

PYRIDYL-CONTAINING COMPOUND

CROSS-REFERENCE TO RELATED APPLICATIONS

The present application claims the benefits and priority of the Chinese Patent Application No. 202111269381.X filed with China National Intellectual Property Administration on October 29, 2021, the Chinese Patent Application No. 202210233624.2 filed with China National Intellectual Property Administration on March 10, 2022, the Chinese Patent Application No. 202210849103.X filed with China National Intellectual Property Administration on July 19, 2022, and the Chinese Patent Application No. 202211274771.0 filed with China National Intellectual Property Administration on October 18, 2022, the content of each of which is incorporated herein by reference in its entirety.

TECHNICAL FIELD

The present application belongs to the field of pharmaceutical chemistry, provides a pyridinyl-containing compound (an exportin inhibitor) and a preparation method therefor, and relates to use thereof for preparing a medicament for treating tumors.

BACKGROUND

Exportin-1 (also known as CRM-1 and XPO-1) has become a key “carrier” protein for transporting some crucial growth-regulatory proteins and tumor suppressor factors from the nucleus to the cytoplasm of eukaryotic cells. When efflux of the exportin-1 becomes abnormally high (e.g., due to the production of overexpressed XPO-1), depletion of these nuclear regulator factors can trigger a wide variety of diseases.

XPO1 is the sole nuclear export factor transporting tumor suppressor factors (e.g., p53, p27, FOXO1, and IκB), and it is overexpressed in various solid tumors and hematological malignant tumors (e.g., GBM, ovarian cancer, pancreatic cancer, cervical cancer, AML, MM, CLL, and NHL). Here, the main key point of XPO1 for carcinogenesis is overexpression of the XPO1 protein in multiple types of cancer cells, and its association with the proliferated cell cycle, depleting tumor suppressor proteins (e.g., p53, p27, FOXO1, and IκB) in the cell nucleus, which allows growth of cancer cells (e.g., M. L. Crochiere et al., *Oncotarget* v.7, pages 1863-1877 (2015)). Generally, selective inhibitor of nuclear export (SINE) compounds are a class of small molecules that inhibit nuclear export of cargo proteins by covalently binding to cysteine at position 528 (Cys528) in the cargo-binding

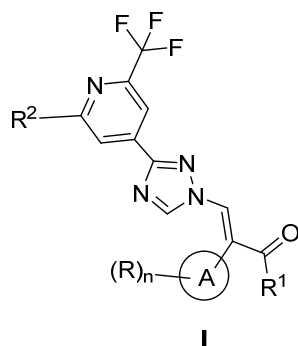
pocket of exportin 1 (XPO1, also known as chromosome maintenance protein 1 (CRM1)) and exert anti-proliferative effects. The interaction between XPO1 and the activated small G-protein Ran (Ran-GTP) in the nucleus facilitates the binding to cargo proteins that comprise short amino acid sequences of hydrophobic residues known as a nuclear export signal (NES).

According to preclinical results, many inflammatory, neurodegenerative and autoimmune diseases also involve similar pathologies. Thus, for example, glucocorticoids are widely used anti-inflammatory and immunomodulatory drugs, the efficacy/mechanism of action of which is based primarily on the restoration of sufficient steroid-activated glucocorticoid receptors (GRs) to interfere with the overactivity of transcription factors such as NF- κ B in the cell nucleus.

Nowadays, although drugs that inhibit diseases caused by excessive efflux of XPO-1 have been demonstrated to have clinical efficacy by the U.S. FDA, new drug therapies are still urgently needed for many diseases.

SUMMARY

The present application provides a compound of formula I, a pharmaceutically acceptable salt thereof, or a stereoisomer thereof:



wherein,

R^1 is selected from the group consisting of $-NH_2$, C_{1-6} alkyl-O-, C_{1-6} alkyl-NH-, and $(C_{1-6}$ alkyl) $_2$ N-;

ring A is selected from the group consisting of a C_{6-10} aromatic ring group and a 5- to 10-membered heteroaromatic ring group;

R is selected from the group consisting of halogen, CN, OH, NH_2 , C_{1-6} alkyl, C_{1-6} alkyl-O-, C_{1-6} alkyl-S-, C_{1-6} haloalkyl-O-, C_{1-6} haloalkyl-S-, C_{1-6} haloalkyl, C_{1-6} alkyl substituted with 3- to 10-membered heterocycloalkyl, R^aNH- , and $(R^a)_2N-$;

R^a is selected from the group consisting of C_{1-6} alkyl, C_{3-10} cycloalkyl, and 3- to 10-membered heterocycloalkyl, and R^a is optionally substituted with one or more groups selected from the group

consisting of halogen, CN, OH, NH₂, C₁₋₆ alkyl, C₁₋₆ alkyl-O-, and 5- to 6-membered heterocycloalkyl;

n is selected from the group consisting of 0, 1, 2, 3, and 4;

R² is selected from the group consisting of cyclopropyl and trifluoromethyl.

In some embodiments, R¹ is selected from the group consisting of -NH₂, C₁₋₄ alkyl-O-, C₁₋₄ alkyl-NH-, and (C₁₋₄ alkyl)₂N-.

In some embodiments, R¹ is selected from the group consisting of -NH₂, C₁₋₃ alkyl-O-, C₁₋₃ alkyl-NH-, and (C₁₋₃ alkyl)₂N-.

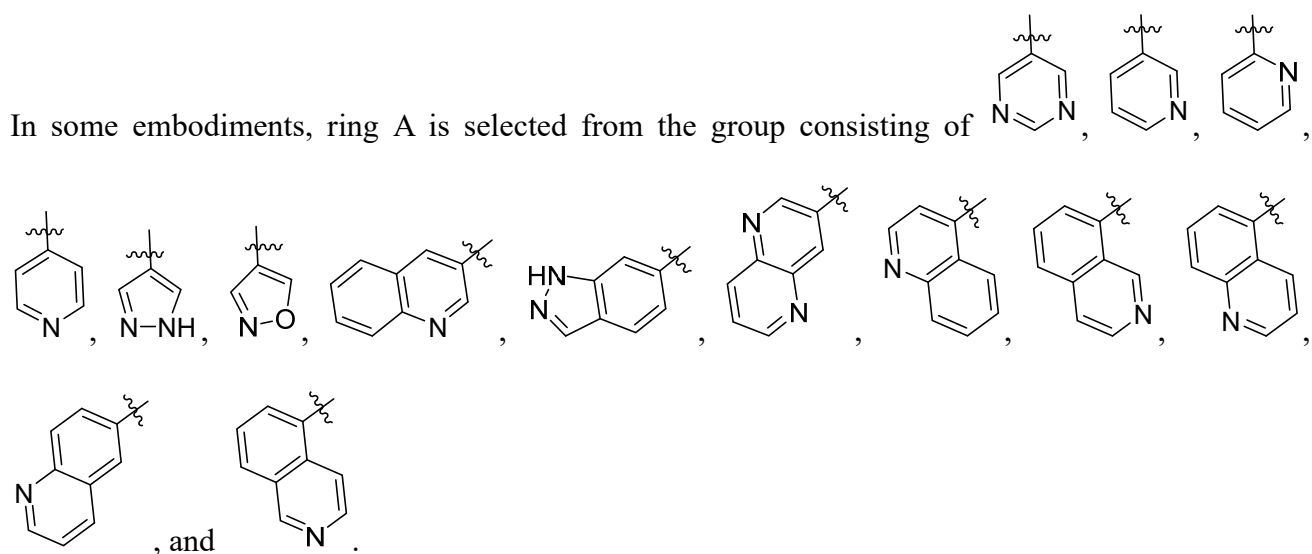
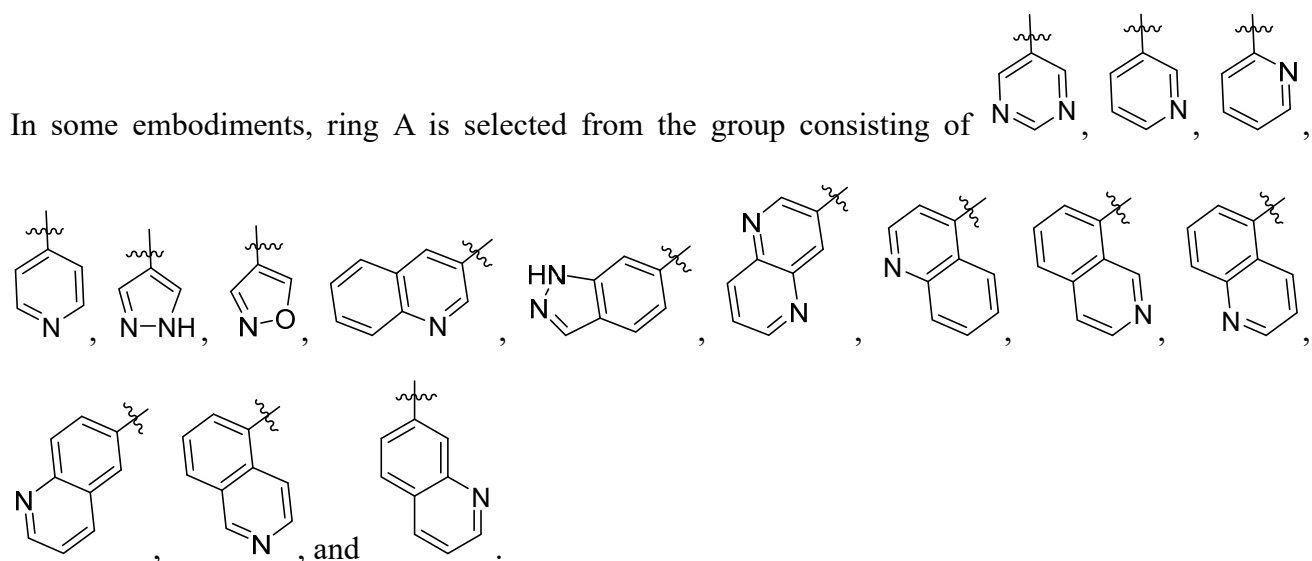
In some embodiments, R¹ is selected from the group consisting of -NH₂, isopropyl-O-, and methyl-NH-. In some embodiments, R¹ is selected from the group consisting of -NH₂ and isopropyl-O-. In some embodiments, R¹ is selected from -NH₂.

In some embodiments, ring A is selected from the group consisting of phenyl and a 5- to 10-membered heteroaromatic ring group. In some embodiments, ring A is selected from the group consisting of 5-, 6-, 7-, 8-, 9-, and 10-membered heteroaromatic ring groups. In some embodiments, ring A is selected from the group consisting of 5- to 6-membered and 9- to 10-membered heteroaromatic ring groups. In some embodiments, ring A is selected from the group consisting of 6- and 10-membered heteroaromatic ring groups. In some embodiments, ring A is selected from a 10-membered heteroaromatic ring group. In some embodiments, ring A is selected from the group consisting of 5- to 6-membered heteroaromatic ring groups. In some embodiments, ring A is selected from a 6-membered heteroaromatic ring group.

In some embodiments, ring A is selected from the group consisting of pyrimidinyl, pyridinyl, pyrazolyl, isoxazolyl, oxazolyl, quinolyl, indazolyl, pyridazinyl, thiazolyl, furanyl, pyranal, thienyl, pyrrolyl, pyrazinyl, isothiazolyl, oxazolyl, indolyl, naphthyridinyl, isoquinolyl, quinazolinyl, and benzofuranyl.

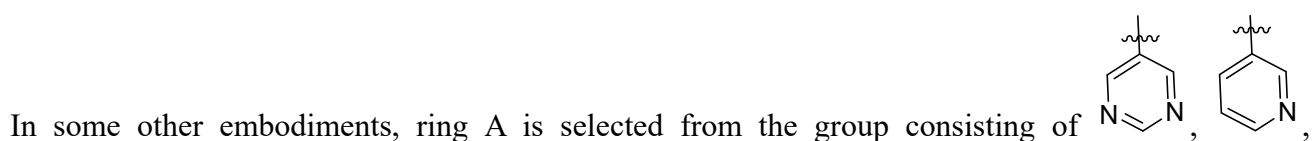
In some embodiments, ring A is selected from the group consisting of pyrimidinyl, pyridinyl, pyrazolyl, isoxazolyl, quinolyl, indazolyl, naphthyridinyl, and isoquinolyl. In some specific embodiments, ring A is selected from the group consisting of pyrimidinyl and pyridinyl; in some specific embodiments, ring A is selected from pyrimidinyl; in some specific embodiments, ring A is selected from pyridinyl; in some specific embodiments, ring A is selected from the group consisting of pyrazolyl and isoxazolyl; in some specific embodiments, ring A is selected from the group

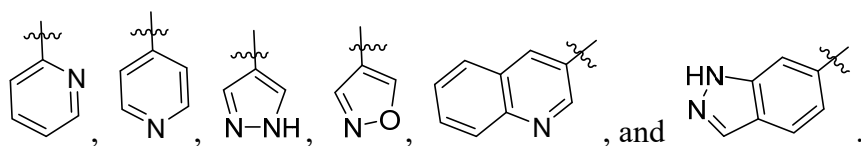
consisting of quinolyl, indazolyl, naphthyridinyl, and isoquinolyl; in some specific embodiments, ring A is selected from the group consisting of quinolyl and naphthyridinyl.

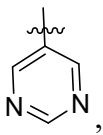
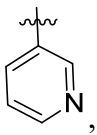
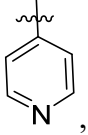


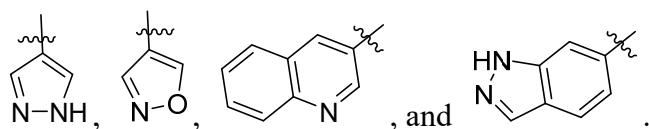
In some other embodiments, ring A is selected from the group consisting of pyrimidinyl, pyridinyl, pyrazolyl, isoxazolyl, quinolyl, indazolyl, pyridazinyl, thiazolyl, furanyl, thienyl, pyrrolyl, pyrazinyl, isothiazolyl, oxazolyl, and indolyl.

In some other embodiments, ring A is selected from the group consisting of pyrimidinyl, pyridinyl, pyrazolyl, isoxazolyl, quinolyl, and indazolyl.





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



In some embodiments, R is selected from the group consisting of halogen, CN, OH, NH₂, C₁₋₄ alkyl, C₁₋₄ alkyl-O-, C₁₋₄ alkyl-S-, C₁₋₄ haloalkyl-O-, C₁₋₄ haloalkyl-S-, C₁₋₄ haloalkyl, R^aNH-, and (R^a)₂N-.

In some embodiments, R is selected from the group consisting of halogen, CN, OH, NH₂, C₁₋₃ alkyl, C₁₋₃ alkyl-O-, C₁₋₃ alkyl-S-, C₁₋₃ haloalkyl-O-, C₁₋₃ haloalkyl-S-, C₁₋₃ haloalkyl, R^aNH-, and (R^a)₂N-.

In some embodiments, R is selected from the group consisting of fluorine, chlorine, CN, OH, NH₂, C₁₋₃ alkyl, C₁₋₃ alkyl-O-, C₁₋₃ haloalkyl, and R^aNH-.

In some embodiments, R is selected from the group consisting of fluorine, CN, NH₂, methyl, methoxy, trifluoromethyl, and R^aNH-.

In some embodiments, R^a is selected from the group consisting of C₁₋₄ alkyl, C₃₋₆ cycloalkyl, and 3- to 6-membered heterocycloalkyl, and R^a is optionally substituted with one or more groups selected from the group consisting of halogen, CN, OH, NH₂, and 5- to 6-membered heterocycloalkyl.

In some embodiments, R^a is selected from the group consisting of C₁₋₃ alkyl, C₅₋₆ cycloalkyl, and 5- to 6-membered heterocycloalkyl, and R^a is optionally substituted with one or more groups selected from the group consisting of halogen, CN, OH, NH₂, and 5- to 6-membered heterocycloalkyl.

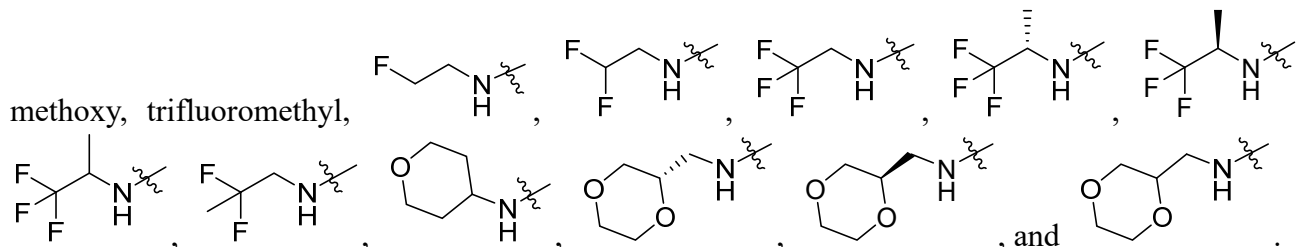
In some embodiments, R^a is selected from the group consisting of C₁₋₃ alkyl and 5- to 6-membered heterocycloalkyl, and R^a is optionally substituted with one or more groups selected from the group consisting of halogen, CN, OH, NH₂, and 5- to 6-membered heterocycloalkyl.

In some embodiments, R^a is selected from the group consisting of C₁₋₃ alkyl and 6-membered heterocycloalkyl, and R^a is optionally substituted with one or more groups selected from the group consisting of fluorine, chlorine, bromine, CN, OH, NH₂, and 6-membered heterocycloalkyl.

In some embodiments, R^a is selected from the group consisting of methyl, ethyl, propyl, and tetrahydropyranyl, and R^a is optionally substituted with one or more fluorine or dioxane.

In some embodiments, R^a is selected from the group consisting of FCH_2CH_2- , F_2CHCH_2- , F_3CCH_2- , $CF_3CH(CH_3)-$, $CH_3CF_2CH_2-$, tetrahydropyranyl, and dioxane- CH_2- .

In some embodiments, R is selected from the group consisting of fluorine, CN, NH_2 , methyl,

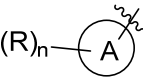


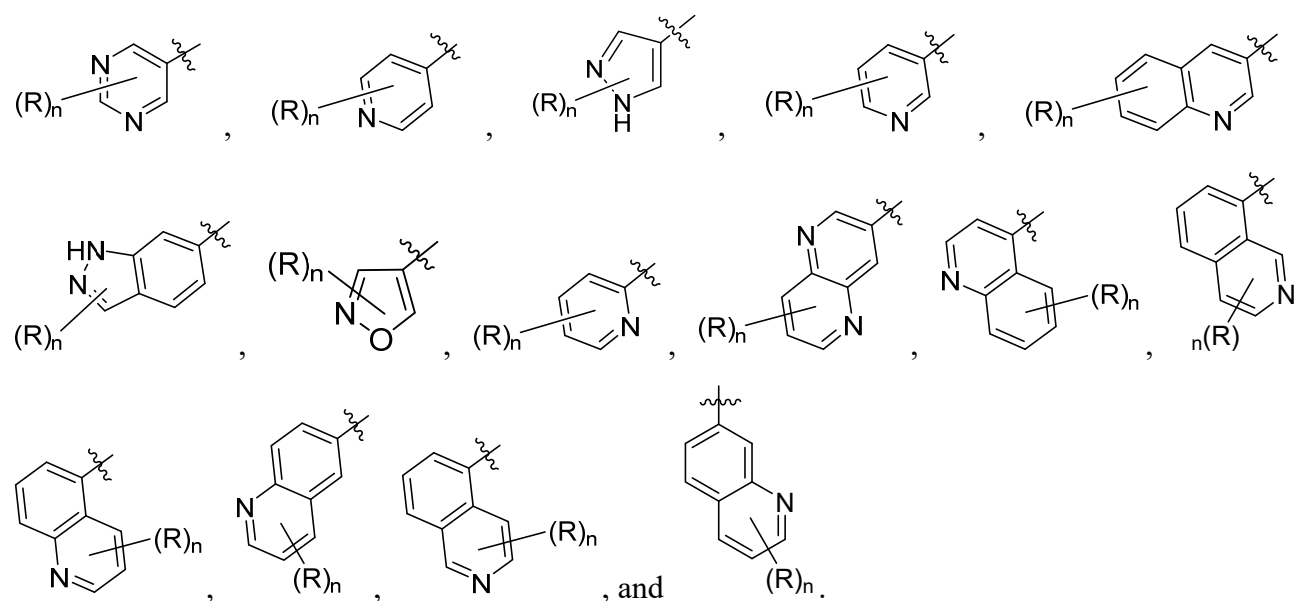
In some embodiments, n is selected from the group consisting of 0, 1, 2, and 3.

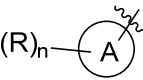
In some embodiments, n is selected from the group consisting of 0, 1, and 2.

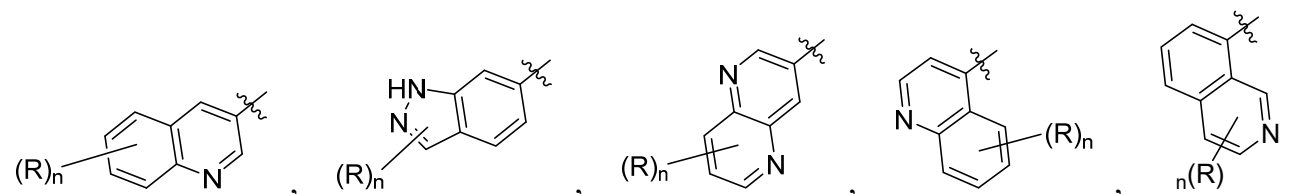
In some embodiments, n is selected from the group consisting of 0 and 1. In some embodiments, n is selected from 0. In some embodiments, n is selected from 1.

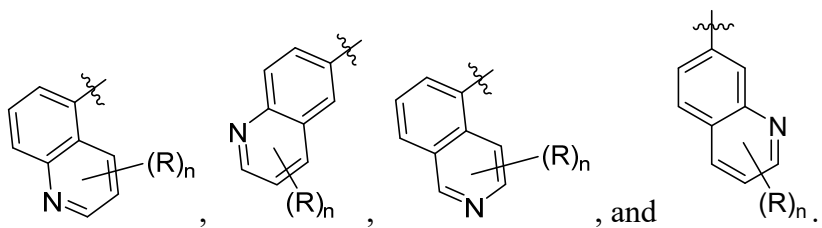
In some embodiments, R^2 is selected from cyclopropyl.

In some embodiments, structural unit $(R)_n$  is selected from the group consisting of

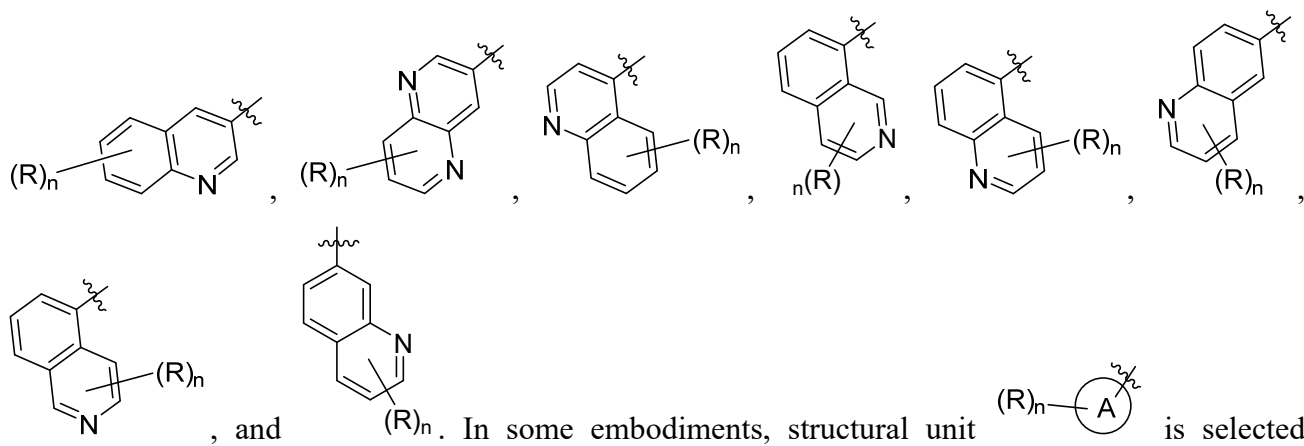


In some embodiments, structural unit $(R)_n$  is selected from the group consisting of

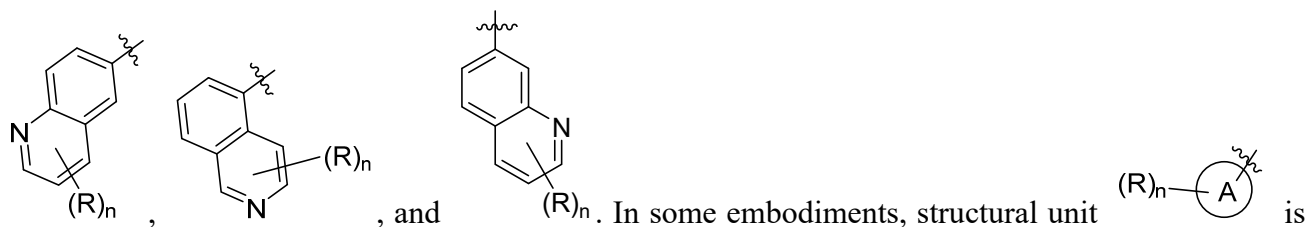




In some embodiments, structural unit $(R)_n$ -A is selected from the group consisting of

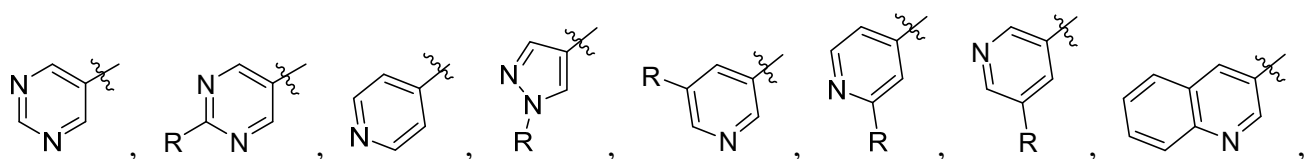


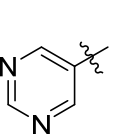
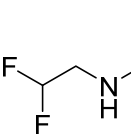
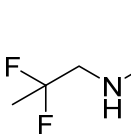
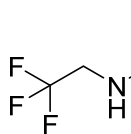
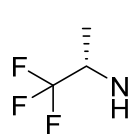
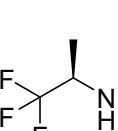
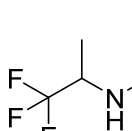
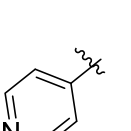
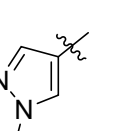
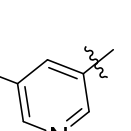
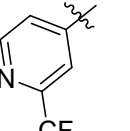
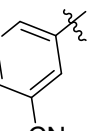
from the group consisting of

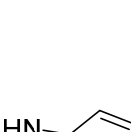


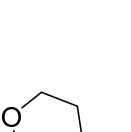
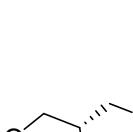
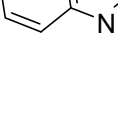
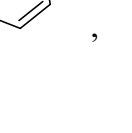
selected from

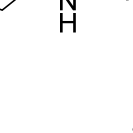
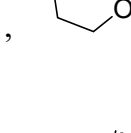
In some embodiments, structural unit $(R)_n$ -A is selected from the group consisting of

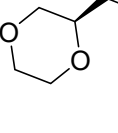
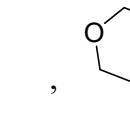
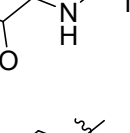
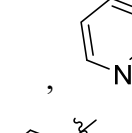
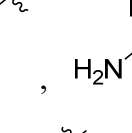
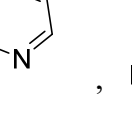
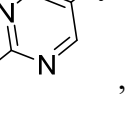
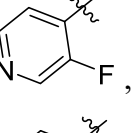
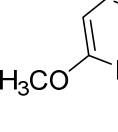
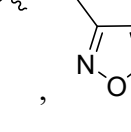
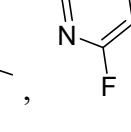
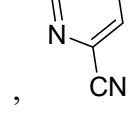
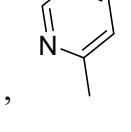
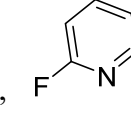
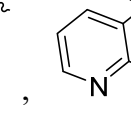
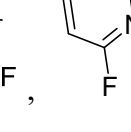


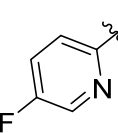
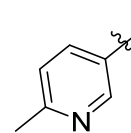
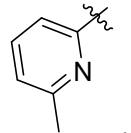
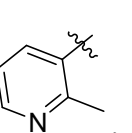
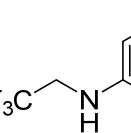
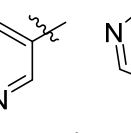
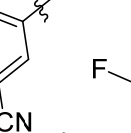
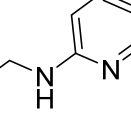













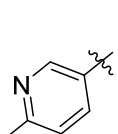
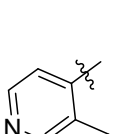
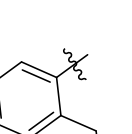
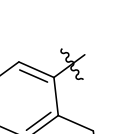
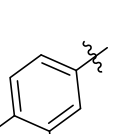
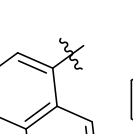
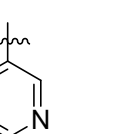
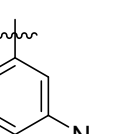


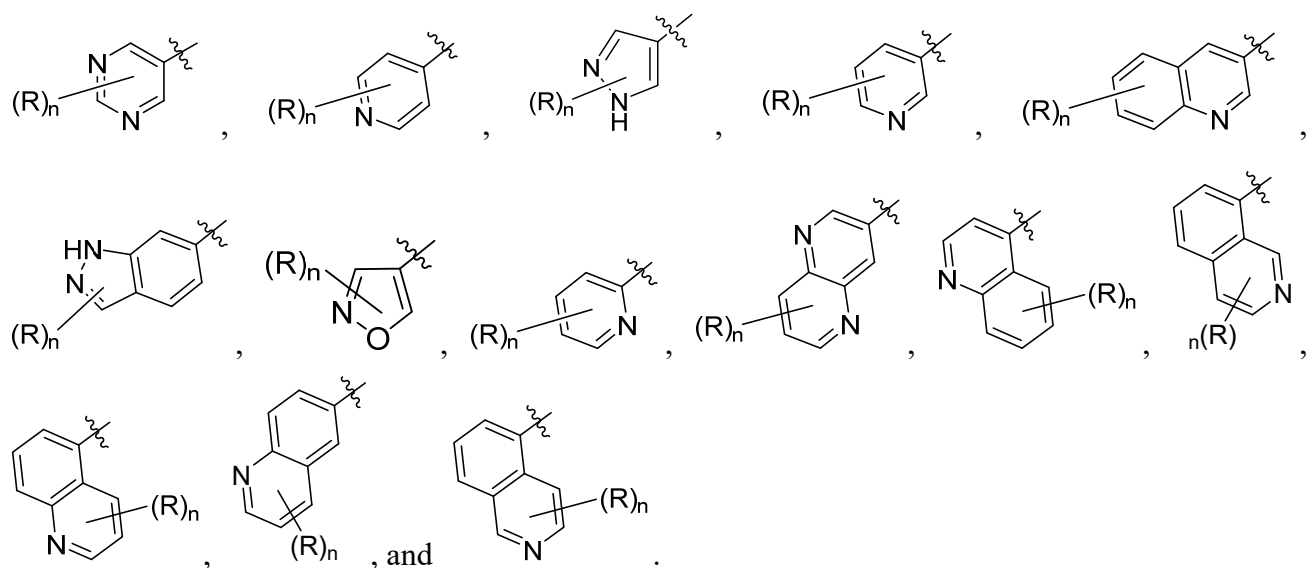



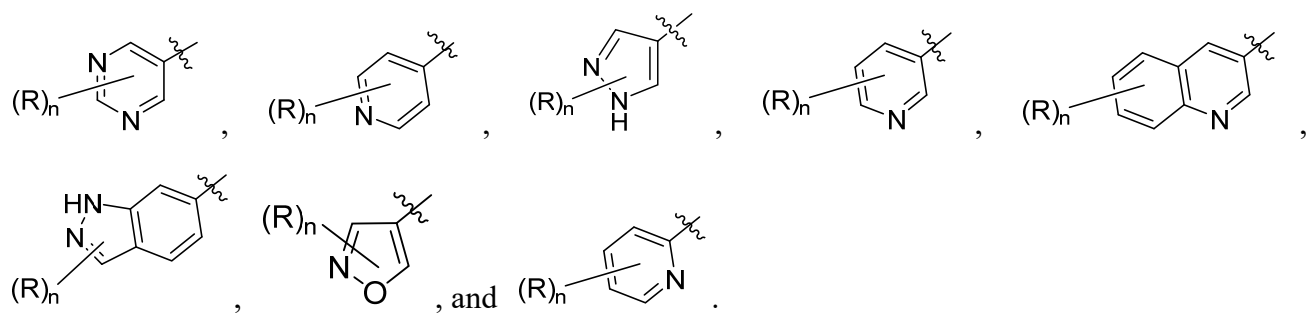









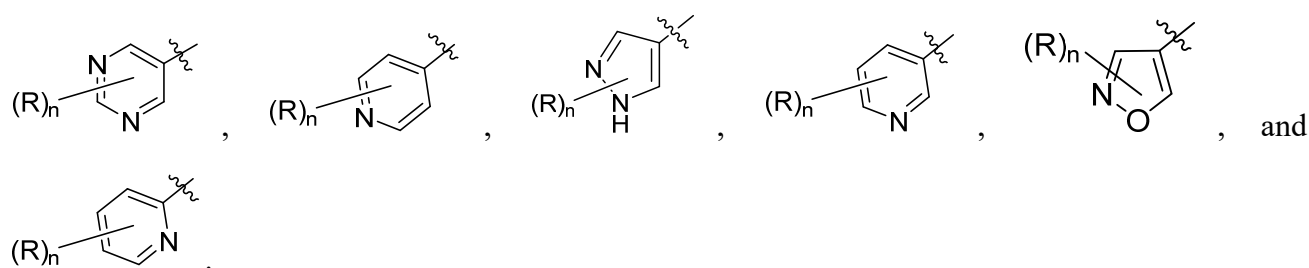

In some embodiments, structural unit $(R)_n$ - A is selected from the group consisting of



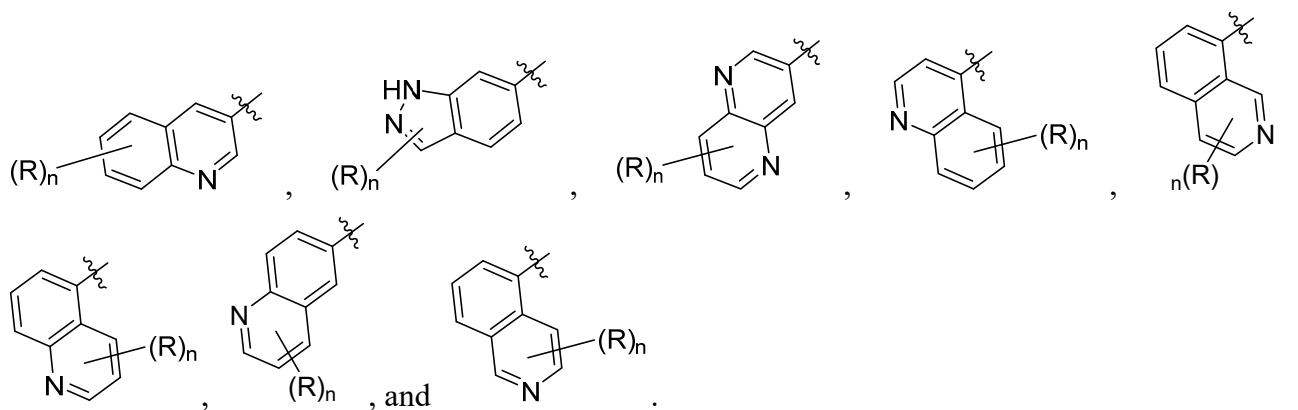
In some other embodiments, structural unit $(R)_n$ - A is selected from the group consisting of



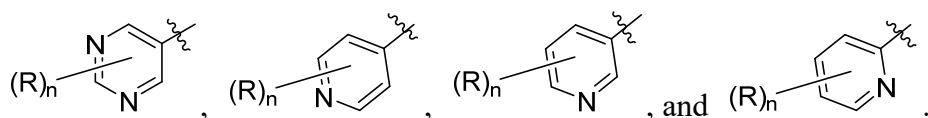
In some embodiments, structural unit $(R)_n$ - A is selected from the group consisting of



In some embodiments, structural unit $(R)_n$ - A is selected from the group consisting of



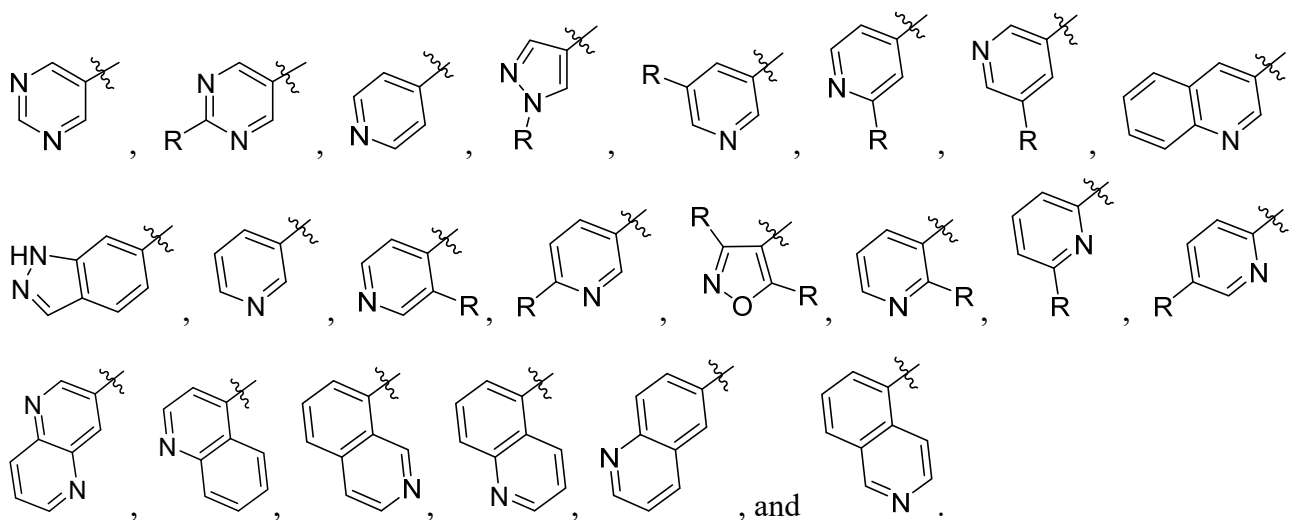
In some embodiments, structural unit $(R)_n$ -A is selected from the group consisting of



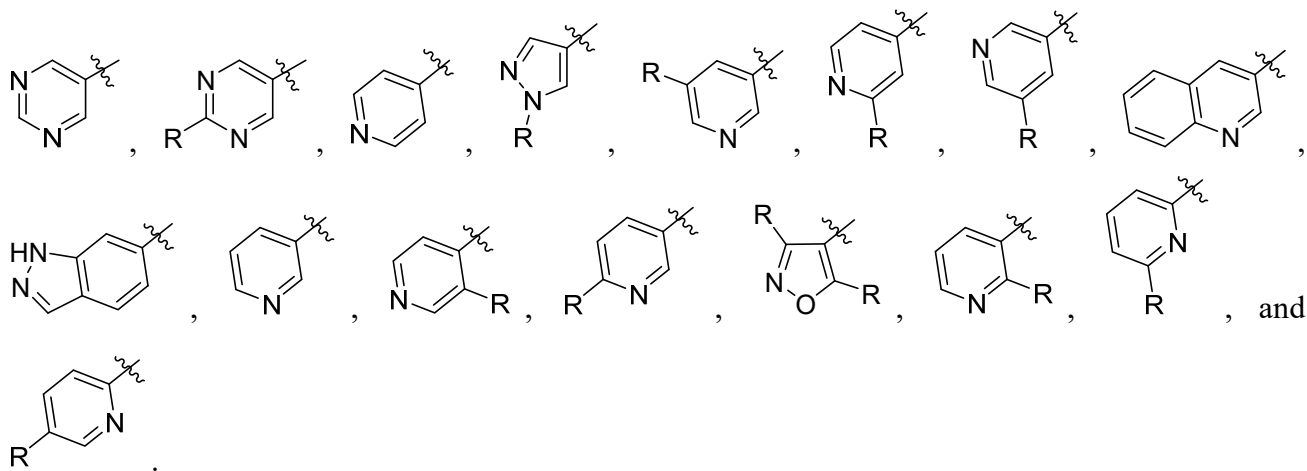
In some embodiments, structural unit $(R)_n$ -A is selected from $(R)_n$ -pyridine. In some

embodiments, structural unit $(R)_n$ -A is selected from $(R)_n$ -pyridine.

