure further relates to use of the compound represented by any one of formulae (I), (IIa) to (IIg), and (III), or the stereoisomer or pharmaceutically acceptable salt thereof, or the pharmaceutical composition thereof in the preparation of a medicament for treating or preventing diseases mediated by KIF18A.

In another aspect, the present disclosure further relates to the compound represented by any one of formulae (I), (IIa) to (IIg), and (III), or the stereoisomer or pharmaceutically acceptable salt thereof, or the pharmaceutical composition thereof for use in treating or preventing diseases mediated by KIF18A.

In still another aspect, the present disclosure further relates to a method for treating or preventing diseases mediated by KIF18A in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of the compound represented by any one of formulae (I), (IIa) to (IIg), and (III), or the stereoisomer or pharmaceutically acceptable salt thereof, or the pharmaceutical composition thereof.

In yet another aspect, the present disclosure further relates to use of the compound represented by any one of formulae (I), (IIa) to (IIg), and (III), or the stereoisomer or pharmaceutically acceptable salt thereof, or the pharmaceutical composition thereof in the treatment or prevention of diseases mediated by KIF18A.

In some embodiments, the diseases mediated by KIF18A are tumors. In some embodiments, the tumors are chromosomally unstable tumors. In some embodiments, the tumors are selected from the group consisting of breast cancer, ovarian cancer, endometrial cancer, cervical cancer, prostate cancer, lung cancer, colorectal cancer, pancreatic cancer, bladder cancer, head and neck cancer, gastric cancer, esophageal cancer, and skin cancer. In some embodiments, the tumors are selected from the group consisting of breast cancer, ovarian cancer, endometrial cancer, cervical cancer, prostate cancer, lung cancer, colorectal cancer, pancreatic cancer, bladder cancer, and head and neck cancer. In some embodiments, the lung cancer is selected from the group consisting of lung squamous cell carcinoma, lung adenocarcinoma, large cell lung cancer, and small cell lung cancer.

Definitions

Unless otherwise stated, the following terms and phrases used herein are intended to have the following meanings. A specific term or phrase without a specific definition should not be considered indefinite or ambiguous, but should be understood according to its ordinary meaning prevailing in the art.

The term “pharmaceutically acceptable” refers to those compounds, materials, compositions, and/or dosage forms which, within the scope of sound medical judgment, are suitable for contact with the tissues of humans and animals without excessive toxicity, irritation, allergic response, or other problems or complications, and are commensurate with a reasonable benefit/risk ratio.

The term "pharmaceutically acceptable salt" refers to a derivative of the compound of the present disclosure prepared by reacting such compound with a relatively non-toxic acid or base. These salts can be prepared during the synthesis, separation, or purification of the compound, or are prepared separately by reacting the purified compound in its free form with a suitable acid or base. Where the compound contains a relatively acidic functional group (such as -COOH, -OH, $-SO_3H$, and the like), a base addition salt can be obtained by reaction with a suitable inorganic or organic cation (base), including, for example, a salt formed with an alkali metal or an alkaline earth metal, an ammonium salt formed with an amine or a derivative thereof, and a salt formed with an amino acid, and the like. Where the compound contains a relatively basic functional group (such as $-NH_2$), an acid addition salt can be obtained by reaction with a suitable inorganic or organic anion (acid), including a salt formed with an inorganic acid or an organic acid (such as a carboxylic acid).

The term "pharmaceutically acceptable carrier" refers to a substance generally accepted in the art for delivering a biologically active agent to an animal, particularly a mammal, and includes, depending on the route of administration and the nature of the dosage form, for example, adjuvants, excipients, or vehicles, such as diluents, preservatives, fillers, flow regulators, disintegrants, wetting agents, emulsifiers, suspending agents, sweeteners, flavoring agents, fragrant agents, antibacterial agents, antifungal agents, lubricants, and dispersing agents. Pharmaceutically acceptable carriers are formulated within the purview of one of ordinary skill in the art considering a multitude of factors, which include, but are not limited to: the type and nature of the active agent being formulated; the subject to whom the composition containing the agent is to be administered; the intended route of administration of the composition; and the targeted therapeutic indication. Pharmaceutically acceptable carriers include both aqueous and non-aqueous media, as well as substances required to

formulate various solid and semi-solid dosage forms. In addition to the active agent, such carriers include many different ingredients and additives; such additional ingredients included in the formulation for various reasons (e.g., for stabilizing the active agent, or as binders, etc.) are well known to those of ordinary skill in the art.

The term “prophylactically or therapeutically effective amount” refers to an adequate amount of the compound, or the pharmaceutically acceptable salt or stereoisomer thereof of the present disclosure which is suitable for the treatment of a disorder with a reasonable effect/risk ratio of any medical treatment and/or prevention. However, it should be understood that the total daily dosage of the compound represented by any one of formulae (I), (IIa) to (IIg), and (III), or the pharmaceutically acceptable salt thereof and the composition of the present disclosure shall be determined by an attending physician within the scope of reliable medical judgment. For any particular patient, the specific therapeutically effective dosage level must be determined based on multiple factors, including the disorder being treated and the seventy of the disorder; the activity of the specific compound used; the specific composition used, the age, weight, general health status, gender, and diet of a patient; the specific administration time, administration route, and excretion rate of the compound used; duration of treatment; medicaments used in combination or simultaneously with specific compounds used; and similar factors commonly known in the medical field.

The "isomers" of the compounds of the present disclosure include geometric isomers and stereoisomers, such as atropisomers, cis-trans isomers, enantiomers, diastereomers, tautomers, and racemic mixtures and other mixtures thereof, all of which fall within the scope of the present disclosure. The term "enantiomer" refers to stereoisomers that are mirror images of each other. The term “tautomer” refers to a type of functional group isomer that differs in the attachment point of hydrogen via the shift of one or more double bonds. For example, a ketone and its enol form are keto-enol tautomers. The term "diastereomer" refers to stereoisomers wherein the molecules have two or more chiral centers and the molecules are non-mirror images of each other. The term "cis-trans isomer" refers to a different spatial configuration existing due to the inability of double bonds or single bonds of ring carbon atoms in a molecule to rotate freely. The term "atropisomer" refers to a stereoisomer that can be isolated as a result of hindered or very slow rotation around a single bond.

Stereoisomers of the compounds of the present disclosure can be prepared by chiral synthesis, chiral reagents, or other conventional techniques. For instance, one enantiomer of a compound of the present disclosure can be prepared using asymmetric catalytic techniques or chiral auxiliary derivatization techniques. Alternatively, a single stereoisomeric compound can be obtained from a mixture using chiral resolution techniques, or can be prepared directly using chiral starting materials. The separation of optically pure compounds in the present disclosure is typically accomplished using preparative chromatography with a chiral column to achieve the separation of chiral compounds.

The absolute stereoconfiguration of a compound can be confirmed by conventional technical means in the art. For example, the absolute configuration of the compound can be verified through single-crystal X-ray diffraction, or can be confirmed based on the chiral structure of a raw material and the reaction mechanism of asymmetric synthesis. Alternatively, the stereoconfiguration of the compound can be determined by comparison with a product with an established absolute configuration after resolution. Herein a compound marked as "absolute configuration not known/determined" is typically obtained by resolving a racemic compound into a single isomer using chiral preparative SFC, followed by characterization and testing.

The term "isotopic derivative" refers to a compound in which at least one atom is replaced

with an atom having the same atomic number but a different atomic mass. Examples of isotopes that may be incorporated into the compounds of the present disclosure include stable and radioactive isotopes, such as hydrogen, carbon, nitrogen, oxygen, phosphorus, sulfur, fluorine, chlorine, bromine, iodine and the like, such as ^{2}H (deuterium, D), ^{3}H (tritium, T), ^{11}C, ^{13}C, ^{14}C, ^{15}N, ^{17}O, ^{18}O, ^{32}p, ^{33}p, ^{33}S, ^{34}S, ^{35}S, ^{36}S, ^{18}F, ^{36}Cl, ^{82}Br, ^{123}I, ^{124}I, ^{125}I, ^{129}I, and ^{131}I, with deuterium being preferred . Compared with a non-deuterated drug, a deuterated drug possesses one or more advantages, such as reduced toxic and side effects, improved drug stability, enhanced therapeutic efficacy, and prolonged biological half-life of the drug. All variations in the isotopic composition of the compounds of the present disclosure, whether radioactive or not, are encompassed within the scope of the present disclosure. Each available hydrogen atom bonded to a carbon atom may be independently replaced with a deuterium atom, wherein the deuterium replacement may be partial or complete, and the partial deuterium replacement means that at least one hydrogen atom is replaced with at least one deuterium atom.

The term "nitrogen oxide" or "N-oxide" refers to a derivative formed by further oxidation of the nitrogen atom in a nitrogen-containing group. Common N-oxides include N-oxides of tertiary amines or N-oxides of nitrogen atoms present in nitrogen-containing heterocycles. Synthetic methods of N-oxides are well known to those skilled in the art, including oxidation of heterocycles and tertiary amines using peroxy acids such as peroxyacetic acid and m-chloroperoxybenzoic acid, hydrogen peroxide, alkyl hydroperoxides such as tert-butyl hydroperoxide, sodium perborate, and dioxirane such as dimethyl dioxirane.

The term "prodrug" refers to certain derivatives of the compounds of the present disclosure that possess little or no pharmacological activity per se, bear a cleavable group and decompose via solvolysis or under physiological conditions to yield the compounds of the present disclosure. Types of the aforementioned prodrugs include, but are not limited to, amides, esters, anhydrides, salts and the like. The term "ester" herein means a derivative formed from the compound of the present disclosure and a suitable alcohol when the compound contains an acidic group (such as a carboxylic acid); or a derivative formed from the compound of the present disclosure and a suitable acid (including organic acids or inorganic acids) when the compound contains a hydroxyl group. Methods for preparing prodrugs are well known to those skilled in the art.

The compounds of the present disclosure may exist in unsolvated and solvated forms, and the solvated forms include hydrate forms. In general, solvated forms are equivalent to unsolvated forms and are encompassed within the scope of the present disclosure.

The compounds of the present disclosure include stereoisomers, isotopic derivatives, solvates, N-oxides, prodrugs, or pharmaceutically acceptable salts thereof.

The compounds of the present disclosure and salts thereof may exist in the form of isotopic derivatives, and the compounds of the present disclosure encompass various isotopic derivatives and mixtures thereof.

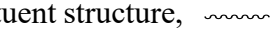
The compounds of the present disclosure and salts thereof may exist in the form of solvates, such as hydrates, and the compounds of the present disclosure encompass various solvates and mixtures thereof.

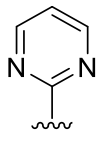
The compounds of the present disclosure and salts thereof may exist in the form of "N-oxides", and the compounds of the present disclosure encompass various N-oxides and mixtures thereof.

The compounds according to the present disclosure, pharmaceutically acceptable salts,

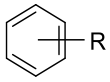
isotopic derivatives, solvates and N-oxides thereof possess the same or similar biological activities, all of which are encompassed within the scope of the present disclosure.

The term "optionally substituted" used herein refers to two scenarios: one or more hydrogen atoms of a group to be substituted may be "unsubstituted" or "substituted" with one or more substituents.

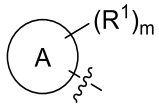
When appearing in a substituent structure,  denotes that such atom serves as the point



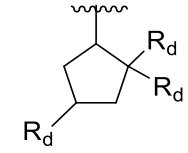
of attachment. By way of example, denotes that the carbon atom on the pyrimidine ring is the atom for attachment. A dash "-" shown in a substituent structure indicates the point of attachment of the substituent. For instance, -CH_3 is attached via its carbon atom. "" and "" represent the absolute configuration of a stereocenter, i.e., the R or S configuration. "" or "" represent the cis or trans configuration. A pair of solid double bonds or a pair of dashed double bonds both indicate the cis configuration, while one solid bond together with one dashed bond indicates the trans configuration.

When the bond of a substituent traverses a ring, it indicates that such substituent may bond to any atom on the ring. For example, the structural unit 

means that the substituent R can be attached at any position on the benzene ring.

When m in the structural unit 

is 0, ring A is substituted with hydrogen by default. When m is 1, 2 or 3, R^1 represents a substituent other than hydrogen. Where a listed substituent does not specify the atom through which it is attached to a given group or a given structural formula, the substituent may be attached via any bondable atom thereof.

When any variable (e.g., R_d) occurs more than one time in the composition or structure of a compound, its definition in each occurrence is independent. For example, 

denotes cyclopentyl substituted with three R_d groups, and each R_d has independent selection options.

Unless otherwise specified, the term "halogen" means a fluorine, chlorine, bromine or iodine atom.

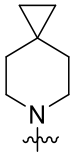
Unless otherwise specified, the term "alkyl" refers to a group derived by removing one hydrogen atom from a branched or straight-chain saturated aliphatic alkane having the specified number of carbon atoms. For example, the "C_{1-10} alkyl" includes C_1, C_2, C_3, C_4, C_5, C_6, C_7, C_8, C_9, and C_{10} alkyl, "C_{1-6} alkyl," "C_{1-4} alkyl," and "C_{1-3} alkyl"; and specific examples thereof include, but are not limited to: methyl, ethyl, n-propyl, isopropyl, sec-butyl, 2-methylbutyl, 1,1-dimethylbutyl, etc.

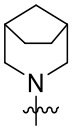
Unless otherwise specified, the term "haloalkyl" refers to an alkyl group in which one or more hydrogen atoms are replaced by halogen atoms, preferably C_{1-6} haloalkyl, and more preferably C_{1-4} haloalkyl. Examples of haloalkyl include, but are not limited to, monofluoromethyl, difluoromethyl, trifluoromethyl, trichloromethyl, tribromomethyl, 2,2,2-trifluoroethyl, 2,2,2-trichloroethyl, and the like. The alkyl group is as defined above.

Unless otherwise specified, the term "alkoxy" refers to an alkyl group as defined herein attached to another group via an oxygen atom, i.e., "alkyl-O-," including "C_{1-6} alkoxy" (having the structure C_{1-6} alkyl-O-) and "C_{1-4} alkoxy," and specific examples thereof include, but are not limited to, methoxy, ethoxy, propoxy, 1-methylethoxy, butoxy, 2-methylbutoxy, 3-methylbutoxy, 1,1-dimethylpropoxy, 1,2-dimethylpropoxy, etc. Preferably, the "alkoxy" according to the present disclosure is C_{1-4} alkoxy, more preferably C_{1-3} alkoxy.

Unless otherwise specified, the term "haloalkoxy" refers to a group obtained by replacing one or more hydrogens in an alkoxy group with halogen atoms. Preferably, the "haloalkoxy" according to the present disclosure is "C_{1-6} haloalkoxy" or "C_{1-4} haloalkoxy." Specific examples according to the present disclosure include: fluoromethoxy (including monofluoromethoxy, difluoromethoxy, and trifluoromethoxy), $-OCH_2CF_3$, $-OCHFCH_3$, etc. The alkoxy group is as defined above.

Unless otherwise specified, the term "cycloalkyl" refers to a saturated cyclic alkyl group derived by removing a hydrogen atom from a cycloalkane, including monocyclic or polycyclic saturated hydrocarbon groups. The polycyclic saturated hydrocarbon groups denote polycyclic groups formed by linking two or more cyclic alkyl structures via spiro, bridged or fused arrangements. Carbon atoms in the cycloalkyl may be further oxidized to form C(O). Unless specifically stated otherwise, any "membered cycloalkyl" described herein is understood to mean a monocyclic cycloalkyl; and polycyclic species will be specifically indicated as spiro, fused or bridged ring groups. The cycloalkyl includes C_{3-8} cycloalkyl, C_{3-6} cycloalkyl and C_{3-5} cycloalkyl. Preferably, the cycloalkyl is of monocyclic saturated structure. Specific examples include, but are not limited to: cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl.

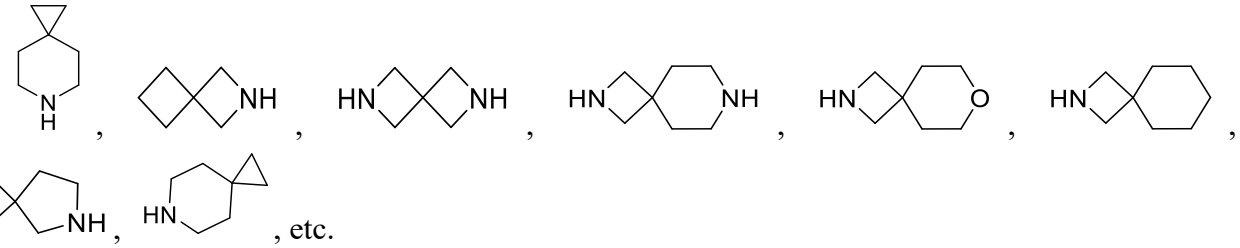
Unless otherwise specified, the term "heterocyclyl" refers to a saturated cyclic group derived by replacing one or more ring carbon atoms of a cycloalkyl group with heteroatoms and/or heteroatom groups. Such heteroatoms and/or heteroatom groups are generally selected from N, O, S, NO, SO, $S(O)_2$, P(O), and NR (R is hydrogen or another substituent as defined herein). The carbon atoms in the heterocycle may be optionally oxidized to form -C(O). Preferably, the heteroatoms are independently selected from 1 to 3 nitrogen and/or oxygen atoms. Heterocyclyl encompasses monocyclic heterocyclyl, fused heterocyclyl, spiro heterocyclyl and bridged heterocyclyl. Heterocyclyl groups include "3- to 8-membered heterocyclyl," "3- to 6-membered heterocyclyl," "3- to 5-membered heterocyclyl," "4- to 6-membered heterocyclyl," and "5- to 6-membered heterocyclyl." Specific examples include, but are not limited to: azetidinyl, pyrrolidinyl, tetrahydrofuranyl, piperidinyl, piperazinyl, tetrahydropyranyl, morpholinyl, 

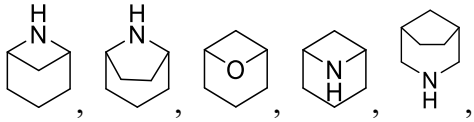
, 

, etc.

Unless otherwise specified, the term "fused heterocyclyl" refers to a saturated non-aromatic cyclic group formed by two or more cyclic structures sharing two adjacent atoms with one another, wherein at least one ring atom is a heteroatom. Such heteroatoms are generally selected from N, O and S. Ring carbon atoms and heteroatoms in the fused heterocycle may be further oxidized to form cyclic groups containing C(O), NO, SO, or $S(O)_2$ groups, which are also encompassed within the definition of heterocyclyl as described in the present disclosure. The fusion modes contemplated herein include: a 5-6 membered heterocyclyl fused to a 5-6 membered heterocyclyl, a 5-6 membered heterocyclyl fused to a 5-6 membered cycloalkyl, a benzene ring fused to a 5-6 membered

heterocyclyl, a benzene ring fused to a 5-6 membered saturated heterocyclyl, a 5-6 membered heteroaryl fused to a 5-6 membered heterocyclyl, a 5-6 membered heteroaryl fused to a 5-6 membered saturated heterocyclyl, a benzene fused to 5-6 membered heterocyclyl fused to a 5-6 membered heterocyclyl, a 5-6 membered heteroaryl fused to 5-6 membered heterocyclyl fused to a 5-6membered heterocyclyl, a benzene fused to 5-6 membered cycloalkyl fused to a 5-6 membered heterocyclyl, and a 5-6 membered heteroaryl fused to 5-6 membered cycloalkyl fused to a 5-6 membered heterocyclyl.