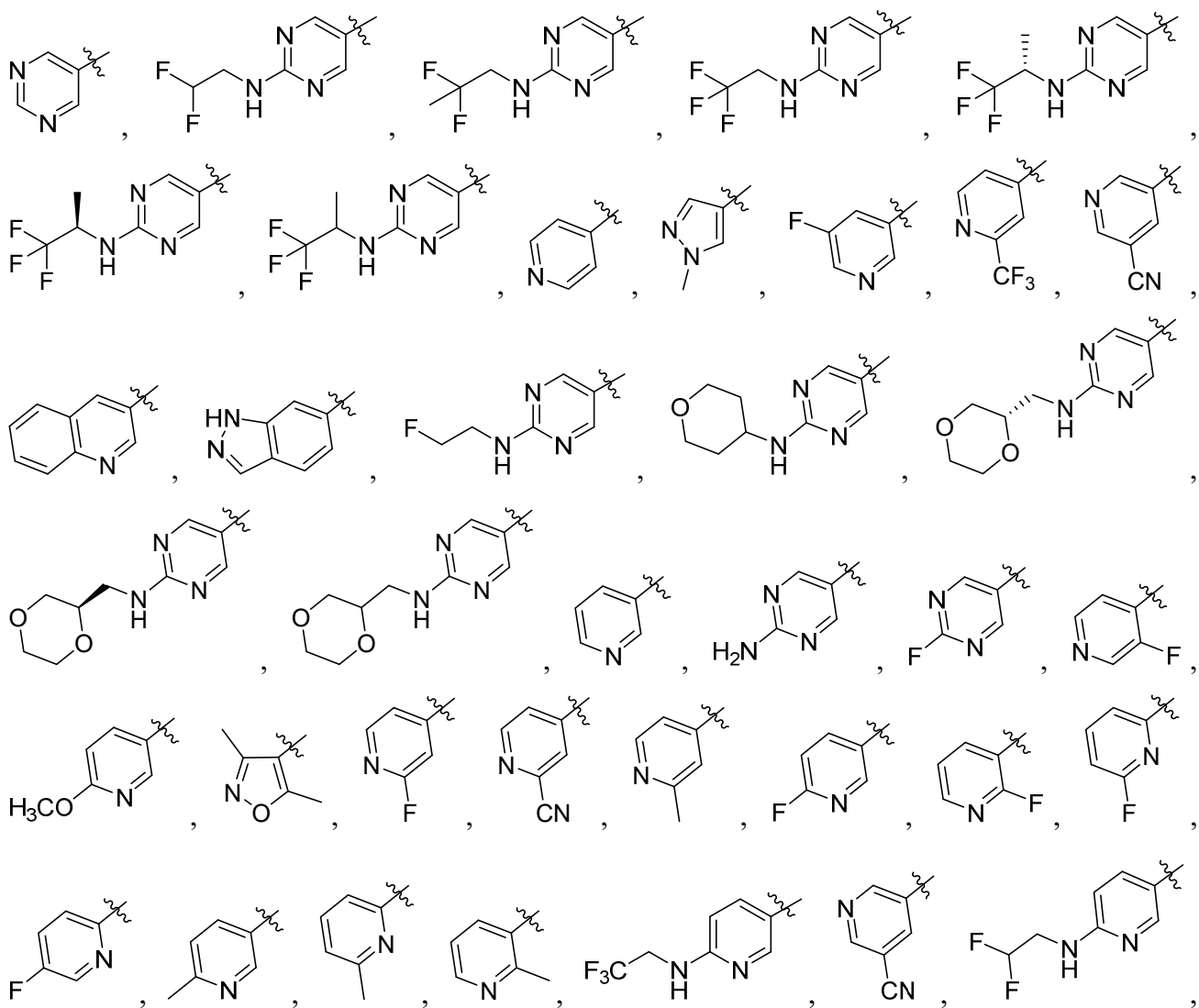
In some embodiments, structural unit $(R)_n$ -A is selected from the group consisting of



In some other embodiments, structural unit $(R)_n$ -A is selected from the group consisting of



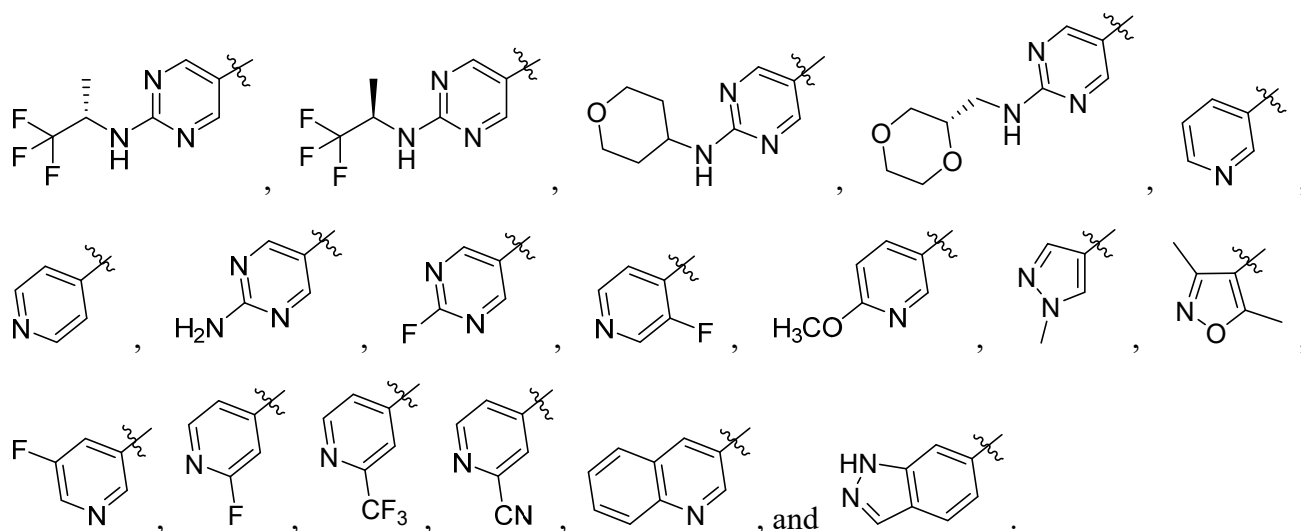
In some embodiments, structural unit  is selected from the group consisting of



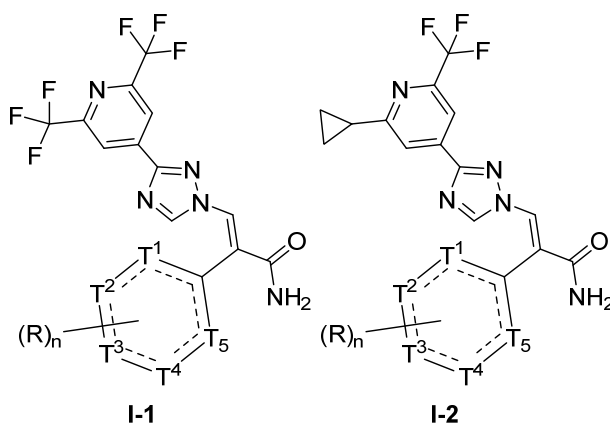
[illegible]





In some embodiments, the compound of formula I, the pharmaceutically acceptable salt thereof, or the stereoisomer thereof is selected from the group consisting of a compound of formula I-1 or I-2, a pharmaceutically acceptable salt thereof, or a stereoisomer thereof,



wherein R and n are as described in the present application;

T¹, T², T³, T⁴, and T⁵ are each independently selected from the group consisting of a bond, O, S, N, and CH, no more than one of which is selected from a bond and at least one of which is selected from N;

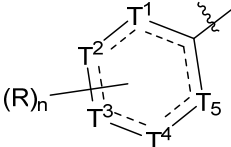
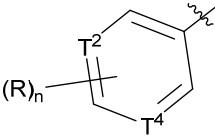
--- represents a single bond or double bond.

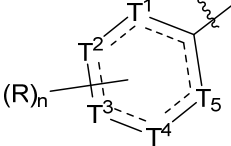
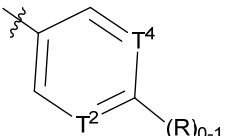
In some embodiments, T¹, T², T³, T⁴, and T⁵ are each independently selected from the group consisting of N and CH, at least one of which is selected from N.

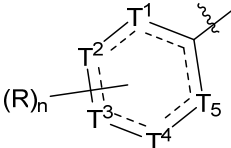
In some embodiments, T² and T⁴ are selected from N, and T¹, T³, and T⁵ are selected from CH.

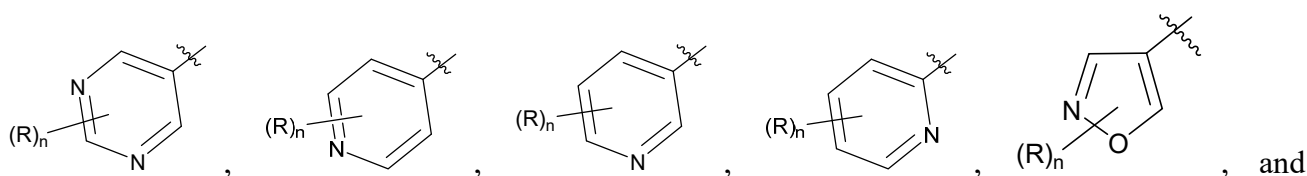
In some embodiments, T³ is selected from N, and T¹, T², T⁴, and T⁵ are selected from CH.

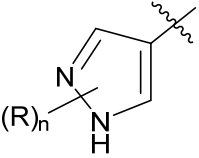
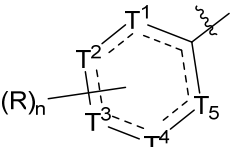
In some embodiments, T² is selected from N, and T¹, T³, T⁴, and T⁵ are selected from CH.

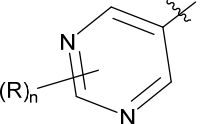
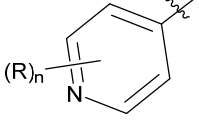
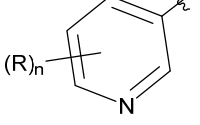
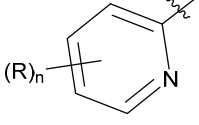
In some embodiments, structural unit  is selected from .

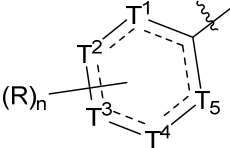
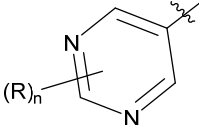
In some embodiments, structural unit  is selected from .

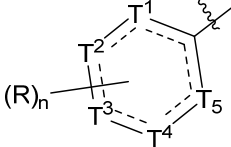
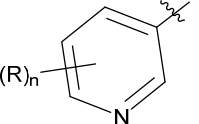
In some embodiments, structural unit  is selected from the group consisting of



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

consisting of , , , and . In some

embodiments, structural unit  is selected from . In some

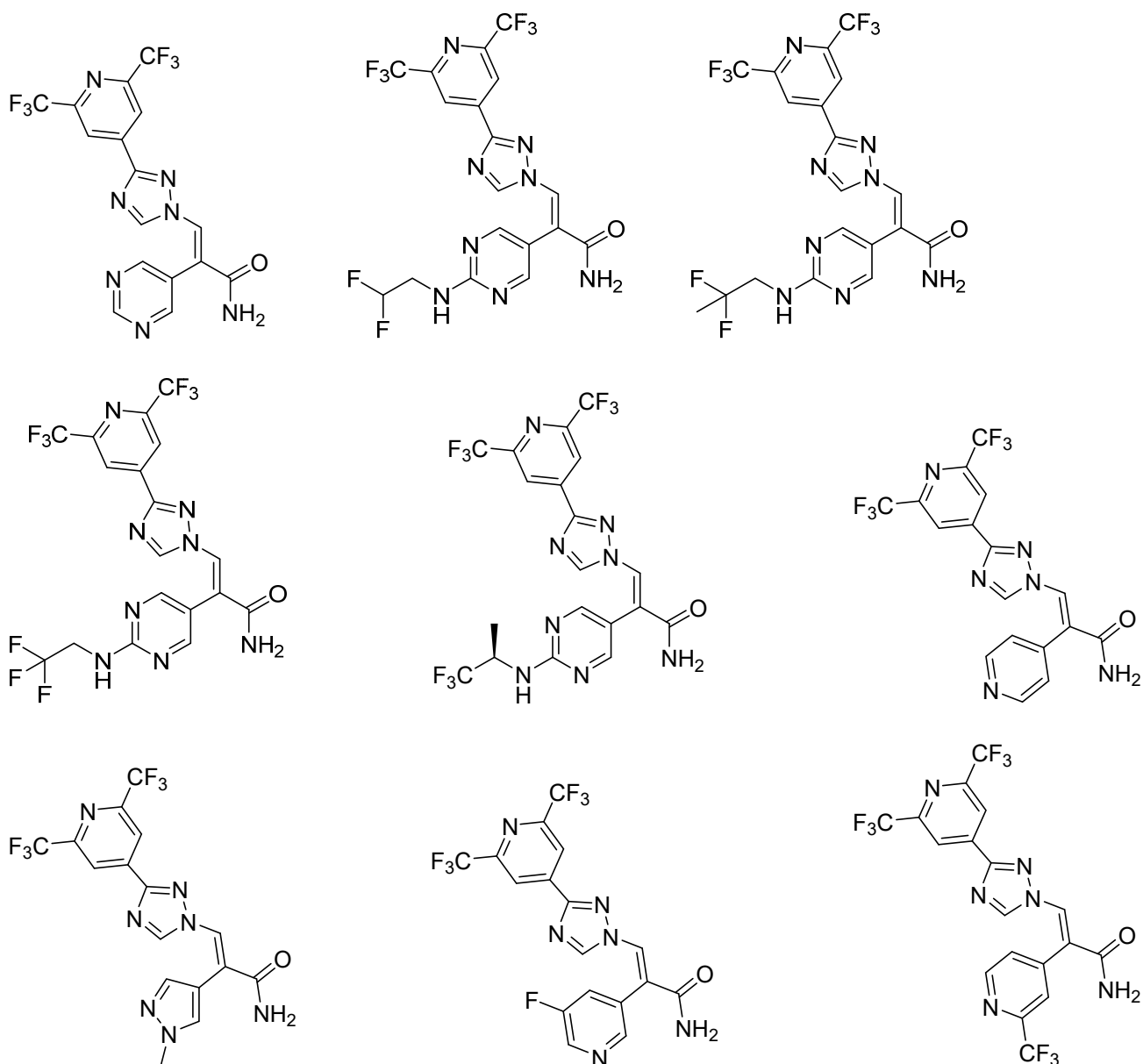
embodiments, structural unit  is selected from .

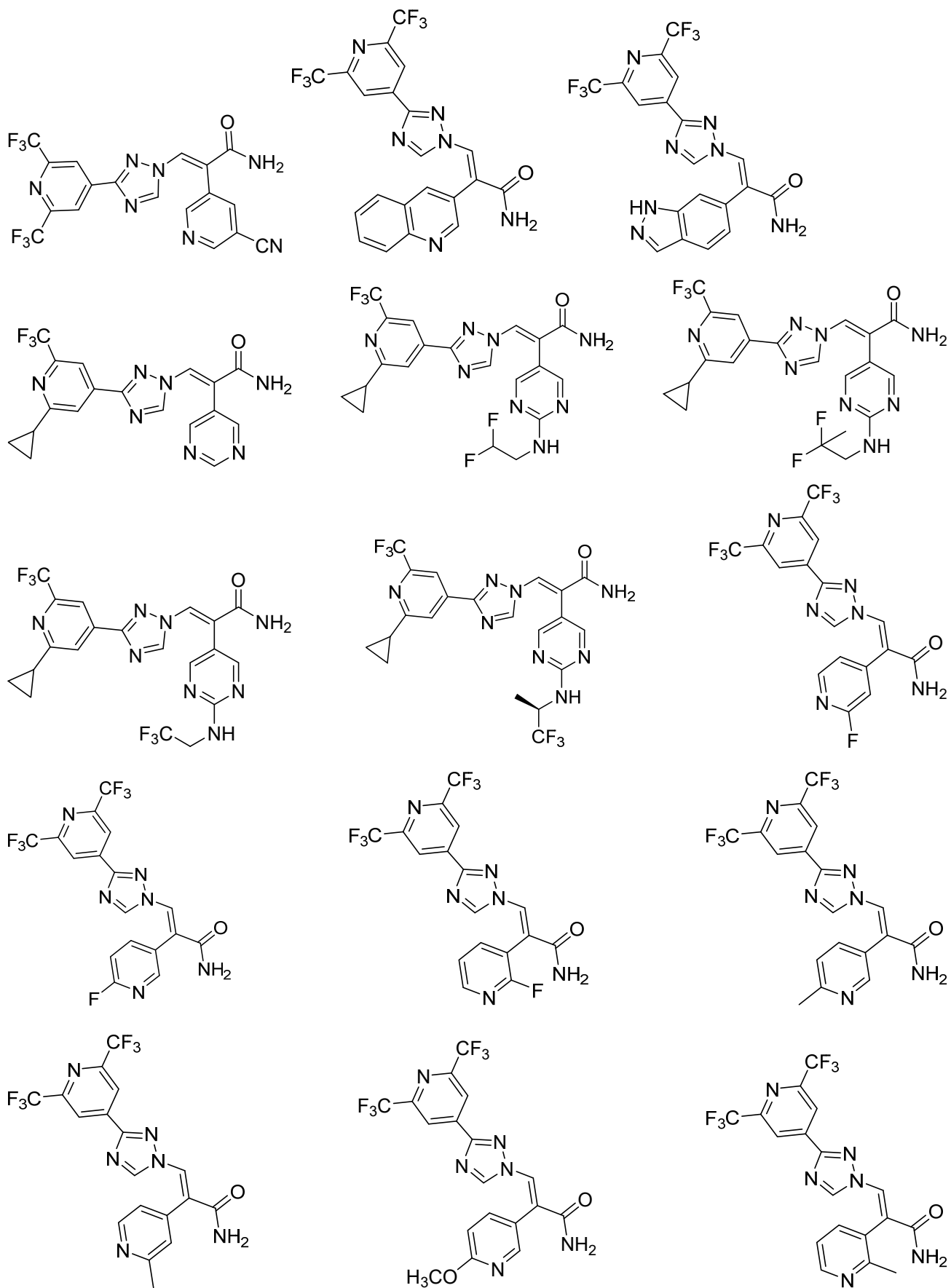
In some embodiments, the present application encompasses the variables defined above and embodiments thereof, as well as any combination thereof.

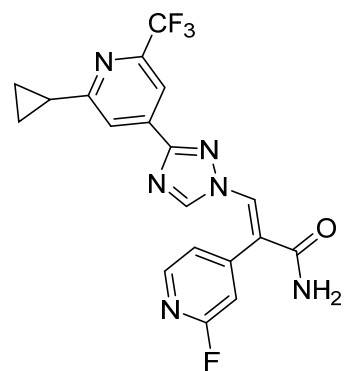
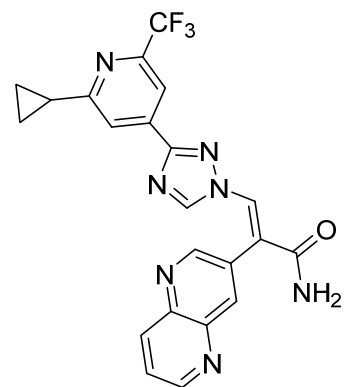
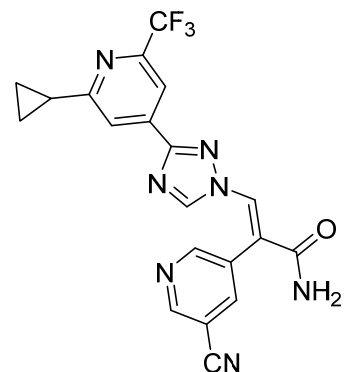
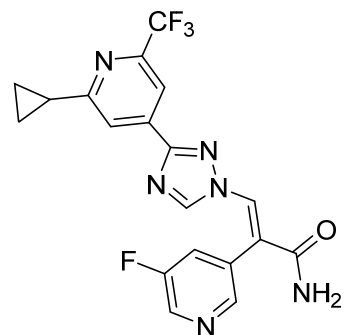
The heteroatom in the heterocycloalkyl or heteroaromatic ring group described above is selected from the group consisting of nitrogen, oxygen, and sulfur, and the remaining ring atoms are selected

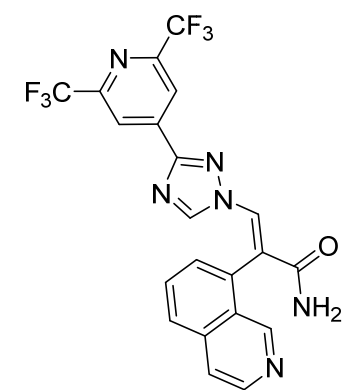
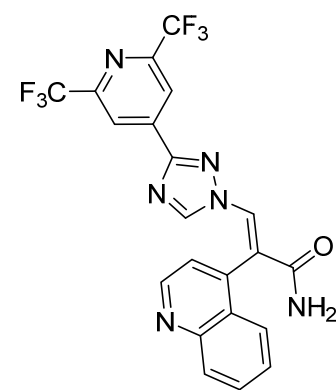
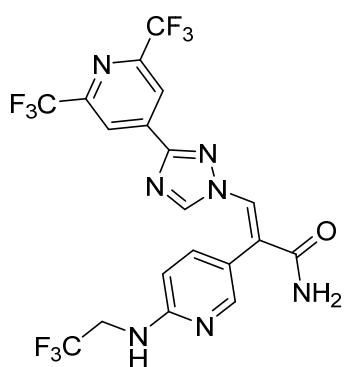
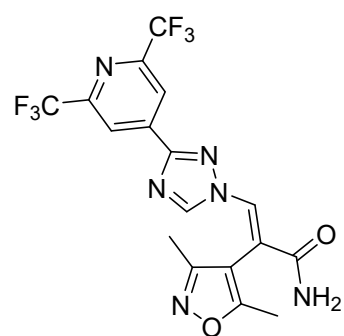
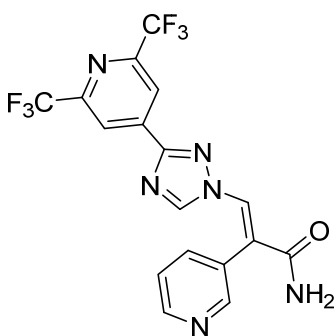
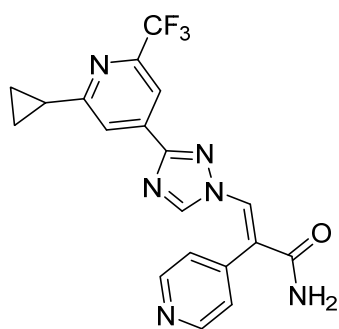
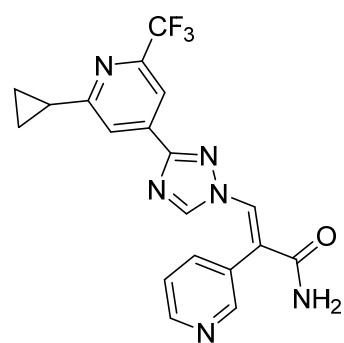
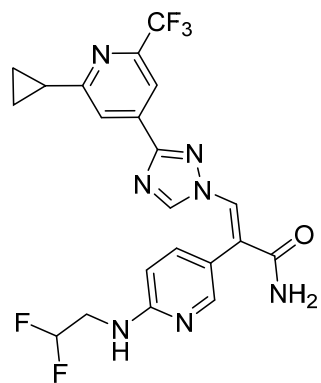
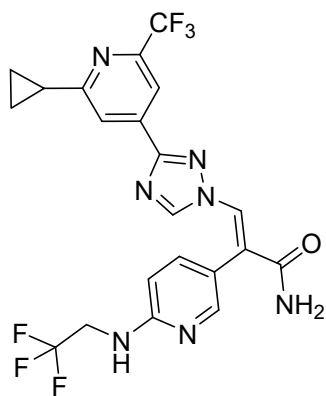
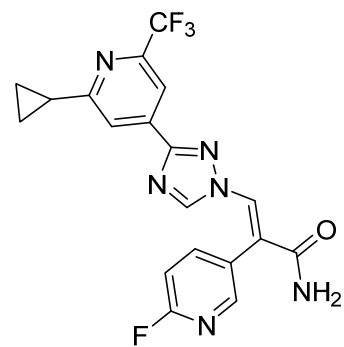
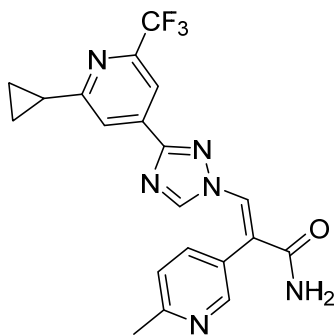
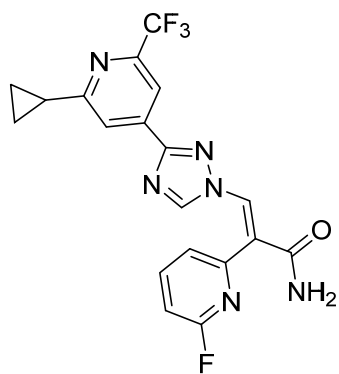
from carbon. The heteroatom in the heterocycloalkyl or heteroaromatic ring group described above is selected from the group consisting of nitrogen and oxygen, and the remaining ring atoms are selected from carbon. The heteroatom in the heterocycloalkyl or heteroaromatic ring group described above is selected from nitrogen, and the remaining ring atoms are selected from carbon. In some embodiments, the number of the heteroatom is selected from the group consisting of 1, 2, 3, and 4. In some embodiments, the number of the heteroatom is selected from the group consisting of 1, 2, and 3. In some embodiments, the number of the heteroatom is selected from the group consisting of 1 and 2.

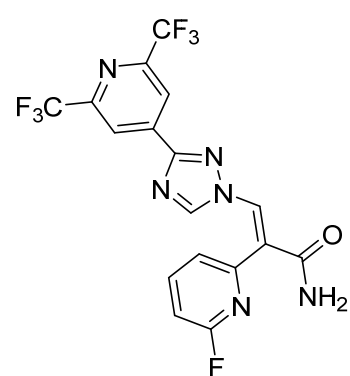
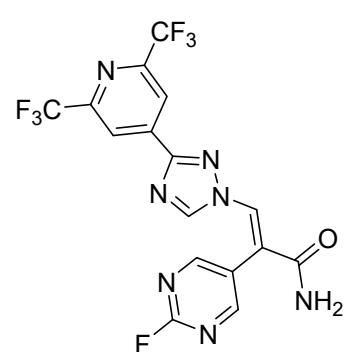
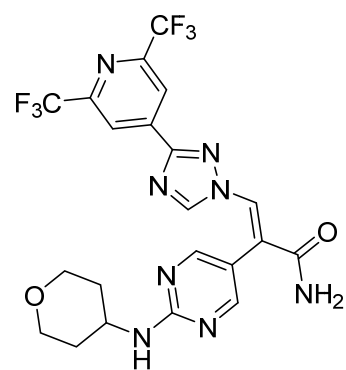
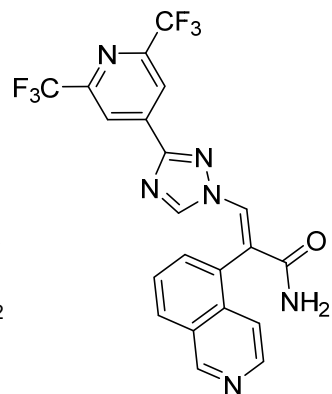
The present application provides compounds, pharmaceutically acceptable salts thereof, or stereoisomers thereof as follows:

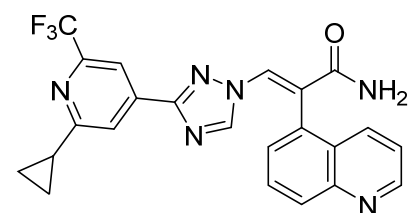
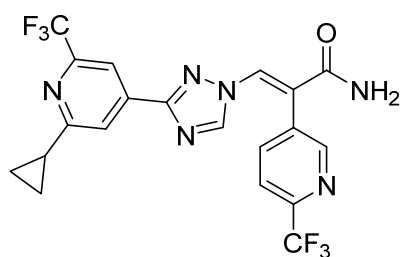
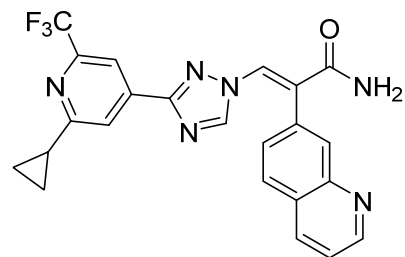
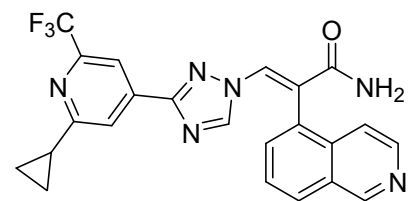
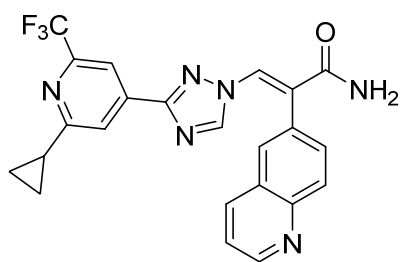
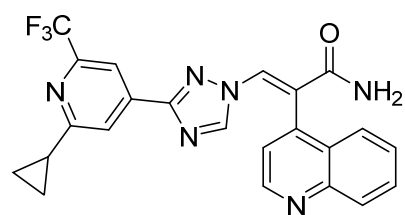
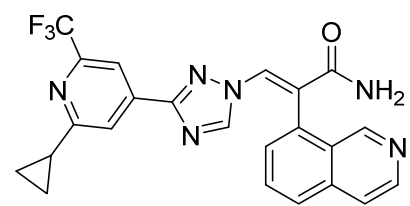
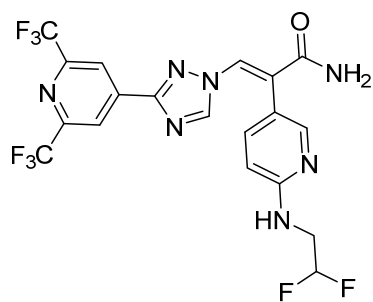
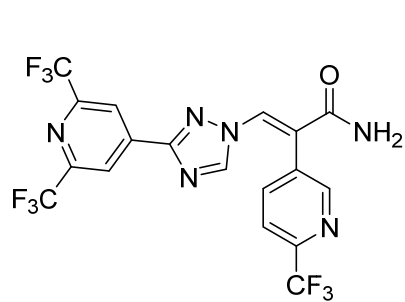
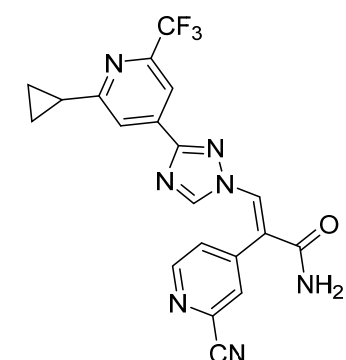
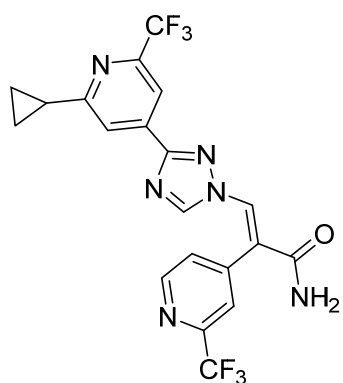
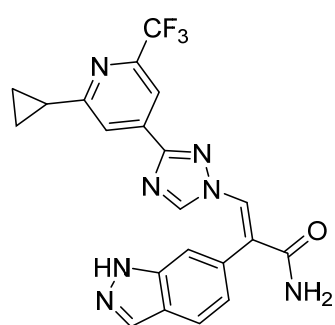
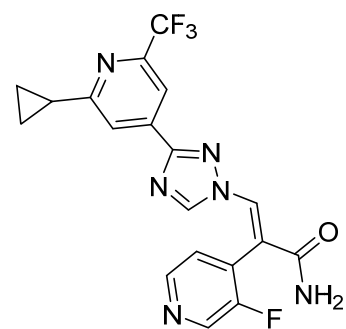
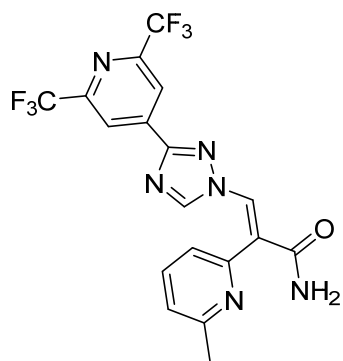
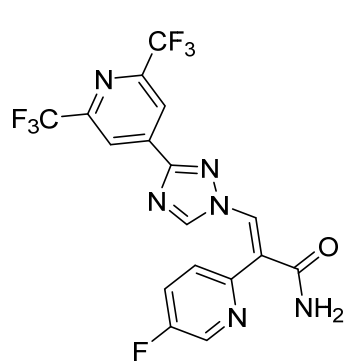


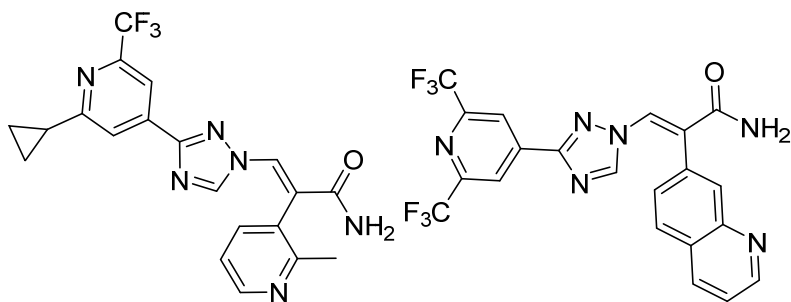












In another aspect, the present application further provides a pharmaceutical composition comprising the compound or the pharmaceutically acceptable salt thereof or the stereoisomer thereof of the present application described above. In some embodiments, the pharmaceutical composition disclosed herein further comprises a pharmaceutically acceptable excipient.