Unless otherwise specified, the term "spiroheterocyclyl" refers to a cyclic structure derived by replacing at least one carbon atom in a "spirocycloalkyl" with a heteroatom/heteroatom group. The heteroatoms/heteroatom groups are selected from the group consisting of N, O, S, P, NO, SO, $S(O)_2$, P(O), and NR, wherein R is hydrogen or any available substituent. Such structures include, but are not limited to, cyclic structures formed by a heterocycle spiro-fused to another heterocycle, or a heterocycle spiro-fused to a cycloalkane. The spiroheterocyclyl preferably contains 1 to 2 heteroatoms selected from NR and/or O; more preferably, it contains one NR together with 0 or 1 additional NR or O heteroatom. Preferred spiroheterocyclyl groups are "nitrogen-containing spiroheterocyclyl", which denotes spiroheterocyclyl wherein at least one ring atom is NR. The spiroheterocyclic ring includes 7- to 11-membered spiroheterocyclic ring, 7- to 9-membered spiroheterocyclic ring, 7- to 11-membered nitrogen-containing spiroheterocyclic ring, and 7- to 9-membered nitrogen-containing spiroheterocyclic ring. Specific examples include, but are not limited to: , etc.

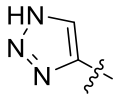
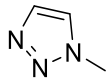
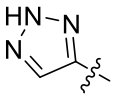
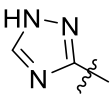
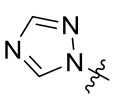
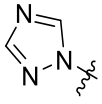
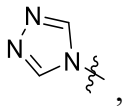
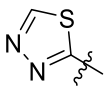
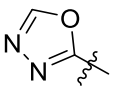
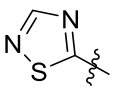
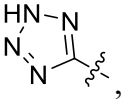
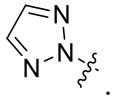
Unless otherwise specified, the term "bridged heterocyclyl" refers to a cyclic structure derived by replacing at least one carbon atom in a "bridged cycloalkyl" with a heteroatom or heteroatom group. The heteroatoms and heteroatom groups are selected from the group consisting of N, O, S, P, NO, SO, $S(O)_2$, P(O), and NR, wherein R is hydrogen or any available substituent. Preferred bridged heterocyclyl groups are "nitrogen-containing bridged heterocyclyl", which denotes heterocyclyl containing at least one ring atom of NR. The bridged heterocyclic ring includes, e.g., "6- to 10-membered bridged heterocyclic ring" or "6- to 8-membered bridged heterocyclic ring," and specific examples include, but are not limited to: , etc.

Unless otherwise specified, the term "aryl" refers to an unsaturated, typically aromatic hydrocarbon group, which may be monocyclic ring or fused polycyclic ring. Preferably, the term "aryl" denotes a carbocyclic ring system in which all ring atoms are carbon atoms. Preferred aryl groups are C_{5-10} aryl or C_{6-10} aryl; more preferred are C_{5-8} aryl or C_{6-8} aryl; most preferred are monocyclic C_{5-6} aryl or C_6 aryl. Examples of aryl include, but are not limited to, phenyl and naphthyl.

Unless otherwise specified, the term "fused aryl" refers to a fused ring group formed by two or more aromatic rings sharing two adjacent carbon atoms with one another, including naphthyl, anthracenyl, phenanthrenyl and the like.

The term "heteroaryl" as used herein refers to a monocyclic aromatic group wherein at least one ring atom is a heteroatom and/or heteroatom group. Such heteroatoms and/or heteroatom groups

are generally selected from the group consisting of N, O, S, P, NO, SO, $S(O)_2$, P(O), and NR, wherein R is hydrogen or any available substituent. The carbon atoms in the heteroaromatic ring may be optionally oxidized to form -C(O). Preferably, the heteroatoms are independently selected from 1 to 3 nitrogen and/or oxygen atoms. The heteroaryl includes "5- to 6-membered heteroaryl"; and specific examples thereof include, but are not limited to, pyrrolyl, furanyl, thienyl, pyrazolyl, imidazolyl, pyrazinyl, pyridazinyl, triazinyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyridyl and pyrimidinyl.

The "5- to 6-membered heteroaryl" as used herein preferably contains at least three heteroatoms selected from the group consisting of N, O, and S, and specific examples include, but are not limited to , , , , , , , , , , , and .

Combinations of substituents and/or variables described in the present disclosure are permissible only when such combinations yield stable compounds or usable synthetic intermediates. A stable compound or stable structure refers to a compound that is sufficiently stable to undergo chemical reactions, can be isolated in a useful purity, and can be formulated into therapeutically effective medicaments.

EXAMPLES

In the examples of the present disclosure, the nomenclature of the title compound is converted from the compound structure by means of Chemdraw. If there is any inconsistency between the compound name and the compound structure, it may be determined by synthesizing relevant information and reaction routes; if it cannot be confirmed by other methods, the given structural formula of the compound shall prevail. The preparation methods of some compounds in the present disclosure refer to the preparation methods of the aforementioned similar compounds. Those skilled in the art should know that when using or referring to the preparation methods cited therein, the feed ratio of reactants, reaction solvent, reaction temperature, etc. may be appropriately adjusted according to the different reactants.

The compounds of the present disclosure can be prepared by a variety of synthetic methods known to those skilled in the art, including the specific examples listed below, the examples formed by their combination with other chemical synthesis methods, and equivalent alternatives known to those skilled in the art, preferred embodiments include but are not limited to the examples of the present disclosure.

Experimental instruments:

The structures of the compounds disclosed herein are confirmed by Nuclear Magnetic Resonance (NMR), and/or Liquid Chromatography-Mass Spectrometry (LC-MS), or Ultra-Performance Liquid Chromatography-Mass Spectrometry (UPLC-MS). NMR chemical shifts (δ) are reported in parts per million (ppm). NMR spectra are recorded on a Bruker Neo 400M or Bruker Ascend 400 spectrometer. The deuterated solvents include deuterated dimethyl sulfoxide (DMSO-d_6), deuterated methanol (CD_3OD), deuterated chloroform ($CDCl_3$) and deuterium oxide (D_2O), with tetramethylsilane (TMS) as the internal standard.

LC-MS analyses are performed on an Agilent 1260-6125B single quadrupole mass spectrometer equipped with a Welch Biomate column (C18, 2.7 μm, 4.6×50 mm), or a Waters H-

Class SQD2 mass spectrometer equipped with a Welch Ultimate column (XB-C18, 1.8 μm, 2.1×50 mm), with electrospray ionization as the ion source.

UPLC-MS analyses are performed on a Waters UPLC H-Class SQD mass spectrometer with electrospray ionization as the ion source.

HPLC analyses are carried out using Waters e2695-2998, Waters ARC, Agilent 1260 or Agilent Poroshell HPH high-performance liquid chromatography systems.

Preparative HPLC employs Waters 2555-2489 (10 μm, ODS, 250 mm × 5 cm) or GILSON Trilution LC systems equipped with a Welch XB-C18 column (5 μm, 21.2 × 150 mm).

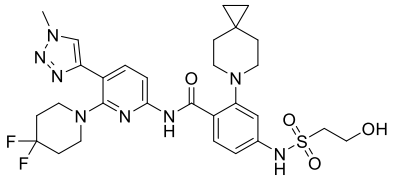
Thin-layer chromatography (TLC) silica gel plates are GF254 silica gel plates supplied by Yantai Jiangyou Silica Gel Development Co., Ltd. or Rushan Shangbang New Materials Co., Ltd. The thickness of TLC plates ranges from 0.15 mm to 0.20 mm, and preparative TLC plates are 20 × 20 cm in size. Column chromatography generally employs 200-300 mesh silica gel from Yucheng Chemical Industry as the stationary phase carrier.

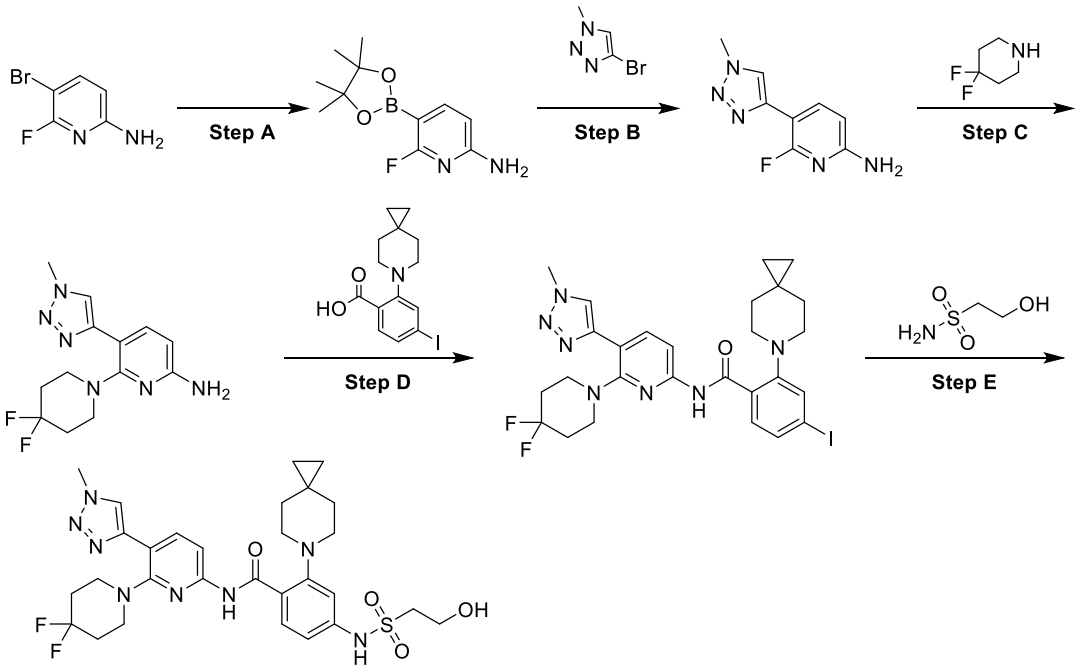
Starting materials used in the Examples of the present disclosure are known and commercially available, or can be synthesized by using or following methods as known in the art. Unless otherwise specified, all reactions in the present disclosure are carried out under continuous magnetic stirring under an atmosphere of dry nitrogen or argon with dry solvents, and reaction temperatures are expressed in degrees Celsius or °C.

Abbreviations and corresponding full names used in the Examples are listed below:

Abbreviation	Name
t-Bu	Tert-butyl
Boc	Tert-butoxycarbonyl
THF	Tetrahydrofuran
LiHMDS	Lithium bis(trimethylsilyl)amide
NaH	Sodium hydride
Dioxane	Dioxane
DCM	Dichloromethane
TFA	Trifluoroacetic acid
Bn	Benzyl

Example 1 *N*-(6-(4,4-difluoropiperidin-1-yl)-5-(1-methyl-1*H*-1,2,3-triazol-4-yl)pyridin-2-yl)-4-((2-hydroxyethyl)sulfonamido)-2-(6-azaspiro[2.5]octan-6-yl)benzamide





Compound 1

Step A: To a solution of 5-bromo-6-fluoropyridin-2-amine (20 g, 0.1 mol) in 1,4-dioxane (500 mL) were added [1,1'-bis(diphenylphosphino)ferrocene]palladium dichloride (7.7 g, 0.01 mol), bis(pinacolato)diboron (38 g, 0.15 mol), and potassium acetate (29 g, 0.3 mol) sequentially at room temperature. After purging with nitrogen, the reaction mixture reacted with stirring at 110°C for 16 h. After the reaction was completed, the reaction mixture was cooled to room temperature, and extracted with ethyl acetate (500 mL×3). The organic phases were combined, washed with saturated brine (300 mL×3), dried over anhydrous sodium sulfate, and filtered. The filtrate was then concentrated under reduced pressure, and the residue was purified by column chromatography on silica gel (petroleum ether/ethyl acetate=1/1), to afford 6-fluoro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-amine (16 g). MS (ESI) M/Z: 239.2 $[M+H]^+$.

Step B: To a solution of 6-fluoro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-amine (3 g, 12.6 mmol) in a mixture of 1,4-dioxane and water (5/1, v/v, 50 mL) were added 4-bromo-1-methyl-1*H*-1,2,3-triazole (3 g, 18.8 mmol), [1,1'-bis(diphenylphosphino)ferrocene]palladium dichloride (1.84 g, 2.52 mmol), and potassium carbonate (5.2 g, 37.8 mmol) sequentially at room temperature. After purging with nitrogen, the reaction mixture reacted at 100°C for 3 h. After the reaction was completed, the reaction mixture was cooled to room temperature, quenched with ice water, and extracted with ethyl acetate (100 mL×3). The organic phases were combined, washed with saturated brine (100 mL×3), dried over anhydrous sodium sulfate, and filtered. The filtrate was then concentrated under reduced pressure, and the resulting residue was purified by column chromatography on silica gel (5% methanol/dichloromethane), to afford 6-fluoro-5-(1-methyl-1*H*-1,2,3-triazol-4-yl)pyridin-2-amine (1.3 g). MS (ESI) M/Z: 194.1 $[M+H]^+$.

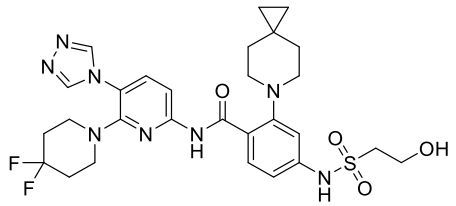
Step C: To a solution of 6-fluoro-5-(1-methyl-1*H*-1,2,3-triazol-4-yl)pyridin-2-amine (1.3 g, 6.7 mmol) in dimethyl sulfoxide (15 mL) were added 4,4-difluoropiperidine (2.43 g, 20.1 mmol) and potassium carbonate (2.8 g, 20.1 mmol) sequentially. After purging with nitrogen, the reaction mixture reacted at 160°C under microwave irradiation for 16 h. The reaction mixture was cooled to room temperature, and purified directly by a C18 reversed-phase column (acetonitrile/water=40/60), to afford 6-(4,4-difluoropiperidin-1-yl)-5-(1-methyl-1*H*-1,2,3-triazol-4-yl)pyridin-2-amine (0.6 g).

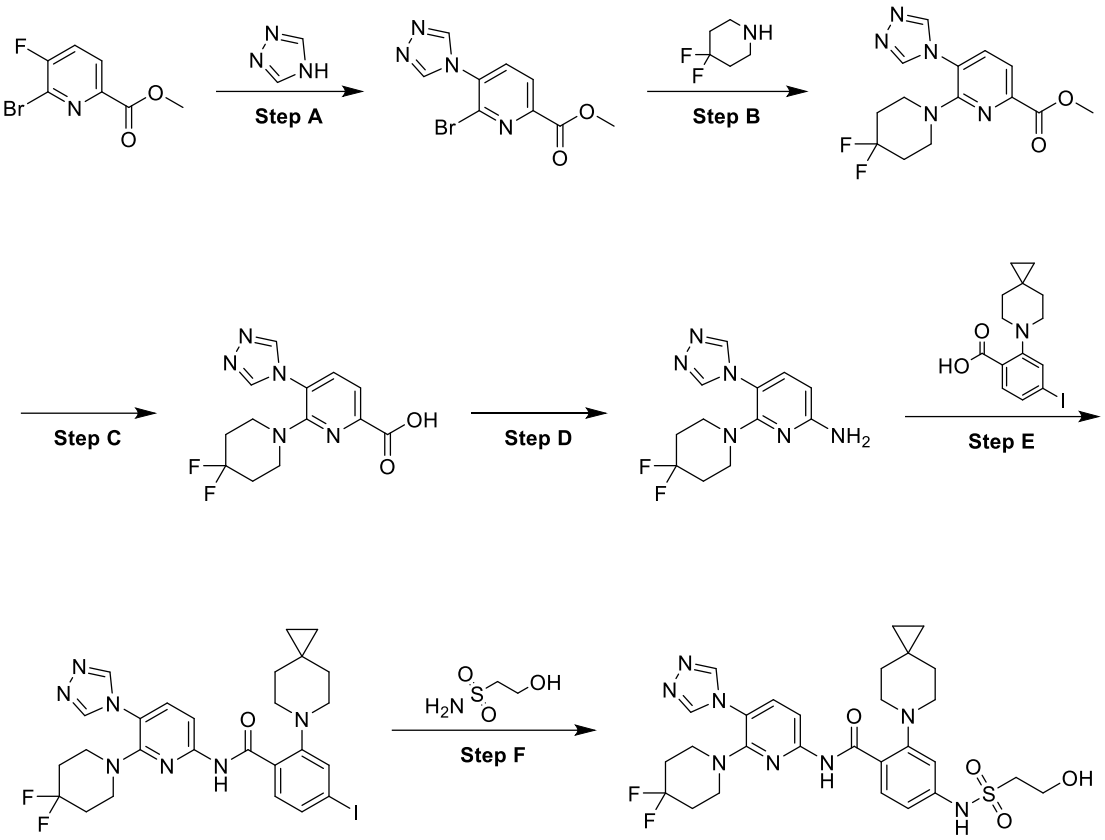
MS (ESI) M/Z: 295.2 $[M+H]^+$.

Step D: To a solution of 4-iodo-2-(6-azaspiro[2.5]octan-6-yl)benzoic acid (0.12 g, 0.34 mmol) in tetrahydrofuran (2 mL) was added dropwise thionyl chloride (0.12 g, 1.02 mmol) at room temperature, and then to the reaction system was added a catalytic amount of *N,N*-dimethylformamide (3 mg, 0.034 mmol). The reaction system reacted at 70 °C for 2 h, and then was directly concentrated to dryness to obtain a residue. Then, a solution of 6-(4,4-difluoropiperidin-1-yl)-5-(1-methyl-1*H*-1,2,3-triazol-4-yl)pyridin-2-amine (0.1*g,* 0.34 mmol) in tetrahydrofuran (2 mL) was added to the residue obtained from the previous step, and then potassium tert-butoxide (1.7 mL, 1.7 mmol, 1 M tetrahydrofuran solution) was added to the reaction system. Finally, the reaction mixture was stirred at room temperature for 16 h, quenched with ice water, and extracted with ethyl acetate (30 mL×3). The organic phases were combined, washed with saturated brine (50 mL×3), dried over anhydrous sodium sulfate, and filtered. The filtrate was then concentrated under reduced pressure, and the resulting residue was purified by column chromatography on silica gel (5% methanol/dichloromethane), to afford the target compound *N*-(6-(4,4-difluoropiperidin-1-yl)-5-(1-methyl-1*H*-1,2,3-triazol-4-yl)pyridin-2-yl)-4-iodo-2-(6-azaspiro[2.5]octan-6-yl)benzamide (68 mg). MS (ESI) M/Z: 634.2 $[M+H]^+$.

Step E: To a solution of *N*-(6-(4,4-difluoropiperidin-1-yl)-5-(1-methyl-1*H*-1,2,3-triazol-4-yl)pyridin-2-yl)-4-iodo-2-(6-azaspiro[2.5]octan-6-yl)benzamide (68 mg, 0.1 mmol) in *N,N*-dimethylformamide (2 mL) were added 2-hydroxyethane-1-sulfonamide (25 mg, 0.2 mmol), cuprous iodide (19 mg, 0.1 mmol), sarcosine (9 mg, 0.1 mmol), and potassium phosphate (85 mg, 0.4 mmol) sequentially at room temperature. After purging with nitrogen, the reaction system reacted at 120°C for 16 h, and was cooled to room temperature. The reaction mixture was purified directly by high performance liquid chromatography, to afford the target product *N*-(6-(4,4-difluoropiperidin-1-yl)-5-(1-methyl-1*H*-1,2,3-triazol-4-yl)pyridin-2-yl)-4-((2-hydroxyethyl)sulfonamido)-2-(6-azaspiro[2.5]octan-6-yl)benzamide (18.2 mg). MS (ESI) M/Z: 631.3 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO) δ 13.29 (s, 1H), 8.53 (s, 1H), 8.26 (d, *J*=8.3 Hz, 1H), 8.06 (dd, *J*=14.8, 8.5 Hz, 2H), 7.26 (d, *J*=1.9 Hz, 1H), 7.12 (dd, *J*=8.6, 2.0 Hz, 1H), 4.13 (s, 3H), 3.76 (t, *J*=6.5 Hz, 2H), 3.36 (s, 2H), 3.18-3.14 (m, 4H), 3.00 (s, 4H), 2.21-2.12 (m, 4H), 1.97-1.49 (m, 4H), 0.40 (s, 4H).

Example 2 *N*-(6-(4,4-difluoropiperidin-1-yl)-5-(4*H*-1,2,4-triazol-4-yl)pyridin-2-yl)-4-((2-hydroxyethyl)sulfonamido)-2-(6-azaspiro[2.5]octan-6-yl)benzamide





Compound 2

Step A: To a solution of methyl 6-bromo-5-fluoropicolinate (2 g, 8.6 mmol) and 4*H*-1,2,4-triazole (0.59 g, 8.6 mmol) in *N,N*-dimethylformamide (30 mL) was added potassium carbonate (3.56 g, 25.8 mmol) at room temperature, and then the reaction mixture reacted with stirring at 80°C for 2 h. After the reaction was completed, the reaction mixture was cooled to room temperature, quenched with ice water, and extracted with ethyl acetate (50 mL×3). The organic phases were combined, washed with saturated brine (50 mL×3), dried over anhydrous sodium sulfate, and filtered. The filtrate was then concentrated under reduced pressure, and the resulting residue was purified by column chromatography on silica gel (petroleum ether/ethyl acetate=5/1), to afford the target compound methyl 6-bromo-5-(4*H*-1,2,4-triazol-4-yl)picolinate (2 g). MS (ESI) M/Z: 283.0 $[M+H]^+$.

Step B: To a solution of methyl 6-bromo-5-(4*H*-1,2,4-triazol-4-yl)picolinate (2 g, 7.1 mmol) in *N,N*-dimethylformamide (30 mL) were added 4,4-difluoropiperidine (1 g, 8.5 mmol) and potassium carbonate (2.9 g, 21.3 mmol) at room temperature. Then, the reaction mixture was transferred to an oil bath, and reacted with stirring at 100°C for 4 h. After the reaction was completed, the reaction mixture was cooled to room temperature, quenched with ice water (50 mL), and extracted with ethyl acetate (50 mL×3). The organic phases were combined, washed with saturated brine (50 mL×3), dried over anhydrous sodium sulfate, and filtered. The filtrate was then concentrated under reduced pressure, and the resulting residue was purified by column chromatography on silica gel (petroleum ether/ethyl acetate=3/1), to afford the target compound methyl 6-(4,4-difluoropiperidin-1-yl)-5-(4*H*-1,2,4-triazol-4-yl)picolinate (2 g). MS (ESI) M/Z: 324.0 $[M+H]^+$.

Step C: To a solution of methyl 6-(4,4-difluoropiperidin-1-yl)-5-(4*H*-1,2,4-triazol-4-yl)picolinate (2 g, 6.2 mmol) in a mixture of tetrahydrofuran/methanol/water=4/2/1 (20 mL) was added lithium hydroxide (0.74 g, 31 mmol) at room temperature. The reaction mixture reacted with

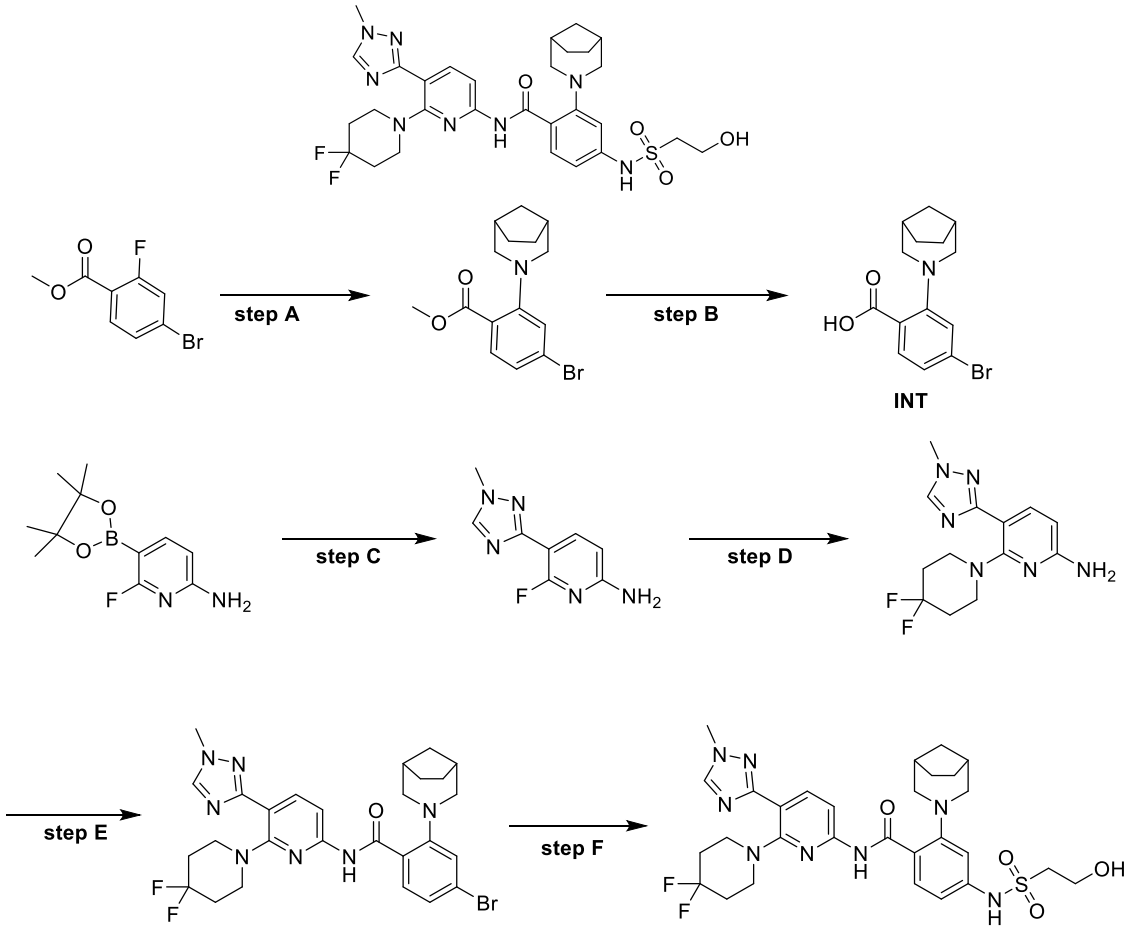
stirring at room temperature for 1 h. After the reaction was completed, the reaction mixture was concentrated by rotary evaporation to remove the solvent, thus affording a residue, which was adjusted with dilute hydrochloric acid (1 M) to pH of 5-6, and then a solid precipitated out. After filtration, the filter cake was washed with methyl tert-butyl ether, and then lyophilized, to afford the target compound 6-(4,4-difluoropiperidin-1-yl)-5-(4*H*-1,2,4-triazol-4-yl)picolinic acid (1.5 g). MS (ESI) M/Z: 310.0 $[M+H]^+$.

Step D: To a solution of 6-(4,4-difluoropiperidin-1-yl)-5-(4*H*-1,2,4-triazol-4-yl)picolinic acid (1.5 g, 4.8 mmol) in *N,N*-dimethylformamide (30 mL) were added diisopropylethylamine (0.89 g, 6.9 mmol) and diphenyl azidophosphate (1.9 g, 6.9 mmol) at room temperature. The reaction mixture was then transferred to an oil bath, and reacted with stirring at 90°C for 5 mins. Water (0.43 g, 24 mmol) was then added. The reaction mixture reacted with stirring continuously at this temperature for additional 2 h, and then was cooled to room temperature, quenched with ice water (50 mL), and extracted with ethyl acetate (50 mL×3). The organic phases were combined, washed with saturated brine (50 mL×3), dried over anhydrous sodium sulfate, and filtered. The filtrate was then concentrated under reduced pressure, and the resulting residue was purified by column chromatography on silica gel (dichloromethane/methanol=20/1), to afford the target compound 6-(4,4-difluoropiperidin-1-yl)-5-(4*H*-1,2,4-triazol-4-yl)pyridin-2-amine (1.2 g). MS (ESI) M/Z: 281.0 $[M+H]^+$.

Step E: To a solution of 4-iodo-2-(6-azaspiro[2.5]octan-6-yl)benzoic acid (0.64 g, 1.8 mmol) in tetrahydrofuran (10 mL) was added dropwise thionyl chloride (0.64 g, 5.4 mmol) at room temperature, and then to the reaction system was added a catalytic amount of *N,N*-dimethylformamide (13 mg, 0.18 mmol). The reaction system reacted at 70°C for 2 h, and then was concentrated directly to obtain a residue. Subsequently, to the residue obtained from the previous step was added a solution of 6-(4,4-difluoropiperidin-1-yl)-5-(4*H*-1,2,4-triazol-4-yl)pyridin-2-amine (0.5 *g,*1.8 mmol) in tetrahydrofuran (5 mL). Then, to the reaction system was added potassium tert-butoxide (9 mL, 9 mmol, 1 M tetrahydrofuran solution). The reaction mixture was stirred at room temperature for 16 h, quenched with ice water, and extracted with ethyl acetate (50 mL×3). The organic phases were combined, washed with saturated brine (50 mL×3), dried over anhydrous sodium sulfate, and filtered. The filtrate was then concentrated under reduced pressure, and the resulting residue was purified by column chromatography on silica gel (dichloromethane/methanol=20/1), to afford the target compound *N*-(6-(4,4-difluoropiperidin-1-yl)-5-(4*H*-1,2,4-triazol-4-yl)pyridin-2-yl)-4-iodo-2-(6-azaspiro[2.5]octan-6-yl)benzamide (0.5 g). MS (ESI) M/Z: 620.2 $[M+H]^+$.

Step F: To a solution of *N*-(6-(4,4-difluoropiperidin-1-yl)-5-(4*H*-1,2,4-triazol-4-yl)pyridin-2-yl)-4-iodo-2-(6-azaspiro[2.5]octan-6-yl)benzamide (0.5 g, 0.81 mmol) in *N,N*-dimethylformamide (5 mL) were added 2-hydroxyethane-1-sulfonamide (202 mg, 1.62 mmol), cuprous iodide (153 mg, 0.81 mmol), sarcosine (72 mg, 0.81 mmol), and potassium phosphate (686 mg, 3.24 mmol) sequentially at room temperature. After purging with nitrogen, the reaction system reacted at 120°C for 16 h, and was cooled to room temperature. The reaction mixture was purified directly by high performance liquid chromatography, to afford the target product *N*-(6-(4,4-difluoropiperidin-1-yl)-5-(4*H*-1,2,4-triazol-4-yl)pyridin-2-yl)-4-((2-hydroxyethyl)sulfonamido)-2-(6-azaspiro[2.5]octan-6-yl)benzamide (107.52 mg). MS (ESI) M/Z: 617.3 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.39 (s, 1H), 9.02 (s, 1H), 8.29 (s, 1H), 8.09 (d, *J*=8.6 Hz, 1H), 7.99 (d, *J*=8.4 Hz, 1H), 7.83 (d, *J*=8.4 Hz, 1H), 7.29 (d, *J*=1.8 Hz, 1H), 7.14 (dd, *J*=8.6, 1.9 Hz, 1H), 3.77 (t, *J*=6.5 Hz, 2H), 3.36 (t, *J*=6.5 Hz, 2H), 3.10-3.04 (m, 4H), 3.03-2.99 (m, 4H), 2.02-1.93 (m, 4H), 1.91-1.32 (m, 4H), 0.40 (s, 4H).

Example 3 2-3-Azabicyclo[3.2.1]octan-3-yl)-*N*-(6-(4,4-difluoropiperidin-1-yl)-5-(1-methyl-1*H*-1,2,4-triazol-3-yl)pyridin-2-yl)-4-((2-hydroxyethyl)sulfonamido)benzamide



Step A: Methyl 4-bromo-2-fluorobenzoate (5 g, 21.46 mmol), 3-azabicyclo[3.2.1]octane hydrochloride (4.75 g, 32.19 mmol), and *N,N*-diisopropylethylamine (13.87 g, 107.30 mmol) were dissolved in dimethyl sulfoxide (100 mL). The reaction mixture was heated to 120°C, stirred for 12 h, then cooled to room temperature, and diluted with a mixture of ethyl acetate/water (200 mL/100 mL). The mixed solution was extracted with ethyl acetate three times. The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated. The residue was purified by a flash silica gel column (ethyl acetate/petroleum ether=5%), to afford methyl 2-(3-azabicyclo[3.2.1]octan-3-yl)-4-bromobenzoate as a yellow solid (6.4 g). MS (ESI) M/Z: 324.0 $[M+H]^+$.

Step B: To a solution of methyl 2-(3-azabicyclo[3.2.1]octan-3-yl)-4-bromobenzoate (6.4 g, 19.74 mmol) dissolved in a mixture of tetrahydrofuran (80 mL) and water (20 mL) was added sodium hydroxide (4.74 g, 118.44 mmol). The reaction mixture was then heated to 80°C, stirred for 36 h, then cooled to room temperature, concentrated under reduced pressure, and adjusted with hydrochloric acid (2 M) to pH of 5-6. Then, a white solid precipitated out. After filtration, the filter cake was dried, to afford 2-(3-azabicyclo[3.2.1]octan-3-yl)-4-bromobenzoic acid as a white solid (5.2 g). MS (ESI) M/Z: 310.0 $[M+H]^+$.

Step C: To a mixed solution of 6-fluoro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaboran-2-yl)pyridin-2-amine (4 g, 16.80 mmol), 3-bromo-1-methyl-1*H*-1,2,4-triazole (3.27 g, 20.16 mmol), and potassium carbonate (6.97 g, 50.40 mmol) dissolved in a mixture of dioxane (60 mL) and water (15 mL) was added [1,1'-bis(diphenylphosphino)ferrocene]palladium dichloride-dichloromethane

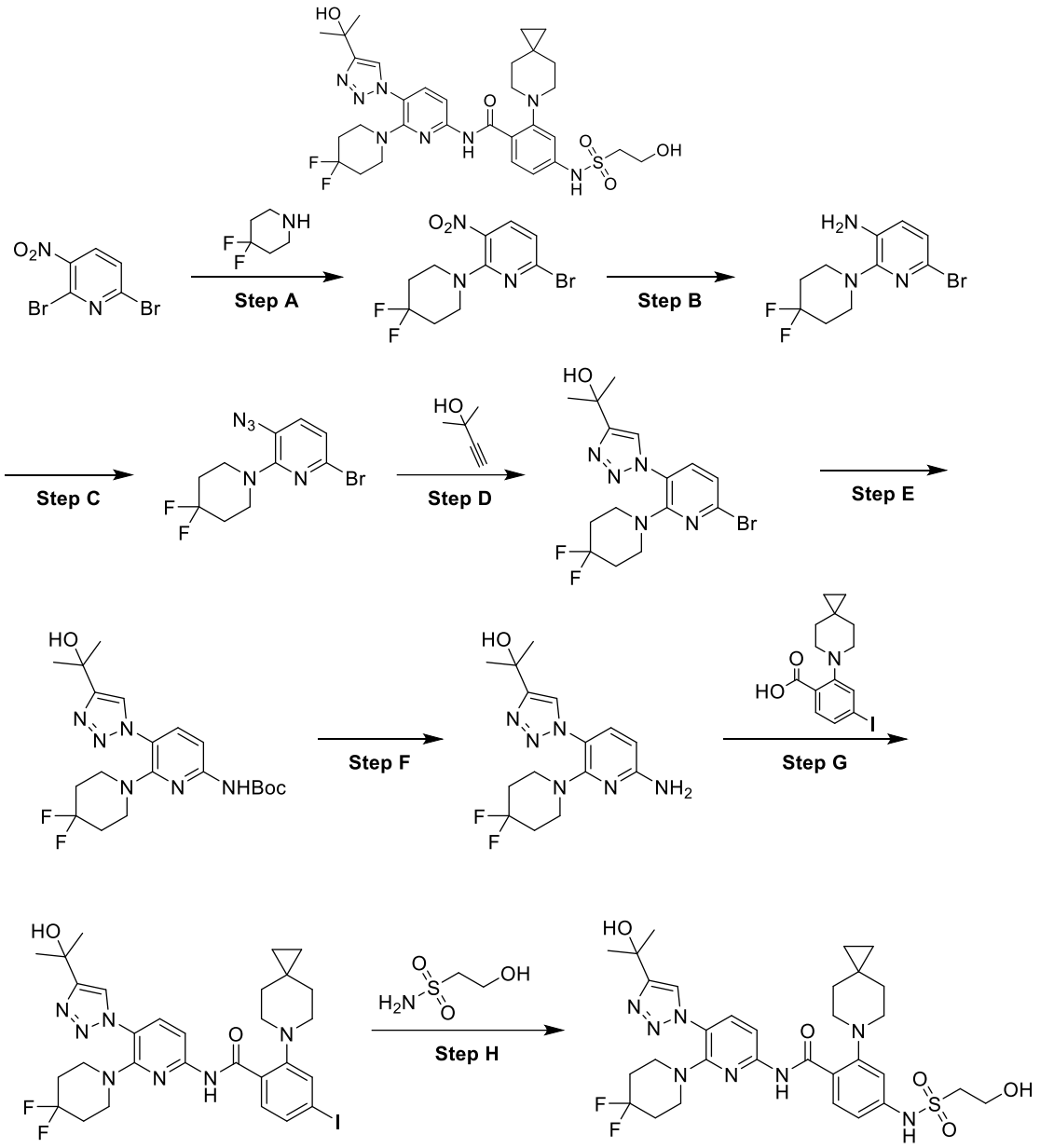
complex (1.37 g, 1.68 mmol) under the protection of nitrogen atmosphere. After purging with nitrogen three times, the reaction mixture reacted at 100°C for 4 h, and then was cooled to room temperature, and diluted with a mixture of ethyl acetate/water (200 mL/100 mL). The mixed solution was extracted with ethyl acetate three times. The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated. The residue was purified by a flash silica gel column (methanol/dichloromethane=5%), to afford 6-fluoro-5-(1-methyl-1*H*-1,2,4-triazol-3-yl)pyridin-2-amine (800 mg). MS (ESI) M/Z: 194.1 $[M+H]^+$.

Step D: A solution of 6-fluoro-5-(1-methyl-1*H*-1,2,4-triazol-3-yl)pyridin-2-amine (400 mg, 2.07 mmol), 4,4-difluoropiperidine (0.75 g, 6.21 mmol), and *N,N*-diisopropylethylamine (1.34 g, 10.35 mmol) dissolved in dimethyl sulfoxide (10 mL) reacted with heating under microwave irradiation at 160°C for 5 h. Then, the reaction mixture was cooled to room temperature, and diluted with a mixture of ethyl acetate/water (100 mL/50 mL). The mixed solution was extracted with ethyl acetate three times. The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated. The residue was purified by a flash silica gel column (methanol/dichloromethane=5%), to afford 6-(4,4-difluoropiperidin-1-yl)-5-(1-methyl-1*H*-1,2,4-triazol-3-yl)pyridin-2-amine as a yellow solid (290 mg). MS (ESI) M/Z: 295.1 $[M+H]^+$.