In another aspect, the present application further provides a method for treating various XPO-1-related diseases, comprising administering to a mammal, preferably a human, in need of the treatment a therapeutically effective amount of the compound, the pharmaceutically acceptable salt thereof, or the stereoisomer thereof, or the pharmaceutical composition thereof of the present application described above.

In another aspect, the present application further provides use of the compound or the pharmaceutically acceptable salt thereof or the stereoisomer thereof, or the pharmaceutical composition thereof of the present application described above for preparing a medicament for treating various XPO-1-related diseases.

In another aspect, the present application further provides use of the compound or the pharmaceutically acceptable salt thereof or the stereoisomer thereof, or the pharmaceutical composition thereof of the present application described above for treating various XPO-1-related diseases.

In another aspect, the present application further provides the compound, the pharmaceutically acceptable salt thereof, or the stereoisomer thereof, or the pharmaceutical composition thereof of the present application described above for treating various XPO-1-related diseases.

In some embodiments, the various XPO-1-related diseases are selected from the group consisting of tumors; in some embodiments, the various XPO-1-related diseases are selected from the group consisting of leukemia and lymphoma.

Technical Effects

The compound of the present application has cell proliferation inhibitory activity (e.g., against Jurkat cells and/or OCI-LY10 cells); stable *in vitro* liver microsome metabolism and good stability in human whole blood; good *in vivo* pharmacokinetic data (e.g., parameters such as AUC, C_{max}, T_{max}, or absolute bioavailability), *in vivo* pharmacodynamic data, and *in vivo* safety data (parameters such as brain-to-blood ratio).

Definitions

Unless otherwise stated, the following terms used in the present application shall have the following meanings. A certain term, unless otherwise specifically defined, should not be considered ambiguous or unclear, but construed according to its common meaning in the art. When referring to a trade name, it is intended to refer to its corresponding commercial product or its active ingredient.

When certain structural units or groups in the present application have a covalent bond that is not connected to a specific atom, it means that the covalent bond can be connected to any atom within that structural unit or group, as long as it adheres to the rules of valence bonding.

The term “substituted” means that any one or more hydrogen atoms on a specific atom are substituted with substituents, as long as the valence of the specific atom is normal and the resulting compound is stable. When the substituent is oxo (namely =O), it means that two hydrogen atoms are substituted and oxo is not available on an aromatic group.

The term “optional” or “optionally” means that the subsequently described event or circumstance may, but does not necessarily, occur. The description includes instances where the event or circumstance occurs and instances where it does not. For example, ethyl being “optionally” substituted with halogen means that the ethyl may be unsubstituted (CH₂CH₃), monosubstituted (for example, CH₂CH₂F), polysubstituted (for example, CHFCH₂F, CH₂CHF₂, and the like), or fully substituted (CF₂CF₃). It will be appreciated by those skilled in the art that for any groups comprising one or more substituents, any substitutions or substituting patterns that may not exist and/or cannot be synthesized spatially are not introduced.

“One or more” used herein refers to an integer ranging from one to ten. For example, “one or more” refers to one, two, three, four, five, six, seven, eight, nine, or ten; or “one or more” refers to one, two, three, four, five, or six; or “one or more” refers to one, two, or three.

C_{m-n} used herein means that the moiety has an integer number of carbon atoms in the given range. For example, “C₁₋₆” means that the group may have 1 carbon atom, 2 carbon atoms, 3 carbon atoms,

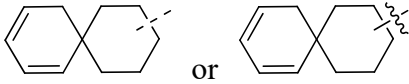
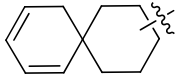
4 carbon atoms, 5 carbon atoms, or 6 carbon atoms. For example, C_{1-3} means that the group may have 1 carbon atom, 2 carbon atoms, or 3 carbon atoms.

When any variable (e.g., R) occurs once or more in the constitution or structure of a compound, the definition of the variable in each case is independent. Therefore, for example, if a group is substituted with 2 R, the definition of each R is independent.

When the number of connecting groups is 0, for example, $-(CH_2)_0-$, it means that the connecting group is a covalent bond.

When one of the variables is selected from a covalent bond, it means that the two groups connected to it are directly linked. For example, in A-L'-Z, where L' represents a covalent bond, it means that the structure is actually A-Z.

When a bond of a substituent is crosslinked to two atoms on a ring, the substituent can be bonded to

any atoms on the ring. For example, structural unit  or  represents that substitution may occur at any one position of cyclohexyl or cyclohexadienyl.

The term “halo-” or “halogen” refers to fluorine, chlorine, bromine, and iodine.

The term “alkyl” refers to hydrocarbyl with a general formula of C_nH_{2n+1} . The alkyl may be linear or branched. For example, the term “ C_{1-6} alkyl” refers to alkyl containing 1 to 6 carbon atoms (for example, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, n-pentyl, 1-methylbutyl, 2-methylbutyl, 3-methylbutyl, neopentyl, hexyl, 2-methylpentyl, and the like). Likewise, the alkyl moieties (namely alkyl) of alkoxy, alkylamino, dialkylamino, alkylsulfonyl and alkylthio have the same definition as those described above. As another example, the term “ C_{1-3} alkyl” refers to alkyl containing 1 to 3 carbon atoms (e.g., methyl, ethyl, propyl, and isopropyl).

The term “alkoxy” refers to -O-alkyl.

The term “cycloalkyl” refers to a carbon ring that is fully saturated and may exist as a monocyclic, bridged cyclic, or spiro cyclic structure. Unless otherwise indicated, the carbon ring is generally a 3- to 10-membered ring (e.g., a 3-, 4-, 5-, 6-, 7-, 8-, 9-, or 10-membered ring). Non-limiting examples of cycloalkyl include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, norbornyl (bicyclo[2.2.1]heptyl), bicyclo[2.2.2]octyl, adamantyl, dicyclo[1.1.1]pentan-1-yl, and the like. For example, C_{3-4} cycloalkyl includes cyclopropyl and cyclobutyl.

The term “heterocycloalkyl” refers to a fully saturated cyclic group that may exist in the form of a

monocyclic, bridged cyclic (including fused ring), or spiro cyclic structure. Unless otherwise indicated, the heterocyclyl is generally a 3- to 7-membered ring (e.g., a 3-, 4-, 5-, 6-, or 7-membered ring) containing 1 to 3 heteroatoms (preferably 1 or 2 heteroatoms) independently selected from the group consisting of sulfur, oxygen, and/or nitrogen. Examples of 3-membered heterocycloalkyl include, but are not limited to, oxiranyl, thiiranyl, and aziranyl. Non-limiting examples of 4-membered heterocycloalkyl include, but are not limited to, azetidiny, oxetanyl, and thietanyl. Examples of 5-membered heterocycloalkyl include, but are not limited to, tetrahydrofuranyl, tetrahydrothienyl, pyrrolidinyl, isoxazolidinyl, oxazolidinyl, isothiazolidinyl, thiazolidinyl, imidazolidinyl, and tetrahydropyrazolyl. Examples of 6-membered heterocycloalkyl include, but are not limited to, piperidinyl, tetrahydropyranyl, tetrahydrothiapyranyl, morpholinyl, piperazinyl, 1,4-oxathianyl, 1,4-dioxanyl, sulfomorpholinyl, 1,3-dithianyl, and 1,4-dithianyl. Examples of 7-membered heterocycloalkyl include, but are not limited to, azepanyl, oxepanyl, and thiepanyl. Monocyclic heterocycloalkyl having 5 or 6 ring atoms is preferred.

The term “aryl” refers to an all-carbon aromatic monocyclic or fused polycyclic group having a conjugated π -electron system. For example, aryl may have 6-20 carbon atoms, 6-14 carbon atoms, or 6-12 carbon atoms. Non-limiting examples of aryl include, but are not limited to, phenyl, naphthyl, anthryl, 1,2,3,4-tetrahydronaphthalene, and the like.

The term “heteroaryl” or “heteroaromatic ring group” refers to a monocyclic or fused polycyclic system which contains at least one ring atom selected from the group consisting of N, O, and S, with the remaining ring atoms being C, and which has at least one aromatic ring. Preferably, heteroaryl has a single 5- to 8-membered ring (e.g., a 5-, 6-, 7-, or 8-membered ring), or has a plurality of fused rings containing 6 to 14 ring atoms, particularly 6 to 10 ring atoms (e.g., 6-, 7-, 8-, 9-, or 10-membered rings). Non-limiting examples of heteroaryl include, but are not limited to, pyrrolyl, furanyl, thienyl, imidazolyl, oxazolyl, isoxazolyl, pyrazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, quinolyl, isoquinolyl, tetrazolyl, triazolyl, triazinyl, benzofuranyl, benzothienyl, indolyl, naphthyridinyl, indazolyl, isoindolyl, and the like.

The term “treat” or “treatment” means administering a compound or formulation described herein to ameliorate or eliminate a disease or one or more symptoms associated with the disease, including:

- (i) inhibiting a disease or disease state, i.e., arresting its progression; and
- (ii) alleviating a disease or disease state, i.e., causing its regression.

The term “prevent” or “prevention” means administering a compound or formulation described herein to prevent a disease or one or more symptoms associated with the disease, including preventing the occurrence of the disease or disease state in a mammal, particularly when such a mammal is predisposed to the disease state but has not yet been diagnosed with it.

The term “therapeutically effective amount” refers to an amount of the compound disclosed herein for (i) treating or preventing a specific disease, condition, or disorder; (ii) alleviating, ameliorating, or eliminating one or more symptoms of a specific disease, condition, or disorder, or (iii) preventing or delaying onset of one or more symptoms of a specific disease, condition, or disorder described herein. The amount of the compound disclosed herein composing the “therapeutically effective amount” varies depending on the compound, the disease state and its severity, the administration regimen, and the age of the mammal to be treated, but can be determined routinely by those skilled in the art in accordance with their knowledge and the present disclosure.

The term “pharmaceutically acceptable” is used herein for those compounds, materials, compositions, and/or dosage forms that are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problems or complications, and commensurate with a reasonable benefit/risk ratio.

A pharmaceutically acceptable salt, for example, may be a metal salt, an ammonium salt, a salt formed with an organic base, a salt formed with an inorganic acid, a salt formed with an organic acid, a salt formed with a basic or acidic amino acid, and the like.

The term “pharmaceutical composition” refers to a mixture consisting of one or more of the compounds or the salts thereof of the present application and a pharmaceutically acceptable excipient. The pharmaceutical composition is intended to facilitate the administration of the compound of the present application to an organism.

The term “pharmaceutically acceptable excipient” refers to those that do not have a significant irritating effect on an organism and do not impair the biological activity and properties of the active compound. Suitable excipients are well known to those skilled in the art, for example, carbohydrate, wax, water-soluble and/or water-swelling polymers, hydrophilic or hydrophobic material, gelatin, oil, solvent, water, or the like.

The word “comprise” and variations thereof such as “comprises” or “comprising” will be understood

in an open, non-exclusive sense, i.e., “including but not limited to”.

The compounds and intermediates disclosed herein may also exist in different tautomeric forms, and all such forms are included within the scope of the present application. The term “tautomer” or “tautomeric form” refers to structural isomers of different energies that can interconvert via a low energy barrier. For example, a proton tautomer (also referred to as prototropic tautomer) includes interconversion via proton transfer, such as keto-enol isomerism and imine-enamine isomerization. A specific example of a proton tautomer is an imidazole moiety where a proton can transfer between two ring nitrogens. A valence tautomer includes the interconversion via recombination of some bonding electrons.

The present application also comprises isotopically labeled compounds of the present application which are identical to those recited herein but have one or more atoms replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number generally found in nature. Examples of isotopes that can be incorporated into the compounds of the present application include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorus, sulfur, fluorine, iodine and chlorine, such as ^2H , ^3H , ^{11}C , ^{13}C , ^{14}C , ^{13}N , ^{15}N , ^{15}O , ^{17}O , ^{18}O , ^{31}P , ^{32}P , ^{35}S , ^{18}F , ^{123}I , ^{125}I , and ^{36}Cl .

Certain isotopically labeled compounds of the present application (e.g., those labeled with ^3H and ^{14}C) can be used to analyze compounds and/or substrate tissue distribution. Tritiated (i.e., ^3H) and carbon-14 (i.e., ^{14}C) isotopes are particularly preferred for their ease of preparation and detectability. Positron emitting isotopes, such as ^{15}O , ^{13}N , ^{11}C , and ^{18}F , can be used in positron emission tomography (PET) studies to determine substrate occupancy. Isotopically labeled compounds of the present application can generally be prepared by following procedures analogous to those disclosed in the schemes and/or examples below while substituting a non-isotopically labeled reagent with an isotopically labeled reagent.

Furthermore, substitution with heavier isotopes such as deuterium (i.e., ^2H) may provide certain therapeutic advantages (e.g., increased *in vivo* half-life or reduced dosage) resulting from greater metabolic stability and hence may be preferred in some circumstances in which deuterium substitution may be partial or complete, wherein partial deuterium substitution refers to substitution of at least one hydrogen with at least one deuterium, and all such forms of the compounds are included within the scope of the present application.

The compound disclosed herein can be asymmetrical, for example, having one or more

stereoisomers. Unless otherwise stated, all stereoisomers are included, for example, enantiomers and diastereoisomers. The compound with asymmetrical carbon atoms disclosed herein can be separated in an optically pure form or in a racemic form. The optically pure form can be separated from a racemic mixture or can be synthesized using a chiral raw material or a chiral reagent.

The pharmaceutical composition of the present application can be prepared by combining the compound of the present application with a suitable pharmaceutically acceptable excipient, and can be formulated, for example, into a solid, semisolid, liquid or gaseous formulation such as tablet, pill, capsule, powder, granule, ointment, emulsion, suspension, suppository, injection, inhalant, gel, microsphere, aerosol, and the like.

Typical routes of administration of the compound or the pharmaceutically acceptable salt thereof or the pharmaceutical composition thereof of the present application include, but are not limited to, oral, rectal, local, inhalation, parenteral, sublingual, intravaginal, intranasal, intraocular, intraperitoneal, intramuscular, subcutaneous and intravenous administration.

The pharmaceutical composition of the present application can be manufactured using methods well known in the art, such as conventional mixing, dissolving, granulating, dragee-making, levigating, emulsifying, and lyophilizing.

In some embodiments, the pharmaceutical composition is in an oral form. For oral administration, the pharmaceutical composition can be formulated by mixing the active compounds with pharmaceutically acceptable excipients well known in the art. These excipients enable the compounds of the present application to be formulated into tablets, pills, pastilles, dragees, capsules, liquids, gels, slurries, suspensions, and the like for oral administration to a patient.

A solid oral composition can be prepared by conventional mixing, filling or tableting. For example, it can be obtained by the following method: mixing the active compounds with solid excipients, optionally grinding the resulting mixture, adding additional suitable excipients if desired, and processing the mixture into granules to get the core parts of tablets or dragees. Suitable excipients include, but are not limited to: binders, diluents, disintegrants, lubricants, glidants, sweeteners or flavoring agents, and the like.

The pharmaceutical composition may also be suitable for parenteral administration, such as a sterile solution, a suspension, or a lyophilized product in a suitable unit dosage form.

Therapeutic dosages of the compound of the present application may be determined by, for example,

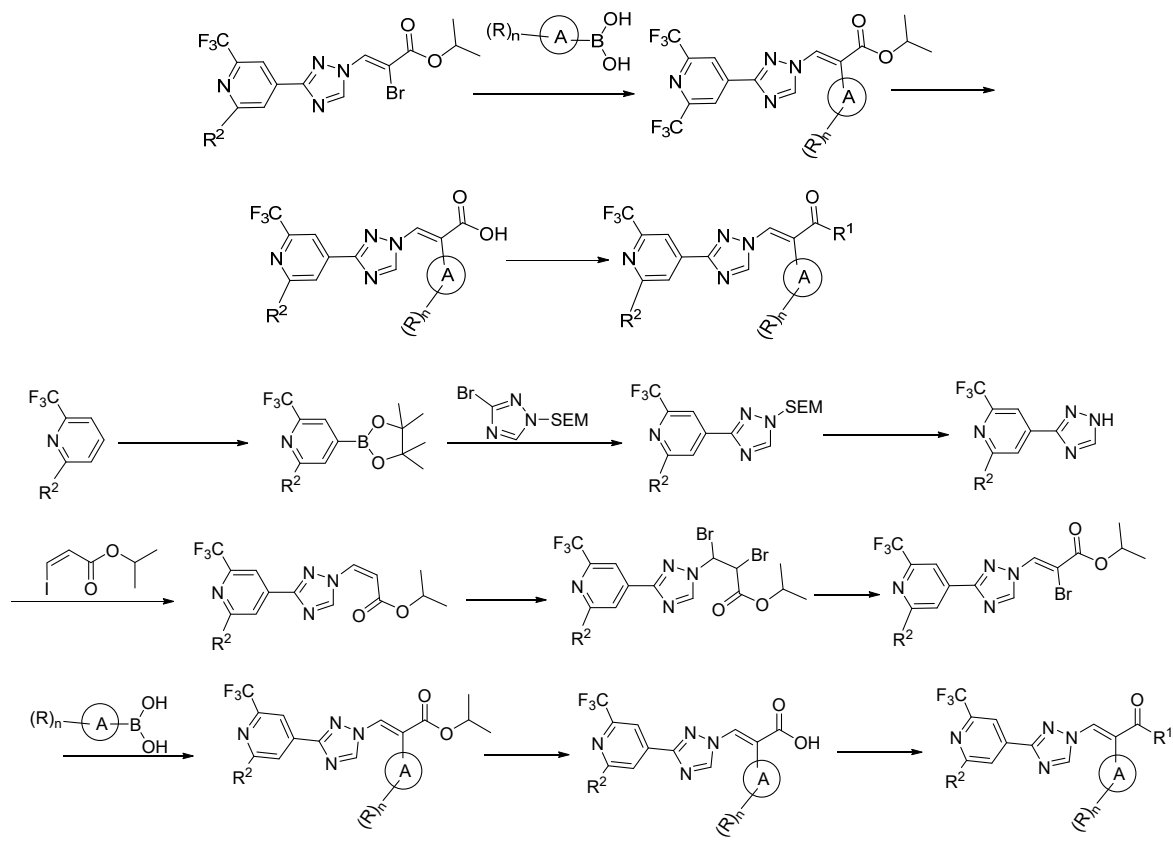
the specific use of a treatment, the route of administration of the compound, the health and condition of a patient, and the judgment of a prescribing physician. The proportion or concentration of the compound disclosed herein in a pharmaceutical composition may not be constant and depends on a variety of factors including dosages, chemical properties (e.g., hydrophobicity), and routes of administration. For example, the compound of the present application may be provided for parenteral administration by a physiological buffered aqueous solution containing about 0.1-10%w/v of the compound. Certain typical dosages range from about 1 µg/kg body weight/day to about 1 g/kg body weight/day. In certain embodiments, the dosage ranges from about 0.01 mg/kg body weight/day to about 100 mg/kg body weight/day. The dosage is likely to depend on such variables as the type and degree of progression of the disease or disorder, the general health condition of a particular patient, the relative biological potency of the compound selected, the excipient formulation, and its route of administration. Effective doses can be extrapolated from dose-response curves derived from *in vitro* or animal model test systems.

The compounds disclosed herein can be prepared using a variety of synthetic methods well known to those skilled in the art, including the specific embodiments listed below, embodiments formed by combinations thereof with other chemical synthetic methods, and equivalents thereof known to those skilled in the art. The preferred embodiments include, but are not limited to, the examples of the present application.

The chemical reactions of the specific embodiments of the present application are conducted in a proper solvent that must be suitable for the chemical changes in the present application and the reagents and materials required. In order to obtain the compounds of the present application, it is sometimes necessary for those skilled in the art to modify or select a synthesis procedure or a reaction process based on the existing embodiments.

An important consideration in synthetic route planning in the art is the selection of suitable protecting groups for reactive functional groups (e.g., amino in the present application). For example, reference may be made to Greene's Protective Groups in Organic Synthesis (4th Ed.) Hoboken, New Jersey: John Wiley & Sons, Inc.

In some embodiments, the compound disclosed herein may be prepared using the following preparation routes in combination with methods known in the art:



wherein ring A, R, n, R^2 , and R^1 are as defined in the present application.

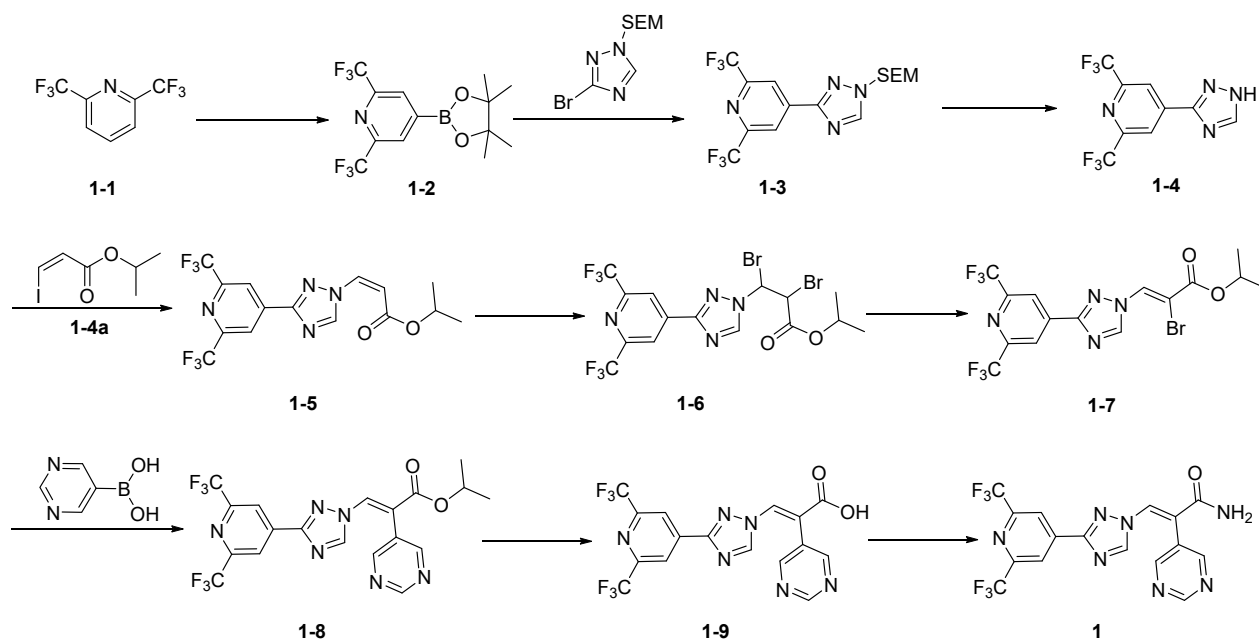
The following abbreviations are used in this application:

Pd(dppf)Cl_2 represents [1,1'-bis(diphenylphosphino)ferrocene]palladium dichloride; DMF represents N,N-dimethylformamide; DABCO represents triethylenediamine; THF represents tetrahydrofuran; SEM represents trimethylsilylethoxymethyl.

For clarity, the present application is further described with the following examples, which are, however, not intended to limit the scope of the present application. All reagents used in the present application are commercially available and can be used without further purification.

DETAILED DESCRIPTION

Example 1



(1) Preparation of compound 1-2

Bis(pinacolato)diboron (2.13 g), 4,4'-di-*tert*-butyl-2,2'-bipyridine (18.7 mg), and (1,5-cyclooctadiene)(methoxy)iridium(I) dimer (23.1 mg) were added to cyclohexane (30 mL). Under nitrogen atmosphere, the mixture was stirred for 10 min, and 3,5-bis(trifluoromethyl)pyridine (compound **1-1**, 3.0 g) was added. The resulting mixture was stirred at 55 °C under nitrogen atmosphere. After the reaction was completed, the reaction solution was quenched with ice water (20 mL) and extracted with ethyl acetate (30 mL $\times$ 3). The organic phase was collected, dried over anhydrous sodium sulfate, and filtered, and the filtrate was evaporated to dryness under reduced pressure to give compound **1-2**, which was directly used in the next step.

(2) Preparation of compound 1-3

Compound **1-2** (4.7 g) was added to ethylene glycol dimethyl ether (50 mL), and 3-bromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-1,2,4-triazole (3.9 g) and an aqueous solution (10 mL) of potassium carbonate (5.8 g) were added. The mixture was stirred at room temperature under nitrogen atmosphere. After 1 h, tetrakis(triphenylphosphine)palladium (805.8 mg) was added, and the resulting mixture was stirred at 90 °C under nitrogen atmosphere. After the reaction was completed, the reaction solution was quenched with ice water (40 mL) and extracted with ethyl acetate (100 mL). The organic phase was collected and washed with brine (50 mL $\times$ 2). The organic layer was dried over anhydrous sodium sulfate and filtered, and the filtrate was evaporated to dryness under reduced pressure to give compound **1-3**, which was directly used in the next step.

(3) Preparation of compound 1-4

Compound **1-3** (5.7 g) was dispersed in 4 M HCl/dioxane (50 mL), and the mixture was stirred at 60 °C. After the reaction was completed, the reaction solution was slowly poured into an ice saturated sodium bicarbonate solution. The resulting mixture was adjusted to pH = 6-7 with sodium bicarbonate and extracted with ethyl acetate (100 mL $\times$ 3). The organic phase was washed with saturated brine (100 mL), dried over anhydrous sodium sulfate, concentrated under reduced pressure until no liquid flowed out, and purified by column chromatography to give compound **1-4**.

(4) Preparation of compound 1-5

Compound **1-4** (900 mg) was dispersed in DMF (20 mL), and DABCO (716 mg) was added. The mixture was stirred at 20-25 °C for 30 min and then cooled to 0-10 °C, and compound **1-4a** (1.15 g) was added dropwise. After addition, the resulting mixture was stirred at 20-25 °C for 1.5 h. After the reaction was completed, the reaction solution was poured into water (50 mL), and the resulting mixture was extracted with ethyl acetate (50 mL $\times$ 2). The organic phases were combined, dried over anhydrous sodium sulfate, and purified by column chromatography to give compound **1-5** (750 mg).

(5) Preparation of compound 1-6

Compound **1-5** (750 mg) was added to dichloromethane (20 mL), and the mixture was cooled to 0 °C. Liquid bromine (605 mg) was added dropwise within 15 min. After addition, the mixture was slowly heated to room temperature and stirred for 4 h. After the reaction was completed, the reaction mixture was poured into ice water (30 mL), and the resulting mixture was extracted with dichloromethane (30 mL $\times$ 3). The organic phases were combined, washed with a saturated sodium bisulfite solution (30 mL), dried over anhydrous sodium sulfate, concentrated under reduced pressure until no liquid flowed out, and purified by column chromatography to give compound **1-6**.

(6) Preparation of compound 1-7

Compound **1-6** (1.05 g) was added to THF (20 mL), and the mixture was cooled to 0 °C. Triethylamine (383.5 mg) was added dropwise. After addition, the mixture was slowly heated to room temperature and reacted for 12 h. After the reaction was completed, the reaction solution was diluted with water (20 mL) and extracted with ethyl acetate (30 mL $\times$ 3). The organic phases were combined, dried over anhydrous sodium sulfate, and purified by column chromatography to give compound **1-7**.

(7) Preparation of compound 1-8

Compound **1-7** (700 mg), 5-pyrimidineboronic acid (220 mg), potassium acetate (435.7 mg), and Pd(dppf)Cl₂ (54 mg) were added to dioxane (20 mL) and water (2 mL). The mixture was heated to 90 °C and reacted under nitrogen atmosphere. After the reaction was completed, the reaction solution was diluted with water (20 mL) and extracted with ethyl acetate (30 mL × 3). The organic phase was collected, dried over anhydrous sodium sulfate, and filtered, and the filtrate was evaporated to dryness under reduced pressure and purified by column chromatography to give compound **1-8** (200 mg).

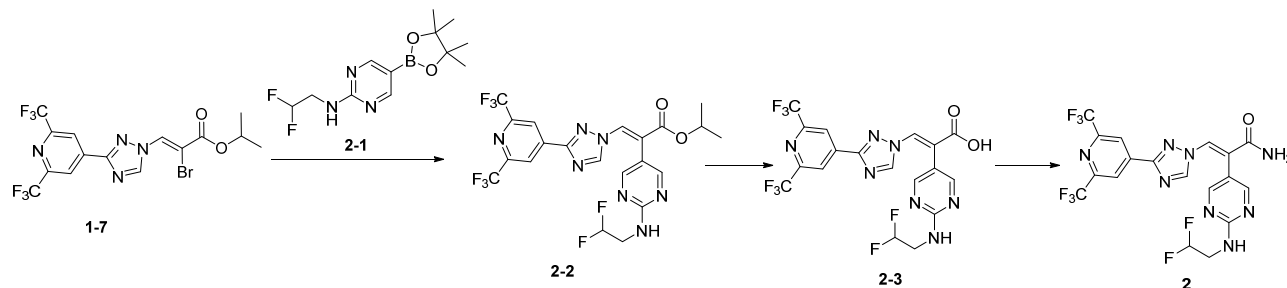
(8) Preparation of compound 1-9

Compound **1-8** (200 mg) was dissolved in tetrahydrofuran (15 mL), a solution of sodium hydroxide (33.9 mg) and water (15 mL) was added dropwise in an ice-water bath, and the mixture was reacted at room temperature overnight. The reaction solution was adjusted to acidity (pH 3-5) with hydrochloric acid, extracted with ethyl acetate (30 mL × 3), dried over anhydrous sodium sulfate, and filtered, and the filtrate was evaporated to dryness under reduced pressure to give compound **1-9**, which was directly used in the next step.

(9) Preparation of Example 1

Compound **1-9** (182 mg) was added to tetrahydrofuran (15 mL), N-methylmorpholine (85.6 mg) and isobutyl chloroformate (115.5 mg) were added in an ice-water bath, and the mixture was stirred for 30 min. Ammonium hydroxide (88.8 mg) was added dropwise, and the mixture was reacted in an ice-water bath for 10 min. Water was added to quench the reaction, and the resulting mixture was extracted with ethyl acetate (30 mL × 3), dried over anhydrous sodium sulfate, concentrated until no liquid flowed out, and purified by preparative liquid chromatography to give Example **1** (13 mg). ESI-MS: $m/z = 430.26$ [M+H]⁺. ¹H NMR (500 MHz, DMSO-*d*₆) δ 9.22 (d, *J* = 9.8 Hz, 2H), 8.74 (s, 2H), 8.45 (s, 1H), 8.07 (s, 2H), 7.68 (s, 1H), 7.44 (s, 1H).

Example 2



(1) Preparation of compound 2-2:

Compounds **1-7** (394 mg) and **2-1** (285 mg) were dispersed in 1,4-dioxane (8 mL), and potassium acetate (244 mg), Pd(dppf)Cl₂ (29 mg), and water (0.8 mL) were added. The mixture was heated to 90 °C and reacted under nitrogen atmosphere. After the reaction was completed, the reaction solution was concentrated under reduced pressure and purified by column chromatography to give compound **2-2**.

(2) Preparation of compound 2-3:

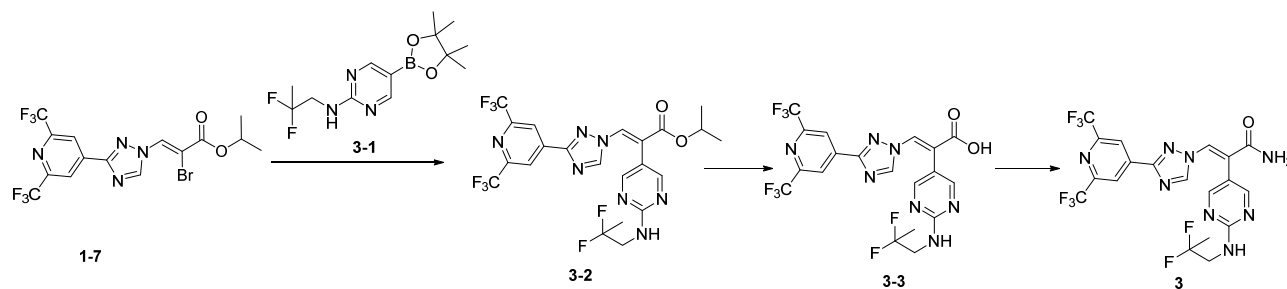
Compound **2-2** (100 mg) was dissolved in tetrahydrofuran (5 mL), a solution of lithium hydroxide hydrate (38.1 mg) and water (5 mL) was added dropwise in an ice-water bath, and the mixture was reacted at room temperature for 2 h. The reaction solution was adjusted to pH 3-5 with hydrochloric acid, extracted with ethyl acetate (20 mL × 2), dried over anhydrous sodium sulfate, and filtered, and the filtrate was evaporated to dryness under reduced pressure to give compound **2-3**, which was directly used in the next step.

(3) Preparation of compound 2:

Compound **2-3** (91 mg) was dispersed in tetrahydrofuran (5 mL), N-methylmorpholine (36 mg) and isobutyl chloroformate (49 mg) were added in an ice-water bath, and the mixture was stirred for 30 min. Ammonium hydroxide (38 mg) was added dropwise, and the mixture was reacted in an ice-water bath for 10 min. Water was added to quench the reaction, and the resulting mixture was extracted with ethyl acetate (20 mL × 2), dried over anhydrous sodium sulfate, concentrated until no liquid flowed out, and purified by preparative liquid chromatography to give compound **2** (41 mg). ESI-MS: $m/z = 509.32 [M+H]^+$.

¹H NMR (500 MHz, DMSO-*d*₆) δ 9.14 (s, 1H), 8.25 (d, $J = 10.4$ Hz, 5H), 7.76 (t, $J = 6.2$ Hz, 1H), 7.58 (s, 1H), 7.43 (s, 1H), 6.09 (tt, $J = 56.5, 4.2$ Hz, 1H), 3.74 (dddd, $J = 19.0, 14.9, 8.2, 5.2$ Hz, 2H).

Example 3



(1) Preparation of compound 3-2:

Compounds **1-7** (394 mg) and **3-1** (299 mg) were dispersed in 1,4-dioxane (8 mL), and potassium

acetate (244 mg), Pd(dppf)Cl₂ (29 mg), and water (0.8 mL) were added. The mixture was heated to 90 °C and reacted under nitrogen atmosphere. After the reaction was completed, the reaction solution was concentrated under reduced pressure and purified by column chromatography to give compound **3-2**.

(2) Preparation of compound 3-3:

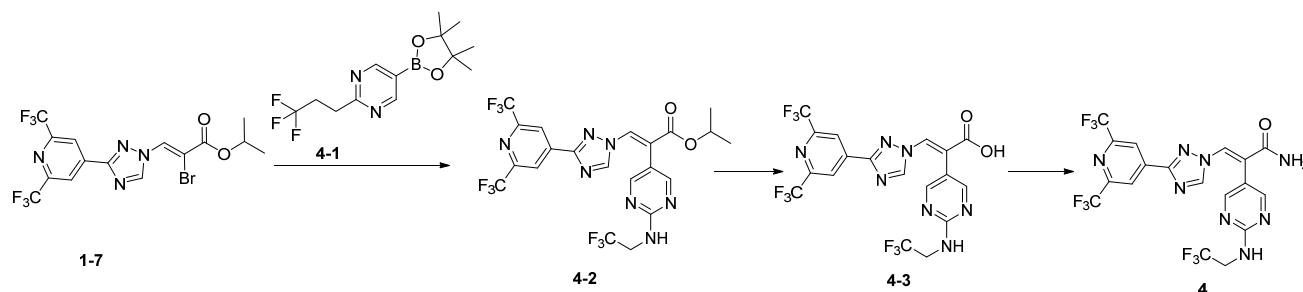
Compound **3-2** (360 mg) was dissolved in tetrahydrofuran (5 mL), a solution of lithium hydroxide hydrate (133.6 mg) and water (5 mL) was added dropwise in an ice-water bath, and the mixture was reacted at room temperature for 2 h. The reaction solution was adjusted to pH 3-5 with hydrochloric acid, extracted with ethyl acetate (20 mL × 2), dried over anhydrous sodium sulfate, and filtered, and the filtrate was evaporated to dryness under reduced pressure to give compound **3-3**, which was directly used in the next step.

(3) Preparation of compound 3:

Compound **3-3** (335 mg) was dispersed in tetrahydrofuran (10 mL), N-methylmorpholine (129 mg) and isobutyl chloroformate (175 mg) were added in an ice-water bath, and the mixture was stirred for 30 min. Ammonium hydroxide (134 mg) was added dropwise, and the mixture was reacted in an ice-water bath for 10 min. Water was added to quench the reaction, and the resulting mixture was extracted with ethyl acetate (20 mL × 2), dried over anhydrous sodium sulfate, concentrated until no liquid flowed out, and purified by preparative liquid chromatography to give compound **3** (90 mg). ESI-MS: $m/z = 523.37 [M+H]^+$.

¹H NMR (500 MHz, DMSO-*d*₆) δ 9.14 (s, 1H), 8.26 (s, 2H), 8.21 (d, *J* = 5.5 Hz, 3H), 7.76 (t, *J* = 6.6 Hz, 1H), 7.57 (s, 1H), 7.45 (s, 1H), 3.83 (td, *J* = 13.6, 6.6 Hz, 2H), 1.61 (t, *J* = 19.0 Hz, 3H).

Example 4



(1) Preparation of compound 4-2:

Compounds **1-7** (300 mg) and **4-1** (230 mg) were dispersed in 1,4-dioxane (8 mL), and potassium

acetate (186.6 mg), Pd(dppf)Cl₂ (46 mg), and water (0.8 mL) were added. The mixture was heated to 90 °C and reacted under nitrogen atmosphere. After the reaction was completed, the reaction solution was concentrated under reduced pressure and purified by column chromatography to give compound **4-2**.

(2) Preparation of compound 4-3:

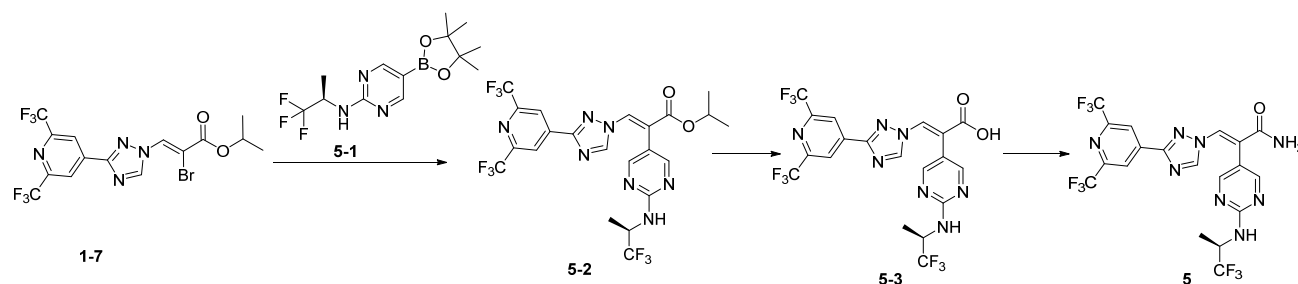
Compound **4-2** (302 mg) was dissolved in tetrahydrofuran (10 mL), a solution of lithium hydroxide hydrate (44.6 mg) and water (10 mL) was added dropwise in an ice-water bath, and the mixture was reacted at room temperature for 3 h. The reaction solution was adjusted to pH 3-5 with hydrochloric acid, extracted with ethyl acetate (20 mL × 2), dried over anhydrous sodium sulfate, and filtered, and the filtrate was evaporated to dryness under reduced pressure to give compound **4-3**, which was directly used in the next step.

(3) Preparation of compound 4:

Compound **4-3** (280 mg) was dispersed in tetrahydrofuran (15 mL), N-methylmorpholine (107 mg) and isobutyl chloroformate (145 mg) were added in an ice-water bath, and the mixture was stirred for 30 min. Ammonium hydroxide (111 mg) was added dropwise, and the mixture was reacted in an ice-water bath for 10 min. Water was added to quench the reaction, and the resulting mixture was extracted with ethyl acetate (20 mL × 2), dried over anhydrous sodium sulfate, concentrated until no liquid flowed out, and purified by preparative liquid chromatography to give compound **4** (30 mg). ESI-MS: $m/z = 527.17 [M+H]^+$.

¹H NMR (500 MHz, DMSO-*d*₆) δ 9.16 (s, 1H), 8.24 (d, *J* = 4.6 Hz, 5H), 7.99 (t, *J* = 6.7 Hz, 1H), 7.57 (s, 1H), 7.45 (s, 1H), 4.18 (q, *J* = 8.7, 8.3 Hz, 2H).

Example 5



(1) Preparation of compound 5-2:

Compounds **1-7** (300 mg) and **5-1** (241 mg) were dispersed in 1,4-dioxane (8 mL), and potassium acetate (187 mg), Pd(dppf)Cl₂ (23 mg), and water (0.8 mL) were added. The mixture was heated to

90 °C and reacted under nitrogen atmosphere. After the reaction was completed, the reaction solution was concentrated under reduced pressure and purified by column chromatography to give compound **5-2**.

(2) Preparation of compound 5-3:

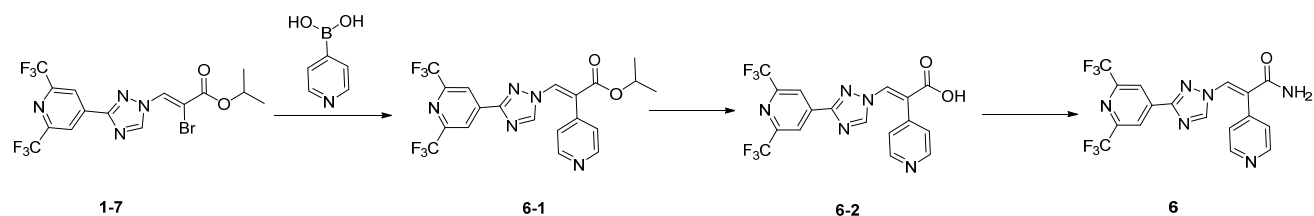
Compound **5-2** (200 mg) was dissolved in tetrahydrofuran (10 mL), a solution of lithium hydroxide hydrate (29 mg) and water (10 mL) was added dropwise in an ice-water bath, and the mixture was reacted at 0-10 °C for 3 h. The reaction solution was adjusted to pH 3-5 with hydrochloric acid, extracted with ethyl acetate (20 mL × 2), dried over anhydrous sodium sulfate, and filtered, and the filtrate was evaporated to dryness under reduced pressure to give compound **5-3**, which was directly used in the next step.

(3) Preparation of compound 5:

Compound **5-3** (185 mg) was dispersed in tetrahydrofuran (15 mL), N-methylmorpholine (69 mg) and isobutyl chloroformate (94 mg) were added in an ice-water bath, and the mixture was stirred for 30 min. Ammonium hydroxide (72 mg) was added dropwise, and the mixture was reacted in an ice-water bath for 10 min. Water was added to quench the reaction, and the resulting mixture was extracted with ethyl acetate (20 mL × 2), dried over anhydrous sodium sulfate, concentrated until no liquid flowed out, and purified by preparative liquid chromatography to give compound **5** (50 mg). ESI-MS: $m/z = 541.25 [M+H]^+$.

^1H NMR (500 MHz, DMSO- d_6) δ 9.17 (d, $J = 3.5$ Hz, 1H), 8.25 (q, $J = 3.8$ Hz, 5H), 7.96 (dd, $J = 9.3, 3.2$ Hz, 1H), 7.58 (s, 1H), 7.47 (s, 1H), 5.02 – 4.86 (m, 1H), 1.36 (dd, $J = 7.3, 3.2$ Hz, 3H).

Example 6



(1) Preparation of compound 6-1:

Compound **1-7** (200 mg) and pyridine-4-boronic acid (62.35 mg) were dispersed in 1,4-dioxane (10 mL), and potassium acetate (124.4 mg), Pd(dppf)Cl₂ (15.5 mg), and water (1 mL) were added. The mixture was heated to 90 °C and reacted under nitrogen atmosphere. After the reaction was completed, the reaction solution was concentrated under reduced pressure and purified by column

chromatography to give compound **6-1**.

(2) Preparation of compound 6-2:

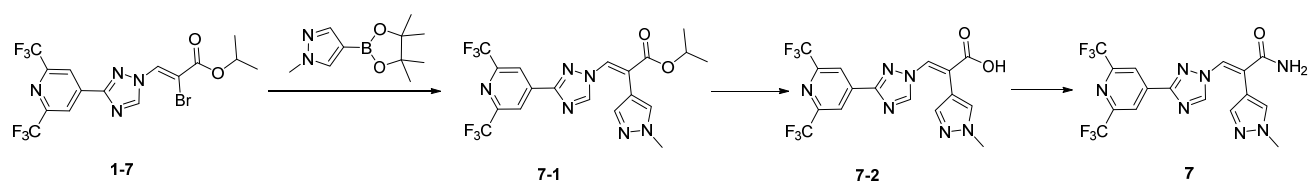
Compound **6-1** (150 mg) was dissolved in tetrahydrofuran (10 mL), a solution of lithium hydroxide hydrate (67.14 mg) and water (10 mL) was added dropwise in an ice-water bath, and the mixture was reacted at room temperature for 3 h. The reaction solution was adjusted to pH 3-5 with hydrochloric acid, extracted with ethyl acetate (20 mL $\times$ 2), dried over anhydrous sodium sulfate, and filtered, and the filtrate was evaporated to dryness under reduced pressure to give compound **6-2**, which was directly used in the next step.

(3) Preparation of compound 6:

Compound **6-2** (137.4 mg) was dispersed in tetrahydrofuran (10 mL), N-methylmorpholine (64.74 mg) and isobutyl chloroformate (87.41 mg) were added in an ice-water bath, and the mixture was stirred for 30 min. Ammonium hydroxide (67.2 mg) was added dropwise, and the mixture was reacted in an ice-water bath for 10 min. Water was added to quench the reaction, and the resulting mixture was extracted with ethyl acetate (20 mL $\times$ 2), dried over anhydrous sodium sulfate, concentrated until no liquid flowed out, and purified by preparative liquid chromatography to give compound **6** (10 mg). ESI-MS: $m/z = 429.19 [M+H]^+$.

^1H NMR (500 MHz, DMSO- d_6) δ 9.02 (s, 1H), 8.65 (d, $J = 5.0$ Hz, 2H), 8.26 (s, 1H), 8.10 (s, 2H), 7.66 (s, 1H), 7.32 (d, $J = 5.0$ Hz, 2H), 7.23 (s, 1H).

Example 7



(1) Preparation of compound 7-1:

Compound **1-7** (300 mg) and 1-methylpyrazole-4-boronic acid pinacol ester (158.3 mg) were dispersed in 1,4-dioxane (8 mL), and potassium acetate (186.6 mg), Pd(dppf)Cl₂ (46 mg), and water (0.8 mL) were added. The mixture was heated to 90 °C and reacted under nitrogen atmosphere. After the reaction was completed, the reaction solution was concentrated under reduced pressure to give compound **7-1**, which was directly used in the next step.

(2) Preparation of compound 7-2:

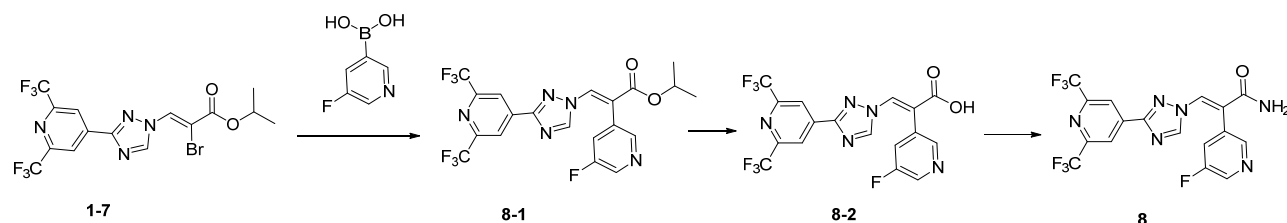
Compound **7-1** (298 mg) was dissolved in tetrahydrofuran (10 mL), a solution of lithium hydroxide hydrate (52.87 mg) and water (10 mL) was added dropwise in an ice-water bath, and the mixture was reacted at room temperature for 3 h. The reaction solution was adjusted to pH 3-5 with hydrochloric acid, extracted with ethyl acetate (20 mL $\times$ 2), dried over anhydrous sodium sulfate, and filtered, and the filtrate was evaporated to dryness under reduced pressure to give compound **7-2**, which was directly used in the next step.

(3) Preparation of compound 7:

Compound **7-2** (270 mg) was dispersed in tetrahydrofuran (15 mL), N-methylmorpholine (127.45 mg) and isobutyl chloroformate (154.41 mg) were added in an ice-water bath, and the mixture was stirred for 30 min. Ammonium hydroxide (132.3 mg) was added dropwise, and the mixture was reacted in an ice-water bath for 10 min. Water was added to quench the reaction, and the resulting mixture was extracted with ethyl acetate (20 mL $\times$ 2), dried over anhydrous sodium sulfate, concentrated until no liquid flowed out, and purified by preparative liquid chromatography to give compound **7** (77 mg). ESI-MS: $m/z = 432.18 [M+H]^+$.

^1H NMR (500 MHz, DMSO- d_6) δ 8.87 (s, 1H), 8.48 (s, 2H), 7.84 (s, 1H), 7.73 (s, 1H), 7.58 (s, 1H), 7.54 (s, 1H), 7.26 (d, $J = 0.9$ Hz, 1H), 3.85 (s, 3H).

Example 8



(1) Preparation of compound 8-1:

Compound **1-7** (200 mg) and 5-fluoro-3-pyridineboronic acid (75.03 mg) were dispersed in 1,4-dioxane (10 mL), and potassium acetate (124.4 mg), Pd(dppf)Cl₂ (15.5 mg), and water (1 mL) were added. The mixture was heated to 90 °C and reacted under nitrogen atmosphere. After the reaction was completed, the reaction solution was concentrated under reduced pressure and purified by column chromatography to give compound **8-1**.

(2) Preparation of compound 8-2:

Compound **8-1** (150 mg) was dissolved in tetrahydrofuran (10 mL), a solution of lithium hydroxide hydrate (65.1 mg) and water (10 mL) was added dropwise in an ice-water bath, and the mixture was

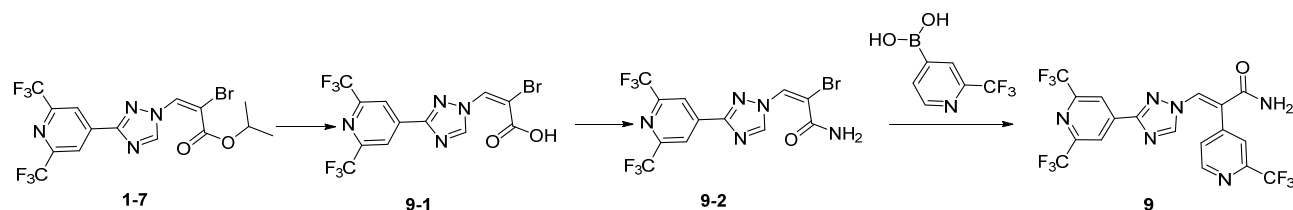
reacted at room temperature for 3 h. The reaction solution was adjusted to pH 3-5 with hydrochloric acid, extracted with ethyl acetate (20 mL $\times$ 2), dried over anhydrous sodium sulfate, and filtered, and the filtrate was evaporated to dryness under reduced pressure to give compound **8-2**, which was directly used in the next step.

(3) Preparation of compound **8**:

Compound **8-2** (138.65 mg) was dispersed in tetrahydrofuran (10 mL), N-methylmorpholine (62.71 mg) and isobutyl chloroformate (84.68 mg) were added in an ice-water bath, and the mixture was stirred for 30 min. Ammonium hydroxide (65.1 mg) was added dropwise, and the mixture was reacted in an ice-water bath for 10 min. Water was added to quench the reaction, and the resulting mixture was extracted with ethyl acetate (20 mL $\times$ 2), dried over anhydrous sodium sulfate, concentrated until no liquid flowed out, and purified by preparative liquid chromatography to give compound **8** (43 mg). ESI-MS: $m/z = 447.14$ $[M+H]^+$.

^1H NMR (500 MHz, DMSO- d_6) δ 9.15 (s, 1H), 8.63 (d, $J = 2.8$ Hz, 1H), 8.39 (s, 1H), 8.34 (d, $J = 1.8$ Hz, 1H), 8.09 (s, 2H), 7.76 (dt, $J = 10.0, 2.2$ Hz, 1H), 7.67 (s, 1H), 7.28 (s, 1H).

Example 9



(1) Preparation of compound **9-1**:

Compound **1-7** (500 mg) was dissolved in tetrahydrofuran (12 mL), a solution of sodium hydroxide (84.5 mg) and water (12 mL) was added dropwise in an ice-water bath, and the mixture was reacted at room temperature overnight. The reaction solution was adjusted to pH 3-5 with hydrochloric acid, extracted with ethyl acetate (30 mL $\times$ 2), dried over anhydrous sodium sulfate, and filtered, and the filtrate was evaporated to dryness under reduced pressure to give compound **9-1**, which was directly used in the next step.

(2) Preparation of compound **9-2**:

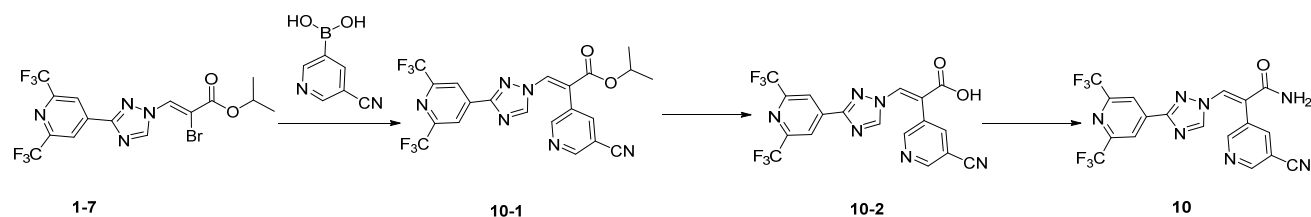
Compound **9-1** (455 mg) was dispersed in tetrahydrofuran (15 mL), N-methylmorpholine (213.7 mg) and isobutyl chloroformate (288.6 mg) were added in an ice-water bath, and the mixture was stirred for 30 min. Ammonium hydroxide (222 mg) was added dropwise, and the mixture was reacted in an

ice-water bath for 10 min. Water was added to quench the reaction, and the resulting mixture was extracted with ethyl acetate (20 mL $\times$ 2), dried over anhydrous sodium sulfate, and concentrated until no liquid flowed out to give compound **9-2**. ESI-MS: m/z = 430.04/432.06 $[M+H]^+$.

(3) Preparation of compound 9:

Compound **9-2** (180 mg) and 4-boronic acid-2-trifluoromethylpyridine (95.9 mg) were dispersed in 1,4-dioxane (6 mL), and potassium acetate (123 mg), Pd(dppf)Cl₂ (15.3 mg), and water (0.6 mL) were added. The mixture was heated to 90 °C and reacted under nitrogen atmosphere. After the reaction was completed, the reaction solution was concentrated under reduced pressure and purified by preparative liquid chromatography to give compound **9** (18 mg). ESI-MS: m/z = 497.09 $[M+H]^+$. ¹H NMR (500 MHz, DMSO-*d*₆) δ 9.21 (s, 1H), 8.83 (d, J = 4.9 Hz, 1H), 8.39 (s, 1H), 7.99 (s, 2H), 7.89 (s, 1H), 7.69 (s, 1H), 7.62 (d, J = 4.9 Hz, 1H), 7.29 (s, 1H).

Example 10



(1) Preparation of compound 10-1:

Compound **1-7** (200 mg) and 5-cyano-3-pyridinylboronic acid (75.03 mg) were dispersed in 1,4-dioxane (10 mL), and potassium acetate (124.4 mg), Pd(dppf)Cl₂ (15.5 mg), and water (1 mL) were added. The mixture was heated to 90 °C and reacted under nitrogen atmosphere. After the reaction was completed, the reaction solution was concentrated under reduced pressure and purified by column chromatography to give compound **10-1**.

(2) Preparation of compound 10-2:

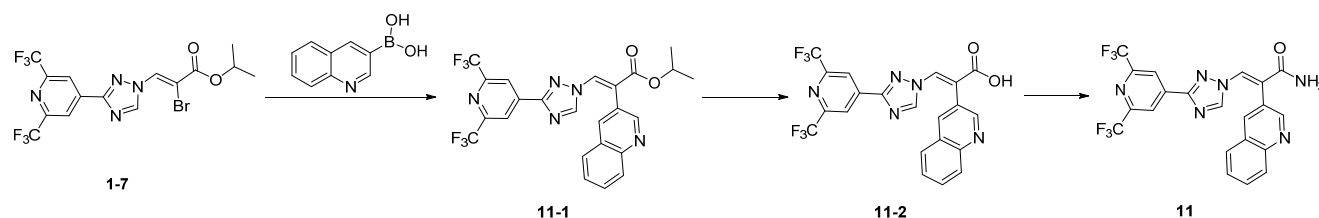
Compound **10-1** (173 mg) was dissolved in tetrahydrofuran (10 mL), a solution of lithium hydroxide hydrate (73.12 mg) and water (10 mL) was added dropwise in an ice-water bath, and the mixture was reacted at room temperature for 3 h. The reaction solution was adjusted to pH 3-5 with hydrochloric acid, extracted with ethyl acetate (20 mL $\times$ 2), dried over anhydrous sodium sulfate, and filtered, and the filtrate was evaporated to dryness under reduced pressure to give compound **10-2**, which was directly used in the next step.

(3) Preparation of compound 10:

Compound **10-2** (159 mg) was dispersed in tetrahydrofuran (10 mL), N-methylmorpholine (70.8 mg) and isobutyl chloroformate (95.6 mg) were added in an ice-water bath, and the mixture was stirred for 30 min. Ammonium hydroxide (73.5 mg) was added dropwise, and the mixture was reacted in an ice-water bath for 10 min. Water was added to quench the reaction, and the resulting mixture was extracted with ethyl acetate (20 mL $\times$ 2), dried over anhydrous sodium sulfate, concentrated until no liquid flowed out, and purified by preparative liquid chromatography to give compound **10** (23 mg). ESI-MS: $m/z = 454.20 [M+H]^+$.

^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 9.21 (s, 1H), 9.09 (d, $J = 2.0$ Hz, 1H), 8.76 (d, $J = 2.1$ Hz, 1H), 8.45 (s, 1H), 8.36 (t, $J = 2.1$ Hz, 1H), 8.05 (s, 2H), 7.70 (s, 1H), 7.30 (s, 1H).

Example 11



(1) Preparation of compound 11-1:

Compound **1-7** (300 mg) and 3-quinolineboronic acid (131.61 mg) were dispersed in 1,4-dioxane (8 mL), and potassium acetate (186.6 mg), $\text{Pd}(\text{dppf})\text{Cl}_2$ (46 mg), and water (0.8 mL) were added. The mixture was heated to 90 °C and reacted under nitrogen atmosphere. After the reaction was completed, the reaction solution was concentrated under reduced pressure to give compound **11-1**, which was directly used in the next step.

(2) Preparation of compound 11-2:

Compound **11-1** (328 mg) was dissolved in tetrahydrofuran (10 mL), a solution of lithium hydroxide hydrate (52.87 mg) and water (10 mL) was added dropwise in an ice-water bath, and the mixture was reacted at room temperature for 3 h. The reaction solution was adjusted to pH 3-5 with hydrochloric acid, extracted with ethyl acetate (20 mL $\times$ 2), dried over anhydrous sodium sulfate, and filtered, and the filtrate was evaporated to dryness under reduced pressure to give compound **11-2**, which was directly used in the next step.

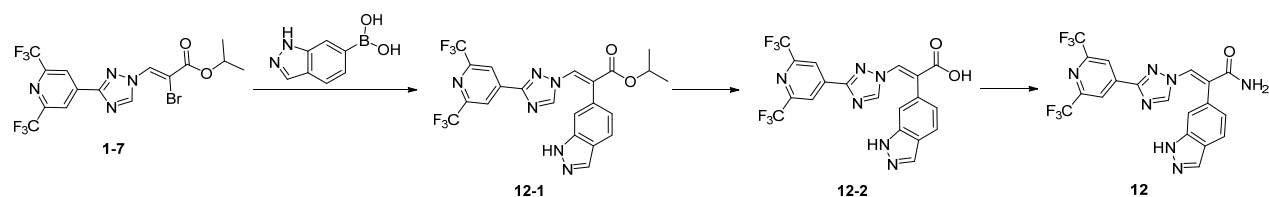
(3) Preparation of compound 11:

Compound **11-2** (301 mg) was dispersed in tetrahydrofuran (15 mL), N-methylmorpholine (127.45 mg) and isobutyl chloroformate (154.41 mg) were added in an ice-water bath, and the mixture was

stirred for 30 min. Ammonium hydroxide (132.3 mg) was added dropwise, and the mixture was reacted in an ice-water bath for 10 min. Water was added to quench the reaction, and the resulting mixture was extracted with ethyl acetate (20 mL $\times$ 2), dried over anhydrous sodium sulfate, concentrated until no liquid flowed out, and purified by preparative liquid chromatography to give compound **11** (30 mg); ESI-MS: m/z = 479.31 $[M+H]^+$.

^1H NMR (500 MHz, DMSO- d_6) δ 9.17 (s, 1H), 8.76 (d, J = 2.2 Hz, 1H), 8.43 (s, 1H), 8.30 (d, J = 2.2 Hz, 1H), 8.08 (d, J = 8.4 Hz, 1H), 8.01 (dd, J = 8.1, 1.4 Hz, 1H), 7.88 (s, 2H), 7.84 (ddd, J = 8.5, 6.9, 1.5 Hz, 1H), 7.70 – 7.62 (m, 2H), 7.36 (s, 1H).

Example 12



(1) Preparation of compound 12-1:

Compound **1-7** (300 mg) and indazole-6-boronic acid (123.22 mg) were dispersed in 1,4-dioxane (8 mL), and potassium acetate (186.6 mg), Pd(dppf)Cl₂ (46 mg), and water (0.8 mL) were added. The mixture was heated to 90 °C and reacted under nitrogen atmosphere. After the reaction was completed, the reaction solution was concentrated under reduced pressure to give compound **12-1**, which was directly used in the next step.

(2) Preparation of compound 12-2:

Compound **12-1** (321 mg) was dissolved in tetrahydrofuran (10 mL), a solution of lithium hydroxide hydrate (52.87 mg) and water (10 mL) was added dropwise in an ice-water bath, and the mixture was reacted at room temperature for 3 h. The reaction solution was adjusted to pH 3-5 with hydrochloric acid, extracted with ethyl acetate (20 mL $\times$ 2), dried over anhydrous sodium sulfate, and filtered, and the filtrate was evaporated to dryness under reduced pressure to give compound **12-2**, which was directly used in the next step.

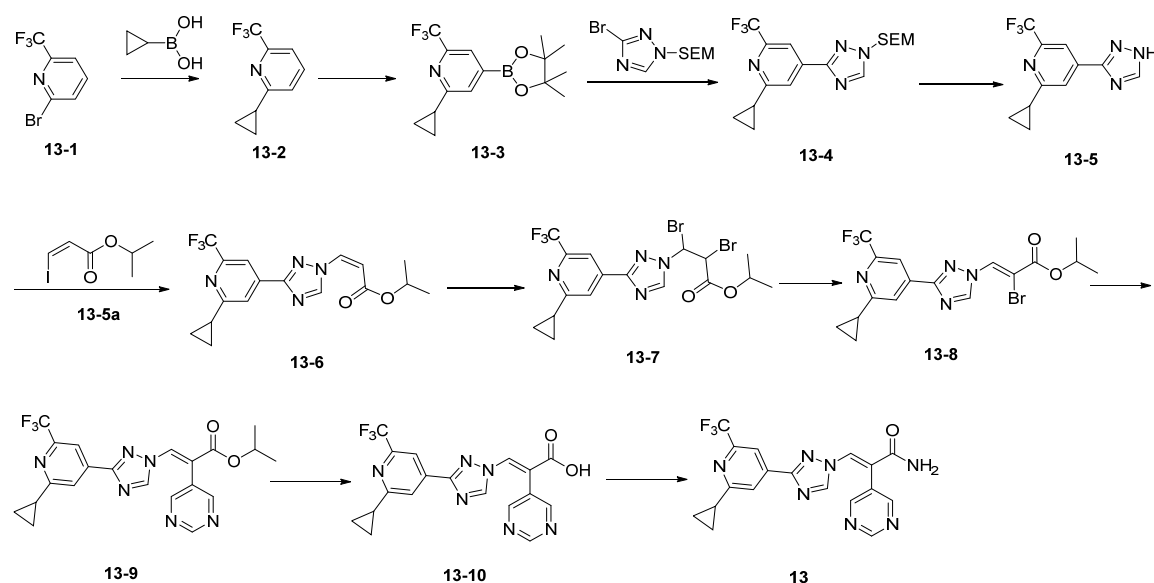
(3) Preparation of compound 12:

Compound **12-2** (295 mg) was dispersed in tetrahydrofuran (15 mL), N-methylmorpholine (127.45 mg) and isobutyl chloroformate (154.41 mg) were added in an ice-water bath, and the mixture was stirred for 30 min. Ammonium hydroxide (132.3 mg) was added dropwise, and the mixture was reacted in an ice-water bath for 10 min. Water was added to quench the reaction, and the resulting

mixture was extracted with ethyl acetate (20 mL $\times$ 2), dried over anhydrous sodium sulfate, concentrated until no liquid flowed out, and purified by preparative liquid chromatography to give compound **12** (40 mg). ESI-MS: m/z = 468.22 $[M+H]^+$.

^1H NMR (500 MHz, DMSO- d_6) δ 13.11 (s, 1H), 8.63 (s, 1H), 8.19 (s, 1H), 8.13 (t, J = 1.3 Hz, 1H), 8.09 (s, 2H), 7.82 (d, J = 8.2 Hz, 1H), 7.62 (s, 1H), 7.47 – 7.43 (m, 1H), 7.11 (s, 1H), 6.95 (dd, J = 8.3, 1.4 Hz, 1H).

Example 13



(1) Preparation of compound 13-2:

Compound **13-1** (15 g), cyclopropylboronic acid (11.4 g), potassium carbonate (27.5 g), and Pd(dppf)Cl₂ (2.4 g) were dispersed in dioxane (150 mL) and water (15 mL). The mixture was heated to 90 °C and reacted under nitrogen atmosphere. After the reaction was completed, the reaction solution was diluted with water (1000 mL) and extracted with ethyl acetate (100 mL $\times$ 3). The organic phase was collected, dried over anhydrous sodium sulfate, and filtered, and the filtrate was evaporated to dryness under reduced pressure and purified by column chromatography to give compound **13-2**.

(2) Preparation of compound 13-3:

Bis(pinacolato)diboron (6.51 g), 4,4'-di-*tert*-butyl-2,2'-bipyridine (76.16 mg), and (1,5-cyclooctadiene)(methoxy)iridium(I) dimer (70.82 mg) were dispersed in cyclohexane (80 mL). The mixture was stirred for 10 min under nitrogen atmosphere, and compound **13-2** (8.0 g) was added. The resulting mixture was stirred at 55 °C under nitrogen atmosphere. After the reaction was

completed, the reaction solution was quenched with ice water (80 mL) and extracted with ethyl acetate (80 mL $\times$ 3). The organic phase was collected, dried over anhydrous sodium sulfate, and filtered, and the filtrate was evaporated to dryness under reduced pressure to give compound **13-3**, which was directly used in the next step.

(3) Preparation of compound 13-4:

Compound **13-3** (10.7 g) was dispersed in ethylene glycol dimethyl ether (80 mL), and 3-bromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-1,2,4-triazole (10.5 g) and an aqueous solution (16 mL) of potassium carbonate (14.18 g) were added. The mixture was stirred at room temperature under nitrogen atmosphere. After 1 h, tetrakis(triphenylphosphine)palladium (1.97 g) was added, and the resulting mixture was stirred at 90 °C under nitrogen atmosphere. After the reaction was completed, the reaction solution was quenched with ice water (60 mL) and extracted with ethyl acetate (100 mL $\times$ 3). The organic phase was collected and washed with brine (60 mL $\times$ 2). The organic layer was dried over anhydrous sodium sulfate and filtered, and the filtrate was evaporated to dryness under reduced pressure to give compound **13-4**, which was directly used in the next step.

(4) Preparation of compound 13-5:

Compound **13-4** (6.0 g) was dispersed in a solution of hydrogen chloride in 1,4-dioxane (4.0 M, 50 mL), and the mixture was stirred at 60 °C until the reaction was completed. The reaction solution was slowly poured into an ice saturated sodium bicarbonate solution. The resulting mixture was adjusted to pH = 7-8 with sodium bicarbonate and extracted with ethyl acetate (100 mL $\times$ 3). The organic phase was washed with saturated brine (100 mL), dried over anhydrous sodium sulfate, concentrated under reduced pressure until no liquid flowed out, and purified by column chromatography to give compound **13-5**.