Step E: 2-(3-azabicyclo[3.2.1]octan-3-yl)-4-bromobenzoic acid (0.30 g, 0.97 mmol) was dissolved in *N,N*-dimethylformamide (10 mL), and 2-(7-azabenzotriazole)-*N,N,N′,N′*-tetramethyluronium hexafluorophosphate (0.50 g, 1.32 mmol) was added. The reaction mixture was stirred for 10 mins, and then 6-(4,4-difluoropiperidin-1-yl)-5-(1-methyl-1*H*-1,2,4-triazol-3-yl)pyridin-2-amine (260 mg, 0.88 mmol) and *N,N*-diisopropylethylamine (0.23 g, 1.76 mmol) were added. The reaction mixture was heated with stirring under microwave irradiation at 50°C for 4 h, then cooled to room temperature, and diluted with a mixture of ethyl acetate/water (100 ml/50 ml). The mixed solution was extracted with ethyl acetate three times. The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated. The residue was purified by a flash silica gel column (ethyl acetate/petroleum ether=50%), to afford 2-(3-azabicyclo[3.2.1]octan-3-yl)-4-bromo-*N*-(6-(4,4-difluoropiperidin-1-yl)-5-(1-methyl-1*H*-1,2,4-triazol-3-yl)pyridin-2-yl)benzamide (370 mg, yield=71.41%). MS (ESI) M/Z: 586.2 $[M+H]^+$.

Step F: To a solution of 2-(3-azabicyclo[3.2.1]octan-3-yl)-4-bromo-*N*-(6-(4,4-difluoropiperidin-1-yl)-5-(1-methyl-1*H*-1,2,4-triazol-3-yl)pyridin-2-yl)benzamide (60 mg, 0.10 mmol) and 2-hydroxyethane-1-sulfonamide (37.55 mg, 0.30 mmol) dissolved in dimethyl sulfoxide (3 mL) were added cuprous iodide (38.09 mg, 0.20 mmol), potassium phosphate (42.45 mg, 0.20 mmol), and (1*R*,2*R*)-(-)-*N,N*'-dimethyl-1,2-cyclohexanediamine (28.45 mg, 0.20 mmol) sequentially. Then, the reaction mixture was heated to 150°C under microwave irradiation under the protection of nitrogen atmosphere and reacted for 1 h. The reaction mixture was cooled to room temperature, diluted with water (50 mL), and then extracted with ethyl acetate (50 mL). The organic phase was concentrated under reduced pressure, to afford the crude product. The crude product was purified and separated by high performance liquid chromatography (formic acid), to afford 2-(3-azabicyclo[3.2.1]octan-3-yl)-*N*-(6-(4,4-difluoropiperidin-1-yl)-5-(1-methyl-1*H*-1,2,4-triazol-3-yl)pyridin-2-yl)-4-((2-hydroxyethyl)sulfonamido)benzamide (19.95 mg). MS (ESI) M/Z: 631.2 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.85 (s, 1H), 8.53 (s, 1H), 8.11 (d, *J*=8.4 Hz, 1H), 7.94 (d, *J*=8.4 Hz, 1H), 7.71 (d, *J*=8.5 Hz, 1H), 7.14 (d, *J*=2.1 Hz, 1H), 6.98 (dd, *J*=8.4, 2.0 Hz, 1H), 3.92 (s, 3H), 3.75 (t, *J*=6.6 Hz, 2H), 3.29 (t, *J*=6.6 Hz, 6H), 3.05-2.95 (m, 2H), 2.83-2.79 (m, 2H), 2.25 (s, 2H), 2.08-1.99 (m, 6H), 1.65-1.46 (m, 4H).

Example 4 *N*-(6-(4,4-difluoropiperidin-1-yl)-5-(4-(2-hydroxyprop-2-yl)-1*H*-1,2,3-triazol-1-yl)pyridin-2-yl)-4-((2-hydroxyethyl)sulfonamido)-2-(6-azaspiro[2.5]octan-6-yl)benzamide



Compound 4

Step A: To a solution of 2,6-dibromo-3-nitropyridine (10 g, 35.7 mmol) and 4,4-difluoropiperidine (4.3 g, 35.7 mmol) in tetrahydrofuran (100 mL) was added potassium carbonate (14.5 g, 107.1 mmol) at room temperature, and then the reaction mixture reacted with stirring at room temperature for 16 h. After the reaction was completed, the reaction mixture was quenched with ice water, and extracted with ethyl acetate (100 mL×3). The organic phases were combined, washed with saturated brine (100 mL×3), dried over anhydrous sodium sulfate, and filtered. The filtrate was then concentrated under reduced pressure, and the resulting residue was purified by column chromatography on silica gel (petroleum ether/ethyl acetate=10/1), to afford the target compound 6-bromo-2-(4,4-difluoropiperidin-1-yl)-3-nitropyridine (6 g). MS (ESI) M/Z: 322.0 $[M+H]^+$.

Step B: To a solution of 6-bromo-2-(4,4-difluoropiperidin-1-yl)-3-nitropyridine (6 g, 18.6

mmol) in *N,N*-dimethylformamide (60 mL) was added bipyridine (0.3 g, 1.9 mmol) in an ice bath. After complete dissolution, $B_2(OH)_4$ (8.3 g, 93 mmol) was added portionwise to the system. During the addition, the reaction mixture changed from pale yellow to dark brown and then back to pale yellow over 10 mins, and then the reaction was completed. The reaction mixture was cooled to room temperature, quenched with ice water (100 mL), and extracted with ethyl acetate (100 mL×3). The organic phases were combined, washed with saturated brine (100 mL×3), dried over anhydrous sodium sulfate, and filtered. The filtrate was then concentrated under reduced pressure, and the resulting residue was purified by column chromatography on silica gel (petroleum ether/ethyl acetate=5/1), to afford the target compound 6-bromo-2-(4,4-difluoropiperidin-1-yl)pyridin-3-amine (2.9 g). MS (ESI) M/Z: 292.0 $[M+H]^+$.

Step C: To a solution of 6-bromo-2-(4,4-difluoropiperidin-1-yl)pyridin-3-amine (2.9 g, 1 mmol) in acetonitrile (40 mL) was added tert-butyl nitrite (1.5 g, 1.5 mmol) in an ice bath. After the mixture reacted with stirring for 10 mins, azidotrimethylsilane (1.7 g, 1.5 mmol) was added to the system. The reaction mixture reacted with stirring continuously for additional 1 h, and then was cooled to room temperature, quenched with ice water (100 mL), and extracted with ethyl acetate (100 mL×3). The organic phases were combined, washed with saturated brine (100 mL×3), dried over anhydrous sodium sulfate, and filtered. The filtrate was then concentrated under reduced pressure, and the resulting residue was purified by column chromatography on silica gel (petroleum ether/ethyl acetate=5/1), to afford the target compound 3-azido-6-bromo-2-(4,4-difluoropiperidin-1-yl)pyridine (1.8 g). MS (ESI) M/Z: 318.0 $[M+H]^+$.

Step D: To a solution of 3-azido-6-bromo-2-(4,4-difluoropiperidin-1-yl)pyridine (1.8 g, 5.7 mmol) in tetrahydrofuran (20 mL) were added 2-methylbut-3-yn-2-ol (0.5 g, 6 mmol), copper acetate (0.1 g, 0.6 mmol), sodium ascorbate (0.1 g, 0.6 mmol), and water (0.5 g, 28.5 mmol) sequentially at room temperature. After purging with nitrogen, the reaction mixture reacted with stirring at room temperature for 16 h, quenched with ice water (50 mL), and extracted with dichloromethane/methanol=10/1 (100 mL×3). The organic phases were combined, washed with saturated brine (100 mL×3), dried over anhydrous sodium sulfate, and filtered. The filtrate was then concentrated under reduced pressure, and the resulting residue was purified by column chromatography on silica gel (dichloromethane/methanol=20/1), to afford the target compound 2-(1-(6-bromo-2-(4,4-difluoropiperidin-1-yl)pyridin-3-yl)-1*H*-1,2,3-triazol-4-yl)propan-2-ol (1.2 g). MS (ESI) M/Z: 402.0 $[M+H]^+$.

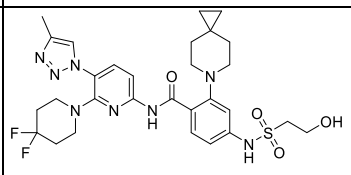
Step E: To a solution of 2-(1-(6-bromo-2-(4,4-difluoropiperidin-1-yl)pyridin-3-yl)-1*H*-1,2,3-triazol-4-yl)propan-2-ol (1.2 g, 3 mmol) in 1,4-dioxane (20 mL) were added tris(dibenzylideneacetone)dipalladium (0.24 g, 0.3 mmol), 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (0.22 g, 0.45 mmol), cesium carbonate (2.9 g, 9 mmol), and tert-butyl carbamate (0.7 g, 6 mmol) at room temperature. After purging with nitrogen, the reaction mixture reacted with stirring at 100°C for additional 2 h. After the reaction was completed, the reaction mixture was cooled to room temperature, quenched with ice water (50 mL), and extracted with ethyl acetate (50 mL×3). The organic phases were combined, washed with saturated brine (30 mL×3), dried over anhydrous sodium sulfate, and filtered. The filtrate was then concentrated under reduced pressure, and the resulting residue was purified by column chromatography on silica gel (dichloromethane/methanol=20/1), to afford the target compound tert-butyl (6-(4,4-difluoropiperidin-1-yl)-5-(4-(2-hydroxypropan-2-yl)-1*H*-1,2,3-triazol-1-yl)pyridin-2-yl)carbamate (1 g). MS (ESI) M/Z: 439.2 $[M+H]^+$.

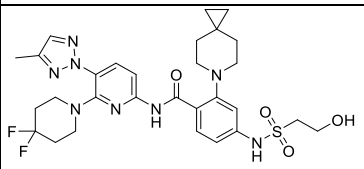
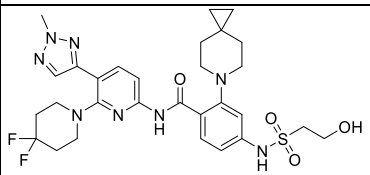
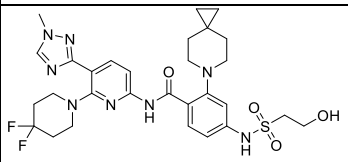
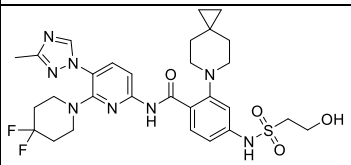
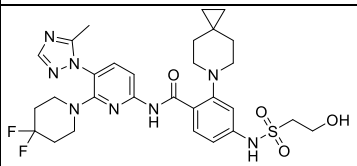
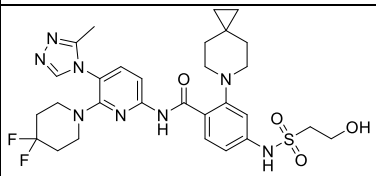
Step F: To a solution of tert-butyl (6-(4,4-difluoropiperidin-1-yl)-5-(4-(2-hydroxypropan-2-yl)-1*H*-1,2,3-triazol-1-yl)pyridin-2-yl)carbamate (1 g, 2.3 mmol) in dichloromethane (10 mL) was added trifluoroacetic acid (5 mL) at room temperature, and the reaction mixture reacted with stirring at room temperature for 1 h. After the reaction was completed, the reaction mixture was concentrated directly by rotary evaporation to remove the solvent, to afford the target compound 2-(1-(6-amino-2-(4,4-difluoropiperidin-1-yl)pyridin-3-yl)-1*H*-1,2,3-triazol-4-yl)propan-2-ol trifluoroacetate(0.8 g). MS (ESI) M/Z: 339.0 $[M+H]^+$.

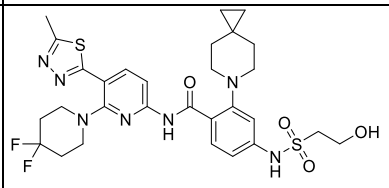
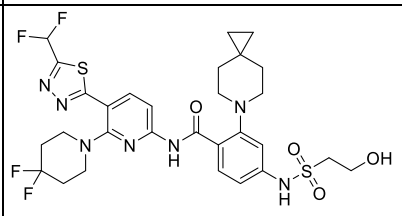
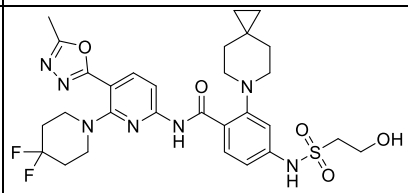
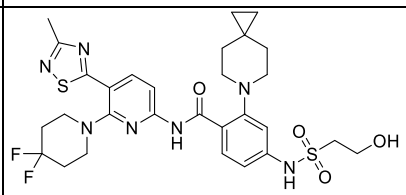
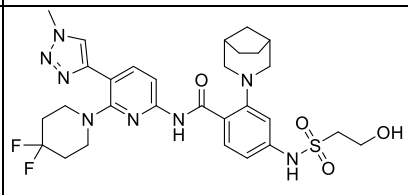
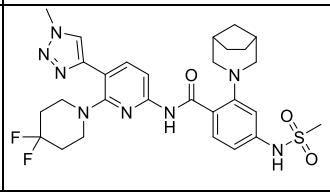
Step G: To a solution of 4-iodo-2-(6-azaspiro[2.5]octan-6-yl)benzoic acid (0.86 g, 2.4 mmol) in tetrahydrofuran (10 mL) was added dropwise thionyl chloride (0.86 g, 7.2 mmol) at room temperature, and then to the reaction system was added a catalytic amount of *N,N*-dimethylformamide (15 mg, 0.2 mmol). The reaction system reacted at 70°C for 2 h, and then was concentrated directly to obtain a residue. Then, to the residue obtained from the previous step was added a solution of 2-(1-(6-amino-2-(4,4-difluoropiperidin-1-yl)pyridin-3-yl)-1*H*-1,2,3-triazol-4-yl)propan-2-ol trifluoroacetate (0.8 g, 2.4 mmol) in tetrahydrofuran (10 mL), and then to the reaction system was added potassium tert-butoxide (12 mL, 12 mmol, 1 M tetrahydrofuran solution). The reaction mixture was stirred at room temperature for 16 h, quenched with ice water, and extracted with ethyl acetate (100 mL×3). The organic phases were combined, washed with saturated brine (100 mL×3), dried over anhydrous sodium sulfate, and filtered. The filtrate was then concentrated under reduced pressure, and the resulting residue was purified by column chromatography on silica gel (dichloromethane/methanol=20/1), to afford the target compound *N*-(6-(4,4-difluoropiperidin-1-yl)-5-(4-(2-hydroxypropan-2-yl)-1*H*-1,2,3-triazol-1-yl)pyridin-2-yl)-4-iodo-2-(6-azaspiro[2.5]octan-6-yl)benzamide (0.8 g). MS (ESI) M/Z: 678.2 $[M+H]^+$.

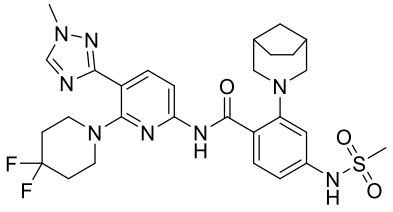
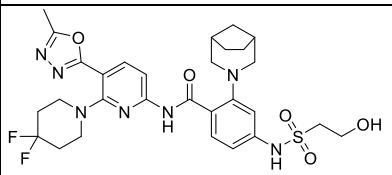
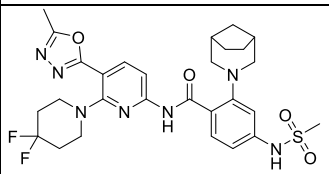
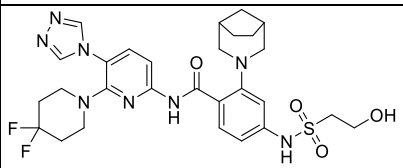
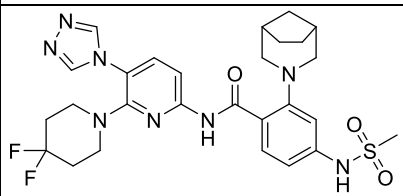
Step H: To a solution of *N*-(6-(4,4-difluoropiperidin-1-yl)-5-(4-2-hydroxypropan-2-yl)-1*H*-1,2,3-triazol-1-yl)pyridin-2-yl)-4-iodo-2-(6-azaspiro[2.5]octan-6-yl)benzamide (0.2 g, 0.3 mmol) in *N,N*-dimethylformamide (5 mL) were added 2-hydroxyethane-1-sulfonamide (75 mg, 0.6 mmol), cuprous iodide (57 mg, 0.3 mmol), sarcosine (27 mg, 0.3 mmol), and potassium phosphate (254 mg, 1.2 mmol) sequentially at room temperature. After purging with nitrogen, the reaction system reacted at 120°C for 16 h, and then was cooled to room temperature. The reaction mixture was purified directly by high performance liquid chromatography, to afford the target product *N*-(6-(4,4-difluoropiperidin-1-yl)-5-(4-(2-hydroxypropan-2-yl)-1*H*-1,2,3-triazol-1-yl)pyridin-2-yl)-4-((2-hydroxyethyl)sulfonamido)-2-(6-azaspiro[2.5]octan-6-yl)benzamide (83.95 mg). MS (ESI) M/Z: 675.2 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.44 (s, 1H), 8.30 (s, 1H), 8.10 (d, *J*=8.6 Hz, 1H), 8.00 (d, *J*=8.4 Hz, 1H), 7.88 (d, *J*=8.4 Hz, 1H), 7.29 (d, *J*=1.9 Hz, 1H), 7.15 (dd, *J*=8.7, 2.0 Hz, 1H), 5.27 (s, 1H), 3.77 (t, *J*=6.5 Hz, 2H), 3.36 (t, *J*=6.5 Hz, 2H), 3.03-2.97 (m, 8H), 2.01-1.94 (m, 4H), 1.90-1.61 (m, 4H), 1.54 (s, 6H), 0.40 (s, 4H).

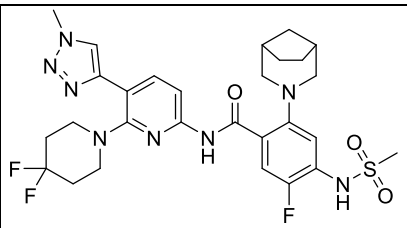
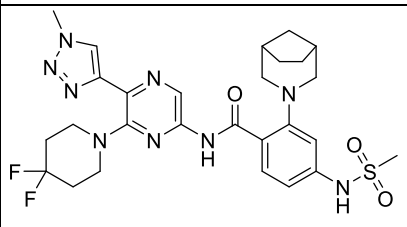
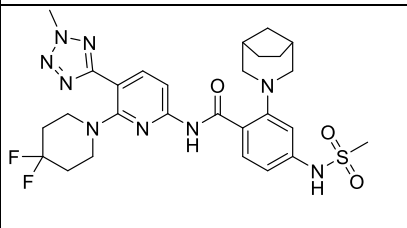
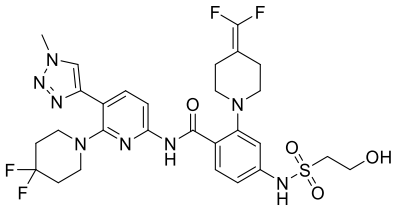
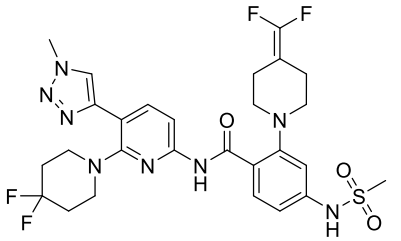
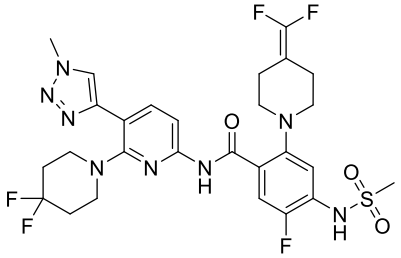
The following target compounds were prepared with reference to the synthetic procedures described in the foregoing Examples.