(5) Preparation of compound 13-6:

Compound **13-5** (4 g) was dispersed in DMF (20 mL) and dioxane (20 mL), and DABCO (3.5 g) was added. The mixture was stirred at 20-25 °C for 30 min and then cooled to 0-10 °C, and compound **13-5a** (5.6 g) was added dropwise. After addition, the resulting mixture was stirred at 20-25 °C for 1.5 h. After the reaction was completed, the reaction solution was poured into water (100 mL), and the resulting mixture was extracted with ethyl acetate (100 mL $\times$ 2). The organic phases were combined, dried over anhydrous sodium sulfate, and purified by column chromatography to give compound **13-6** (3.0 g).

(6) Preparation of compound 13-7:

Compound **13-6** (3 g) was dispersed in dichloromethane (30 mL), and the mixture was cooled to 0 °C. Liquid bromine (2.6 g) was added dropwise within 15 min. After addition, the mixture was slowly heated to room temperature and stirred for 6 h. After the reaction was completed, the reaction mixture was poured into ice water (40 mL), and the resulting mixture was extracted with dichloromethane (40 mL $\times$ 3). The organic phases were combined, washed with a saturated sodium bisulfite solution (30 mL), dried over anhydrous sodium sulfate, concentrated under reduced pressure until no liquid flowed out, and purified by column chromatography to give compound **13-7**.

(7) Preparation of compound 13-8:

Compound **13-7** (4.3 g) was dispersed in tetrahydrofuran (40 mL), and the mixture was cooled to 0 °C. Triethylamine (1.65 g) was added dropwise. After addition, the mixture was slowly heated to room temperature and reacted for 6 h. After the reaction was completed, the reaction solution was diluted with water (40 mL) and extracted with ethyl acetate (40 mL $\times$ 3). The organic phases were combined, dried over anhydrous sodium sulfate, and purified by column chromatography to give compound **13-8** (2 g).

(8) Preparation of compound 13-9:

Compound **13-8** (300 mg), 5-pyrimidineboronic acid (100 mg), potassium acetate (198 mg), and Pd(dppf)Cl₂ (24.6 mg) were dispersed in dioxane (8 mL) and water (0.8 mL). The mixture was heated to 90 °C and reacted under nitrogen atmosphere. After the reaction was completed, the reaction solution was diluted with water (15 mL) and extracted with ethyl acetate (20 mL $\times$ 3). The organic phase was collected, dried over anhydrous sodium sulfate, and filtered, and the filtrate was evaporated to dryness under reduced pressure and purified by column chromatography to give compound **13-9** (200 mg).

(9) Preparation of compound 13-10:

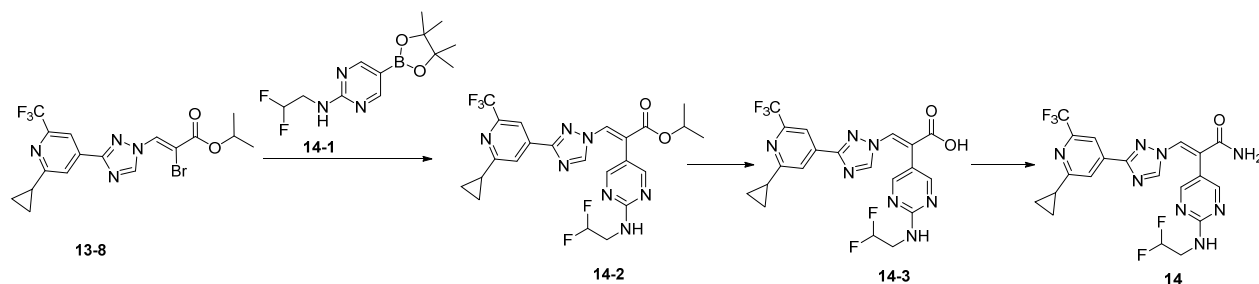
Compound **13-9** (200 mg) was dissolved in tetrahydrofuran (8 mL), a solution of sodium hydroxide (36 mg) and water (8 mL) was added dropwise in an ice-water bath, and the mixture was reacted at room temperature overnight. The reaction solution was adjusted to pH 3-5 with hydrochloric acid, extracted with ethyl acetate (20 mL $\times$ 3), dried over anhydrous sodium sulfate, and filtered, and the filtrate was evaporated to dryness under reduced pressure to give compound **13-10**, which was directly used in the next step.

(10) Preparation of compound 13:

Compound **13-10** (181 mg) was dispersed in tetrahydrofuran (10 mL), N-methylmorpholine (91 mg) and isobutyl chloroformate (123 mg) were added in an ice-water bath, and the mixture was stirred for 30 min. Ammonium hydroxide (95 mg) was added dropwise, and the mixture was reacted in an ice-water bath for 10 min. Water was added to quench the reaction, and the resulting mixture was extracted with ethyl acetate (20 mL $\times$ 3), dried over anhydrous sodium sulfate, concentrated until no liquid flowed out, and purified by preparative liquid chromatography to give compound **13** (57 mg). ESI-MS: $m/z = 402.27 [M+H]^+$.

^1H NMR (500 MHz, DMSO- d_6) δ 9.24 (s, 1H), 9.13 (s, 1H), 8.73 (s, 2H), 8.42 (s, 1H), 7.69 (s, 1H), 7.65 (s, 1H), 7.49 (s, 1H), 7.41 (s, 1H), 2.28 (tt, $J = 8.3, 4.7$ Hz, 1H), 1.10 (dq, $J = 6.6, 3.8$ Hz, 2H), 0.99 – 0.91 (m, 2H).

Example 14



(1) Preparation of compound 14-2:

Compounds **13-8** (300 mg) and **14-1** (228 mg) were dispersed in 1,4-dioxane (15 mL), and potassium acetate (196 mg), Pd(dppf)Cl₂ (22 mg), and water (1.5 mL) were added. The mixture was heated to 90 °C and reacted under nitrogen atmosphere. After the reaction was completed, the reaction solution was concentrated under reduced pressure and purified by column chromatography to give compound **14-2**.

(2) Preparation of compound 14-3:

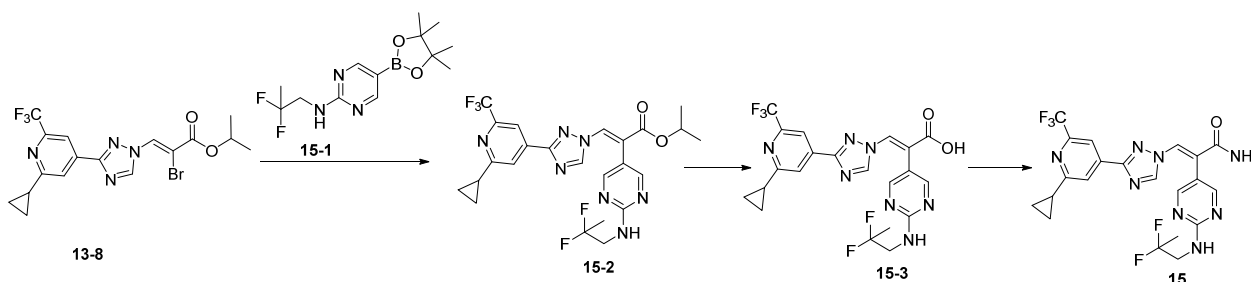
Compound **14-2** (100 mg) was dissolved in tetrahydrofuran (5 mL), a solution of lithium hydroxide hydrate (40.1 mg) and water (5 mL) was added dropwise in an ice-water bath, and the mixture was reacted at room temperature for 2 h. The reaction solution was adjusted to pH 3-5 with hydrochloric acid, extracted with ethyl acetate (20 mL $\times$ 2), dried over anhydrous sodium sulfate, and filtered, and the filtrate was evaporated to dryness under reduced pressure to give compound **14-3**, which was directly used in the next step.

(3) Preparation of compound 14:

Compound **14-3** (60 mg) was dispersed in tetrahydrofuran (5 mL), N-methylmorpholine (26 mg) and isobutyl chloroformate (35 mg) were added in an ice-water bath, and the mixture was stirred for 30 min. Ammonium hydroxide (27 mg) was added dropwise, and the mixture was reacted in an ice-water bath for 10 min. Water was added to quench the reaction, and the resulting mixture was extracted with ethyl acetate (20 mL $\times$ 2), dried over anhydrous sodium sulfate, concentrated until no liquid flowed out, and purified by preparative liquid chromatography to give compound **14** (10 mg). ESI-MS: $m/z = 481.3 [M+H]^+$.

^1H NMR (500 MHz, DMSO- d_6) δ 9.05 (s, 1H), 8.21 (s, 3H), 7.84 (d, $J = 1.3$ Hz, 1H), 7.76 (t, $J = 6.2$ Hz, 1H), 7.71 (d, $J = 1.3$ Hz, 1H), 7.55 (s, 1H), 7.40 (s, 1H), 6.10 (tt, $J = 56.5, 4.2$ Hz, 1H), 3.74 (tdd, $J = 15.0, 6.2, 4.1$ Hz, 2H), 2.30 (tt, $J = 8.1, 4.7$ Hz, 1H), 1.08 (dt, $J = 8.1, 3.2$ Hz, 2H), 0.99 – 0.95 (m, 2H).

Example 15



(1) Preparation of compound 15-2:

Compounds **13-8** (371 mg) and **15-1** (299 mg) were dispersed in 1,4-dioxane (55 mL), and potassium acetate (244 mg), Pd(dppf)Cl₂ (30 mg), and water (1.5 mL) were added. The mixture was heated to 90 °C and reacted under nitrogen atmosphere. After the reaction was completed, the reaction solution was concentrated under reduced pressure and purified by column chromatography to give compound **15-2**.

(2) Preparation of compound 15-3:

Compound **15-2** (340 mg) was dissolved in tetrahydrofuran (5 mL), a solution of lithium hydroxide hydrate (132.7 mg) and water (5 mL) was added dropwise in an ice-water bath, and the mixture was reacted at room temperature for 2 h. The reaction solution was adjusted to pH 3-5 with hydrochloric acid, extracted with ethyl acetate (20 mL $\times$ 2), dried over anhydrous sodium sulfate, and filtered, and the filtrate was evaporated to dryness under reduced pressure to give compound **15-3**, which was

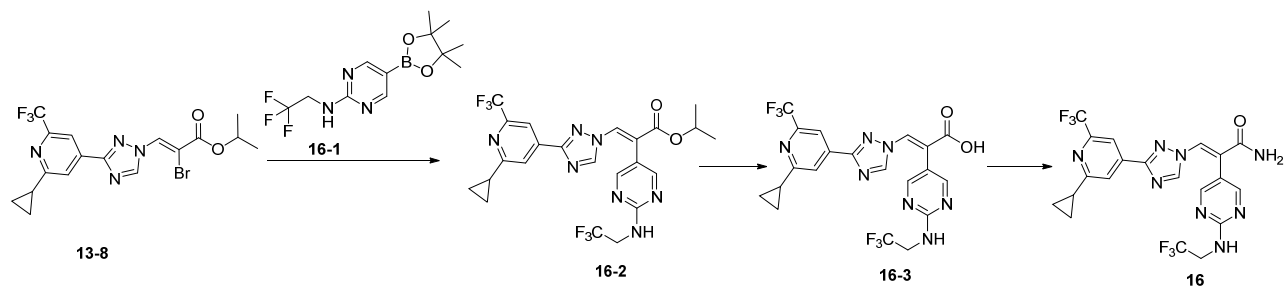
directly used in the next step.

(3) Preparation of compound 15:

Compound **15-3** (312 mg) was dispersed in tetrahydrofuran (5 mL), N-methylmorpholine (127 mg) and isobutyl chloroformate (172 mg) were added in an ice-water bath, and the mixture was stirred for 30 min. Ammonium hydroxide (132 mg) was added dropwise, and the mixture was reacted in an ice-water bath for 10 min. Water was added to quench the reaction, and the resulting mixture was extracted with ethyl acetate (20 mL $\times$ 2), dried over anhydrous sodium sulfate, concentrated until no liquid flowed out, and purified by preparative liquid chromatography to give compound **15** (70 mg). ESI-MS: $m/z = 495.39 [M+H]^+$.

^1H NMR (500 MHz, DMSO- d_6) δ 9.05 (s, 1H), 8.20 (d, $J = 3.2$ Hz, 3H), 7.84 (d, $J = 1.2$ Hz, 1H), 7.77 (t, $J = 6.6$ Hz, 1H), 7.73 (d, $J = 1.3$ Hz, 1H), 7.54 (s, 1H), 7.42 (s, 1H), 3.83 (td, $J = 13.6, 6.6$ Hz, 2H), 2.29 (tt, $J = 8.3, 4.7$ Hz, 1H), 1.61 (t, $J = 19.0$ Hz, 3H), 1.08 (dt, $J = 8.0, 3.2$ Hz, 2H), 1.00 – 0.94 (m, 2H).

Example 16



(1) Preparation of compound 16-2:

Compounds **13-8** (400 mg) and **16-1** (327 mg) were dispersed in 1,4-dioxane (15 mL), and potassium acetate (264 mg), Pd(dppf)Cl₂ (65.7 mg), and water (1.5 mL) were added. The mixture was heated to 90 °C and reacted under nitrogen atmosphere. After the reaction was completed, the reaction solution was concentrated under reduced pressure and purified by column chromatography to give compound **16-2**.

(2) Preparation of compound 16-3:

Compound **16-2** (300 mg) was dissolved in tetrahydrofuran (10 mL), a solution of lithium hydroxide hydrate (46.5 mg) and water (10 mL) was added dropwise in an ice-water bath, and the mixture was reacted at room temperature for 3 h. The reaction solution was adjusted to pH 3-5 with hydrochloric acid, extracted with ethyl acetate (20 mL $\times$ 2), dried over anhydrous sodium sulfate, and filtered, and

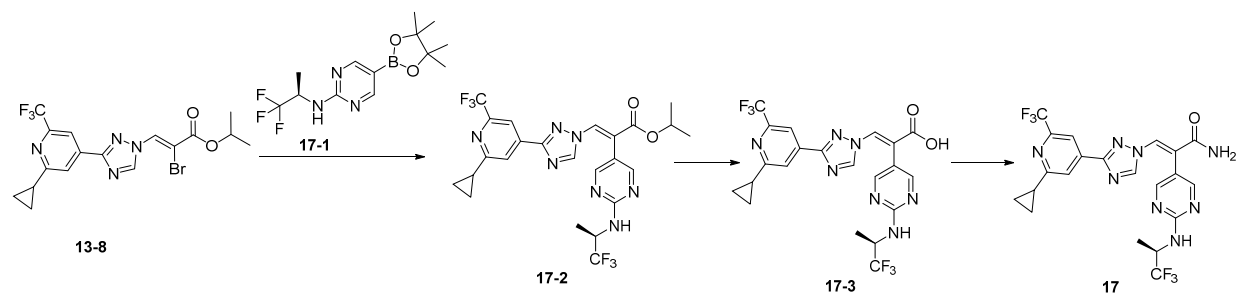
the filtrate was evaporated to dryness under reduced pressure to give compound **16-3**, which was directly used in the next step.

(3) Preparation of compound 16:

Compound **16-3** (276 mg) was dispersed in tetrahydrofuran (15 mL), N-methylmorpholine (112 mg) and isobutyl chloroformate (151 mg) were added in an ice-water bath, and the mixture was stirred for 30 min. Ammonium hydroxide (116 mg) was added dropwise, and the mixture was reacted in an ice-water bath for 10 min. Water was added to quench the reaction, and the resulting mixture was extracted with ethyl acetate (20 mL $\times$ 2), dried over anhydrous sodium sulfate, concentrated until no liquid flowed out, and purified by preparative liquid chromatography to give compound **16** (58.4 mg). ESI-MS: $m/z = 499.28 [M+H]^+$.

^1H NMR (500 MHz, DMSO- d_6) δ 9.07 (s, 1H), 8.23 (d, $J = 6.1$ Hz, 3H), 8.00 (t, $J = 6.7$ Hz, 1H), 7.83 (d, $J = 1.3$ Hz, 1H), 7.70 (d, $J = 1.3$ Hz, 1H), 7.55 (s, 1H), 7.42 (s, 1H), 4.18 (qd, $J = 9.5, 6.6$ Hz, 2H), 2.28 (tt, $J = 8.1, 4.7$ Hz, 1H), 1.08 (dt, $J = 8.0, 3.2$ Hz, 2H), 0.99 – 0.94 (m, 2H).

Example 17



(1) Preparation of compound 17-2:

Compounds **13-8** (400 mg) and **17-1** (342 mg) were dispersed in 1,4-dioxane (15 mL), and potassium acetate (264 mg), Pd(dppf)Cl₂ (65.7 mg), and water (1.5 mL) were added. The mixture was heated to 90 °C and reacted under nitrogen atmosphere. After the reaction was completed, the reaction solution was concentrated under reduced pressure and purified by column chromatography to give compound **17-2**.

(2) Preparation of compound 17-3:

Compound **17-2** (400 mg) was dissolved in tetrahydrofuran (10 mL), and a solution of lithium hydroxide hydrate (91 mg) and water (10 mL) was added dropwise in an ice-water bath. The temperature was controlled at 0-10 °C, and the mixture was reacted for 3 h. The reaction solution was adjusted to pH 3-5 with hydrochloric acid, extracted with ethyl acetate (20 mL $\times$ 2), dried over

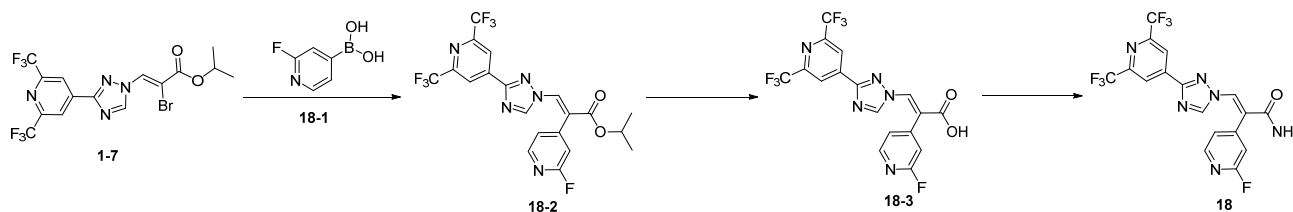
anhydrous sodium sulfate, and filtered, and the filtrate was evaporated to dryness under reduced pressure to give compound **17-3**, which was directly used in the next step.

(3) Preparation of compound 17:

Compound **17-3** (370 mg) was dispersed in tetrahydrofuran (15 mL), N-methylmorpholine (146 mg) and isobutyl chloroformate (197 mg) were added in an ice-water bath, and the mixture was stirred for 30 min. Ammonium hydroxide (151 mg) was added dropwise, and the mixture was reacted in an ice-water bath for 10 min. Water was added to quench the reaction, and the resulting mixture was extracted with ethyl acetate (20 mL $\times$ 2), dried over anhydrous sodium sulfate, concentrated until no liquid flowed out, and purified by preparative liquid chromatography to give compound **17** (49 mg). ESI-MS: $m/z = 513.33$ $[M+H]^+$.

^1H NMR (500 MHz, DMSO- d_6) δ 9.07 (s, 1H), 8.23 (d, $J = 7.2$ Hz, 3H), 7.96 (d, $J = 9.1$ Hz, 1H), 7.85 (s, 1H), 7.71 (d, $J = 1.3$ Hz, 1H), 7.54 (s, 1H), 7.43 (s, 1H), 4.95 (h, $J = 7.2$ Hz, 1H), 2.29 (tt, $J = 8.3, 4.7$ Hz, 1H), 1.35 (d, $J = 7.0$ Hz, 3H), 1.07 (dt, $J = 8.3, 3.1$ Hz, 2H), 0.98 (dq, $J = 7.0, 3.4$ Hz, 2H).

Example 18



(1) Preparation of compound 18-2:

Compound **1-7** (300 mg) and 2-fluoropyridine-4-boronic acid (**18-1**, 107 mg) were dispersed in 1,4-dioxane (8 mL), and potassium acetate (186.6 mg), Pd(dppf)Cl₂ (23.2 mg), and water (0.8 mL) were added. The mixture was heated to 90 °C and reacted under nitrogen atmosphere. After the starting materials were consumed completely as detected by TLC, the reaction solution was concentrated under reduced pressure and purified by column chromatography to give compound **18-2**.

(2) Preparation of compound 18-3:

Compound **18-2** (240 mg) was dissolved in tetrahydrofuran (10 mL), a solution of lithium hydroxide hydrate (61.7 mg) and water (10 mL) was added dropwise in an ice-water bath, and the mixture was reacted at 0-5 °C for 2 h. The reaction solution was adjusted to pH 6-7 with hydrochloric acid,

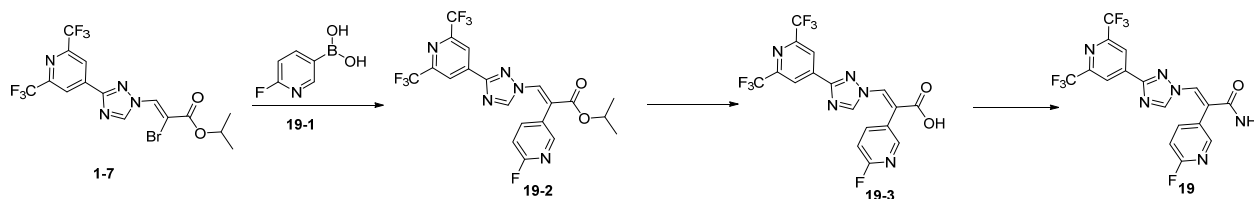
extracted with ethyl acetate, dried over anhydrous sodium sulfate, and filtered, and the filtrate was evaporated to dryness under reduced pressure to give compound **18-3**, which was directly used in the next step.

(3) Preparation of compound 18:

Compound **18-3** (219 mg) was dispersed in tetrahydrofuran (15 mL), N-methylmorpholine (99 mg) and isobutyl chloroformate (133.8 mg) were added in an ice-water bath, and the mixture was stirred for 30 min. Ammonium hydroxide (102.9 mg) was added dropwise, and the mixture was reacted in an ice-water bath for 10 min. Water was added to quench the reaction, and the resulting mixture was extracted with ethyl acetate, dried over anhydrous sodium sulfate, concentrated until no liquid flowed out, and purified by preparative liquid chromatography to give compound **18** (57 mg). ESI-MS: $m/z = 447.17 [M+H]^+$.

^1H NMR (500 MHz, DMSO- d_6) δ 9.13 (s, 1H), 8.34 (s, 1H), 8.30 (d, $J = 5.1$ Hz, 1H), 8.09 (s, 2H), 7.68 (s, 1H), 7.26 (dt, $J = 5.1, 1.7$ Hz, 1H), 7.21 (s, 1H), 7.19 (d, $J = 1.6$ Hz, 1H).

Example 19



(1) Preparation of compound 19-2:

Compound **1-7** (200 mg) and 2-fluoropyridine-5-boronic acid (**19-1**, 71.5 mg) were dispersed in 1,4-dioxane (10 mL), and potassium acetate (124.4 mg), Pd(dppf)Cl₂ (15.5 mg), and water (1 mL) were added. The mixture was heated to 90 °C and reacted under nitrogen atmosphere. After the starting materials were consumed completely as detected by TLC, the reaction solution was concentrated under reduced pressure and purified by column chromatography to give compound **19-2**.

(2) Preparation of compound 19-3:

Compound **19-2** (205 mg) was dissolved in tetrahydrofuran (10 mL), a solution of lithium hydroxide hydrate (35.4 mg) and water (10 mL) was added dropwise in an ice-water bath, and the mixture was reacted at room temperature for 3 h. The reaction solution was adjusted to pH 6-7 with hydrochloric acid, extracted with ethyl acetate, dried over anhydrous sodium sulfate, and filtered, and the filtrate

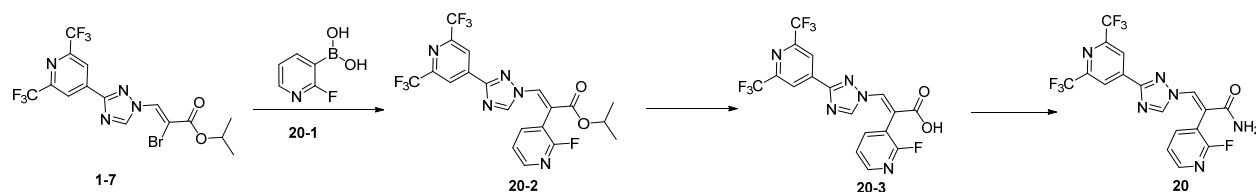
was evaporated to dryness under reduced pressure to give compound **19-3**, which was directly used in the next step.

(3) Preparation of compound 19:

Compound **19-3** (137.4 mg) was dispersed in tetrahydrofuran (10 mL), N-methylmorpholine (64.74 mg) and isobutyl chloroformate (87.41 mg) were added in an ice-water bath, and the mixture was stirred for 30 min. Ammonium hydroxide (67.2 mg) was added dropwise, and the mixture was reacted in an ice-water bath for 10 min. Water was added to quench the reaction, and the resulting mixture was extracted with ethyl acetate, dried over anhydrous sodium sulfate, concentrated until no liquid flowed out, and purified by preparative liquid chromatography to give compound **19** (70 mg). ESI-MS: $m/z = 447.15 [M+H]^+$.

^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 9.14 (s, 1H), 8.37 (s, 1H), 8.14 (d, $J = 2.4$ Hz, 1H), 8.11 (s, 2H), 7.89 (td, $J = 8.1, 2.5$ Hz, 1H), 7.64 (s, 1H), 7.27 (dd, $J = 8.4, 2.7$ Hz, 2H).

Example 20



(1) Preparation of compound 20-2:

Compound **1-7** (200 mg) and 2-fluoropyridine-3-boronic acid (**20-1**, 71.5 mg) were dispersed in 1,4-dioxane (10 mL), and potassium acetate (124.4 mg), $\text{Pd}(\text{dppf})\text{Cl}_2$ (15.5 mg), and water (1 mL) were added. The mixture was heated to 90 °C and reacted under nitrogen atmosphere. After the starting materials were consumed completely as detected by TLC, the reaction solution was concentrated under reduced pressure and purified by column chromatography to give compound **20-2**.

(2) Preparation of compound 20-3:

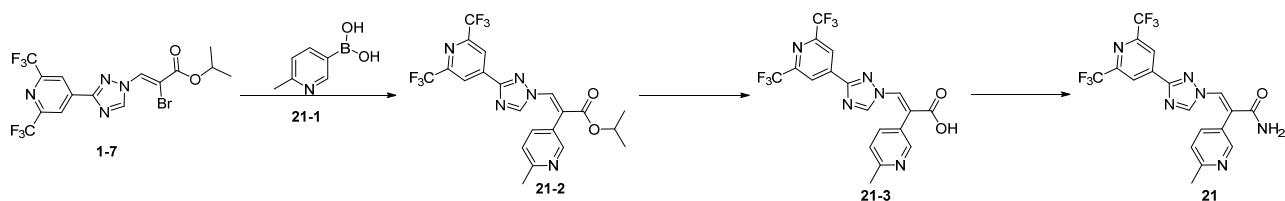
Compound **20-2** (205 mg) was dissolved in tetrahydrofuran (10 mL), a solution of lithium hydroxide hydrate (35.4 mg) and water (10 mL) was added dropwise in an ice-water bath, and the mixture was reacted at room temperature for 3 h. The reaction solution was adjusted to pH 6-7 with hydrochloric acid, extracted with ethyl acetate, dried over anhydrous sodium sulfate, and filtered, and the filtrate was evaporated to dryness under reduced pressure to give compound **20-3**, which was directly used

in the next step.

(3) Preparation of compound 20:

Compound **20-3** (137.4 mg) was dispersed in tetrahydrofuran (10 mL), N-methylmorpholine (64.74 mg) and isobutyl chloroformate (87.41 mg) were added in an ice-water bath, and the mixture was stirred for 30 min. Ammonium hydroxide (67.2 mg) was added dropwise, and the mixture was reacted in an ice-water bath for 10 min. Water was added to quench the reaction, and the resulting mixture was extracted with ethyl acetate, dried over anhydrous sodium sulfate, concentrated until no liquid flowed out, and purified by preparative liquid chromatography to give compound **20** (15 mg). ESI-MS: $m/z = 447.16 [M+H]^+$.

Example 21



(1) Preparation of compound 21-2:

Compound **1-7** (300 mg) and 6-methylpyridine-3-boronic acid (**21-1**, 104 mg) were dispersed in 1,4-dioxane (8 mL), and potassium acetate (186.6 mg), Pd(dppf)Cl₂ (23.2 mg), and water (0.8 mL) were added. The mixture was heated to 90 °C and reacted under nitrogen atmosphere. After the starting materials were consumed completely as detected by TLC, the reaction solution was concentrated under reduced pressure and purified by column chromatography to give compound **21-2**.

(2) Preparation of compound 21-3:

Compound **21-2** (120 mg) was dissolved in tetrahydrofuran (10 mL), a solution of lithium hydroxide hydrate (20.7 mg) and water (10 mL) was added dropwise in an ice-water bath, and the mixture was reacted at 0-5 °C for 2 h. The reaction solution was adjusted to pH 6-7 with hydrochloric acid, extracted with ethyl acetate, dried over anhydrous sodium sulfate, and filtered, and the filtrate was evaporated to dryness under reduced pressure to give compound **21-3**, which was directly used in the next step.

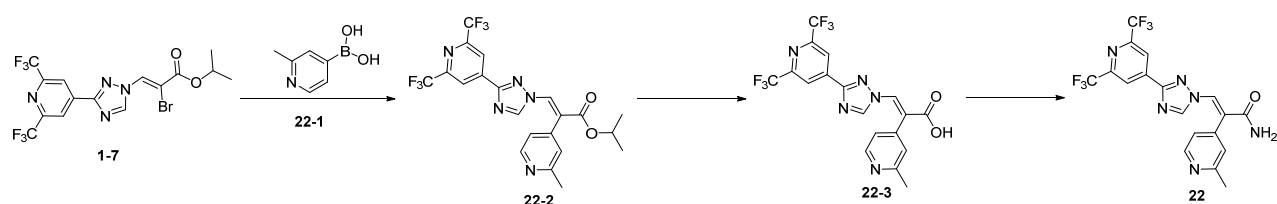
(3) Preparation of compound 21:

Compound **21-3** (109 mg) was dispersed in tetrahydrofuran (15 mL), N-methylmorpholine (50 mg)

and isobutyl chloroformate (67.5 mg) were added in an ice-water bath, and the mixture was stirred for 30 min. Ammonium hydroxide (51.9 mg) was added dropwise, and the mixture was reacted in an ice-water bath for 10 min. Water was added to quench the reaction, and the resulting mixture was extracted with ethyl acetate, dried over anhydrous sodium sulfate, concentrated until no liquid flowed out, and purified by preparative liquid chromatography to give compound **21** (42 mg). ESI-MS: $m/z = 443.17 [M+H]^+$.

^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 9.05 (s, 1H), 8.32 (d, $J = 2.1$ Hz, 1H), 8.29 (s, 1H), 8.11 (s, 2H), 7.61 (s, 1H), 7.57 (dd, $J = 7.9, 2.3$ Hz, 1H), 7.34 (d, $J = 7.9$ Hz, 1H), 7.23 (s, 1H), 2.54 (s, 3H).

Example 22



(1) Preparation of compound 22-2:

Compound **1-7** (300 mg) and 2-methylpyridine-4-boronic acid (**22-1**, 104 mg) were dispersed in 1,4-dioxane (8 mL), and potassium acetate (186.6 mg), $\text{Pd}(\text{dppf})\text{Cl}_2$ (23.2 mg), and water (0.8 mL) were added. The mixture was heated to 90 °C and reacted under nitrogen atmosphere. After the starting materials were consumed completely as detected by TLC, the reaction solution was concentrated under reduced pressure and purified by column chromatography to give compound **22-2**.

(2) Preparation of compound 22-3:

Compound **22-2** (170 mg) was dissolved in tetrahydrofuran (10 mL), a solution of lithium hydroxide hydrate (29 mg) and water (10 mL) was added dropwise in an ice-water bath, and the mixture was reacted at 0-5 °C for 2 h. The reaction solution was adjusted to pH 6-7 with hydrochloric acid, extracted with ethyl acetate, dried over anhydrous sodium sulfate, and filtered, and the filtrate was evaporated to dryness under reduced pressure to give compound **22-3**, which was directly used in the next step.

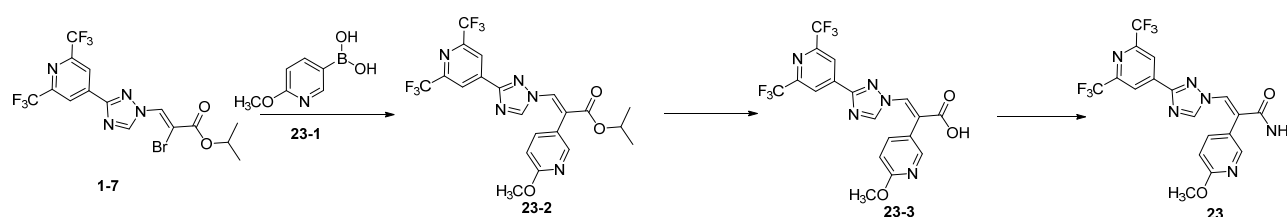
(3) Preparation of compound 22

Compound **22-3** (155 mg) was dispersed in tetrahydrofuran (15 mL), N-methylmorpholine (70.8 mg) and isobutyl chloroformate (95.6 mg) were added in an ice-water bath, and the mixture was stirred

for 30 min. Ammonium hydroxide (73.5 mg) was added dropwise, and the mixture was reacted in an ice-water bath for 10 min. Water was added to quench the reaction, and the resulting mixture was extracted with ethyl acetate, dried over anhydrous sodium sulfate, concentrated until no liquid flowed out, and purified by preparative liquid chromatography to give compound **22** (57 mg). ESI-MS: $m/z = 443.16 [M+H]^+$.

^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 8.99 (s, 1H), 8.49 (dd, $J = 5.0, 0.8$ Hz, 1H), 8.23 (s, 1H), 8.12 (s, 2H), 7.64 (s, 1H), 7.21 – 7.19 (m, 1H), 7.17 (s, 1H), 7.06 (dd, $J = 5.1, 1.6$ Hz, 1H), 2.49 (s, 3H).

Example 23



(1) Preparation of compound 23-2

Compound **1-7** (300 mg) and 6-methoxy-3-pyridineboronic acid (**23-1**, 116.23 mg) were dispersed in 1,4-dioxane (10 mL), and potassium acetate (186.7 mg), $\text{Pd}(\text{dppf})\text{Cl}_2$ (23.2 mg), and water (1 mL) were added. The mixture was heated to 90 °C and reacted under nitrogen atmosphere. After the starting materials were consumed completely as detected by TLC, the reaction solution was concentrated under reduced pressure and purified by column chromatography to give compound **23-2**.

(2) Preparation of compound 23-3

Compound **23-2** (306 mg) was dissolved in tetrahydrofuran (10 mL), a solution of lithium hydroxide hydrate (53.2 mg) and water (10 mL) was added dropwise in an ice-water bath, and the mixture was reacted at room temperature for 3 h. The reaction solution was adjusted to pH 6-7 with hydrochloric acid, extracted with ethyl acetate, dried over anhydrous sodium sulfate, and filtered, and the filtrate was evaporated to dryness under reduced pressure to give compound **23-3**, which was directly used in the next step.

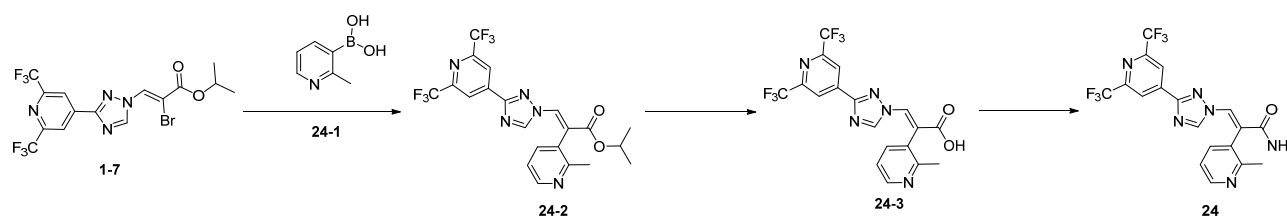
(3) Preparation of compound 23

Compound **23-3** (289 mg) was dispersed in tetrahydrofuran (10 mL), *N*-methylmorpholine (128.3 mg) and isobutyl chloroformate (173.2 mg) were added in an ice-water bath, and the mixture was stirred for 30 min. Ammonium hydroxide (133.1 mg) was added dropwise, and the mixture was

reacted in an ice-water bath for 10 min. Water was added to quench the reaction, and the resulting mixture was extracted with ethyl acetate, dried over anhydrous sodium sulfate, concentrated until no liquid flowed out, and purified by preparative liquid chromatography to give compound **23** (100 mg). ESI-MS: $m/z = 459.22$ $[M+H]^+$.

^1H NMR (500 MHz, DMSO- d_6) δ 9.04 (s, 1H), 8.25 (s, 1H), 8.17 (s, 2H), 8.07 – 8.04 (m, 1H), 7.58 (dd, $J = 8.5, 2.5$ Hz, 2H), 7.23 (s, 1H), 6.90 (dd, $J = 8.6, 0.7$ Hz, 1H), 3.91 (s, 3H).

Example 24



(1) Preparation of compound 24-2

Compound **1-7** (300 mg) and 2-methylpyridine-3-boronic acid (**24-1**, 104 mg) were dispersed in 1,4-dioxane (8 mL), and potassium acetate (186.6 mg), Pd(dppf)Cl₂ (23.2 mg), and water (0.8 mL) were added. The mixture was heated to 90 °C and reacted under nitrogen atmosphere. After the starting materials were consumed completely as detected by TLC, the reaction solution was concentrated under reduced pressure and purified by column chromatography to give compound **24-2**.

(1) Preparation of compound 24-3

Compound **24-2** (150 mg) was dissolved in tetrahydrofuran (10 mL), a solution of lithium hydroxide hydrate (38.9 mg) and water (10 mL) was added dropwise in an ice-water bath, and the mixture was reacted at 0-25 °C for 2 h. The reaction solution was adjusted to pH 6-7 with hydrochloric acid, extracted with ethyl acetate, dried over anhydrous sodium sulfate, and filtered, and the filtrate was evaporated to dryness under reduced pressure to give compound **24-3**, which was directly used in the next step.

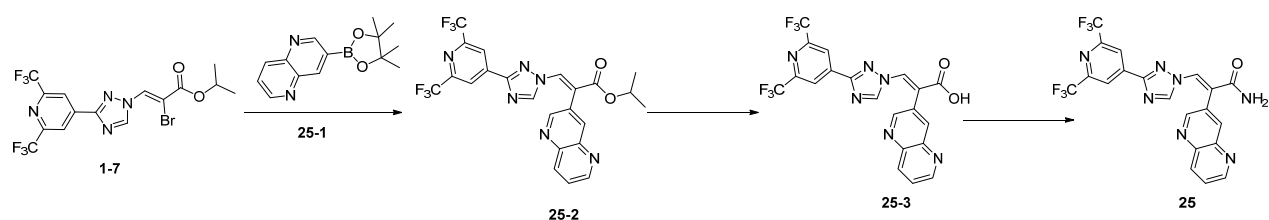
(3) Preparation of compound 24

Compound **24-3** (137 mg) was dispersed in tetrahydrofuran (15 mL), N-methylmorpholine (62.5 mg) and isobutyl chloroformate (84.4 mg) were added in an ice-water bath, and the mixture was stirred for 30 min. Ammonium hydroxide (64.9 mg) was added dropwise, and the mixture was reacted in an ice-water bath for 10 min. Water was added to quench the reaction, and the resulting mixture was

extracted with ethyl acetate, dried over anhydrous sodium sulfate, concentrated until no liquid flowed out, and purified by preparative liquid chromatography to give compound **24** (82 mg). ESI-MS: $m/z = 443.28 [M+H]^+$.

^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 9.07 (s, 1H), 8.51 (dd, $J = 4.9, 1.7$ Hz, 1H), 8.34 (s, 1H), 8.05 (s, 2H), 7.59 (s, 1H), 7.51 (dd, $J = 7.6, 1.7$ Hz, 1H), 7.29 (dd, $J = 7.6, 4.9$ Hz, 1H), 7.18 (s, 1H), 2.28 (s, 3H).

Example 25



(1) Preparation of compound 25-2:

Compounds **1-7** (300 mg) and **25-1** (195 mg) were dispersed in 1,4-dioxane (8 mL), and potassium acetate (186.6 mg), $\text{Pd}(\text{dppf})\text{Cl}_2$ (46 mg), and water (0.8 mL) were added. The mixture was heated to 90 °C and reacted under nitrogen atmosphere. After the starting materials were consumed completely as detected by TLC, the reaction solution was concentrated under reduced pressure to give compound **25-2**.

(2) Preparation of compound 25-3:

Compound **25-2** (240 mg) was dissolved in tetrahydrofuran (10 mL), a solution of lithium hydroxide hydrate (57.8 mg) and water (10 mL) was added dropwise in an ice-water bath, and the mixture was reacted at room temperature for 3 h. The reaction solution was adjusted to pH 6-7 with hydrochloric acid, extracted with ethyl acetate, dried over anhydrous sodium sulfate, and filtered, and the filtrate was evaporated to dryness under reduced pressure to give compound **25-3**, which was directly used in the next step.

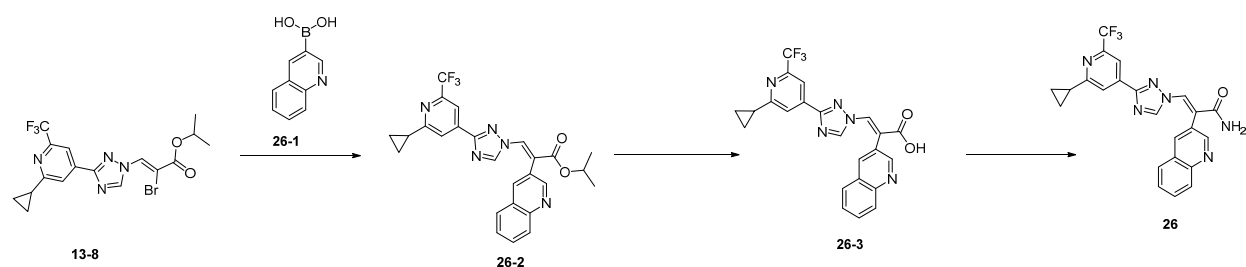
(3) Preparation of compound 25:

Compound **25-3** (220 mg) was dispersed in tetrahydrofuran (15 mL), N-methylmorpholine (93 mg) and isobutyl chloroformate (125 mg) were added in an ice-water bath, and the mixture was stirred for 30 min. Ammonium hydroxide (96 mg) was added dropwise, and the mixture was reacted in an ice-water bath for 10 min. Water was added to quench the reaction, and the resulting mixture was extracted with ethyl acetate, dried over anhydrous sodium sulfate, concentrated until no liquid

flowed out, and purified by preparative liquid chromatography to give compound **25** (86 mg). ESI-MS: $m/z = 480.24 [M+H]^+$.

^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 9.22 (s, 1H), 9.04 (dd, $J = 4.2, 1.7$ Hz, 1H), 8.89 (d, $J = 2.1$ Hz, 1H), 8.53 – 8.45 (m, 2H), 8.34 (d, $J = 2.1$ Hz, 1H), 7.88 (dd, $J = 8.5, 4.2$ Hz, 1H), 7.82 (s, 2H), 7.70 (s, 1H), 7.38 (s, 1H).

Example 26



(1) Preparation of compound 26-2:

Compound **13-8** (200 mg) and 3-quinolineboronic acid (**26-1**, 76.6 mg) were dispersed in 1,4-dioxane (5 mL), and potassium acetate (132.5 mg), $\text{Pd}(\text{dppf})\text{Cl}_2$ (14.6 mg), and water (0.5 mL) were added. The mixture was heated to 90 °C and reacted under nitrogen atmosphere. After the starting materials were consumed completely as detected by TLC, the reaction solution was concentrated under reduced pressure and purified by column chromatography to give compound **26-2**.

(2) Preparation of compound 26-3:

Compound **26-2** (120 mg) was dissolved in tetrahydrofuran (4 mL), a solution of lithium hydroxide hydrate (30.6 mg) and water (4 mL) was added dropwise in an ice-water bath, and the mixture was reacted at room temperature for 4 h. The reaction solution was adjusted to pH 6-7 with hydrochloric acid, extracted with ethyl acetate, dried over anhydrous sodium sulfate, and filtered, and the filtrate was evaporated to dryness under reduced pressure to give compound **26-3**, which was directly used in the next step.

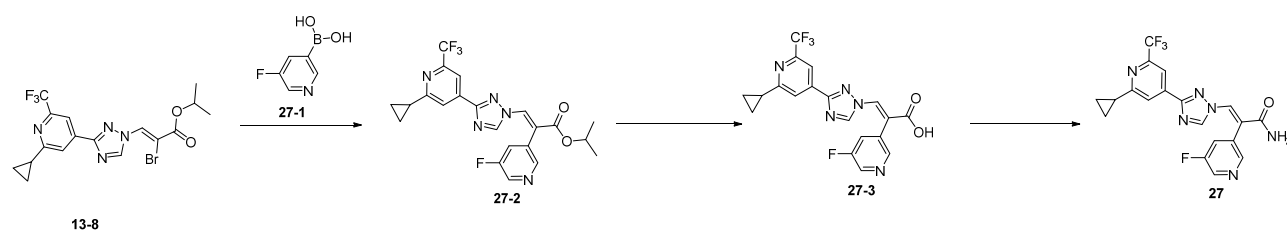
(3) Preparation of compound 26:

Compound **26-3** (100 mg) was dispersed in tetrahydrofuran (5 mL), *N*-methylmorpholine (44.5 mg) and isobutyl chloroformate (60.1 mg) were added in an ice-water bath, and the mixture was stirred for 30 min. Ammonium hydroxide (46.2 mg) was added dropwise, and the mixture was reacted in an ice-water bath for 10 min. Water was added to quench the reaction, and the resulting mixture was

extracted with ethyl acetate, dried over anhydrous sodium sulfate, concentrated until no liquid flowed out, and purified by preparative liquid chromatography to give compound **26** (40 mg); ESI-MS: $m/z = 451.20$ $[M+H]^+$.

^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 9.07 (s, 1H), 8.74 (d, $J = 2.2$ Hz, 1H), 8.40 (s, 1H), 8.29 (d, $J = 2.2$ Hz, 1H), 8.09 (dd, $J = 8.4, 1.1$ Hz, 1H), 8.01 (dd, $J = 8.1, 1.5$ Hz, 1H), 7.82 (ddd, $J = 8.5, 6.9, 1.5$ Hz, 1H), 7.64 (ddd, $J = 8.1, 6.9, 1.2$ Hz, 2H), 7.48 (d, $J = 1.4$ Hz, 1H), 7.33 (s, 1H), 7.29 (d, $J = 1.3$ Hz, 1H), 2.07 (tt, $J = 8.1, 4.7$ Hz, 1H), 1.06 – 0.97 (m, 2H), 0.83 – 0.75 (m, 2H).

Example 27



(1) Preparation of compound 27-2:

Compound **13-8** (200 mg) and 5-fluoro-3-pyridineboronic acid (**27-1**, 76.1 mg) were dispersed in 1,4-dioxane (5 mL), and potassium acetate (132.5 mg), $\text{Pd}(\text{dppf})\text{Cl}_2$ (14.6 mg), and water (0.5 mL) were added. The mixture was heated to 90 °C and reacted under nitrogen atmosphere. After the starting materials were consumed completely as detected by TLC, the reaction solution was concentrated under reduced pressure and purified by column chromatography to give compound **27-2**.

(2) Preparation of compound 27-3:

Compound **27-2** (120 mg) was dissolved in tetrahydrofuran (4 mL), a solution of lithium hydroxide hydrate (32.8 mg) and water (4 mL) was added dropwise in an ice-water bath, and the mixture was reacted at room temperature for 4 h. The reaction solution was adjusted to pH 6-7 with hydrochloric acid, extracted with ethyl acetate, dried over anhydrous sodium sulfate, and filtered, and the filtrate was evaporated to dryness under reduced pressure to give compound **27-3**, which was directly used in the next step.

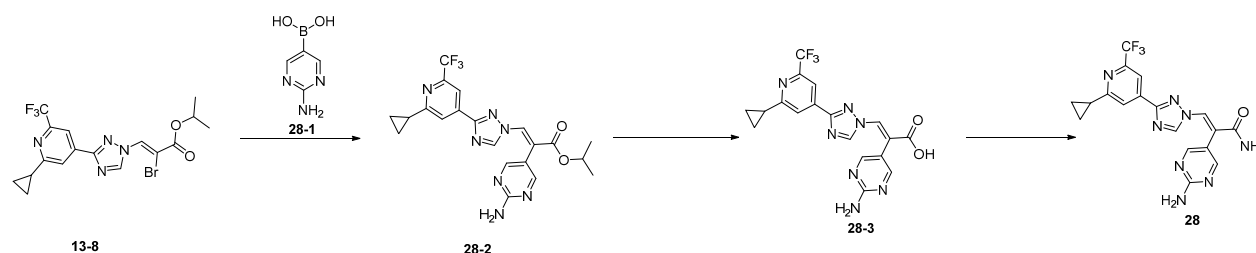
(3) Preparation of compound 27:

Compound **27-3** (100 mg) was dispersed in tetrahydrofuran (5 mL), *N*-methylmorpholine (48.6 mg) and isobutyl chloroformate (65.6 mg) were added in an ice-water bath, and the mixture was stirred

for 30 min. Ammonium hydroxide (50.4 mg) was added dropwise, and the mixture was reacted in an ice-water bath for 10 min. Water was added to quench the reaction, and the resulting mixture was extracted with ethyl acetate, dried over anhydrous sodium sulfate, concentrated until no liquid flowed out, and purified by preparative liquid chromatography to give compound **27** (40 mg). ESI-MS: $m/z = 419.22 [M+H]^+$.

^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 9.05 (s, 1H), 8.63 (d, $J = 2.8$ Hz, 1H), 8.34 (d, $J = 19.3$ Hz, 2H), 7.79 – 7.69 (m, 2H), 7.64 (s, 1H), 7.51 (s, 1H), 7.25 (s, 1H), 2.28 (tt, $J = 8.4, 4.7$ Hz, 1H), 1.10 (dd, $J = 8.0, 3.0$ Hz, 2H), 0.93 (dd, $J = 4.7, 2.6$ Hz, 2H).

Example 28



(1) Preparation of compound 28-2:

Compound **13-8** (200 mg) and 2-aminopyrimidine-5-boronic acid (**28-1**, 75 mg) were dispersed in 1,4-dioxane (5 mL), and potassium acetate (132.5 mg), $\text{Pd}(\text{dppf})\text{Cl}_2$ (14.6 mg), and water (0.5 mL) were added. The mixture was heated to 90 °C and reacted under nitrogen atmosphere. After the starting materials were consumed completely as detected by TLC, the reaction solution was concentrated under reduced pressure and purified by column chromatography to give compound **28-2**.

(2) Preparation of compound 28-3:

Compound **28-2** (102 mg) was dissolved in tetrahydrofuran (4 mL), a solution of lithium hydroxide hydrate (27.7 mg) and water (4 mL) was added dropwise in an ice-water bath, and the mixture was reacted at room temperature for 4 h. The reaction solution was adjusted to pH 6-7 with hydrochloric acid, extracted with ethyl acetate, dried over anhydrous sodium sulfate, and filtered, and the filtrate was evaporated to dryness under reduced pressure to give compound **28-3**, which was directly used in the next step.

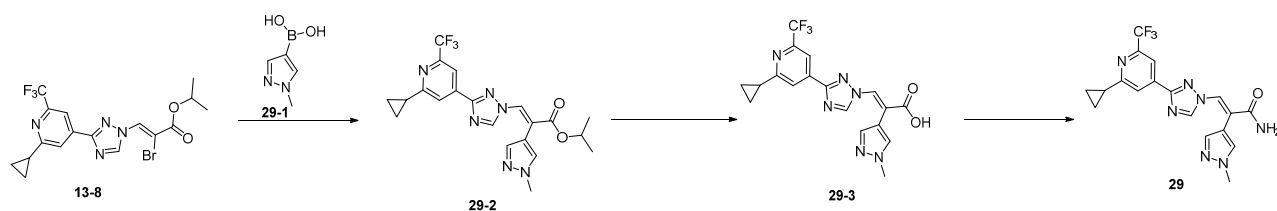
(3) Preparation of compound 28:

Compound **28-3** (100 mg) was dispersed in tetrahydrofuran (5 mL), *N*-methylmorpholine (48.6 mg) and isobutyl chloroformate (65.6 mg) were added in an ice-water bath, and the mixture was stirred

for 30 min. Ammonium hydroxide (50.4 mg) was added dropwise, and the mixture was reacted in an ice-water bath for 10 min. Water was added to quench the reaction, and the resulting mixture was extracted with ethyl acetate, dried over anhydrous sodium sulfate, concentrated until no liquid flowed out, and purified by preparative liquid chromatography to give compound **28** (45 mg); ESI-MS: $m/z = 417.22$ $[M+H]^+$.

^1H NMR (500 MHz, $\text{DMSO-}d_6$) δ 9.00 (s, 1H), 8.15 (s, 1H), 8.08 (s, 2H), 7.85 (d, $J = 1.2$ Hz, 1H), 7.78 (d, $J = 1.3$ Hz, 1H), 7.53 (s, 1H), 7.41 (s, 1H), 6.84 (s, 2H), 2.36 – 2.28 (m, 1H), 1.09 (dt, $J = 8.0, 3.2$ Hz, 2H), 0.98 (dq, $J = 6.9, 3.9$ Hz, 2H).

Example 29



(1) Preparation of compound 29-2:

Compound **13-8** (200 mg) and 1-methyl-1H-pyrazole-4-boronic acid (**29-1**, 68 mg) were dispersed in 1,4-dioxane (5 mL), and potassium acetate (132.5 mg), Pd(dppf)Cl_2 (14.6 mg), and water (0.5 mL) were added. The mixture was heated to 90 °C and reacted under nitrogen atmosphere. After the starting materials were consumed completely as detected by TLC, the reaction solution was concentrated under reduced pressure and purified by column chromatography to give compound **29-2**.

(2) Preparation of compound 29-3:

Compound **29-2** (100 mg) was dissolved in tetrahydrofuran (4 mL), a solution of lithium hydroxide hydrate (27.7 mg) and water (4 mL) was added dropwise in an ice-water bath, and the mixture was reacted at room temperature for 4 h. The reaction solution was adjusted to pH 6-7 with hydrochloric acid, extracted with ethyl acetate, dried over anhydrous sodium sulfate, and filtered, and the filtrate was evaporated to dryness under reduced pressure to give compound **29-3**, which was directly used in the next step.

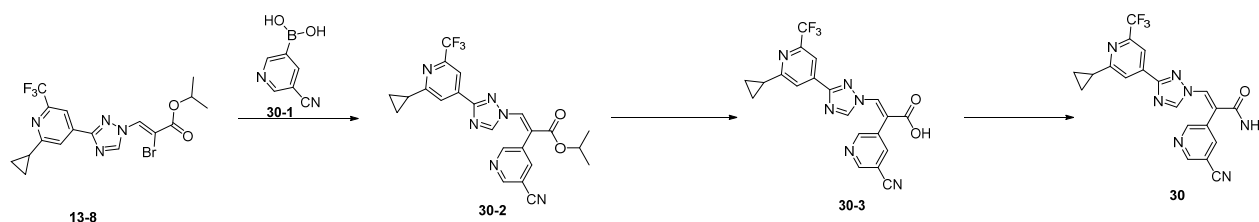
(3) Preparation of compound 29:

Compound **29-3** (88.96 mg) was dispersed in tetrahydrofuran (5 mL), N-methylmorpholine (44.5 mg) and isobutyl chloroformate (60.09 mg) were added in an ice-water bath, and the mixture was

stirred for 30 min. Ammonium hydroxide (46.2 mg) was added dropwise, and the mixture was reacted in an ice-water bath for 10 min. Water was added to quench the reaction, and the resulting mixture was extracted with ethyl acetate, dried over anhydrous sodium sulfate, concentrated until no liquid flowed out, and purified by preparative liquid chromatography to give compound **29** (30 mg). ESI-MS: $m/z = 404.24 [M+H]^+$.

^1H NMR (500 MHz, DMSO- d_6) δ 8.75 (s, 1H), 8.08 – 8.03 (m, 1H), 7.94 (d, $J = 1.3$ Hz, 1H), 7.82 (s, 1H), 7.72 (s, 1H), 7.55 (s, 1H), 7.49 (s, 1H), 7.25 (s, 1H), 3.85 (s, 3H), 2.37 (tt, $J = 8.1, 4.7$ Hz, 1H), 1.10 (dt, $J = 8.1, 3.2$ Hz, 2H), 1.00 (dq, $J = 7.0, 4.3, 3.9$ Hz, 2H).

Example 30



(1) Preparation of compound 30-2:

Compound **13-8** (200 mg) and 5-cyano-pyridine-3-boronic acid (**30-1**, 79.8 mg) were dispersed in 1,4-dioxane (5 mL), and potassium acetate (132.5 mg), Pd(dppf)Cl₂ (14.6 mg), and water (0.5 mL) were added. The mixture was heated to 90 °C and reacted under nitrogen atmosphere. After the starting materials were consumed completely as detected by TLC, the reaction solution was concentrated under reduced pressure and purified by column chromatography to give compound **30-2**.

(2) Preparation of compound 30-3:

Compound **30-2** (150 mg) was dissolved in tetrahydrofuran (4 mL), a solution of lithium hydroxide hydrate (40.28 mg) and water (4 mL) was added dropwise in an ice-water bath, and the mixture was reacted at room temperature for 4 h. The reaction solution was adjusted to pH 6-7 with hydrochloric acid, extracted with ethyl acetate, dried over anhydrous sodium sulfate, and filtered, and the filtrate was evaporated to dryness under reduced pressure to give compound **30-3**, which was directly used in the next step.

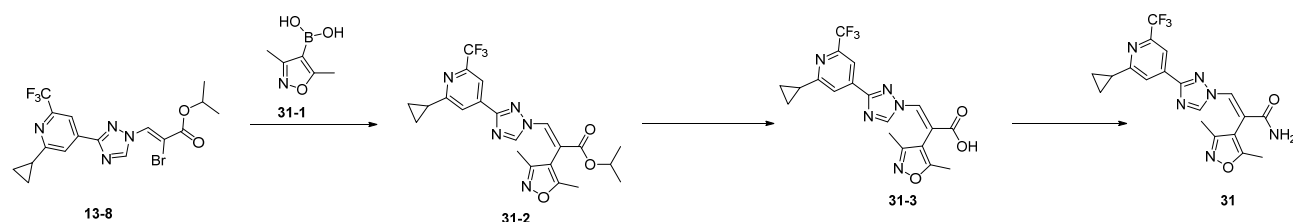
(3) Preparation of compound 30:

Compound **30-3** (136.44 mg) was dispersed in tetrahydrofuran (5 mL), N-methylmorpholine (64.74 mg) and isobutyl chloroformate (87.4 mg) were added in an ice-water bath, and the mixture was

stirred for 30 min. Ammonium hydroxide (67.2 mg) was added dropwise, and the mixture was reacted in an ice-water bath for 10 min. Water was added to quench the reaction, and the resulting mixture was extracted with ethyl acetate, dried over anhydrous sodium sulfate, concentrated until no liquid flowed out, and purified by preparative liquid chromatography to give compound **30** (45 mg). ESI-MS: $m/z = 426.21 [M+H]^+$.

^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 9.12 (s, 1H), 9.09 (d, $J = 2.0$ Hz, 1H), 8.75 (d, $J = 2.1$ Hz, 1H), 8.42 (s, 1H), 8.35 (t, $J = 2.1$ Hz, 1H), 7.70 (d, $J = 1.3$ Hz, 1H), 7.66 (s, 1H), 7.45 (d, $J = 1.3$ Hz, 1H), 7.28 (s, 1H), 2.29 (tt, $J = 8.1, 4.7$ Hz, 1H), 1.10 (dt, $J = 8.1, 3.3$ Hz, 2H), 0.97 – 0.89 (m, 2H).

Example 31



(1) Preparation of compound 31-2:

Compound **13-8** (200 mg) and 3,5-dimethylisoxazole-4-boronic acid (**31-1**, 76.1 mg) were dispersed in 1,4-dioxane (5 mL), and potassium carbonate (186.6 mg), $\text{Pd}(\text{dppf})\text{Cl}_2$ (14.6 mg), and water (0.5 mL) were added. The mixture was heated to 90 °C and reacted under nitrogen atmosphere. After the starting materials were consumed completely as detected by TLC, the reaction solution was concentrated under reduced pressure and purified by column chromatography to give compound **31-2**.

(2) Preparation of compound 31-3:

Compound **31-2** (150 mg) was dissolved in tetrahydrofuran (4 mL), a solution of lithium hydroxide hydrate (41.54 mg) and water (4 mL) was added dropwise in an ice-water bath, and the mixture was reacted at room temperature for 4 h. The reaction solution was adjusted to pH 6-7 with hydrochloric acid, extracted with ethyl acetate, dried over anhydrous sodium sulfate, and filtered, and the filtrate was evaporated to dryness under reduced pressure to give compound **31-3**, which was directly used in the next step.

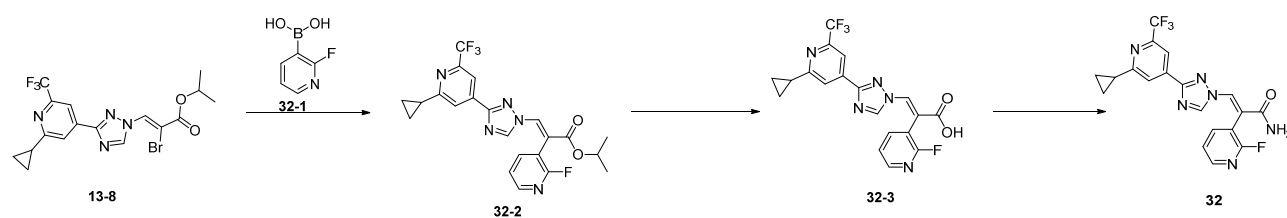
(3) Preparation of compound 31:

Compound **31-3** (134 mg) was dispersed in tetrahydrofuran (5 mL), N-methylmorpholine (64.74 mg) and isobutyl chloroformate (87.4 mg) were added in an ice-water bath, and the mixture was stirred

for 30 min. Ammonium hydroxide (67.2 mg) was added dropwise, and the mixture was reacted in an ice-water bath for 10 min. Water was added to quench the reaction, and the resulting mixture was extracted with ethyl acetate, dried over anhydrous sodium sulfate, concentrated until no liquid flowed out, and purified by preparative liquid chromatography to give compound **31** (30 mg). ESI-MS: $m/z = 419.23 [M+H]^+$.

^1H NMR (500 MHz, DMSO- d_6) δ 9.07 (s, 1H), 8.38 (s, 1H), 7.86 (d, $J = 1.3$ Hz, 1H), 7.78 (d, $J = 1.3$ Hz, 1H), 7.52 (s, 1H), 7.37 (s, 1H), 2.31 (tt, $J = 8.1, 4.7$ Hz, 1H), 2.17 (s, 3H), 1.96 (s, 3H), 1.14 – 1.08 (m, 2H), 1.01 – 0.95 (m, 2H).

Example 32



(1) Preparation of compound 32-2:

Compound **13-8** (200 mg) and 2-fluoro-pyridine-3-boronic acid (**32-1**, 76.1 mg) were dispersed in 1,4-dioxane (5 mL), and potassium carbonate (186.6 mg), Pd(dppf)Cl₂ (14.6 mg), and water (0.5 mL) were added. The mixture was heated to 90 °C and reacted under nitrogen atmosphere. After the starting materials were consumed completely as detected by TLC, the reaction solution was concentrated under reduced pressure and purified by column chromatography to give compound **32-2**.

(2) Preparation of compound 32-3:

Compound **32-2** (70 mg) was dissolved in tetrahydrofuran (4 mL), a solution of lithium hydroxide hydrate (18.9 mg) and water (4 mL) was added dropwise in an ice-water bath, and the mixture was reacted at room temperature for 4 h. The reaction solution was adjusted to pH 6-7 with hydrochloric acid, extracted with ethyl acetate, dried over anhydrous sodium sulfate, and filtered, and the filtrate was evaporated to dryness under reduced pressure to give compound **32-3**, which was directly used in the next step.

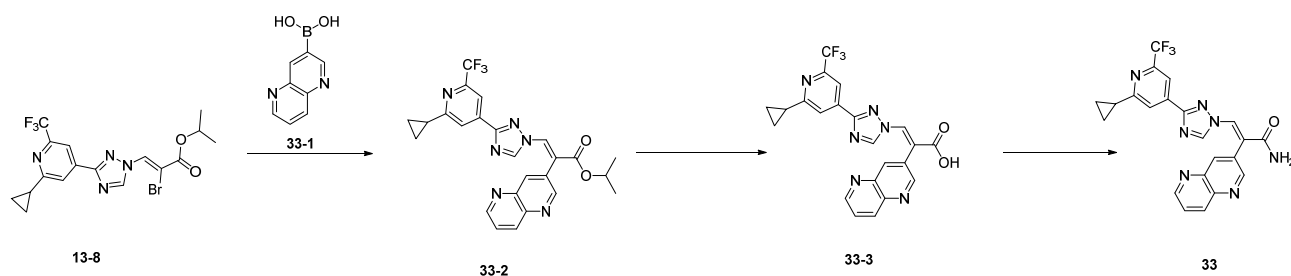
(3) Preparation of compound 32:

Compound **32-3** (50 mg) was dispersed in tetrahydrofuran (5 mL), N-methylmorpholine (24.3 mg) and isobutyl chloroformate (32.7 mg) were added in an ice-water bath, and the mixture was stirred

for 30 min. Ammonium hydroxide (25.2 mg) was added dropwise, and the mixture was reacted in an ice-water bath for 10 min. Water was added to quench the reaction, and the resulting mixture was extracted with ethyl acetate, dried over anhydrous sodium sulfate, concentrated until no liquid flowed out, and purified by preparative liquid chromatography to give compound **32** (10 mg). ESI-MS: $m/z = 419.21$ $[M+H]$

¹H NMR (500 MHz, DMSO-*d*₆) δ 9.13 (s, 1H), 8.39 (s, 1H), 8.32 (dd, *J* = 5.0, 1.9 Hz, 1H), 7.86 (ddd, *J* = 9.5, 7.3, 1.9 Hz, 1H), 7.69 (d, *J* = 1.3 Hz, 1H), 7.59 (s, 1H), 7.50 (d, *J* = 1.3 Hz, 1H), 7.44 (ddd, *J* = 7.1, 4.9, 1.9 Hz, 1H), 7.40 (s, 1H), 2.27 (tt, *J* = 8.2, 4.7 Hz, 1H), 1.10 (dt, *J* = 8.1, 3.3 Hz, 2H), 0.97 – 0.90 (m, 2H).

Example 33



(1) Preparation of compound 33-2:

Compound **13-8** (200 mg) and [1,5]naphthyridine-3-boronic acid (**33-1**, 138.3 mg) were dispersed in 1,4-dioxane (5 mL), and potassium acetate (132.5 mg), Pd(dppf)Cl₂ (14.6 mg), and water (0.5 mL) were added. The mixture was heated to 90 °C and reacted under nitrogen atmosphere. After the starting materials were consumed completely as detected by TLC, the reaction solution was concentrated under reduced pressure and purified by column chromatography to give compound **33-2**.

(2) Preparation of compound 33-3:

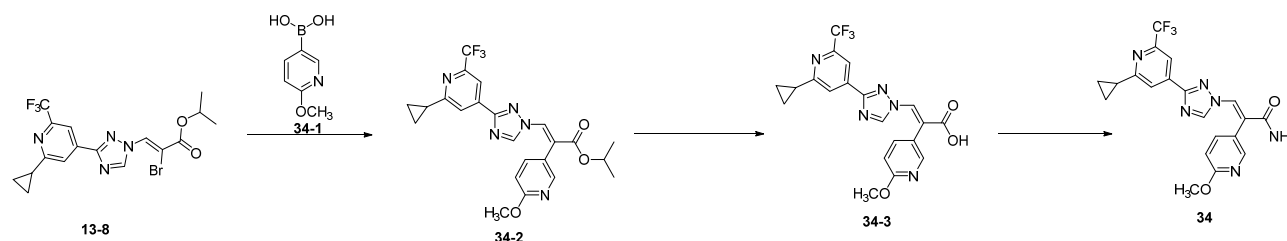
Compound **33-2** (160 mg) was dissolved in tetrahydrofuran (4 mL), a solution of lithium hydroxide hydrate (40.28 mg) and water (4 mL) was added dropwise in an ice-water bath, and the mixture was reacted at room temperature for 4 h. The reaction solution was adjusted to pH 6-7 with hydrochloric acid, extracted with ethyl acetate, dried over anhydrous sodium sulfate, and filtered, and the filtrate was evaporated to dryness under reduced pressure to give compound **33-3**, which was directly used in the next step.

(3) Preparation of compound 33:

Compound **33-3** (144.7 mg) was dispersed in tetrahydrofuran (5 mL), N-methylmorpholine (64.74 mg) and isobutyl chloroformate (87.4 mg) were added in an ice-water bath, and the mixture was stirred for 30 min. Ammonium hydroxide (67.2 mg) was added dropwise, and the mixture was reacted in an ice-water bath for 10 min. Water was added to quench the reaction, and the resulting mixture was extracted with ethyl acetate, dried over anhydrous sodium sulfate, concentrated until no liquid flowed out, and purified by preparative liquid chromatography to give compound **33** (20 mg). ESI-MS: $m/z = 452.21 [M+H]^+$.

^1H NMR (500 MHz, $\text{DMSO-}d_6$) δ 9.12 (s, 1H), 9.03 (dd, $J = 4.2, 1.7$ Hz, 1H), 8.87 (d, $J = 2.2$ Hz, 1H), 8.51 (d, $J = 8.5$ Hz, 1H), 8.46 (s, 1H), 8.31 (d, $J = 2.2$ Hz, 1H), 7.86 (dd, $J = 8.5, 4.2$ Hz, 1H), 7.65 (s, 1H), 7.51 (s, 1H), 7.34 (s, 1H), 7.20 – 7.14 (m, 1H), 2.10 (tt, $J = 8.4, 4.7$ Hz, 1H), 1.01 (dt, $J = 6.4, 3.3$ Hz, 2H), 0.79 (dq, $J = 6.9, 4.0$ Hz, 2H).

Example 34



(1) Preparation of compound 34-2:

Compound **13-8** (200 mg) and 2-methoxypyridine-5-boronic acid (**34-1**, 82.6 mg) were dispersed in 1,4-dioxane (5 mL), and potassium acetate (132.5 mg), Pd(dppf)Cl_2 (14.6 mg), and water (0.5 mL) were added. The mixture was heated to 90 °C and reacted under nitrogen atmosphere. After the starting materials were consumed completely as detected by TLC, the reaction solution was concentrated under reduced pressure and purified by column chromatography to give compound **34-2**.

(2) Preparation of compound 34-3:

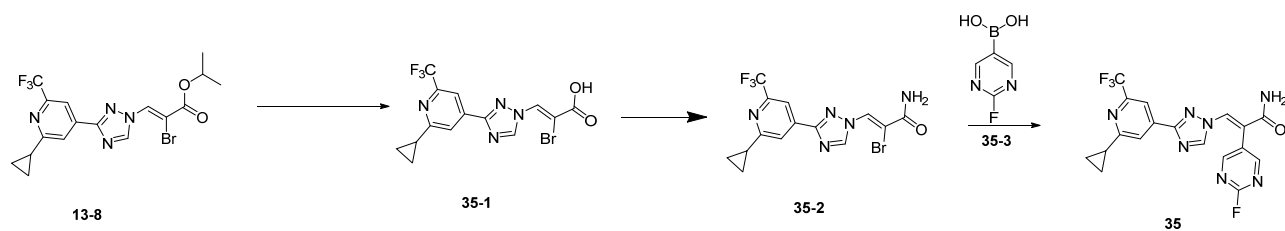
Compound **34-2** (180 mg) was dissolved in tetrahydrofuran (4 mL), a solution of lithium hydroxide hydrate (47.9 mg) and water (4 mL) was added dropwise in an ice-water bath, and the mixture was reacted at room temperature for 4 h. The reaction solution was adjusted to pH 6-7 with hydrochloric acid, extracted with ethyl acetate, dried over anhydrous sodium sulfate, and filtered, and the filtrate was evaporated to dryness under reduced pressure to give compound **34-3**, which was directly used in the next step.