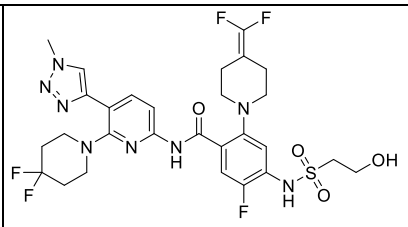
Example No.	Structural formula	^{1}HNMR	MS(ESI)M/Z $[M+H]^+$
5		^{1}H NMR (400 MHz, DMSO-d_6) δ 13.39 (s, 1H), 8.30 (s, 1H), 8.10 (d, *J*=8.6 Hz, 1H), 7.99 (d, *J*=8.4 Hz, 1H), 7.85 (d, *J*=8.4 Hz, 1H), 7.29 (d, *J*=1.9 Hz, 1H), 7.14 (dd, *J*=8.7, 1.9 Hz, 1H), 3.77 (t, *J*=6.5 Hz, 2H), 3.36 (t,	631.3

		J=6.5 Hz, 2H), 3.05-3.01 (m, 8H), 2.35 (s, 3H), 2.02-1.93 (m, 4H), 1.92-1.45 (m, 4H), 0.40 (s, 4H).	
6		^{1}H NMR (400 MHz, DMSO-d_6) δ 13.47 (s, 1H), 8.11 (d, *J*=8.6 Hz, 1H), 8.01 (d, *J*=8.4 Hz, 1H), 7.79 (d, *J*=8.4 Hz, 1H), 7.74 (s, 1H), 7.29 (d, *J*=1.9 Hz, 1H), 7.14 (dd, *J*=8.6, 2.0 Hz, 1H), 3.77 (t, *J*=6.5 Hz, 2H), 3.36 (t, *J*=6.4 Hz, 2H), 3.05-3.01 (m, 8H), 2.21 (s, 3H), 1.94-1.86 (m, 4H), 1.84-1.32 (m, 4H), 0.40 (s, 4H).	631.3
7		^{1}H NMR (400 MHz, DMSO-d_6) δ 13.30 (s, 1H), 8.24 (s, 1H), 8.07 (d, *J*=8.7 Hz, 1H), 8.05-7.99 (m, 2H), 7.26 (d, *J*=1.9 Hz, 1H), 7.12 (dd, *J*=8.7, 1.9 Hz, 1H), 4.21 (s, 3H), 3.76 (t, *J*=6.5 Hz, 2H), 3.35 (d, *J*=6.4 Hz, 2H), 3.21-3.16 (m, 4H), 3.03-2.99 (m, 4H), 2.17-2.08 (m, 4H), 1.89-1.40 (m, 4H), 0.40 (s, 4H).	631.2
8		^{1}H NMR (400 MHz, DMSO-d_6) δ 13.21 (s, 1H), 8.54 (s, 1H), 8.13 (d, *J*=8.3 Hz, 1H), 8.08 (d, *J*=8.6 Hz, 1H), 7.91 (d, *J*=8.3 Hz, 1H), 7.27 (d, *J*=2.0 Hz, 1H), 7.13 (dd, *J*=8.7, 2.0 Hz, 1H), 3.93 (s, 3H), 3.76 (t, *J*=6.5 Hz, 2H), 3.36 (d, *J*=6.4 Hz, 2H), 3.31-3.28 (m, 4H), 3.03-2.99 (s, 4H), 2.13-2.04 (m, 4H), 1.96-1.53 (m, 4H), 0.40 (s, 4H).	631.2
9		^{1}H NMR (400 MHz, DMSO-d_6) δ 13.36 (s, 1H), 8.90 (s, 1H), 8.09 (d, *J*=8.6 Hz, 1H), 7.97 (d, *J*=8.4 Hz, 1H), 7.81 (d, *J*=8.4 Hz, 1H), 7.29 (s, 1H), 7.14 (d, *J*=8.6 Hz, 1H), 3.77 (t, *J*=6.4 Hz, 2H), 3.36 (t, *J*=6.5 Hz, 2H), 3.08 (s, 4H), 3.03-2.99 (s, 4H), 2.37 (s, 3H), 2.04-1.95 (m, 4H), 1.88-1.30 (m, 4H), 0.40 (s, 4H).	631.3
10		^{1}H NMR (400 MHz, DMSO-d_6) δ 13.27 (s, 1H), 8.08 (d, *J*=8.6 Hz, 1H), 7.90 (d, *J*=8.4 Hz, 2H), 7.78 (d, *J*=8.4 Hz, 1H), 7.27 (d, *J*=2.0 Hz, 1H), 7.13 (dd, *J*=8.7, 2.0 Hz, 1H), 3.76 (t, *J*=6.5 Hz, 2H), 3.35 (t, *J*=6.5 Hz, 2H), 3.08-3.03 (m, 4H), 3.03-2.99 (m, 4H), 2.35 (s, 3H), 1.98-1.89 (m, 4H), 1.89-1.25 (m, 4H), 0.40 (s, 4H).	631.3
11		^{1}H NMR (400 MHz, DMSO-d_6) δ 13.43 (s, 1H), 8.16 (s, 1H), 8.10 (d, *J*=8.6 Hz, 1H), 7.98 (d, *J*=8.4 Hz, 1H), 7.76 (d, *J*=8.4 Hz, 1H), 7.29 (s, 1H), 7.14 (d, *J*=8.9 Hz, 1H), 3.77 (t, *J*=6.4 Hz, 2H), 3.36 (t, *J*=6.4 Hz, 2H), 3.11-3.08 (m, 4H), 3.03-2.99 (m, 4H),	631.3

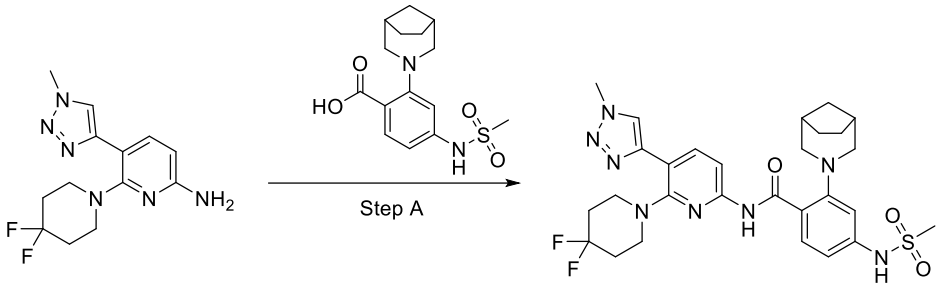
		2.30 (s, 3H), 1.96-1.88 (m, 4H), 1.86-1.48 (m, 4H), 0.40 (s, 4H).	
12		^{1}H NMR (400 MHz, DMSO-d_6) δ 13.62 (s, 1H), 8.44 (d, *J*=8.5 Hz, 1H), 8.17 (d, *J*=8.5 Hz, 1H), 8.10 (d, *J*=8.7 Hz, 1H), 7.29 (d, *J*=1.8 Hz, 1H), 7.14 (dd, *J*=8.7, 1.9 Hz, 1H), 3.77 (t, *J*=6.5 Hz, 2H), 3.36 (t, *J*=6.5 Hz, 2H), 3.33-3.31- (m, 4H), 3.21-3.15 (m, 4H), 3.01-2.97 (m, 4H), 2.76 (s, 3H), 2.26-2.16 (m, 4H), 2.03-1.40 (m, 4H), 0.40 (s, 4H).	648.2
13		^{1}H NMR (400 MHz, DMSO-d_6) δ 13.75 (s, 1H), 8.63 (d, *J*=8.6 Hz, 1H), 8.25 (d, *J*=8.6 Hz, 1H), 8.10 (d, *J*=8.7 Hz, 1H), 7.62 (t, *J*=53.4 Hz, 1H), 7.29 (d, *J*=1.9 Hz, 1H), 7.14 (dd, *J*=8.6, 2.0 Hz, 1H), 3.77 (t, *J*=6.5 Hz, 2H), 3.38-3.35 (m, 2H), 3.23-3.19 (m, 4H), 3.03-2.99 (m, 4H), 2.28-2.19 (m, 4H), 1.96-1.38 (m, 4H), 0.41 (s, 4H).	684.2
14		^{1}H NMR (400 MHz, DMSO-d_6) δ 13.46 (s, 1H), 8.18 (d, *J*=8.3 Hz, 1H), 8.07 (d, *J*=8.6 Hz, 1H), 7.98 (d, *J*=8.2 Hz, 1H), 7.25 (s, 1H), 7.11 (d, *J*=8.7 Hz, 1H), 3.76 (t, *J*=6.3 Hz, 2H), 3.47-3.45 (m, 2H), 3.29-3.16 (m, 4H), 3.01-2.98 (m, 4H), 2.57 (s, 3H), 2.19-2.08 (m, 4H), 1.96-1.47 (m, 4H), 0.40 (s, 4H).	632.2
15		^{1}H NMR (400 MHz, DMSO-d_6) δ 13.85 (s, 1H), 8.61 (d, *J*=8.6 Hz, 1H), 8.29 (d, *J*=8.6 Hz, 1H), 8.10 (d, *J*=8.7 Hz, 1H), 7.30 (d, *J*=2.0 Hz, 1H), 7.16 (dd, *J*=8.7, 2.1 Hz, 1H), 3.77 (t, *J*=6.5 Hz, 2H), 3.37 (t, *J*=6.5 Hz, 2H), 3.21-3.16 (m, 4H), 3.03-2.99 (m, 4H), 2.62 (s, 3H), 2.35-2.25 (m, 4H), 2.03-1.42 (m, 4H), 0.41 (s, 4H).	648.2
16		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.90 (s, 1H), 10.05 (s, 1H), 8.51 (s, 1H), 8.29 (d, *J*=8.4 Hz, 1H), 8.09 (d, *J*=8.4 Hz, 1H), 7.74 (d, *J*=8.5 Hz, 1H), 7.19 (d, *J*=1.4 Hz, 1H), 7.01 (dd, *J*=8.5, 1.7 Hz, 1H), 4.95 (s, 1H), 4.13 (s, 3H), 3.76 (t, *J*=6.5 Hz, 2H), 3.34-3.31 (m, 2H), 3.15-3.11 (m, 4H), 3.03-2.99 (m, 2H), 2.83-2.81 (m, 2H), 2.28-2.25 (m, 2H), 2.18-2.08 (m, 4H), 1.99-1.96 (m, 2H), 1.60-1.49 (m, 4H).	631.2
17		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.95 (s, 1H), 10.15 (s, 1H), 8.57 (s, 1H), 8.35 (d, *J*=8.4 Hz, 1H), 8.15 (d, *J*=8.4 Hz, 1H), 7.81 (d, *J*=8.4 Hz, 1H), 7.23 (s, 1H), 7.08 (dd, *J*=8.5, 1.7 Hz, 1H), 4.18 (s, 3H), 3.18-3.15	601.3

		(m, 4H), 3.14 (s, 3H), 3.08-3.06 (m, 2H), 2.89-2.86 (m, 2H), 2.33-2.29 (m, 2H), 2.24-2.14 (m, 4H), 2.05-2.01 (m, 2H), 1.66-1.53 (m, 4H).	
18		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.85 (s, 1H), 8.57 (s, 1H), 8.11 (d, *J*=8.3 Hz, 1H), 7.94 (d, *J*=8.1 Hz, 1H), 7.73 (d, *J*=8.3 Hz, 1H), 7.13 (s, 1H), 6.99 (d, *J*=8.5 Hz, 1H), 3.92 (s, 3H), 3.27-3.23 (m, 4H), 3.10 - 2.94 (m, 5H), 2.83-2.81 (m, 2H), 2.26 (s, 2H), 2.14 - 1.89 (m, 6H), 1.69 -1.43 (m, 4H).	601.2
19		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.99 (s, 1H), 8.17 (d, *J*=8.5 Hz, 1H), 8.01 (d, *J*=8.6 Hz, 1H), 7.68 (d, *J*=8.4 Hz, 1H), 7.14 (d, *J*=2.1 Hz, 1H), 6.98 (dd, *J*=8.3, 2.0 Hz, 1H), 3.75 (t, *J*=6.6 Hz, 2H), 3.30 (d, *J*=5.9 Hz, 6H), 3.05- 2.94 (m, 2H), 2.83-2.81 (m, 2H), 2.57 (s, 3H), 2.26-2.23 (m, 2H), 2.03-2.01 (m, 2H), 1.94-1.91 (m, 2H), 1.61 - 1.48 (m, 4H).	632.2
20		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.99 (s, 1H), 10.21 (s, 1H), 8.17 (d, *J*=8.5 Hz, 1H), 8.01 (d, *J*=8.6 Hz, 1H), 7.69 (d, *J*=8.4 Hz, 1H), 7.12 (s, 1H), 6.99 (d, *J*=8.5 Hz, 1H), 3.34-3.28 (m, 4H), 3.11 (s, 3H), 3.10-2.94 (m, 2H), 2.83-2.81 (m, 2H), 2.57 (s, 3H), 2.06-2.03 (m, 2H), 2.14-2.00 (m, 4H), 1.93-1.91 (m, 2H), 1.64-1.45 (m, 4H).	602.2
21		^{1}H NMR (400 MHz, DMSO-d_6) δ 11.05 (s, 1H), 9.01 (s, 1H), 8.28 (s, 1H), 8.02 (d, *J*=8.5 Hz, 1H), 7.82 (d, *J*=8.5 Hz, 1H), 7.71 (d, *J*=8.5 Hz, 1H), 7.15 (d, *J*=1.8 Hz, 1H), 6.99 (dd, *J*=8.5, 1.9 Hz, 1H), 3.75 (t, *J*=6.6 Hz, 2H), 3.30 (t, *J*=6.6 Hz, 2H), 3.03-2.97 (m, 6H), 2.83-2.81 (m, 2H), 2.26 (s, 2H), 1.97-1.91 (m, 6H), 1.61-1.49 (m, 4H).	617.3
22		^{1}H NMR (400 MHz, DMSO-d_6) δ 11.04 (s, 1H), 10.22 (s, 1H), 9.01 (s, 1H), 8.29 (s, 1H), 8.02 (d, *J*=8.3 Hz, 1H), 7.82 (d, *J*=8.5 Hz, 1H), 7.72 (d, *J*=8.4 Hz, 1H), 7.14 (s, 1H), 7.00 (d, *J*=8.4 Hz, 1H), 3.06 (s, 3H), 3.03-2.97 (m, 6H), 2.84-2.81 (m, 2H), 2.28-2.25 (m, 2H), 2.01-1.88 (m, 6H), 1.62-1.48 (m, 4H).	587.3

23		^{1}H NMR (400 MHz, DMSO-d_6) δ 11.34 (s, 1H), 10.31 (s, 1H), 8.53 (s, 1H), 8.29 (d, *J*=8.4 Hz, 1H), 8.09 (d, *J*=8.4 Hz, 1H), 7.62 (d, *J*=11.5 Hz, 1H), 7.43 (d, *J*=7.3 Hz, 1H), 4.13 (s, 3H), 3.13-3.10 (m, 4H), 3.05 (s, 3H), 2.96-2.93 (m, 2H), 2.87-2.84 (m, 2H), 2.26-2.23 (m, 2H), 2.19-2.08 (m, 4H), 2.01-1.97 (m, 2H), 1.66-1.53 (m, 4H).	619.2
24		^{1}H NMR (400 MHz, DMSO-d_6) δ 11.44 (s, 1H), 10.35 (s, 1H), 9.17 (s, 1H), 8.56 (s, 1H), 7.81 (d, *J*=8.5 Hz, 1H), 7.18 (s, 1H), 7.03 (dd, *J*=8.5, 1.7 Hz, 1H), 4.13 (s, 3H), 3.28-3.26 (m, 4H), 3.05 (s, 3H), 2.99-2.96 (m, 2H), 2.88-2.84 (m, 2H), 2.28-2.26 (m, 2H), 2.15-2.08 (m, 4H), 2.02-1.93 (m, 2H), 1.64-1.52 (m, 4H).	602.2
25		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.99 (s, 1H), 10.45 (s, 1H), 8.22 (d, J=8.4 Hz, 1H), 8.03 (d, J=8.4 Hz, 1H), 7.72 (d, *J*=8.6 Hz, 1H), 7.12 (s, 1H), 6.98 (d, J=8.5 Hz, 1H), 4.43 (s, 3H), 3.23-3.21 (m, 4H), 3.03-2.99 (m, 5H), 2.85-2.81 (m, 2H), 2.26-2.23 (m, 2H), 2.08-2.05 (m, 4H), 1.99-1.95 (m, 2H), 1.57-1.53 (m, 4H).	602.2
26		^{1}H NMR (400 MHz, DMSO-d_6) δ 12.96 (s, 1H), 8.51 (s, 1H), 8.29 (d, *J*=8.3 Hz, 1H), 8.06-8.03 (m, 2H), 7.17-7.09 (m, 2H), 4.12 (s, 3H), 3.76 (t, *J*=6.5 Hz, 2H), 3.35-3.33 (m, 2H), 3.08-3.06 (m, 2H), 3.03-3.00 (m, 2H), 2.59-2.56 (m, 4H), 2.19-2.02 (m, 4H).	653.2
27		^{1}H NMR (400 MHz, DMSO-d_6) δ 12.95 (s, 1H), 10.40 (s, 1H), 8.51 (s, 1H), 8.29 (d, *J*=8.3 Hz, 1H), 8.06-8.04 (m, 2H), 7.20-7.07 (m, 2H), 4.13 (s, 3H), 3.11 (s, 3H), 3.06-3.03 (m, 8H), 2.59-2.56 (m, 4H), 2.19-2.02 (m, 4H).	623.2
28		^{1}H NMR (400 MHz, DMSO-d_6) δ 13.37 (s, 1H), 10.44 (s, 1H), 8.52 (s, 1H), 8.30 (d, *J*=8.0 Hz, 1H), 8.03 (d, *J*=7.6 Hz, 1H), 7.84 (d, *J*=11.6 Hz, 1H), 7.44 (d, *J*=6.2 Hz, 1H), 4.13 (s, 3H), 3.08-3.01 (m,11H), 2.59-2.56 (m, 4H), 2.13-2.10 (m, 4H).	641.2

29		^{1}H NMR (400 MHz, DMSO) δ 13.36 (s, 1H), 8.52 (s, 1H), 8.30 (d, *J*=8.3 Hz, 1H), 8.03 (d, *J*=8.3 Hz, 1H), 7.85 (d, *J*=11.7 Hz, 1H), 7.48 (d, *J*=7.2 Hz, 1H), 4.13 (s, 3H), 3.79 (t, *J*=6.3 Hz, 2H), 3.36 (d, *J*=6.1 Hz, 2H), 3.05-3.03 (m, 8H), 2.59-2.56 (m, 4H), 2.11-2.08 (m, 4H).	671.2