(3) Preparation of compound 34:

Compound **34-3** (163.9 mg) was dispersed in tetrahydrofuran (5 mL), N-methylmorpholine (76.8 mg) and isobutyl chloroformate (103.8 mg) were added in an ice-water bath, and the mixture was stirred for 30 min. Ammonium hydroxide (79.8 mg) was added dropwise, and the mixture was reacted in an ice-water bath for 10 min. Water was added to quench the reaction, and the resulting mixture was extracted with ethyl acetate, dried over anhydrous sodium sulfate, concentrated until no liquid flowed out, and purified by preparative liquid chromatography to give compound **34** (80 mg). ESI-MS: $m/z = 431.19 [M+H]^+$.

^1H NMR (500 MHz, DMSO- d_6) δ 8.91 (s, 1H), 8.21 (s, 1H), 8.04 (d, $J = 2.4$ Hz, 1H), 7.81 (d, $J = 1.3$ Hz, 1H), 7.61 (d, $J = 1.3$ Hz, 1H), 7.58 (d, $J = 2.4$ Hz, 1H), 7.56 (d, $J = 2.5$ Hz, 1H), 7.55 (s, 1H), 7.20 (s, 1H), 6.89 (d, $J = 8.5$ Hz, 1H), 3.91 (s, 3H), 2.29 (tt, $J = 8.1, 4.8$ Hz, 1H), 1.12 – 1.05 (m, 2H), 0.98 – 0.93 (m, 2H).

Example 35



(1) Preparation of compound 35-1:

Compound **13-8** (200 mg) was dissolved in tetrahydrofuran (4 mL), a solution of lithium hydroxide hydrate (56.65 mg) and water (4 mL) was added dropwise in an ice-water bath, and the mixture was reacted at room temperature for 4 h. The reaction solution was adjusted to pH 6-7 with hydrochloric acid, extracted with ethyl acetate, dried over anhydrous sodium sulfate, and filtered, and the filtrate was evaporated to dryness under reduced pressure to give compound **35-1**, which was directly used in the next step.

(2) Preparation of compound 35-2:

Compound **35-1** (181.4 mg) was dispersed in tetrahydrofuran (5 mL), N-methylmorpholine (91.04 mg) and isobutyl chloroformate (122.9 mg) were added in an ice-water bath, and the mixture was stirred for 30 min. Ammonium hydroxide (94.5 mg) was added dropwise, and the mixture was reacted in an ice-water bath for 10 min. Water was added to quench the reaction, and the resulting mixture was extracted with ethyl acetate, dried over anhydrous sodium sulfate, and concentrated

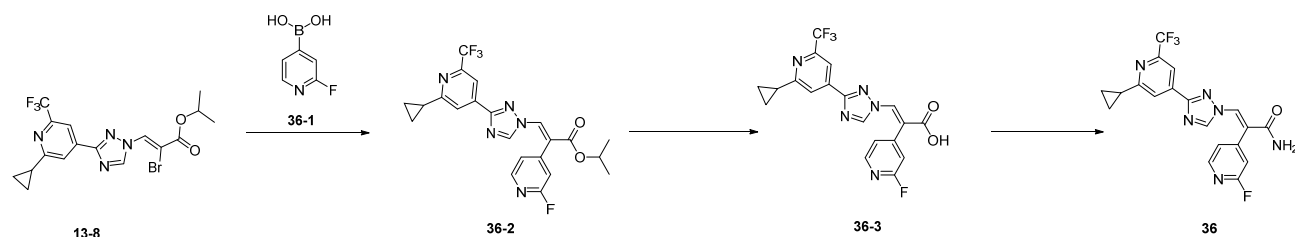
until no liquid flowed out to give compound **35-2**, which was directly used in the next step.

(2) Preparation of compound **35**:

Compound **35-2** (200 mg) and 2-fluoro-pyrimidine-5-boronic acid (**35-3**, 134.4 mg) were dispersed in 1,4-dioxane (5 mL), and potassium acetate (147.21 mg), Pd(dppf)Cl₂ (18.3 mg), and water (0.5 mL) were added. The mixture was heated to 90 °C and reacted under nitrogen atmosphere. After the starting materials were consumed completely as detected by TLC, the reaction solution was concentrated under reduced pressure and purified by preparative liquid chromatography to give compound **35** (30 mg). ESI-MS: $m/z = 420.19 [M+H]^+$.

¹H NMR (500 MHz, DMSO-*d*₆) δ 9.18 (s, 1H), 8.74 (s, 2H), 8.47 (s, 1H), 7.74 (s, 1H), 7.66 (s, 1H), 7.49 (s, 1H), 7.35 (s, 1H), 2.28 (tt, $J = 8.4, 4.7$ Hz, 1H), 1.11 (dq, $J = 6.7, 3.9$ Hz, 2H), 1.00 – 0.89 (m, 2H).

Example 36



(1) Preparation of compound **36-2**:

Compound **13-8** (200 mg) and 2-fluoro-pyridine-4-boronic acid (**36-1**, 76.09 mg) were dispersed in 1,4-dioxane (5 mL), and potassium acetate (132.5 mg), Pd(dppf)Cl₂ (14.6 mg), and water (0.5 mL) were added. The mixture was heated to 90 °C and reacted under nitrogen atmosphere. After the starting materials were consumed completely as detected by TLC, the reaction solution was concentrated under reduced pressure and purified by column chromatography to give compound **36-2**.

(2) Preparation of compound **36-3**:

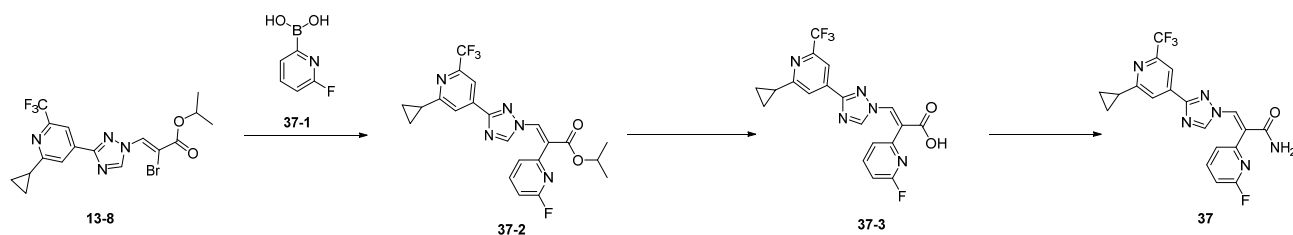
Compound **36-2** (150 mg) was dissolved in tetrahydrofuran (4 mL), a solution of lithium hydroxide hydrate (40.3 mg) and water (4 mL) was added dropwise in an ice-water bath, and the mixture was reacted at room temperature for 4 h. The reaction solution was adjusted to pH 6-7 with hydrochloric acid, extracted with ethyl acetate, dried over anhydrous sodium sulfate, and filtered, and the filtrate was evaporated to dryness under reduced pressure to give compound **36-3**, which was directly used in the next step.

(3) Preparation of compound 36:

Compound **36-3** (100 mg) was dispersed in tetrahydrofuran (5 mL), N-methylmorpholine (48.5 mg) and isobutyl chloroformate (65.5 mg) were added in an ice-water bath, and the mixture was stirred for 30 min. Ammonium hydroxide (50.4 mg) was added dropwise, and the mixture was reacted in an ice-water bath for 10 min. Water was added to quench the reaction, and the resulting mixture was extracted with ethyl acetate, dried over anhydrous sodium sulfate, concentrated until no liquid flowed out, and purified by preparative liquid chromatography to give compound **36** (30 mg). ESI-MS: $m/z = 419.19 [M+H]^+$.

^1H NMR (500 MHz, DMSO- d_6) δ 9.03 (s, 1H), 8.29 (d, $J = 5.3$ Hz, 2H), 7.68 (s, 1H), 7.63 (s, 1H), 7.53 (s, 1H), 7.25 (d, $J = 5.0$ Hz, 1H), 7.18 (d, $J = 6.6$ Hz, 2H), 2.26 (tt, $J = 8.3, 4.7$ Hz, 1H), 1.10 (dq, $J = 6.8, 3.9$ Hz, 2H), 0.94 (dq, $J = 6.7, 4.0$ Hz, 2H).

Example 37



(1) Preparation of compound 37-2:

Compound **13-8** (200 mg) and 6-fluoro-pyridine-2-boronic acid (**37-1**, 76.09 mg) were dispersed in 1,4-dioxane (5 mL), and potassium acetate (132.5 mg), Pd(dppf)Cl₂ (14.6 mg), and water (0.5 mL) were added. The mixture was heated to 90 °C and reacted under nitrogen atmosphere. After the starting materials were consumed completely as detected by TLC, the reaction solution was concentrated under reduced pressure and purified by column chromatography to give compound **37-2**.

(2) Preparation of compound 37-3:

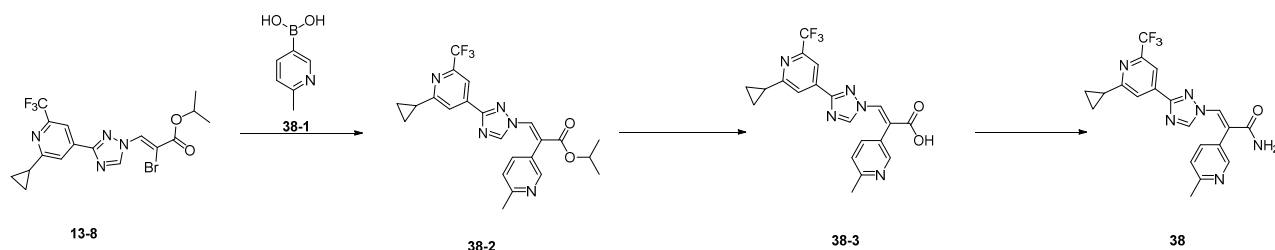
Compound **37-2** (170 mg) was dissolved in tetrahydrofuran (4 mL), a solution of lithium hydroxide hydrate (46.4 mg) and water (4 mL) was added dropwise in an ice-water bath, and the mixture was reacted at room temperature for 4 h. The reaction solution was adjusted to pH 6-7 with hydrochloric acid, extracted with ethyl acetate, dried over anhydrous sodium sulfate, and filtered, and the filtrate was evaporated to dryness under reduced pressure to give compound **37-3**, which was directly used in the next step.

(3) Preparation of compound 37:

Compound **37-3** (155.2 mg) was dispersed in tetrahydrofuran (5 mL), N-methylmorpholine (74.8 mg) and isobutyl chloroformate (101.1 mg) were added in an ice-water bath, and the mixture was stirred for 30 min. Ammonium hydroxide (77.7 mg) was added dropwise, and the mixture was reacted in an ice-water bath for 10 min. Water was added to quench the reaction, and the resulting mixture was extracted with ethyl acetate, dried over anhydrous sodium sulfate, concentrated until no liquid flowed out, and purified by preparative liquid chromatography to give compound **37** (40 mg). ESI-MS: $m/z = 419.19 [M+H]^+$.

^1H NMR (500 MHz, DMSO- d_6) δ 9.01 (d, $J = 1.4$ Hz, 1H), 8.27 (d, $J = 1.4$ Hz, 1H), 8.05 (q, $J = 8.1$ Hz, 1H), 7.73 (s, 1H), 7.60 (s, 1H), 7.51 (d, $J = 1.4$ Hz, 1H), 7.34 (dd, $J = 7.4, 2.3$ Hz, 1H), 7.23 (dd, $J = 8.5, 2.3$ Hz, 2H), 2.29 (tt, $J = 8.4, 4.7$ Hz, 1H), 1.09 (dq, $J = 6.5, 3.8$ Hz, 2H), 0.94 (dt, $J = 5.0, 3.3$ Hz, 2H).

Example 38



(1) Preparation of compound 38-2:

Compound **13-8** (200 mg) and 2-methyl-pyridine-5-boronic acid (**38-1**, 73.95 mg) were dispersed in 1,4-dioxane (5 mL), and potassium acetate (132.5 mg), Pd(dppf)Cl₂ (14.6 mg), and water (0.5 mL) were added. The mixture was heated to 90 °C and reacted under nitrogen atmosphere. After the starting materials were consumed completely as detected by TLC, the reaction solution was concentrated under reduced pressure and purified by column chromatography to give compound **38-2**.

(2) Preparation of compound 38-3:

Compound **38-2** (105 mg) was dissolved in tetrahydrofuran (4 mL), a solution of lithium hydroxide hydrate (28.95 mg) and water (4 mL) was added dropwise in an ice-water bath, and the mixture was reacted at room temperature for 4 h. The reaction solution was adjusted to pH 6-7 with hydrochloric acid, extracted with ethyl acetate, dried over anhydrous sodium sulfate, and filtered, and the filtrate was evaporated to dryness under reduced pressure to give compound **38-3**, which was directly used

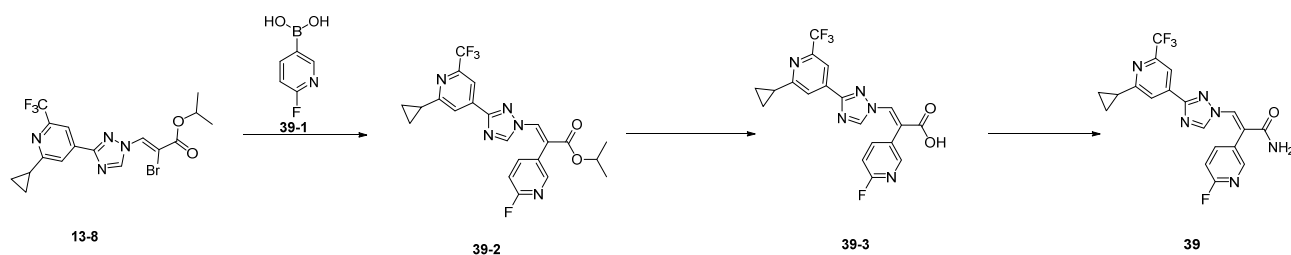
in the next step.

(3) Preparation of compound 38:

Compound **38-3** (95.5 mg) was dispersed in tetrahydrofuran (5 mL), N-methylmorpholine (46.5 mg) and isobutyl chloroformate (62.8 mg) were added in an ice-water bath, and the mixture was stirred for 30 min. Ammonium hydroxide (48.3 mg) was added dropwise, and the mixture was reacted in an ice-water bath for 10 min. Water was added to quench the reaction, and the resulting mixture was extracted with ethyl acetate, dried over anhydrous sodium sulfate, concentrated until no liquid flowed out, and purified by preparative liquid chromatography to give compound **38** (30 mg). ESI-MS: $m/z = 415.24 [M+H]^+$.

^1H NMR (500 MHz, DMSO- d_6) δ 8.93 (s, 1H), 8.30 (d, $J = 2.3$ Hz, 1H), 8.24 (s, 1H), 7.78 (s, 1H), 7.56 (dd, $J = 8.0, 2.4$ Hz, 2H), 7.53 (d, $J = 1.3$ Hz, 1H), 7.33 (d, $J = 7.9$ Hz, 1H), 7.20 (s, 1H), 2.54 (s, 3H), 2.29 (tt, $J = 8.3, 4.7$ Hz, 1H), 1.09 (dt, $J = 8.1, 3.3$ Hz, 2H), 1.00 – 0.89 (m, 2H).

Example 39



(1) Preparation of compound 39-2:

Compound **13-8** (200 mg) and 2-fluoro-pyridine-5-boronic acid (**39-1**, 76.09 mg) were dispersed in 1,4-dioxane (5 mL), and potassium acetate (132.5 mg), Pd(dppf)Cl₂ (14.6 mg), and water (0.5 mL) were added. The mixture was heated to 90 °C and reacted under nitrogen atmosphere. After the starting materials were consumed completely as detected by TLC, the reaction solution was concentrated under reduced pressure and purified by column chromatography to give compound **39-2**.

(2) Preparation of compound 39-3:

Compound **39-2** (180 mg) was dissolved in tetrahydrofuran (4 mL), a solution of lithium hydroxide hydrate (49.1 mg) and water (4 mL) was added dropwise in an ice-water bath, and the mixture was reacted at room temperature for 4 h. The reaction solution was adjusted to pH 6-7 with hydrochloric acid, extracted with ethyl acetate, dried over anhydrous sodium sulfate, and filtered, and the filtrate was evaporated to dryness under reduced pressure to give compound **39-3**, which was directly used

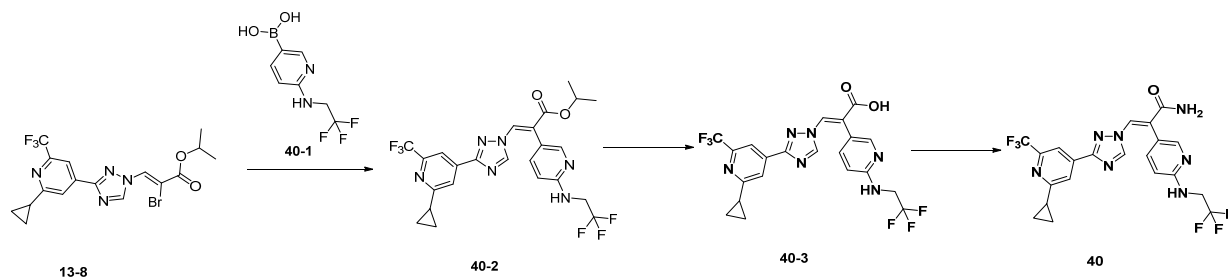
in the next step.

(3) Preparation of compound 39:

Compound **39-3** (163 mg) was dispersed in tetrahydrofuran (5 mL), N-methylmorpholine (78.9 mg) and isobutyl chloroformate (106.5 mg) were added in an ice-water bath, and the mixture was stirred for 30 min. Ammonium hydroxide (81.9 mg) was added dropwise, and the mixture was reacted in an ice-water bath for 10 min. Water was added to quench the reaction, and the resulting mixture was extracted with ethyl acetate, dried over anhydrous sodium sulfate, concentrated until no liquid flowed out, and purified by preparative liquid chromatography to give compound **39** (40 mg). ESI-MS: $m/z = 419.20 [M+H]^+$.

^1H NMR (500 MHz, DMSO- d_6) δ 9.04 (s, 1H), 8.33 (s, 1H), 8.13 (d, $J = 2.4$ Hz, 1H), 7.88 (td, $J = 8.2, 2.5$ Hz, 1H), 7.75 (d, $J = 1.2$ Hz, 1H), 7.61 (s, 1H), 7.52 (d, $J = 1.3$ Hz, 1H), 7.27 (dd, $J = 8.4, 2.7$ Hz, 1H), 7.24 (s, 1H), 2.28 (tt, $J = 8.0, 4.7$ Hz, 1H), 1.09 (dt, $J = 8.0, 3.3$ Hz, 2H), 0.99 – 0.89 (m, 2H).

Example 40



(1) Preparation of compound 40-2:

Compound **13-8** (200 mg, 0.45 mmol, 1.0 eq) and 2-trifluoroethylaminopyridine-5-boronic acid (**40-1**, 118.08 mg) were dispersed in 1,4-dioxane (5 mL), and potassium acetate (132.5 mg), Pd(dppf)Cl₂ (14.6 mg), and water (0.5 mL) were added. The mixture was heated to 90 °C and reacted under nitrogen atmosphere. After the starting materials were consumed completely as detected by TLC, the reaction solution was concentrated under reduced pressure and purified by column chromatography to give compound **40-2**.

(2) Preparation of compound 40-3:

Compound **40-2** (130 mg) was dissolved in tetrahydrofuran (4 mL), a solution of lithium hydroxide hydrate (30.3 mg) and water (4 mL) was added dropwise in an ice-water bath, and the mixture was reacted at room temperature for 4 h. The reaction solution was adjusted to pH 6-7 with hydrochloric

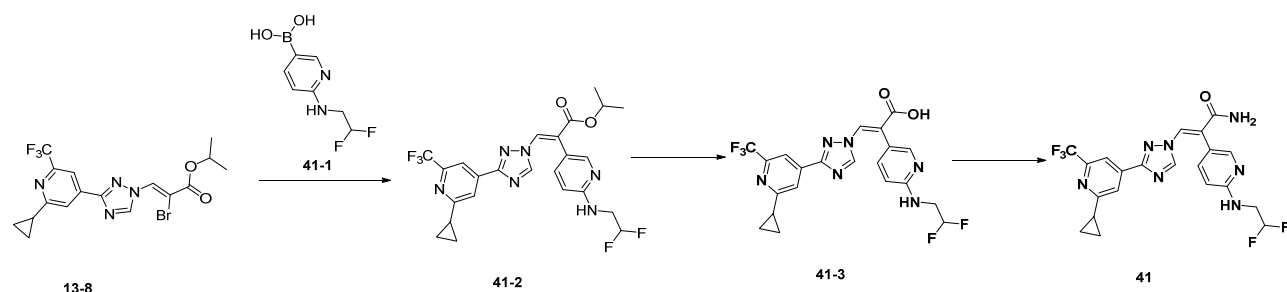
acid, extracted with ethyl acetate, dried over anhydrous sodium sulfate, and filtered, and the filtrate was evaporated to dryness under reduced pressure to give compound **40-3**, which was directly used in the next step.

(3) Preparation of compound 40:

Compound **40-3** (119.6 mg) was dispersed in tetrahydrofuran (5 mL), N-methylmorpholine (48.6 mg) and isobutyl chloroformate (65.6 mg) were added in an ice-water bath, and the mixture was stirred for 30 min. Ammonium hydroxide (50.4 mg) was added dropwise, and the mixture was reacted in an ice-water bath for 10 min. Water was added to quench the reaction, and the resulting mixture was extracted with ethyl acetate, dried over anhydrous sodium sulfate, concentrated until no liquid flowed out, and purified by preparative liquid chromatography to give compound **40** (50 mg). ESI-MS: $m/z = 498.29 [M+H]^+$.

^1H NMR (500 MHz, DMSO- d_6) δ 8.78 (s, 1H), 8.05 (s, 1H), 7.88 (d, $J = 2.0$ Hz, 2H), 7.75 (d, $J = 1.3$ Hz, 1H), 7.56 – 7.49 (m, 1H), 7.39 (t, $J = 6.6$ Hz, 1H), 7.32 (dd, $J = 8.5, 2.4$ Hz, 1H), 7.24 (s, 1H), 6.69 (d, $J = 8.5$ Hz, 1H), 4.19 (qd, $J = 9.7, 6.5$ Hz, 2H), 2.30 (tt, $J = 8.2, 4.7$ Hz, 1H), 1.08 (dt, $J = 8.0, 3.2$ Hz, 2H), 1.02 – 0.91 (m, 2H).

Example 41



(1) Preparation of compound 41-2:

Compound **13-8** (200 mg) and 6-(2,2-difluoroethylamino)pyridine-3-boronic acid (**41-1**, 108.86 mg) were dispersed in 1,4-dioxane (5 mL), and potassium acetate (132.5 mg), Pd(dppf)Cl₂ (14.6 mg), and water (0.5 mL) were added. The mixture was heated to 90 °C and reacted under nitrogen atmosphere. After the starting materials were consumed completely as detected by TLC, the reaction solution was concentrated under reduced pressure and purified by column chromatography to give compound **41-2**.

(2) Preparation of compound 41-3:

Compound **41-2** (120 mg) was dissolved in tetrahydrofuran (4 mL), a solution of lithium hydroxide

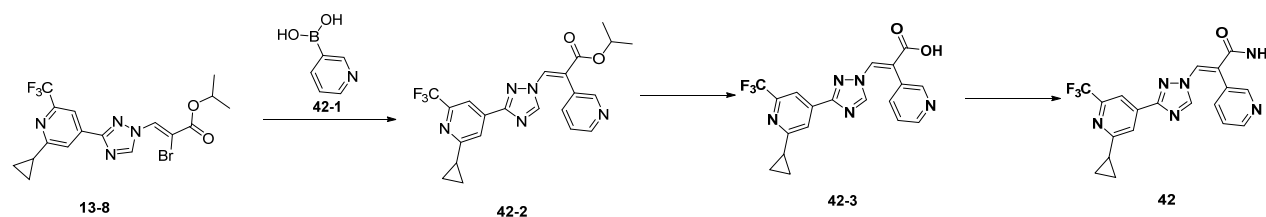
hydrate (28.9 mg) and water (4 mL) was added dropwise in an ice-water bath, and the mixture was reacted at room temperature for 4 h. The reaction solution was adjusted to pH 6-7 with hydrochloric acid, extracted with ethyl acetate, dried over anhydrous sodium sulfate, and filtered, and the filtrate was evaporated to dryness under reduced pressure to give compound **41-3**, which was directly used in the next step.

(3) Preparation of compound 41:

Compound **41-3** (110.5 mg) was dispersed in tetrahydrofuran (5 mL), N-methylmorpholine (46.5 mg) and isobutyl chloroformate (62.8 mg) were added in an ice-water bath, and the mixture was stirred for 30 min. Ammonium hydroxide (48.3 mg) was added dropwise, and the mixture was reacted in an ice-water bath for 10 min. Water was added to quench the reaction, and the resulting mixture was extracted with ethyl acetate, dried over anhydrous sodium sulfate, concentrated until no liquid flowed out, and purified by preparative liquid chromatography to give compound **41** (40 mg). ESI-MS: $m/z = 480.31 [M+H]^+$.

^1H NMR (500 MHz, DMSO- d_6) δ 8.74 (s, 1H), 8.03 (s, 1H), 7.90 (d, $J = 1.3$ Hz, 1H), 7.87 (d, $J = 2.4$ Hz, 1H), 7.77 (d, $J = 1.2$ Hz, 1H), 7.53 (s, 1H), 7.27 (dd, $J = 8.6, 2.4$ Hz, 1H), 7.25 – 7.18 (m, 2H), 6.64 (d, $J = 8.6$ Hz, 1H), 6.09 (tt, $J = 56.6, 4.1$ Hz, 1H), 3.73 (tdd, $J = 15.4, 6.1, 4.1$ Hz, 2H), 2.31 (tt, $J = 8.1, 4.7$ Hz, 1H), 1.08 (dt, $J = 8.0, 3.2$ Hz, 2H), 1.00 – 0.94 (m, 2H).

Example 42



(1) Preparation of compound 42-2:

Compound **13-8** (200 mg) and pyridine-3-boronic acid (**42-1**, 66.37 mg) were dispersed in 1,4-dioxane (5 mL), and potassium acetate (132.5 mg), Pd(dppf)Cl₂ (14.6 mg), and water (0.5 mL) were added. The mixture was heated to 90 °C and reacted under nitrogen atmosphere. After the starting materials were consumed completely as detected by TLC, the reaction solution was concentrated under reduced pressure and purified by column chromatography to give compound **42-2**.

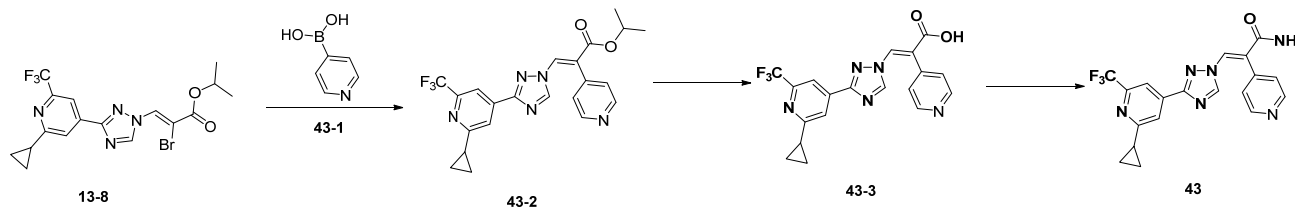
(2) Preparation of compound 42-3:

Compound **42-2** (85 mg) was dissolved in tetrahydrofuran (4 mL), a solution of lithium hydroxide hydrate (24.1 mg) and water (4 mL) was added dropwise in an ice-water bath, and the mixture was reacted at room temperature for 4 h. The reaction solution was adjusted to pH 6-7 with hydrochloric acid, extracted with ethyl acetate, dried over anhydrous sodium sulfate, and filtered, and the filtrate was evaporated to dryness under reduced pressure to give compound **42-3**, which was directly used in the next step.

(3) Preparation of compound 42:

Compound **42-3** (76.28 mg) was dispersed in tetrahydrofuran (5 mL), N-methylmorpholine (38.4 mg) and isobutyl chloroformate (51.9 mg) were added in an ice-water bath, and the mixture was stirred for 30 min. Ammonium hydroxide (39.9 mg) was added dropwise, and the mixture was reacted in an ice-water bath for 10 min. Water was added to quench the reaction, and the resulting mixture was extracted with ethyl acetate, dried over anhydrous sodium sulfate, concentrated until no liquid flowed out, and purified by preparative liquid chromatography to give compound **42** (20 mg). ESI-MS: $m/z = 401.32 [M+H]^+$.

Example 43



(1) Preparation of compound 43-2:

Compound **13-8** (200 mg) and 4-pyridineboronic acid (**43-1**, 66.37 mg) were dispersed in 1,4-dioxane (5 mL), and potassium acetate (132.5 mg), Pd(dppf)Cl₂ (14.6 mg), and water (0.5 mL) were added. The mixture was heated to 90 °C and reacted under nitrogen atmosphere. After the starting materials were consumed completely as detected by TLC, the reaction solution was concentrated under reduced pressure and purified by column chromatography to give compound **43-2**.

(2) Preparation of compound 43-3:

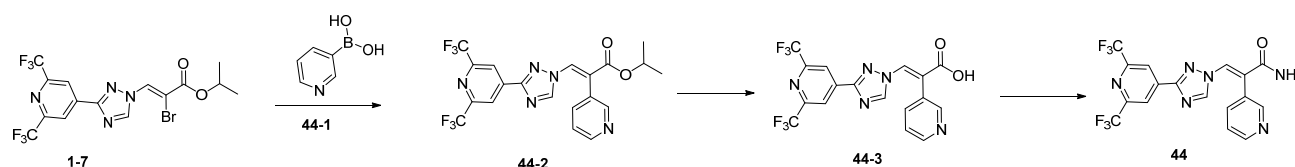
Compound **43-2** (120 mg) was dissolved in tetrahydrofuran (4 mL), a solution of lithium hydroxide hydrate (34.06 mg) and water (4 mL) was added dropwise in an ice-water bath, and the mixture was reacted at room temperature for 4 h. The reaction solution was adjusted to pH 6-7 with hydrochloric

acid, extracted with ethyl acetate, dried over anhydrous sodium sulfate, and filtered, and the filtrate was evaporated to dryness under reduced pressure to give compound **43-3**, which was directly used in the next step.

(3) Preparation of compound 43:

Compound **43-3** (108.4 mg) was dispersed in tetrahydrofuran (5 mL), N-methylmorpholine (54.6 mg) and isobutyl chloroformate (73.7 mg) were added in an ice-water bath, and the mixture was stirred for 30 min. Ammonium hydroxide (56.7 mg) was added dropwise, and the mixture was reacted in an ice-water bath for 10 min. Water was added to quench the reaction, and the resulting mixture was extracted with ethyl acetate, dried over anhydrous sodium sulfate, concentrated until no liquid flowed out, and purified by preparative liquid chromatography to give compound **43** (60 mg). ESI-MS: $m/z = 401.24 [M+H]^+$.

Example 44



(1) Preparation of compound 44-2:

Compound **1-7** (200 mg) and pyridine-3-boronic acid (**44-1**, 62.4 mg) were dispersed in 1,4-dioxane (8 mL), and potassium carbonate (175 mg), Pd(dppf)Cl₂ (15.5 mg), and water (0.8 mL) were added. The mixture was heated to 90 °C and reacted under nitrogen atmosphere. After the starting materials were consumed completely as detected by TLC, the reaction solution was concentrated under reduced pressure and purified by column chromatography to give compound **44-2**.

(2) Preparation of compound 44-3:

Compound **44-2** (100 mg) was dissolved in tetrahydrofuran (5 mL), a solution of lithium hydroxide hydrate (290 mg) and water (5 mL) was added dropwise in an ice-water bath, and the mixture was reacted at room temperature for 2 h. The reaction solution was adjusted to pH 6-7 with hydrochloric acid, extracted with ethyl acetate, dried over anhydrous sodium sulfate, and filtered, and the filtrate was evaporated to dryness under reduced pressure to give compound **44-3**, which was directly used in the next step.

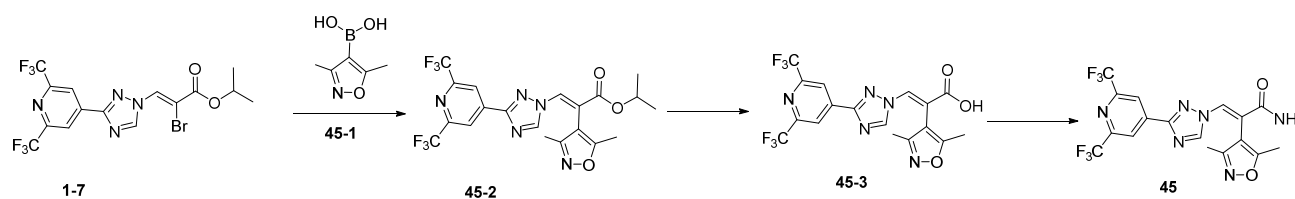
(3) Preparation of compound 44:

Compound **44-3** (91 mg) was dispersed in tetrahydrofuran (10 mL), N-methylmorpholine (42.9 mg)

and isobutyl chloroformate (58 mg) were added in an ice-water bath, and the mixture was stirred for 30 min. Ammonium hydroxide (44.5 mg) was added dropwise, and the mixture was reacted in an ice-water bath for 10 min. Water was added to quench the reaction, and the resulting mixture was extracted with ethyl acetate, dried over anhydrous sodium sulfate, concentrated until no liquid flowed out, and purified by preparative liquid chromatography to give compound **44** (60 mg). ESI-MS: $m/z = 429.29$ $[M+H]^+$.

^1H NMR (500 MHz, $\text{DMSO-}d_6$) δ 9.05 (s, 1H), 8.62 (d, $J = 4.9$ Hz, 1H), 8.46 (d, $J = 2.2$ Hz, 1H), 8.31 (s, 1H), 8.10 (s, 2H), 7.70 (dt, $J = 7.9, 1.9$ Hz, 1H), 7.64 (s, 1H), 7.48 (dd, $J = 7.8, 4.8$ Hz, 1H), 7.28 (s, 1H).

Example 45



(1) Preparation of compound 45-2:

Compound **1-7** (200 mg) and 3,5-dimethylisoxazole-4-boronic acid (**45-1**, 71.6 mg) were dispersed in 1,4-dioxane (8 mL), and potassium carbonate (175 mg), Pd(dppf)Cl_2 (15.5 mg), and water (0.8 mL) were added. The mixture was heated to 90 °C and reacted under nitrogen atmosphere. After the starting materials were consumed completely as detected by TLC, the reaction solution was concentrated under reduced pressure and purified by column chromatography to give compound **45-2**.

(2) Preparation of compound 45-3:

Compound **45-2** (159 mg) was dissolved in tetrahydrofuran (10 mL), a solution of lithium hydroxide hydrate (44.7 mg) and water (10 mL) was added dropwise in an ice-water bath, and the mixture was reacted at room temperature for 2 h. The reaction solution was adjusted to pH 6-7 with hydrochloric acid, extracted with ethyl acetate, dried over anhydrous sodium sulfate, and filtered, and the filtrate was evaporated to dryness under reduced pressure to give compound **45-3**, which was directly used in the next step.