Example 17 2-(3-Azabicyclo[3.2.1]octan-3-yl)-*N*-(6-(4,4-difluoropiperidin-1-yl)-5-(1-methyl-1*H*-1,2,3-triazol-4-yl)pyridin-2-yl)-4-(methylsulfonamido)benzamide

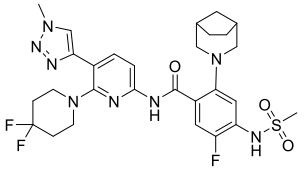


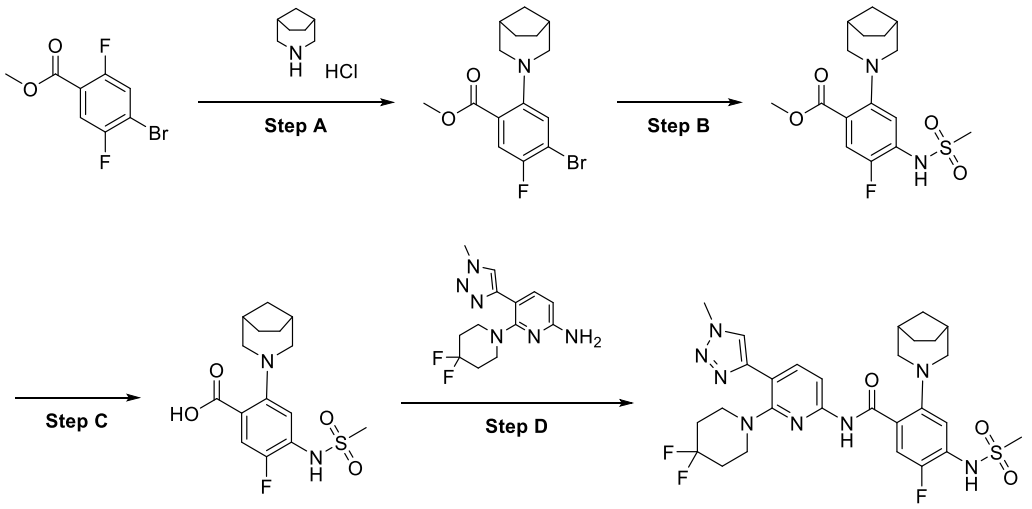
Compound 17

Step A: To a solution of 6-(4,4-difluoropiperidin-1-yl)-5-(1-methyl-1*H*-1,2,3-triazol-4-yl)pyridin-2-amine (1 g, 3.1 mmol) in acetonitrile (20 mL) were added *N*-methylimidazole (0.75 g, 9.3 mmol), tetramethylchlorouronium hexafluorophosphate (1.74 g, 6.2 mmol), and 2-(3-azabicyclo[3.2.1]octan-3-yl)-4-(methylsulfonamido)benzoic acid (0.9 g, 3.1 mmol) sequentially at room temperature. Then, the reaction system reacted at 70°C for 6 h, and then was cooled to room temperature. The reaction mixture was concentrated directly, and the resulting residue was purified by column chromatography on silica gel, to afford the target compound 2-(3-azabicyclo[3.2.1]octan-3-yl)-*N*-(6-(4,4-difluoropiperidin-1-yl)-5-(1-methyl-1*H*-1,2,3-triazol-4-yl)pyridin-2-yl)-4-(methylsulfonamido)benzamide (645) mg). MS (ESI) M/Z: 601.3 $[M+H]^+$.

^{1}H NMR (400 MHz, DMSO-d_6) δ 10.95 (s, 1H), 10.15 (s, 1H), 8.57 (s, 1H), 8.35 (d, *J*=8.4 Hz, 1H), 8.15 (d, *J*=8.4 Hz, 1H), 7.81 (d, *J*=8.4 Hz, 1H), 7.23 (s, 1H), 7.08 (dd, *J*=8.5, 1.7 Hz, 1H), 4.18 (s, 3H), 3.18-3.15 (m, 4H), 3.14 (s, 3H), 3.08-3.06 (m, 2H), 2.89-2.86 (m, 2H), 2.33-2.29 (m, 2H), 2.24-2.14 (m, 4H), 2.05-2.01 (m, 2H), 1.66-1.53 (m, 4H).

Example 23 2-(3-Azabicyclo[3.2.1]octan-3-yl)-*N*-(6-(4,4-difluoropiperidin-1-yl)-5-(1-methyl-1*H*-1,2,3-triazol-4-yl)pyridin-2-yl)-5-fluoro-4-(methylsulfonamido)benzamide





Compound 23

Step A: To a solution of methyl 4-bromo-2,5-difluorobenzoate (2 g, 8 mmol) and 3-azabicyclo[3.2.1]octane hydrochloride (1.3 g, 8.8 mmol) in *N*-methylpyrrolidone (30 mL) was added potassium carbonate (3.3 g, 24 mmol) at room temperature. Then, the reaction mixture reacted with stirring under sealed conditions at 120°C for additional 4 h, and then was cooled to room temperature, quenched with ice water, and extracted with ethyl acetate (100 mL×3). The organic phases were combined, washed with saturated brine (100 mL×3), dried over anhydrous sodium sulfate, and filtered. The filtrate was then concentrated under reduced pressure, and the resulting residue was purified by column chromatography on silica gel using 10% ethyl acetate in petroleum ether as eluent, to afford the target compound methyl 2-(3-azabicyclo[3.2.1]octan-3-yl)-4-bromo-5-fluorobenzoate (1.6 g). MS (ESI) M/Z: 342.0 $[M+H]^+$.

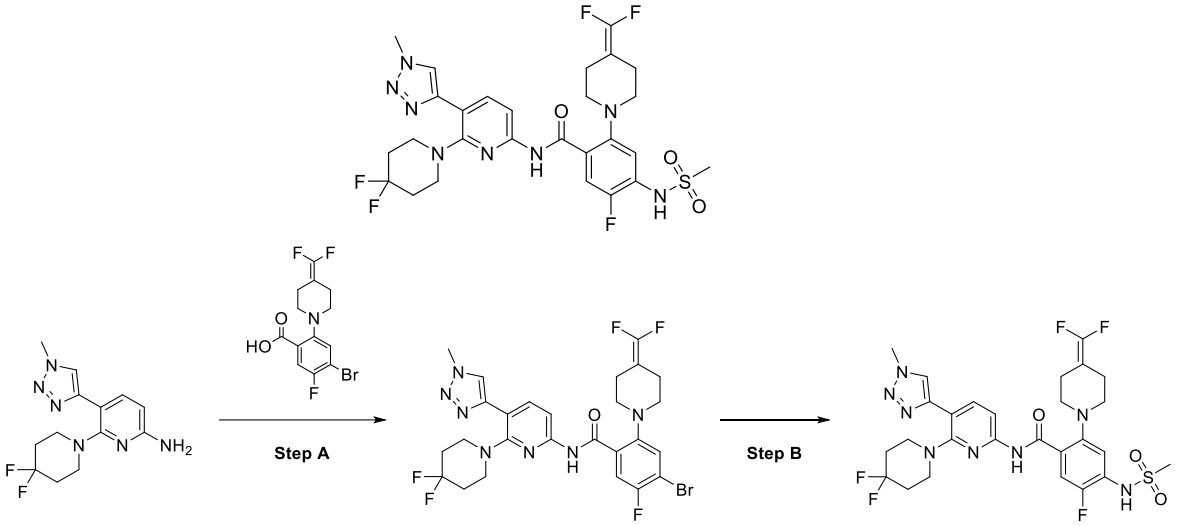
Step B: To a solution of methyl 2-(3-azabicyclo[3.2.1]octan-3-yl)-4-bromo-5-fluorobenzoate (0.6 g, 1.75 mmol) in *N,N*-dimethylformamide (10 mL) were added methylsulfonamide (0.5 g, 5.25mmol), CuI (0.33 g, 1.75 mmol), (1*R*, 2*R*)-(-)-*N,N'*-dimethyl-1,2-cyclohexanediamine (124 mg, 0.87 mmol), and potassium phosphate (1.5 g, 7 mmol) sequentially in an ice bath. After purging with nitrogen, the reaction system reacted with stirring at 120°C for 6 h, and then was cooled to room temperature, quenched with ice water, and extracted with ethyl acetate (100 mL×3). The organic phases were combined, washed with saturated brine (100 mL×3), dried over anhydrous sodium sulfate, and filtered. The filtrate was then concentrated under reduced pressure, and the resulting residue was purified by column chromatography on silica gel using 5% methanol in dichloromethane as eluent, to afford the target compound methyl 2-(3-azabicyclo[3.2.1]octan-3-yl)-5-fluoro-4-(methylsulfonamido)benzoate (0.4 g). MS (ESI) M/Z: 357.2 $[M+H]^+$.

Step C: To a solution of methyl 2-((1*R*,5*S*)-3-azabicyclo[3.2.1]octan-3-yl)-5-fluoro-4-(methylsulfonamido)benzoate (0.4 g, 1.1 mmol) in a mixture of tetrahydrofuran/methanol/water (10 mL) was added sodium hydroxide (0.22 g, 5.5 mmol) at room temperature. Then, the reaction mixture reacted with stirring at 70°C for additional 2 h, and then was cooled to room temperature, and adjusted with hydrochloric acid (1 M) to weakly acidic pH. A white solid precipitated out. After suction filtration, the filter cake was lyophilized, to afford the target compound 2-(3-azabicyclo[3.2.1]octan-3-yl)-5-fluoro-4-(methylsulfonamido)benzoic acid (0.25 g). MS (ESI) M/Z: 343.2 $[M+H]^+$.

Step D: To a solution of 2-(3-azabicyclo[3.2.1]octan-3-yl)-5-fluoro-4-(methylsulfonamido)benzoic acid (0.15 g, 0.44 mmol) in acetonitrile (10 mL) were added *N*-

methylimidazole (108 mg, 1.32 mmol), tetramethylchlorouronium hexafluorophosphate (246 mg, 0.88 mmol), and 6-(4,4-difluoropiperidin-1-yl)-5-(1-methyl-1*H*-1,2,3-triazol-4-yl)pyridin-2-amine (130 mg, 0.44 mmol) sequentially at room temperature. The reaction system reacted at 70°C for 6 h, and then was cooled to room temperature. The reaction mixture was concentrated directly, and the residue was purified by column chromatography on silica gel, to afford the target compound 2-(3-azabicyclo[3.2.1]octan-3-yl)-*N*-(6-(4,4-difluoropiperidin-1-yl)-5-(1-methyl-1*H*-1,2,3-triazol-4-yl)pyridin-2-yl)-5-fluoro-4-(methylsulfonamido)benzamide (65 mg). MS (ESI) M/Z: 619.2 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.34 (s, 1H), 10.31 (s, 1H), 8.53 (s, 1H), 8.29 (d, *J*=8.4 Hz, 1H), 8.09 (d, *J*=8.4 Hz, 1H), 7.62 (d, *J*=11.5 Hz, 1H), 7.43 (d, *J*=7.3 Hz, 1H), 4.13 (s, 3H), 3.13-3.10 (m, 4H), 3.05 (s, 3H), 2.96-2.93 (m, 2H), 2.87-2.84 (m, 2H), 2.26-2.23 (m, 2H), 2.19-2.08 (m, 4H), 2.01-1.97 (m, 2H), 1.66-1.53 (m, 4H).

Example 28 2-(4-(difluoromethylene)piperidin-1-yl)-*N*-(6-(4,4-difluoropiperidin-1-yl)-5-(1-methyl-1*H*-1,2,3-triazol-4-yl)pyridin-2-yl)-5-fluoro-4-(methylsulfonamido)benzamide



Compound 28

Step A: To a solution of 4-bromo-2-(4-(difluoromethylene)piperidin-1-yl)-5-fluorobenzoic acid (0.2 g, 0.56 mmol) in acetonitrile (10 mL) were added *N*-methylimidazole (138 mg, 1.68 mmol), tetramethylchlorouronium hexafluorophosphate (314 mg, 1.12 mmol), and 6-(4,4-difluoropiperidin-1-yl)-5-(1-methyl-1*H*-1,2,3-triazol-4-yl)pyridin-2-amine (165 mg, 0.56 mmol) sequentially at room temperature. The reaction system reacted at 70°C for 4 h, and then was cooled to room temperature. The reaction mixture was concentrated directly, and then purified by column chromatography on silica gel (10% methanol/dichloromethane), to afford the target compound 4-bromo-2-(4-(difluoromethylene)piperidin-1-yl)-*N*-(6-(4,4-difluoropiperidin-1-yl)-5-(1-methyl-1*H*-1,2,3-triazol-4-yl)pyridin-2-yl)-5-fluorobenzamide (0.28 g). MS (ESI) M/Z: 626.2 $[M+H]^+$.

Step B: To a solution of 4-bromo-2-(4-(difluoromethylene)piperidin-1-yl)-*N*-(6-(4,4-difluoropiperidin-1-yl)-5-(1-methyl-1*H*-1,2,3-triazol-4-yl)pyridin-2-yl)-5-fluorobenzamide (80 mg, 0.13 mmol) in dimethyl sulfoxide (2 mL) were added methylsulfonamide (37 mg, 0.39 mmol), cuprous iodide (25 mg, 0.13 mmol), (1*R*,2*R*)-(-)-*N,N*'-dimethyl-1,2-cyclohexanediamine (10 mg, 0.07 mmol), and potassium phosphate (110 mg, 0.52 mmol) sequentially at room temperature. After purging with nitrogen, the reaction system reacted under microwave irradiation at 100°C for 4 h, and then was cooled to room temperature. The reaction mixture was purified directly by preparative high

performance liquid chromatography, to afford the target product 2-(4-(difluoromethylene)piperidin-1-yl)-*N*-(6-(4,4-difluoropiperidin-1-yl)-5-(1-methyl-1*H*-1,2,3-triazol-4-yl)pyridin-2-yl)-5-fluoro-4-(methylsulfonamido)benzamide (17.13 mg). MS (ESI) M/Z: 641.2 [M+H]+.

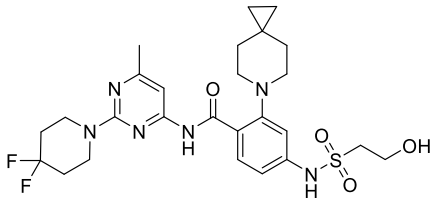
^{1}H NMR (400 MHz, DMSO-d_6) δ 13.37 (s, 1H), 10.44 (s, 1H), 8.52 (s, 1H), 8.30 (d, *J*=8.0 Hz, 1H), 8.03 (d, *J*=7.6 Hz, 1H), 7.84 (d, *J*=11.6 Hz, 1H), 7.44 (d, *J*=6.2 Hz, 1H), 4.13 (s, 3H), 3.08-3.01 (m,11H), 2.59-2.56 (m, 4H), 2.13-2.10 (m, 4H).

Biological Evaluation:

Test Example 1: Evaluation of inhibitory effects of compounds of the present disclosure on human KIF18A actin activity

In this experiment, the ADP-Glo assay was adopted to evaluate the inhibitory activity of the compounds of the present disclosure against human KIF18A actin activity, and the half-maximal inhibitory concentration (IC_{50}) of each compound against KIF18A actin activity was determined.

Positive control compound: AMG-650, having the structure shown below:



AMG-650

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Abbreviations and corresponding names thereof used in the Test Examples are listed below:

Abbreviation	Name
$MgCl_2$	Magnesium chloride
KCl	Potassium chloride
EGTA	Ethylene glycol bis(2-aminoethylether)-*N,N,N',N'*-tetraacetic acid
DTT	Dithiothreitol
BSA	Bovine serum albumin
Tween-20	Polysorbate-20
CP	ChemPartner
ADP-GloR1	ADP-Glo™ Reagent
ADP-GloR2	Kinase Detection Substrate

1. Experimental Materials:

1) $MgCl_2$, KCl, EGTA, DTT, BSA, Tween-20, and PIPES buffer (pH 6.9) purchased from Sigma for preparation of Assay buffer

2) KIF18A purchased from CP

3) MT (tubulin) purchased from Cytoskeleton

4) Paclitaxel purchased from MCE

5) Preparation of assay buffer:

50 mM PIPES, pH 6.9

50 mM KCl

0.5 mM EGTA

5 mM $MgCl_2$

1 mM DTT

0.01% BSA

0.005% Tween-20

5 μM Paclitaxel

6) ADP-Glo reagent, purchased from Promega Company.

2. Experimental Procedures

a) Test compounds or pure DMSO were transferred into a 384-well assay microplate using an Echo 650. Test compounds were subjected to 3-fold serial dilution in DMSO starting from the maximum testing concentration; additional DMSO was supplemented to ensure a consistent final DMSO concentration of 1% in each well.

b) 2.5 μL of KIF18A solution diluted with Assay buffer (final concentration: 10 nM KIF18A) was added, followed by incubation at room temperature for 30 min.

c) 2.5 μL of substrate mixture diluted in Assay buffer was added. The substrate mixture contained 180 μM ATP (supplied within ADP-Glo kit) and 0.1 mg/mL microtubules (MT). The mixture was incubated at room temperature for 60 min.

d) 5 μL of ADP-Glo R1 reagent was added. The plate was briefly centrifuged and incubated at room temperature for 2 h.

e) 10 μL of ADP-Glo R2 reagent was added. The plate was briefly centrifuged and incubated at room temperature for 1 h.

f) Chemiluminescence signals were detected on a PerkinElmer Envision plate reader.

g) Data analysis was performed using GraphPad Prism 6 software to calculate the IC_{50} values of the test compounds.

3. Experimental Results

Inhibitory activities of the compounds of the present disclosure against human KIF18A actin activity were shown in Table 1.

Table 1 Inhibition of KIF18A actin activity

Example No.	KIF18A IC_{50} (nM)
AMG-650	54
Example 1	16
Example 2	9
Example 3	13
Example 4	39
Example 5	15
Example 6	22
Example 7	34
Example 8	17
Example 9	11
Example 10	42
Example 11	23
Example 12	16
Example 13	48
Example 14	14
Example 15	36

Example 16	12
Example 17	25
Example 18	13
Example 19	9
Example 20	30
Example 21	12
Example 22	21
Example 23	13
Example 24	23
Example 25	51
Example 26	14
Example 27	13
Example 28	14
Example 29	8

Conclusion: The compounds of the present disclosure exhibited potent inhibitory activity against human KIF18A actin activity.

Test Example 2: Evaluation of the inhibitory effects of compounds of the present disclosure on the proliferation of ovarian cancer NCIOVCAR3 cells

In this experiment, the CellTiter-Glo (CTG) assay was adopted to evaluate the inhibitory activity of the compounds of the present disclosure against the proliferation of NCIOVCAR3 cells, and the half-maximal inhibitory concentration (IC_{50}) of each compound against cell growth was determined.

1. Experimental Materials

a) RPMI 1640 medium, fetal bovine serum (FBS), and Penicillin-Streptomycin purchased from GIBCO.

b) CellTiter-Glo reagent purchased from Promega Company.

2. Experimental Procedures

a) Day 0: NCIOVCAR3 cells were seeded into a 384-well plate at a density of 500 cells per well in a volume of 50 μL per well.

b) Day 1: Test compounds were added to the culture plate using a TECAN instrument to achieve a final DMSO concentration of 0.5%. DMSO was added to blank control wells to reach a final concentration of 0.5%. The plate was incubated in a cell incubator for 120 hours (37 °C, 5% CO_2).

c) Day 6: 50 μL of CellTiter-Glo reagent was added to each well. The plate was shaken at 500 rpm for 2 minutes and incubated at room temperature in the dark for 10 minutes to stabilize luminescence signals.

d) Chemiluminescence signals were detected on a PerkinElmer Envision plate reader.

e) Data analysis was performed using GraphPad Prism 6 software to calculate the IC_{50} values of the test compounds.

3. Experimental Results

Inhibitory activities of the compounds of the present disclosure against the proliferation of

NCIOVCAR3 ovarian cancer cells were shown in Table 2.

Table 2 Inhibitory activity against proliferation of NCIOVCAR3 cells

Example No.	NCIOVCAR3 IC_{50} (nM)
AMG-650	52
Example 1	4
Example 2	3
Example 3	4
Example 4	30
Example 5	4
Example 6	10
Example 7	10
Example 8	3
Example 9	6
Example 10	10
Example 11	25
Example 12	7
Example 13	42
Example 14	4
Example 15	161
Example 16	4
Example 17	5
Example 18	6
Example 19	7
Example 20	11
Example 21	14
Example 22	20
Example 23	11
Example 24	9
Example 25	10
Example 26	5
Example 27	5
Example 28	17
Example 29	13

Conclusion: The compounds of the present disclosure exhibited potent inhibitory activity against the proliferation of NCIOVCAR3 ovarian cancer cells.

Test Example 3: Evaluation of the inhibitory effects of compounds of the present disclosure on the proliferation of chromosomally unstable tumor cells

Well-established methods known to those skilled in the art, such as the CTG assay, were adopted to evaluate the inhibitory activity of the compounds of the present disclosure against the proliferation ofchromosomally unstable tumor cell lines including OVCAR8, HT29, MDAMB157,

BT549, NCIH23 and Calu6.

3.1 Experimental materials

Reagent and instrument names	Art. No.	Manufacturer
OVCAR8	CBP60289	Nanjing Cobioer
HT29	CBP60011	Nanjing Cobioer
MDAMB157	HTB-24	ATCC
BT549	CBP60357	Nanjing Cobioer
NCIH23	CRL-5800	ATCC
Calu6	HTB-56	ATCC
RPMI 1640 medium	11875093	Gibco™
FBS	10091148	Gibco™
Insulin	T8221	TaoSu
96-well white-bottom clear	3903	Corning
CellTiter Glo	G7573	Promega
Dispenser	Echo 600	Beckman
Microplate reader	Envision	PerkinElmer

3.2 Experimental Procedures

1) Cell culture: All cell lines were cultured in accordance with the supplier's instructions. Specifically, taking HT29 as an example, HT29 cells were cultured in RPMI 1640 medium supplemented with 10% FBS, and passaged every 3-4 days. For passaging, cells were thoroughly dissociated, and the cell suspension was collected and centrifuged at 800 rpm for 3 min. After discarding the supernatant, cells were resuspended in fresh medium and subcultured at a split ratio of approximately 1:4.

2) HT29 cells were harvested, resuspended in culture medium and counted, then seeded into a white 96-well plate with clear bottom at a density of 800 cells per well in 100 μL medium.

3) Test compounds of the present disclosure were dispensed into the 96-well plate using an Echo 650. The top concentration was set at 2 μM with 3-fold serial dilution to generate a total of nine concentration points. The final DMSO concentration was maintained at 0.5%. The plate was incubated in a humidified incubator at 37 °C with 5% CO_2 for 7 days.

4) Upon incubation completion, 50 μL of CTG reagent was added to each well. The plate was shaken for 10 min, and chemiluminescence signals were detected on an Envision plate reader.

GI_{50} Calculation:

The luminescence reading obtained from cell-containing wells treated only with DMSO, measured on the day of test compound treatment prior to compound addition, was defined as the low control. The luminescence reading obtained from cell-containing wells treated only with DMSO, measured on the day of test compound treatment termination, was defined as the high control.

Inhibition rate of compound = $100\%\times((RLU_{\text{high control}}-RLU_{\text{low control}})-(RLU_{\text{compound}}-RLU_{\text{low control}}))/(RLU_{\text{high control}}-RLU_{\text{low control}})$.

The experimental results were shown in Table 3.

Table 3 Inhibitory activity of compounds against proliferation of chromosomally unstable tumor cells

Example Compounds	Cell activity GI_{50} (nM)					
	OVCAR8	HT29	MDAMB157	BT549	NCIH23	Calu6
Example 23	4	5	5	14	8	7
AMG-650	64	38	47	70	157	64

The results demonstrated that compared with AMG-650, the compound of Example 23 exhibited stronger inhibitory activity against the proliferation of chromosomally unstable tumor cells.

Test Example 4: In vivo pharmacodynamic evaluation of the compounds of the present disclosure in an OVCAR3 xenograft tumor model

4.1 Experimental Animals and Housing Conditions

Species: Mouse

Strain: BALB/c Nude mice

Age upon arrival: 6-8 weeks old

Sex: Female

Body weight: 19-24 g

Supplier: Zhejiang Vital River Laboratory Animal Technology Co., Ltd.

Animal license certificate: SCXK (Zhe) 2024-0001; Certificate No. 20240603Ab220619000250

4.2 Experimental Procedures

1) Cell Culture

Human ovarian cancer OVCAR3 cells (ovarian carcinoma, ATCC, Cat No. HTB-161, Lot No. 4470175) were cultured as monolayers in vitro. Cells were cultured in high-glucose RPMI 1640 medium supplemented with 20% heat-inactivated fetal bovine serum, 10 μg/mL insulin, 100 U/mL penicillin and 100 U/mL streptomycin at 37 °C under 5% CO_2. Cells were passaged two to three times weekly. Cells were harvested, counted and inoculated during the exponential growth phase.

2) Tumor Cell Inoculation and Group Allocation

A cell suspension containing 10×10^6 OVCAR3 cells in 100 μL PBS was mixed uniformly with an equal volume (100 μL) of Matrigel (volume ratio = 1:1). The mixture was subcutaneously injected into the dorsal region of the right forelimb of each mouse. On day 31 post-inoculation, when the average tumor volume reached 132 mm^3, animals were randomly grouped and compound administration was initiated. Each group contained 6 mice. Compounds were administered orally once daily for a total of 28 consecutive days. Group information was shown in Table 4.

Table 4 Experimental animal grouping information

Serial No.	Group	Dosage (mg/kg)	Administration volume parameter $(\mu L/g)^2$	Administration route	Administration frequency
1	Vehicle group	/	10	Oral	QDx28D
2	AMG-650	3	10	Oral	QDx28D

3	AMG-650	10	10	Oral	QDx28D
4	Example 23	1	10	Oral	QDx28D
5	Example 23	3	10	Oral	QDx28D

Note: Vehicle group: 5% DMSO + 10% Solutol + 85% Saline.

3) Tumor Measurement and Experimental Endpoints

Tumor diameters were measured twice weekly using a vernier caliper. Tumor volume was calculated according to the formula: $V = 0.5a \times b^2$, wherein a represents the longest tumor diameter and b represents the shortest tumor diameter.

The anti-tumor efficacy of test compounds was evaluated by Tumor Growth Inhibition (TGI, %). Calculation formula for TGI (%): TGI (%) = [1 - (Mean tumor volume of treatment group at the end of treatment − Mean tumor volume of the same treatment group at treatment initiation) / (Mean tumor volume of vehicle control group at the end of treatment - Mean tumor volume of vehicle control group at treatment initiation)] × 100%.

The inhibitory effects of each experimental group on tumors were summarized in Table 5.

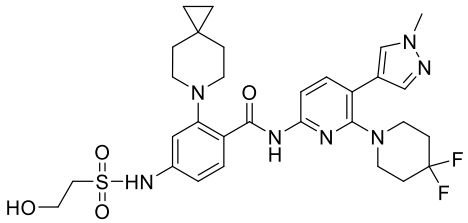
Table 5 Inhibitory effects on the growth of OVCAR3 subcutaneous xenograft tumors

Group	Dosage (mg/kg)	Adiministration frequency	Tumor inhibition rate (%)
Vehicle group	/	QDx28D	/
AMG-650	3	QDx28D	58
AMG-650	10	QDx28D	102
Example 23	1	QDx28D	94
Example 23	3	QDx28D	117

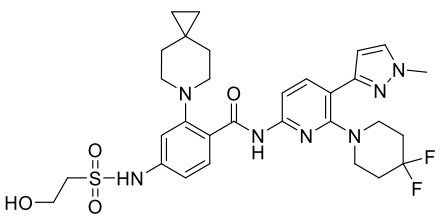
The experimental results demonstrated that the compound of Example 23 exhibitd superior in vivo efficacy against the OVCAR3 xenograft tumor model compared with the positive control AMG-650.

Test Example 5:

Compounds 1 and 5 with the following structures disclosed in CN116554151A were adopted as control compounds for activity testing.



CN116554151A Compound 1



CN116554151A Compound 5

In this experiment, the ADP-Glo assay was adopted to evaluate the inhibitory activity of the compounds against human KIF18A actin activity, and the half-maximal inhibitory concentration (IC_{50}) of each compound against KIF18A actin activity was determined.

1. Experimental Materials

1) $MgCl_2$, KCl, EGTA, DTT, BSA, Tween-20 and PIPES buffer (pH 6.9) purchased from Sigma for preparation of Assay buffer.

2) KIF18A purchased from CP

3) MT (tubulin) purchased from Cytoskeleton, Lot #031

4) Paclitaxel purchased from MCE

5) ADP-Glo reagent, purchased from Promega Company

6) Preparation of assay buffer:

50 mM PIPES, pH 6.9

50 mM KCl

0.5 mM EGTA

5 mM $MgCl_2$

1 mM DTT

0.01% BSA

0.005% Tween-20

5 μM Paclitaxel

2. Experimental Procedures

a) Test compounds or pure DMSO were transferred into a 384-well assay microplate using an Echo 650. Test compounds were subjected to 3-fold serial dilution in DMSO starting from the maximum testing concentration; additional DMSO was supplemented to ensure a consistent final DMSO concentration of 1% in each well.

b) 2.5 μL of KIF18A solution diluted with Assay buffer (final concentration: 10 nM KIF18A) was added, followed by incubation at room temperature for 15 min.

c) 2.5 μL of substrate mixture diluted in Assay buffer was added. The substrate mixture contained 180 μM ATP (supplied within ADP-Glo kit) and 0.1 mg/mL microtubules (MT). The mixture was incubated at room temperature for 60 min.

d) 5 μL of ADP-Glo R1 reagent was added. The plate was briefly centrifuged and incubated at room temperature for 2 h.

e) 10 μL of ADP-Glo R2 reagent was added. The plate was briefly centrifuged and incubated at room temperature for 1 h.

f) Chemiluminescence signals were detected on a PerkinElmer Envision plate reader.

g) Data analysis was performed using GraphPad Prism 6 software to calculate the IC_{50} values of the test compounds.

3. Experimental Results

Inhibitory activities of the compounds of the present disclosure against human KIF18A actin activity were shown in Table 6.

Table 6 Inhibition of KIF18A actin activity

Example No.	KIF18A IC_{50} (nM)
Example 23	9.74
Compound 1 of CN116554151A	35.00
Compound 5 of CN116554151A	35.37

Conclusion: As can be seen from Table 6, the compounds of the present disclosure exhibited stronger inhibitory activity against KIF18A actin.

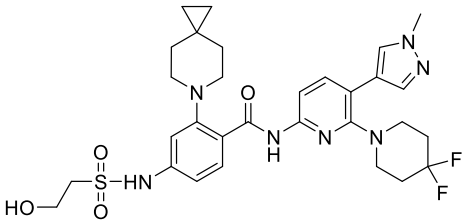
Test Example 6: Determination of pharmacokinetic profiles of test compounds in mice

Mice were used as test animals to investigate the in vivo plasma pharmacokinetic profiles of compounds following intravenous bolus injection at a dose of 1 mg/kg and oral administration at a dose of 10 mg/kg.

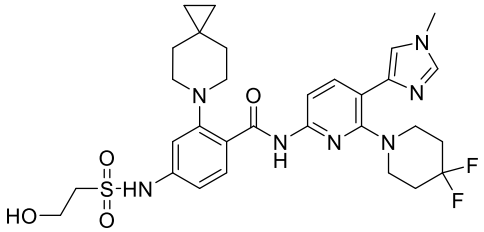
1. Study Protocol

1.1 Test Compounds

The compound of Example 23 of the present disclosure, as well as Compound 1 and Compound 7 from CN116554151A.



CN116554151A Compound 1



CN116554151A Compound 7

1.2 Test Animals

Twelve male CD-1 mice (3 animals per group) were supplied by Shanghai Jihui Laboratory Animal Care Co., Ltd.

1.3 Dosing

A total of 12 male CD-1 mice were used in the study. Mice in the intravenous (IV) dosing group had free access to food and water, whereas mice in the oral (PO) dosing group were fasted. The dose and administration volume were 1 mg/kg and 5 mL/kg for the IV route, and 10 mg/kg and 10 mL/kg for the PO route, respectively.

1.4 Experimental Apparatus

Eppendorf 5810 R centrifuge and Eppendorf pipettes were purchased from Eppendorf AG. Vortex mixer was purchased from Scientific Industries, Inc.

1.5 Sample Collection

Following dosing, approximately 0.1 mL blood samples were collected from mice via saphenous vein puncture at 0.0833 h (only for IV group), 0.25 h, 0.5 h, 1 h, 2 h, 4 h, 8 h and 24 h post-dosing. Blood samples were transferred into EDTA-K2 tubes, and centrifuged at 4600 rpm for 5 min at 4 °C. Plasma was then separated and stored at -80 °C.

1.6 Sample Preparation

1) A 50 μL aliquot of plasma sample was mixed with 200 μL of methanol:acetonitrile (v:v = 1:1) for protein precipitation. After mixing, the mixture was centrifuged at 2773 × g for 15 min.

2) A 50 μL aliquot of the resulting supernatant was diluted with diluent (methanol:water, v:v = 1:1, containing 0.1% formic acid). The concentrations of the test compounds were quantified by LC-MS/MS.

1.7 Liquid Chromatography Conditions

LC system: Shimadzu LC-30AD or LC-40D XS

Mass spectrometer: AB Sciex 5500

Chromatographic column: Phenomenex Kinetex C18 (2.6 μm, 3.0 mm × 50 mm), or ACE C4 (2.1 mm × 50 mm), or Waters XSelect® HSS T3 (2.5 μm, 2.1 mm × 50 mm)

Mobile phase: Mobile phase A: 0.1% formic acid in 5 mM ammonium acetate aqueous solution; Mobile phase B: 0.05% or 0.1% formic acid in acetonitrile

Flow rate: 0.6 mL/min

Elution mode: Gradient elution over 0-3 min.

2. Experimental Results and Analysis

Main pharmacokinetic parameters were calculated using WinNonlin software. The pharmacokinetic parameters after intravenous and oral administration to mice were summarized in Table 7 and Table 8.

Table 7 Pharmacokinetic parameters of test compounds following intravenous administration in mice

Compound No.	Dose (mg/kg)	CL (mL/min/kg)	V_{ss} (L/kg)	$T_{1/2}$ (hr)	AUC (hr*ng/mL)
Example 23	1	0.69	0.83	14.1	16710
Compound 1 of CN116554151A	1	1.27	0.35	2.6	13526
Compound 7 of CN116554151A	1	15	1.91	1.91	1097

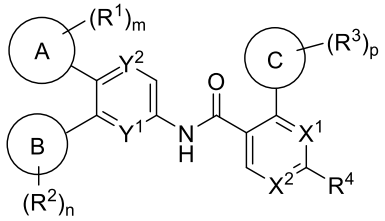
Table 8 Pharmacokinetic parameters of test compounds following oral administration in mice

Compound No.	Dose (mg/kg)	C_{max} (ng/mL)	AUC (hr*ng/mL)	$T_{1/2}$ (hr)
Example 23	10	8753	126021	7.3
Compound 1 of CN116554151A	10	5587	54813	3.0
Compound 7 of CN116554151A	10	1065	3600	1.8

The experimental results indicated that the compound of Example 23 of the present disclosure exhibited obviously superior $T_{1/2}$ and AUC compared with Compound 1 and Compound 7 from CN116554151A, and demonstrated favorable pharmacokinetic properties in mice.

CLAIMS

1. A compound represented by formula (I), or a stereoisomer or pharmaceutically acceptable salt thereof:



(I)

wherein

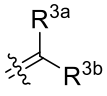
ring A is 5- to 6-membered heteroaryl, and the 5- to 6-membered heteroaryl contains at least 3 heteroatoms selected from the group consisting of N, O, and S;

ring B is 4- to 6-membered heterocyclyl, and the 4- to 6-membered heterocyclyl contains at least one heteroatom selected from the group consisting of N, O, and S;

ring C is 6- to 8-membered heterocyclyl, and the 6- to 8-membered heterocyclyl contains at least one heteroatom selected from the group consisting of N, O, and S;

X^1, X^2, Y^1, and Y^2 are each independently selected from the group consisting of N and CR^x; and the R^x is selected from the group consisting of H, halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, and C_{1-6} alkoxy;

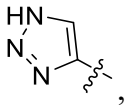
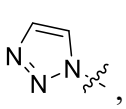
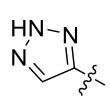
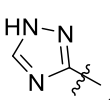
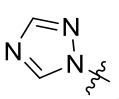
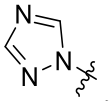
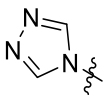
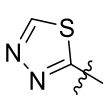
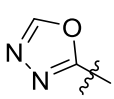
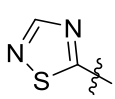
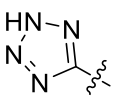
R^1 and R^2 are each independently selected from the group consisting of halogen, C_{1-6} alkyl, and C_{3-6} cycloalkyl, and the C_{1-6} alkyl or C_{3-6} cycloalkyl is optionally substituted with one or more substituents selected from the group consisting of OH, halogen, $-NH_2$, and C_{1-4} alkoxy;

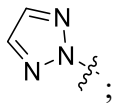
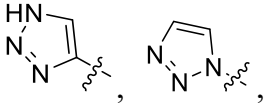
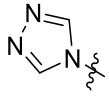
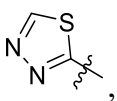
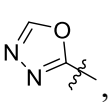
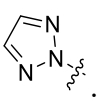
R^3 is halogen, OH, C_{1-6} alkyl, C_{3-6} cycloalkyl, or ;

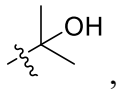
R^{3a} and R^{3b} are each independently selected from the group consisting of H, halogen, and C_{1-6} alkyl, and the C_{1-6} alkyl is optionally substituted with one or more substituents selected from the group consisting of halogen, hydroxy, amino, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxy, C_{3-6} cycloalkyl, 3- to 8-membered heterocyclyl, phenyl, and 5- to 6-membered heteroaryl;

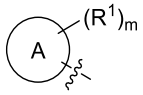
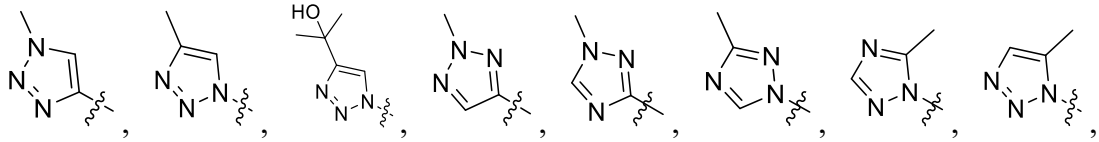
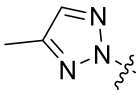
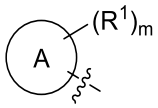
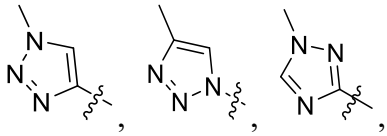
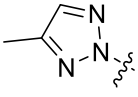
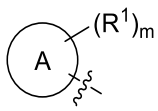
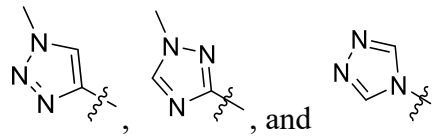
R^4 is selected from $-NHSO_2-C_{1-4}$ alkyl, and the C_{1-4} alkyl is optionally substituted with OH or halogen; and

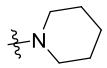
m, n and p are each independently selected from 0, 1, 2, and 3.

2. The compound, or the stereoisomer or pharmaceutically acceptable salt thereof according to claim 1, wherein ring A is 5-membered heteroaryl containing at least 3 heteroatoms selected from the group consisting of N, O, and S; or ring A is 5-membered heteroaryl, which contains 3 heteroatoms selected from N, or 2 heteroatoms selected from N and 1 heteroatom selected from O and S, or 4 heteroatoms selected from N; or ring A is selected from the group consisting of , , , , , , , , , , , and

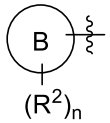
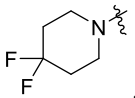
; or ring A is selected from the group consisting of , , , , and .

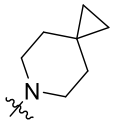
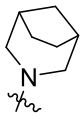
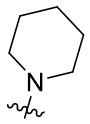
3. The compound, or the stereoisomer or pharmaceutically acceptable salt thereof according to claim 1 or 2, wherein R^1 is selected from C_{1-6} alkyl, and the C_{1-6} alkyl is optionally substituted with one or more substituents selected from the group consisting of OH and halogen, and/or m is selected from 0 and 1; or R^1 is selected from the group consisting of methyl, CHF_2, and , and m is selected from 0 and 1; or R^1 is methyl, and m is selected from 0 and 1.

4. The compound, or the stereoisomer or pharmaceutically acceptable salt thereof according to any one of claims 1 to 3, wherein the structural unit  is selected from the group consisting of , and ; or the structural unit  is selected from the group consisting of , and ; or the structural unit  is selected from the group consisting of .

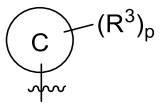
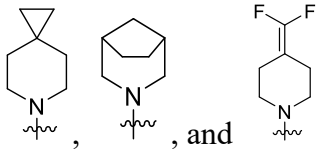
5. The compound, or the stereoisomer or pharmaceutically acceptable salt thereof according to any one of claims 1 to 4, wherein ring B is 6-membered heterocyclyl containing one heteroatom selected from N; or ring B is .

6. The compound, or the stereoisomer or pharmaceutically acceptable salt thereof according to any one of claims 1 to 5, wherein R^2 is halogen, and/or n is selected from 0, 1, and 2; or R^2 is selected from the group consisting of F, Cl, and Br, and n is selected from 0, 1, and 2.

7. The compound, or the stereoisomer or pharmaceutically acceptable salt thereof according to any one of claims 1 to 6, wherein the structural unit  is selected from .

8. The compound, or the stereoisomer or pharmaceutically acceptable salt thereof according to any one of claims 1 to 7, wherein ring C is 6-, 7-, or 8-membered heterocyclyl containing one heteroatom selected from N; or ring C is selected from the group consisting of , , and .

9. The compound, or the stereoisomer or pharmaceutically acceptable salt thereof according to any one of claims 1 to 8, wherein R^3 is , R^{3a} and R^{3b} are each independently selected from the group consisting of H and halogen, and p is selected from 0, 1, and 2; or R^3 is ; and p is selected from 0, 1, and 2.

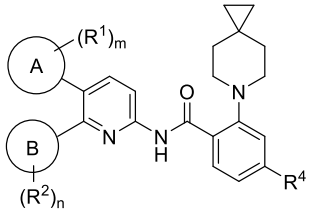
10. The compound, or the stereoisomer or pharmaceutically acceptable salt thereof according to any one of claims 1 to 9, wherein the structural unit  is selected from the group consisting of .

11. The compound, or the stereoisomer or pharmaceutically acceptable salt thereof according to any one of claims 1 to 10, wherein X^1 and X^2 are each independently selected from CR^x, and R^x is selected from the group consisting of H and halogen; or X^1 and X^2 are each independently selected from the group consisting of CH, -CF, and N; or X^1 is CH, and X^2 is CH or -CF.

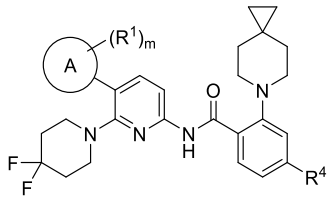
12. The compound, or the stereoisomer or pharmaceutically acceptable salt thereof according to any one of claims 1 to 11, wherein Y^1 and Y^2 are each independently selected from the group consisting of CH and N; or Y^1 is N, and Y^2 is CH; or Y^1 is N, and Y^2 is N.

13. The compound, or the stereoisomer or pharmaceutically acceptable salt thereof according to any one of claims 1 to 12, wherein R^4 is selected from -$NHSO_2$-C_{1-4} alkyl, and the C_{1-4} alkyl is optionally substituted with one or more OH; or R^4 is selected from the group consisting of -$NHSO_2$-CH_2CH_2OH and -$NHSO_2$-CH_3.

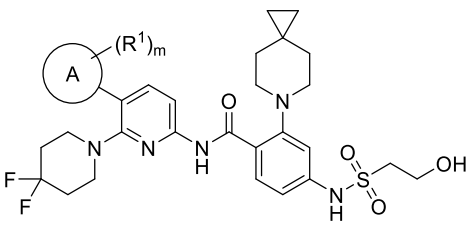
14. The compound, or the stereoisomer or pharmaceutically acceptable salt thereof according to any one of claims 1 to 13, wherein the compound, or the stereoisomer or pharmaceutically acceptable salt thereof is selected from the group consisting of:



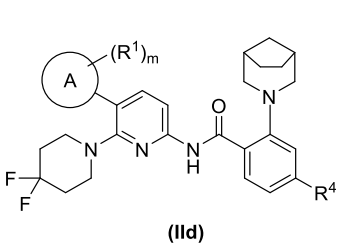
(IIa),



(IIb),

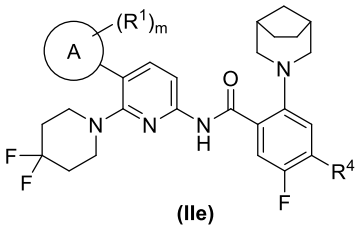


(IIc),



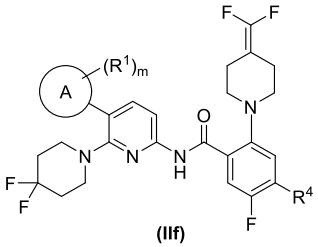
(IId)

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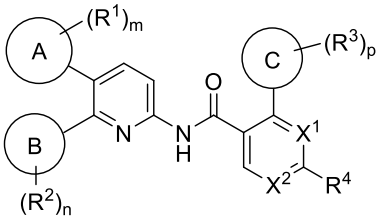
(IIe)

,



(IIf)

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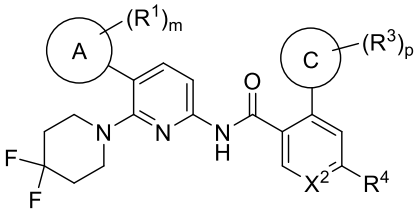


(IIg)

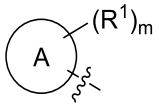
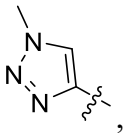
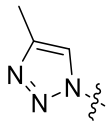
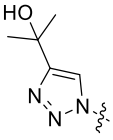
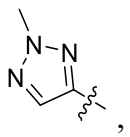
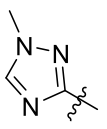
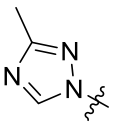
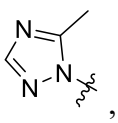
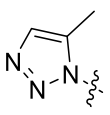
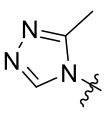
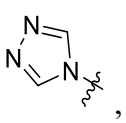
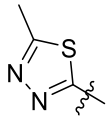
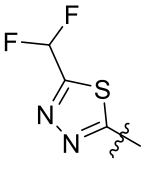
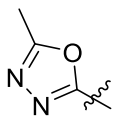
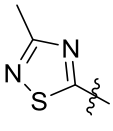
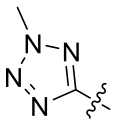
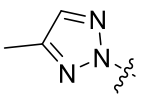
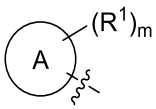
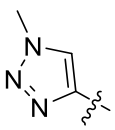
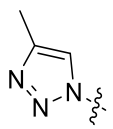
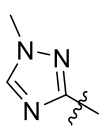
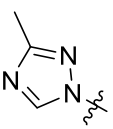
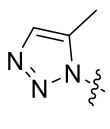
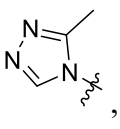
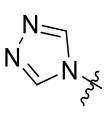
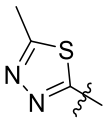
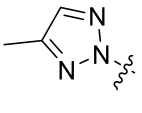
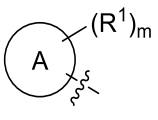
,

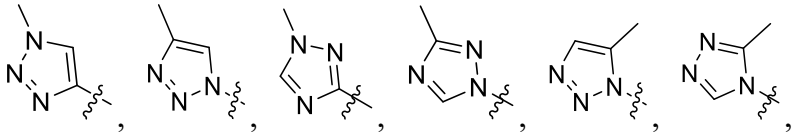
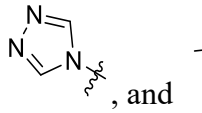
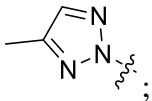
wherein ring A, ring B, ring C, R^1, R^2, R^3, R^4, X^1, X^2, m, p, and n are as defined in any one of claims 1 to 13.

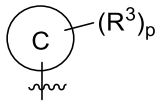
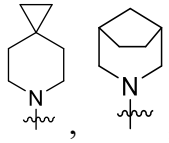
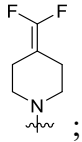
15. The compound, or the stereoisomer or pharmaceutically acceptable salt thereof according to claim 1, wherein the compound, or the stereoisomer or pharmaceutically acceptable salt thereof is selected from:



(III)

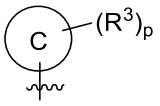
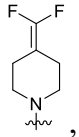
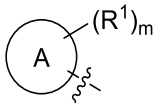
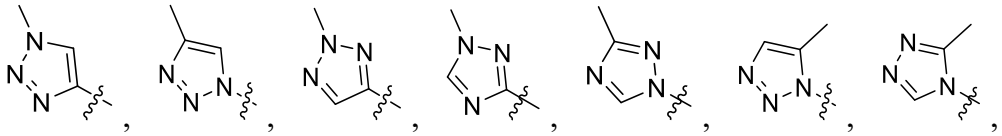
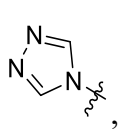
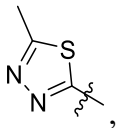
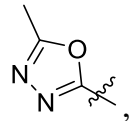
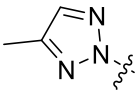
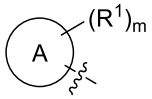
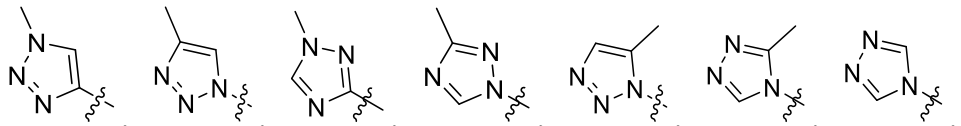
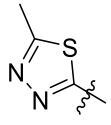
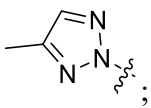
wherein the structural unit  is selected from the group consisting of , , , , , , , , , , , , , , , and ; or the structural unit  is selected from the group consisting of , , , , , , , , and ; or the structural unit  is

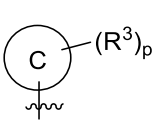
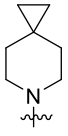
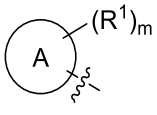
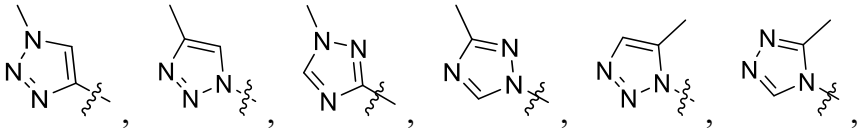
selected from the group consisting of , , and ;

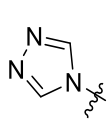
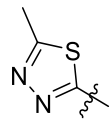
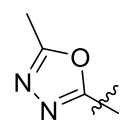
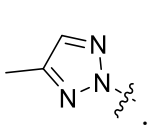
the structural unit  is selected from the group consisting of , and ;

X^2 is selected from the group consisting of CH and -CF; and

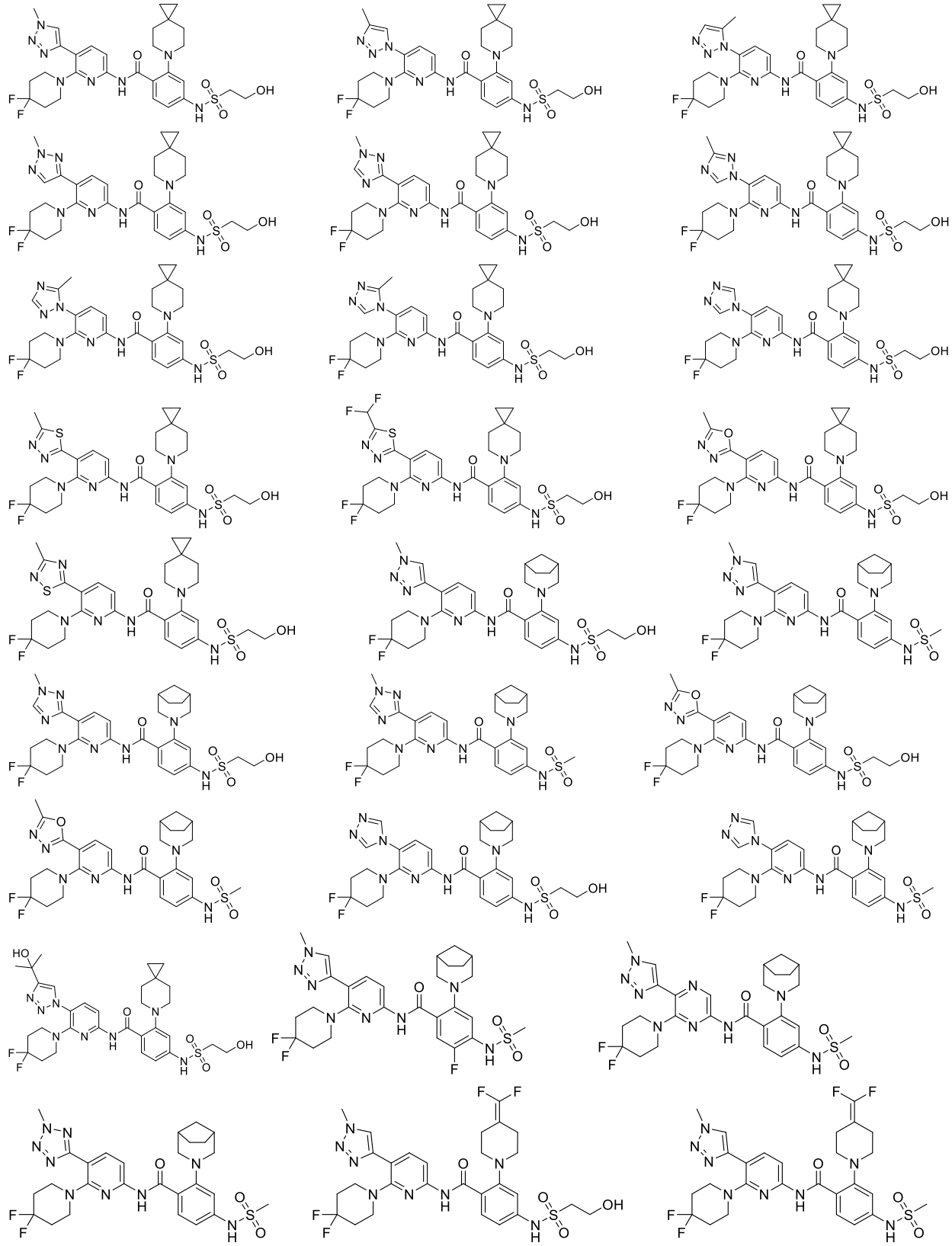
R^4 is selected from the group consisting of $-NHSO_2-CH_2CH_2OH$ and $-NHSO_2-CH_3$.

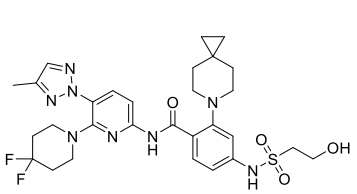
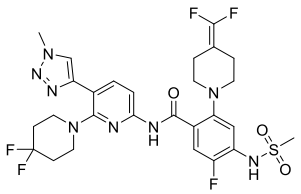
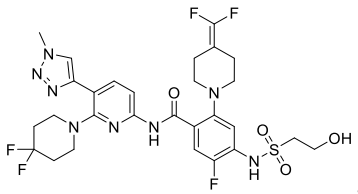
16. The compound, or the stereoisomer or pharmaceutically acceptable salt thereof according to any one of claims 1, 5 to 7, and 11 to 15, wherein the structural unit  is selected from the group consisting of  and , and the structural unit  is selected from the group consisting of , , , , and , or the structural unit  is selected from the group consisting of , , and ; or

the structural unit  is , and the structural unit  is selected from the group consisting of ,

, , , and .

17. A compound, or a stereoisomer or pharmaceutically acceptable salt thereof, selected from the group consisting of:



  and .

18. A pharmaceutical composition, comprising the compound according to any one of claims 1 to 17, or the stereoisomer or pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

19. Use of the compound according to any one of claims 1 to 17, or the stereoisomer or pharmaceutically acceptable salt thereof, or the pharmaceutical composition according to claim 18 in the preparation of a medicament for treating diseases mediated by KIF18A.

20. A method for treating or preventing diseases mediated by KIF18A, comprising administering to a subject in need thereof a therapeutically effective amount of the compound according to any one of claims 1 to 17, or the stereoisomer or pharmaceutically acceptable salt thereof, or the pharmaceutical composition according to claim 18.

21.The compound according to any one of claims 1 to 17, or the stereoisomer or pharmaceutically acceptable salt thereof, or the pharmaceutical composition according to claim 18 for use in the treatment or prevention of diseases mediated by KIF18A.

22. The use according to claim 19 or the method according to claim 20, or the compound, or the stereoisomer or pharmaceutically acceptable salt thereof, or the pharmaceutical composition according to claim 21, wherein the diseases mediated by KIF18A are tumors; or the diseases mediated by KIF18A are chromosomally unstable tumors.

23. The use, or the method, or the compound, or the stereoisomer or pharmaceutically acceptable salt thereof, or the pharmaceutical composition according to claim 22, wherein the tumors are selected from the group consisting of breast cancer, ovarian cancer, endometrial cancer, cervical cancer, prostate cancer, lung cancer, colorectal cancer, pancreatic cancer, bladder cancer, head and neck cancer, gastric cancer, esophageal cancer, and skin cancer; and preferably, the lung cancer is selected from the group consisting of lung squamous cell carcinoma, lung adenocarcinoma, large cell lung cancer, and small cell lung cancer.