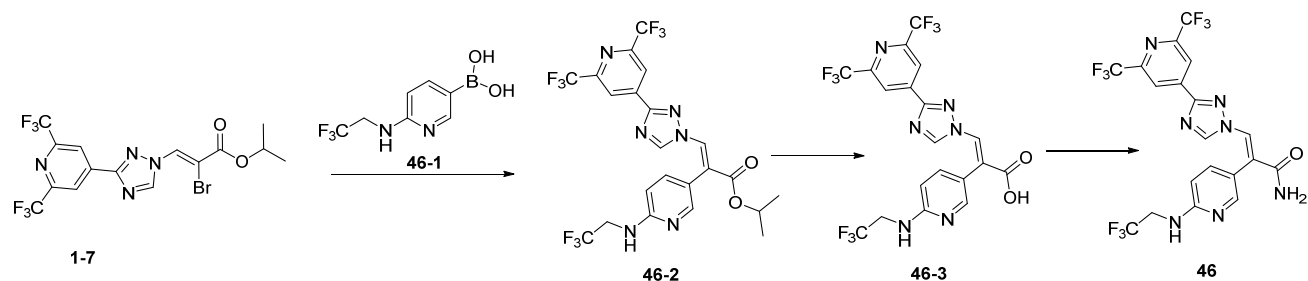
(3) Preparation of compound 45:

Compound **45-3** (145 mg) was dispersed in tetrahydrofuran (10 mL), N-methylmorpholine (65.7 mg)

and isobutyl chloroformate (88.7 mg) were added in an ice-water bath, and the mixture was stirred for 30 min. Ammonium hydroxide (68 mg) was added dropwise, and the mixture was reacted in an ice-water bath for 10 min. Water was added to quench the reaction, and the resulting mixture was extracted with ethyl acetate, dried over anhydrous sodium sulfate, concentrated until no liquid flowed out, and purified by preparative liquid chromatography to give compound **45** (66 mg). ESI-MS: $m/z = 447.29 [M+H]^+$.

^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 9.16 (s, 1H), 8.41 (s, 1H), 8.31 (s, 2H), 7.57 (s, 1H), 7.42 (s, 1H), 2.18 (s, 3H), 1.97 (s, 3H).

Example 46



(1) Preparation of compound 46-2:

Compound **1-7** (250 mg) and 6-(2,2,2-trifluoroethylamino)pyridine-3-boronic acid (**46-1**, 140 mg) were dispersed in 1,4-dioxane (8 mL), and potassium carbonate (219 mg), $\text{Pd}(\text{dppf})\text{Cl}_2$ (19.3 mg), and water (0.8 mL) were added. The mixture was heated to 90 °C and reacted under nitrogen atmosphere. After the starting materials were consumed completely as detected by TLC, the reaction solution was concentrated under reduced pressure and purified by column chromatography to give compound **46-2**.

(2) Preparation of compound 46-3:

Compound **46-2** (220 mg) was dissolved in tetrahydrofuran (10 mL), a solution of lithium hydroxide hydrate (48.7 mg) and water (10 mL) was added dropwise in an ice-water bath, and the mixture was reacted at room temperature for 2 h. The reaction solution was adjusted to pH 6-7 with hydrochloric acid, extracted with ethyl acetate, dried over anhydrous sodium sulfate, and filtered, and the filtrate was evaporated to dryness under reduced pressure to give compound **46-3**, which was directly used in the next step.

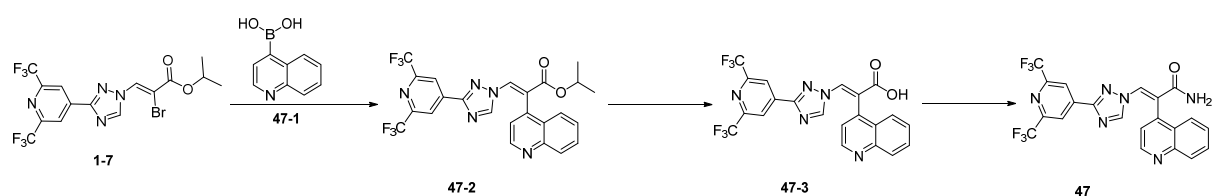
(3) Preparation of compound 46:

Compound **46-3** (203 mg) was dispersed in tetrahydrofuran (10 mL), N-methylmorpholine (78 mg)

and isobutyl chloroformate (106 mg) were added in an ice-water bath, and the mixture was stirred for 30 min. Ammonium hydroxide (81 mg) was added dropwise, and the mixture was reacted in an ice-water bath for 10 min. Water was added to quench the reaction, and the resulting mixture was extracted with ethyl acetate, dried over anhydrous sodium sulfate, concentrated until no liquid flowed out, and purified by preparative liquid chromatography to give compound **46** (30 mg). ESI-MS: $m/z = 526.33$ $[M+H]^+$.

^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 8.91 (s, 1H), 8.28 (s, 2H), 8.08 (s, 1H), 7.89 (d, $J = 2.3$ Hz, 1H), 7.55 (s, 1H), 7.40 (t, $J = 6.5$ Hz, 1H), 7.33 (dd, $J = 8.6, 2.4$ Hz, 1H), 7.27 (s, 1H), 6.68 (d, $J = 8.6$ Hz, 1H), 4.18 (qd, $J = 9.7, 6.4$ Hz, 2H).

Example 47



(1) Preparation of compound 47-2:

Compound **1-7** (200 mg) and 4-quinolineboronic acid (**47-1**, 87.7 mg) were dispersed in 1,4-dioxane (8 mL), and potassium acetate (124 mg), $\text{Pd}(\text{dppf})\text{Cl}_2$ (15.5 mg), and water (0.8 mL) were added. The mixture was heated to 90 °C and reacted under nitrogen atmosphere. After the starting materials were consumed completely as detected by TLC, the reaction solution was concentrated under reduced pressure and purified by column chromatography to give compound **47-2**.

(2) Preparation of compound 47-3:

Compound **47-2** (200 mg) was dissolved in tetrahydrofuran (10 mL), a solution of lithium hydroxide hydrate (48 mg) and water (10 mL) was added dropwise in an ice-water bath, and the mixture was reacted at room temperature for 2 h. The reaction solution was adjusted to pH 6-7 with hydrochloric acid, extracted with ethyl acetate, dried over anhydrous sodium sulfate, and filtered, and the filtrate was evaporated to dryness under reduced pressure to give compound **47-3**, which was directly used in the next step.

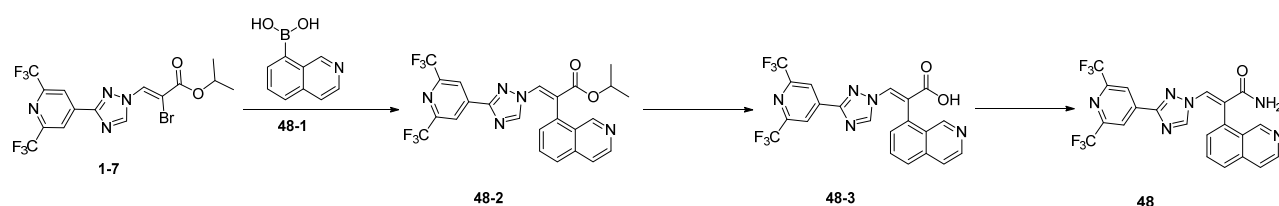
(3) Preparation of compound 47:

Compound **47-3** (184 mg) was dispersed in tetrahydrofuran (10 mL), *N*-methylmorpholine (77.7 mg) and isobutyl chloroformate (105 mg) were added in an ice-water bath, and the mixture was stirred for

30 min. Ammonium hydroxide (80 mg) was added dropwise, and the mixture was reacted in an ice-water bath for 10 min. Water was added to quench the reaction, and the resulting mixture was extracted with ethyl acetate, dried over anhydrous sodium sulfate, concentrated until no liquid flowed out, and purified by preparative liquid chromatography to give compound **47** (90 mg). ESI-MS: $m/z = 479.22$ $[M+H]^+$.

^1H NMR (500 MHz, DMSO- d_6) δ 9.10 (s, 1H), 8.95 (d, $J = 4.4$ Hz, 1H), 8.57 (s, 1H), 8.12 (d, $J = 8.4$ Hz, 1H), 7.77 (dd, $J = 8.4, 1.4$ Hz, 1H), 7.74 (ddd, $J = 8.3, 6.8, 1.4$ Hz, 1H), 7.63 (s, 1H), 7.61 (s, 2H), 7.52 (ddd, $J = 8.2, 6.8, 1.2$ Hz, 1H), 7.42 (d, $J = 4.4$ Hz, 1H), 7.22 (s, 1H).

Example 48



(1) Preparation of compound 48-2:

Compound **1-7** (200 mg) and 8-isoquinolineboronic acid (**48-1**, 87.7 mg) were dispersed in 1,4-dioxane (8 mL), and potassium acetate (124 mg), Pd(dppf)Cl₂ (15.5 mg), and water (0.8 mL) were added. The mixture was heated to 90 °C and reacted under nitrogen atmosphere. After the starting materials were consumed completely as detected by TLC, the reaction solution was concentrated under reduced pressure and purified by column chromatography to give compound **48-2**.

(2) Preparation of compound 48-3:

Compound **48-2** (170 mg) was dissolved in tetrahydrofuran (10 mL), a solution of lithium hydroxide hydrate (41 mg) and water (10 mL) was added dropwise in an ice-water bath, and the mixture was reacted at room temperature for 2 h. The reaction solution was adjusted to pH 6-7 with hydrochloric acid, extracted with ethyl acetate, dried over anhydrous sodium sulfate, and filtered, and the filtrate was evaporated to dryness under reduced pressure to give compound **48-3**, which was directly used in the next step.

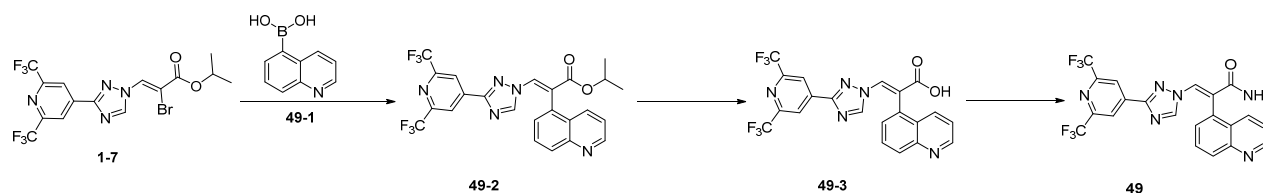
(3) Preparation of compound 48:

Compound **48-3** (156 mg) was dispersed in tetrahydrofuran (10 mL), N-methylmorpholine (66 mg) and isobutyl chloroformate (89 mg) were added in an ice-water bath, and the mixture was stirred for

30 min. Ammonium hydroxide (68 mg) was added dropwise, and the mixture was reacted in an ice-water bath for 10 min. Water was added to quench the reaction, and the resulting mixture was extracted with ethyl acetate, dried over anhydrous sodium sulfate, concentrated until no liquid flowed out, and purified by preparative liquid chromatography to give compound **48** (45 mg). ESI-MS: $m/z = 479.24 [M+H]^+$.

^1H NMR (500 MHz, DMSO- d_6) δ 9.10 (d, $J = 43.7$ Hz, 2H), 8.54 (d, $J = 37.6$ Hz, 2H), 8.08 (d, $J = 8.1$ Hz, 1H), 7.99 – 7.81 (m, 2H), 7.66 (s, 3H), 7.55 (d, $J = 7.0$ Hz, 1H), 7.28 (s, 1H).

Example 49



(1) Preparation of compound 49-2:

Compound **1-7** (200 mg) and 5-quinolineboronic acid (**49-1**, 87.7 mg) were dispersed in 1,4-dioxane (8 mL), and potassium carbonate (175 mg), Pd(dppf)Cl₂ (15.5 mg), and water (0.8 mL) were added. The mixture was heated to 90 °C and reacted under nitrogen atmosphere. After the starting materials were consumed completely as detected by TLC, the reaction solution was concentrated under reduced pressure and purified by column chromatography to give compound **49-2**.

(2) Preparation of compound 49-3:

Compound **49-2** (200 mg) was dissolved in tetrahydrofuran (10 mL), a solution of lithium hydroxide hydrate (48 mg) and water (10 mL) was added dropwise in an ice-water bath, and the mixture was reacted at room temperature for 2 h. The reaction solution was adjusted to pH 6-7 with hydrochloric acid, extracted with ethyl acetate, dried over anhydrous sodium sulfate, and filtered, and the filtrate was evaporated to dryness under reduced pressure to give compound **49-3**, which was directly used in the next step.

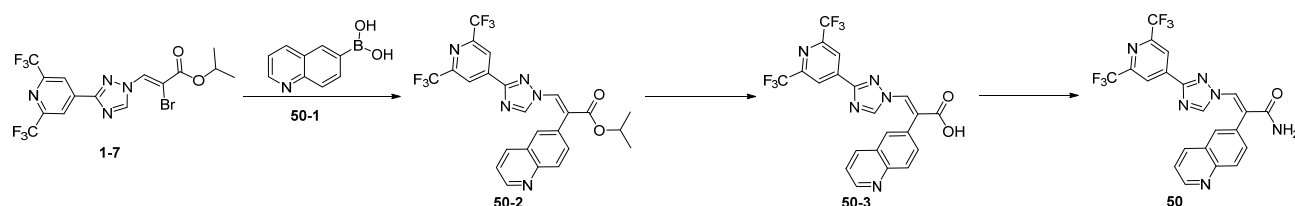
(3) Preparation of compound 49:

Compound **49-3** (184 mg) was dispersed in tetrahydrofuran (10 mL), N-methylmorpholine (77.7 mg) and isobutyl chloroformate (105 mg) were added in an ice-water bath, and the mixture was stirred for 30 min. Ammonium hydroxide (80 mg) was added dropwise, and the mixture was reacted in an ice-water bath for 10 min. Water was added to quench the reaction, and the resulting mixture was

extracted with ethyl acetate, dried over anhydrous sodium sulfate, concentrated until no liquid flowed out, and purified by preparative liquid chromatography to give compound **49** (62 mg). ESI-MS: $m/z = 479.25$ $[M+H]^+$.

^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 8.98 (s, 1H), 8.93 (d, $J = 4.4$ Hz, 1H), 8.56 (s, 1H), 8.18 (dd, $J = 18.0, 8.5$ Hz, 2H), 7.88 (t, $J = 7.8$ Hz, 1H), 7.72 (s, 2H), 7.63 (s, 1H), 7.59 – 7.43 (m, 2H), 7.15 (s, 1H).

Example 50



(1) Preparation of compound **50-2**:

Compound **1-7** (200 mg) and 6-quinolineboronic acid (**50-1**, 87.7 mg) were dispersed in 1,4-dioxane (8 mL), and potassium carbonate (175 mg), $\text{Pd}(\text{dppf})\text{Cl}_2$ (15.5 mg), and water (0.8 mL) were added. The mixture was heated to 90 °C and reacted under nitrogen atmosphere. After the starting materials were consumed completely as detected by TLC, the reaction solution was concentrated under reduced pressure and purified by column chromatography to give compound **50-2**.

(2) Preparation of compound **50-3**:

Compound **50-2** (150 mg) was dissolved in tetrahydrofuran (10 mL), a solution of lithium hydroxide hydrate (36 mg) and water (10 mL) was added dropwise in an ice-water bath, and the mixture was reacted at room temperature for 2 h. The reaction solution was adjusted to pH 6-7 with hydrochloric acid, extracted with ethyl acetate, dried over anhydrous sodium sulfate, and filtered, and the filtrate was evaporated to dryness under reduced pressure to give compound **50-3**, which was directly used in the next step.

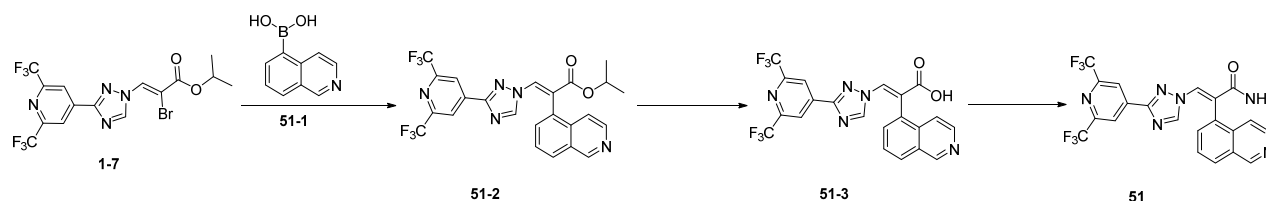
(3) Preparation of compound **50**:

Compound **50-3** (138 mg) was dispersed in tetrahydrofuran (10 mL), *N*-methylmorpholine (58 mg) and isobutyl chloroformate (78.7 mg) were added in an ice-water bath, and the mixture was stirred for 30 min. Ammonium hydroxide (60.5 mg) was added dropwise, and the mixture was reacted in an ice-water bath for 10 min. Water was added to quench the reaction, and the resulting mixture was extracted with ethyl acetate, dried over anhydrous sodium sulfate, concentrated until no liquid

flowed out, and purified by preparative liquid chromatography to give compound **50** (87 mg). ESI-MS: $m/z = 479.22$ $[M+H]^+$.

^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 9.00 (dd, $J = 4.3, 1.7$ Hz, 1H), 8.95 (s, 1H), 8.45 (dd, $J = 8.4, 1.8$ Hz, 1H), 8.32 (s, 1H), 8.09 (d, $J = 8.6$ Hz, 1H), 7.98 (d, $J = 1.9$ Hz, 1H), 7.92 (s, 2H), 7.67 (s, 1H), 7.65 – 7.62 (m, 1H), 7.62 – 7.58 (m, 1H), 7.19 (s, 1H).

Example 51



(1) Preparation of compound **51-2**:

Compound **1-7** (200 mg) and 5-quinolineboronic acid (**51-1**, 87.7 mg) were dispersed in 1,4-dioxane (8 mL), and potassium carbonate (175 mg), $\text{Pd}(\text{dppf})\text{Cl}_2$ (15.5 mg), and water (0.8 mL) were added. The mixture was heated to 90 °C and reacted under nitrogen atmosphere. After the starting materials were consumed completely as detected by TLC, the reaction solution was concentrated under reduced pressure and purified by column chromatography to give compound **51-2**.

(2) Preparation of compound **51-3**:

Compound **51-2** (200 mg) was dissolved in tetrahydrofuran (10 mL), a solution of lithium hydroxide hydrate (48 mg) and water (10 mL) was added dropwise in an ice-water bath, and the mixture was reacted at room temperature for 2 h. The reaction solution was adjusted to pH 6-7 with hydrochloric acid, extracted with ethyl acetate, dried over anhydrous sodium sulfate, and filtered, and the filtrate was evaporated to dryness under reduced pressure to give compound **51-3**, which was directly used in the next step.

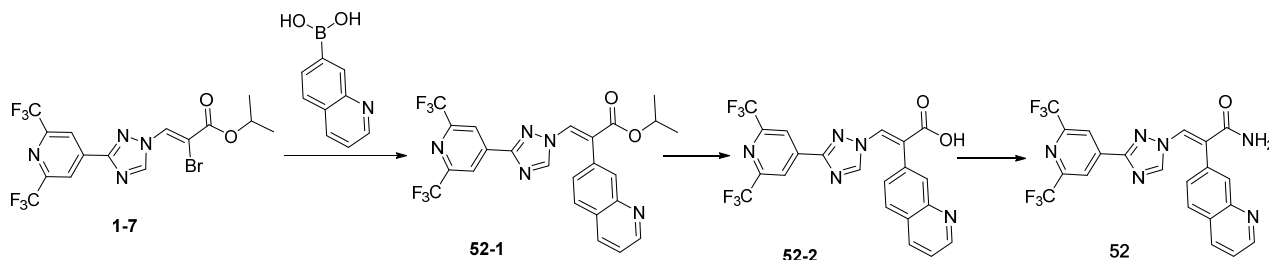
(3) Preparation of compound **51**:

Compound **51-3** (184 mg) was dispersed in tetrahydrofuran (10 mL), *N*-methylmorpholine (77.7 mg) and isobutyl chloroformate (105 mg) were added in an ice-water bath, and the mixture was stirred for 30 min. Ammonium hydroxide (80 mg) was added dropwise, and the mixture was reacted in an ice-water bath for 10 min. Water was added to quench the reaction, and the resulting mixture was extracted with ethyl acetate, dried over anhydrous sodium sulfate, concentrated until no liquid flowed out, and purified by preparative liquid chromatography to give compound **51** (29 mg).

ESI-MS: $m/z = 479.23 [M+H]^+$.

^1H NMR (500 MHz, $\text{DMSO-}d_6$) δ 9.39 (s, 1H), 9.02 (s, 1H), 8.56 (s, 1H), 8.42 (d, $J = 5.8$ Hz, 1H), 8.24 (d, $J = 8.2$ Hz, 1H), 7.90 – 7.49 (m, 6H), 7.16 (s, 1H).

Example 52



(1) Preparation of compound 52-1:

Compound **1-7** (300 mg) and 5-quinolineboronic acid (131.6 mg) were dispersed in 1,4-dioxane (8 mL), and potassium carbonate (263 mg), Pd(dppf)Cl_2 (23.2 mg), and water (0.8 mL) were added. The mixture was heated to 90 °C and reacted under nitrogen atmosphere. After the reaction was completed, the reaction solution was concentrated under reduced pressure and purified by column chromatography to give compound **52-1**.

(2) Preparation of compound 52-2:

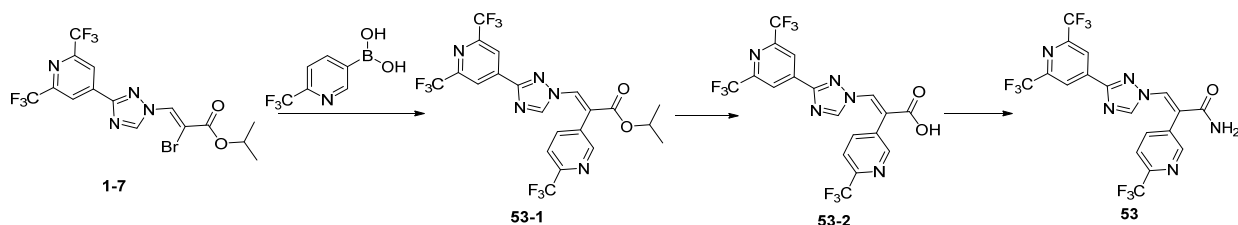
Compound **52-1** (200 mg) was dissolved in tetrahydrofuran (10 mL), a solution of lithium hydroxide hydrate (48 mg) and water (10 mL) was added dropwise in an ice-water bath, and the mixture was reacted at room temperature for 2 h. The reaction solution was adjusted to pH 6-7 with hydrochloric acid, extracted with ethyl acetate (20 mL $\times$ 2), dried over anhydrous sodium sulfate, and filtered, and the filtrate was evaporated to dryness under reduced pressure to give compound **52-2**, which was directly used in the next step.

(3) Preparation of compound 52:

Compound **52-2** (184 mg) was dispersed in tetrahydrofuran (10 mL), N-methylmorpholine (77.7 mg) and isobutyl chloroformate (105 mg) were added in an ice-water bath, and the mixture was stirred for 30 min. Ammonium hydroxide (80 mg) was added dropwise, and the mixture was reacted in an ice-water bath for 10 min. Water was added to quench the reaction, and the resulting mixture was extracted with ethyl acetate (20 mL $\times$ 2), dried over anhydrous sodium sulfate, concentrated until no liquid flowed out, and purified by preparative liquid chromatography to give compound **52** (90 mg in total). ESI-MS: $m/z = 479.14 [M+H]^+$.

^1H NMR (500 MHz, $\text{DMSO-}d_6$) δ 8.96 (s, 1H), 8.92 (dd, $J = 4.2, 1.7$ Hz, 1H), 8.44 (dd, $J = 8.5, 1.8$ Hz, 1H), 8.31 (s, 1H), 8.04 (d, $J = 8.4$ Hz, 1H), 7.94 (d, $J = 1.6$ Hz, 1H), 7.91 (s, 2H), 7.65 (s, 1H), 7.61 (dd, $J = 8.3, 4.2$ Hz, 1H), 7.47 (dd, $J = 8.3, 1.7$ Hz, 1H), 7.19 (s, 1H).

Example 53



(1) Preparation of compound 53-1:

Compound **1-7** (300 mg) and 6-trifluoromethyl-3-pyridineboronic acid (145 mg) were dispersed in 1,4-dioxane (8 mL), and potassium carbonate (138.2 mg), Pd(dppf)Cl_2 (23.2 mg), and water (0.8 mL) were added. The mixture was heated to 90 °C and reacted under nitrogen atmosphere. After the reaction was completed, the reaction solution was concentrated under reduced pressure and purified by column chromatography to give compound **53-1**.

(2) Preparation of compound 53-2:

Compound **53-1** (300 mg) was dissolved in tetrahydrofuran (10 mL), a solution of lithium hydroxide hydrate (70 mg) and water (10 mL) was added dropwise in an ice-water bath, and the mixture was reacted at room temperature for 3 h. The reaction solution was adjusted to pH 6-7 with hydrochloric acid, extracted with ethyl acetate (20 mL $\times$ 2), dried over anhydrous sodium sulfate, and filtered, and the filtrate was evaporated to dryness under reduced pressure to give compound **53-2**, which was directly used in the next step.

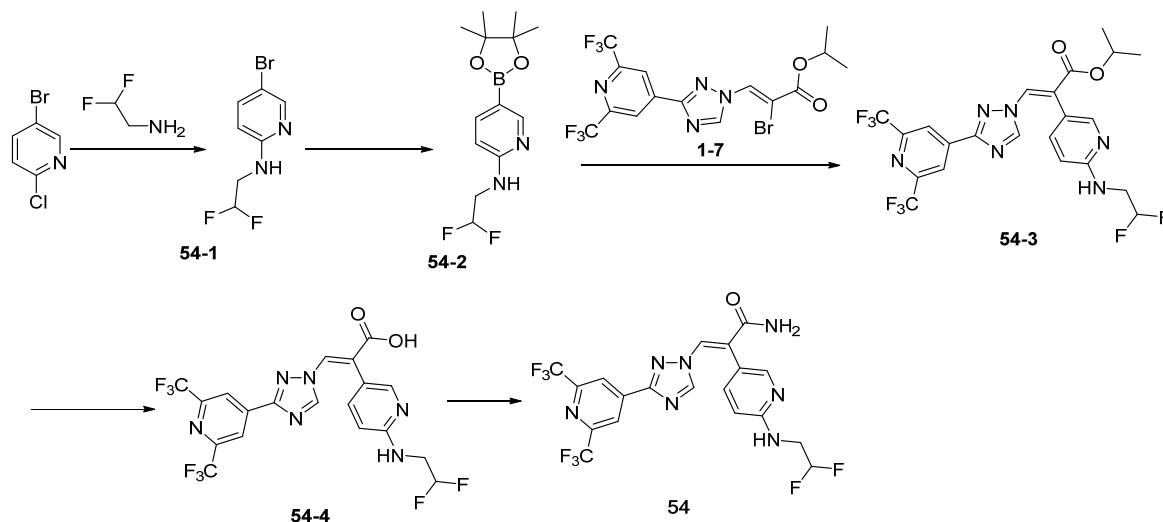
(3) Preparation of compound 53:

Compound **53-2** (276 mg) was dispersed in tetrahydrofuran (10 mL), N-methylmorpholine (112 mg) and isobutyl chloroformate (152 mg) were added in an ice-water bath, and the mixture was stirred for 30 min. Ammonium hydroxide (117 mg) was added dropwise, and the mixture was reacted in an ice-water bath for 10 min. Water was added to quench the reaction, and the resulting mixture was extracted with ethyl acetate (20 mL $\times$ 2), dried over anhydrous sodium sulfate, concentrated until no liquid flowed out, and purified by preparative liquid chromatography to give compound **53** (150 mg in total). ESI-MS: $m/z = 497.05$ $[\text{M}+\text{H}]^+$.

^1H NMR (500 MHz, $\text{DMSO-}d_6$) δ 9.22 (s, 1H), 8.68 (d, $J = 2.0$ Hz, 1H), 8.44 (s, 1H), 8.01 (d, $J = 4.4$

Hz, 3H), 7.98 (d, $J = 8.0$ Hz, 1H), 7.67 (s, 1H), 7.33 (s, 1H).

Example 54



(1) Preparation of compound 54-1:

Compounds 5-bromo-2-chloropyridine (2.4 g) and 2,2-difluoroethylamine (1.76 g) were dispersed in 1,4-dioxane (30 mL), and bis(dibenzylideneacetone)palladium (420 mg), 1,1'-bis(di-*tert*-butylphosphino)ferrocene (710 mg), and potassium *tert*-butoxide (5.6 g) were added. The mixture was heated to 90 °C and reacted under nitrogen atmosphere. After the reaction was completed, the reaction solution was concentrated under reduced pressure and purified by column chromatography to give compound **54-1**.

(2) Preparation of compound 54-2:

Compound **54-1** (200 mg) was dispersed in 1,4-dioxane (10 mL), and bis(pinacolato)diboron (236 mg), potassium acetate (331 mg), and Pd(dppf)Cl₂ (62 mg) were added. The mixture was reacted at 90 °C for 3 h under nitrogen atmosphere. The reaction solution was diluted with water (10 mL), extracted with ethyl acetate (20 mL × 2), dried over anhydrous sodium sulfate, and concentrated until no liquid flowed out to give compound **54-2**.

(3) Preparation of compound 54-3:

Compounds **1-7** (332 mg) and **54-2** (240 mg) were dispersed in 1,4-dioxane (10 mL), and potassium acetate (207 mg), Pd(dppf)Cl₂ (25.7 mg), and water (1 mL) were added. The mixture was heated to 90 °C and reacted under nitrogen atmosphere. After the reaction was completed, the reaction solution was concentrated under reduced pressure and purified by column chromatography to give compound **54-3**.

(4) Preparation of compound 54-4:

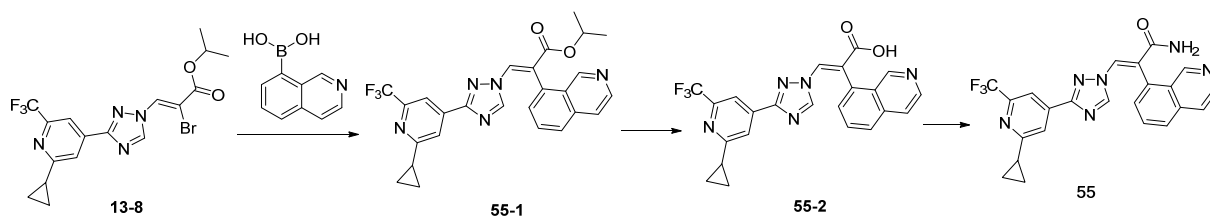
Compound **54-3** (180 mg) was dissolved in tetrahydrofuran (8 mL), a solution of lithium hydroxide hydrate (41 mg) and water (8 mL) was added dropwise in an ice-water bath, and the mixture was reacted at room temperature for 4 h. The reaction solution was adjusted to pH 6-7 with hydrochloric acid, extracted with ethyl acetate (20 mL $\times$ 2), dried over anhydrous sodium sulfate, and filtered, and the filtrate was evaporated to dryness under reduced pressure to give compound **54-4**, which was directly used in the next step.

(5) Preparation of compound 54:

Compound **54-4** (166 mg) was dispersed in tetrahydrofuran (10 mL), N-methylmorpholine (66 mg) and isobutyl chloroformate (89 mg) were added in an ice-water bath, and the mixture was stirred for 30 min. Ammonium hydroxide (69 mg) was added dropwise, and the mixture was reacted in an ice-water bath for 10 min. Water was added to quench the reaction, and the resulting mixture was extracted with ethyl acetate (20 mL $\times$ 2), dried over anhydrous sodium sulfate, concentrated until no liquid flowed out, and purified by preparative liquid chromatography to give compound **54** (73 mg). ESI-MS: $m/z = 508.16 [M+H]^+$.

^1H NMR (500 MHz, DMSO- d_6) δ 8.87 (s, 1H), 8.31 (s, 2H), 8.06 (s, 1H), 7.88 (d, $J = 2.4$ Hz, 1H), 7.55 (s, 1H), 7.31 – 7.19 (m, 3H), 6.64 (dd, $J = 8.6, 0.8$ Hz, 1H), 6.08 (tt, $J = 56.6, 4.1$ Hz, 1H), 3.73 (tdd, $J = 15.4, 6.1, 4.2$ Hz, 2H).

Example 55



(1) Preparation of compound 55-1:

Compound **13-8** (200 mg) and isoquinoline-8-boronic acid (93.4 mg) were dispersed in 1,4-dioxane (5 mL), and potassium carbonate (186.57 mg), Pd(dppf)Cl₂ (14.6 mg), and water (0.5 mL) were added. The mixture was heated to 90 °C and reacted under nitrogen atmosphere. After the reaction was completed, the reaction solution was concentrated under reduced pressure and purified by column chromatography to give compound **55-1**.

(2) Preparation of compound 55-2:

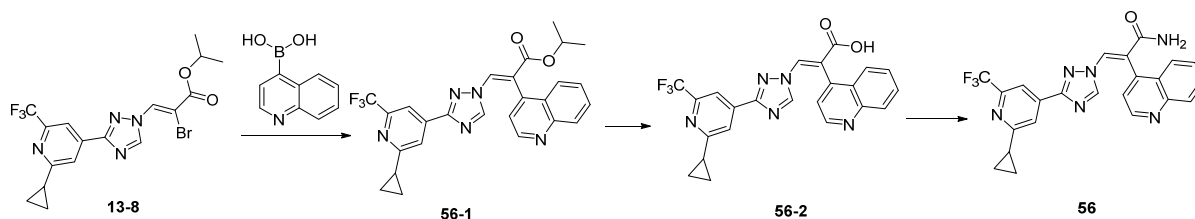
Compound **55-1** (170 mg) was dissolved in tetrahydrofuran (4 mL), a solution of lithium hydroxide hydrate (43.4 mg) and water (4 mL) was added dropwise in an ice-water bath, and the mixture was reacted at room temperature for 4 h. The reaction solution was adjusted to pH 6-7 with hydrochloric acid, extracted with ethyl acetate (20 mL $\times$ 2), dried over anhydrous sodium sulfate, and filtered, and the filtrate was evaporated to dryness under reduced pressure to give compound **55-2**, which was directly used in the next step.

(3) Preparation of compound **55**:

Compound **55-2** (171.5 mg) was dispersed in tetrahydrofuran (5 mL), N-methylmorpholine (76.8 mg) and isobutyl chloroformate (103.8 mg) were added in an ice-water bath, and the mixture was stirred for 30 min. Ammonium hydroxide (79.8 mg) was added dropwise, and the mixture was reacted in an ice-water bath for 10 min. Water was added to quench the reaction, and the resulting mixture was extracted with ethyl acetate (20 mL $\times$ 2), dried over anhydrous sodium sulfate, concentrated until no liquid flowed out, and purified by preparative liquid chromatography to give compound **55** (30 mg). ESI-MS: $m/z = 451.23 [M+H]^+$.

^1H NMR (500 MHz, DMSO- d_6) δ 9.12 (s, 1H), 8.93 (s, 1H), 8.51 (d, $J = 12.6$ Hz, 2H), 8.07 (d, $J = 8.2$ Hz, 1H), 8.01 – 7.76 (m, 2H), 7.71 – 7.47 (m, 2H), 7.38 (s, 1H), 7.22 (s, 1H), 7.03 (s, 1H), 2.18 (s, 1H), 1.05 (d, $J = 8.3$ Hz, 2H), 0.84 (s, 2H).

Example 56



(1) Preparation of compound **56-1**:

Compound **13-8** (200 mg) and quinoline-4-boronic acid (93.4 mg) were dispersed in 1,4-dioxane (5 mL), and potassium carbonate (186.57 mg), Pd(dppf)Cl₂ (14.6 mg), and water (0.5 mL) were added. The mixture was heated to 90 °C and reacted under nitrogen atmosphere. After the reaction was completed, the reaction solution was concentrated under reduced pressure and purified by column chromatography to give compound **56-1**.

(2) Preparation of compound **56-2**:

Compound **56-1** (160 mg) was dissolved in tetrahydrofuran (4 mL), a solution of lithium hydroxide

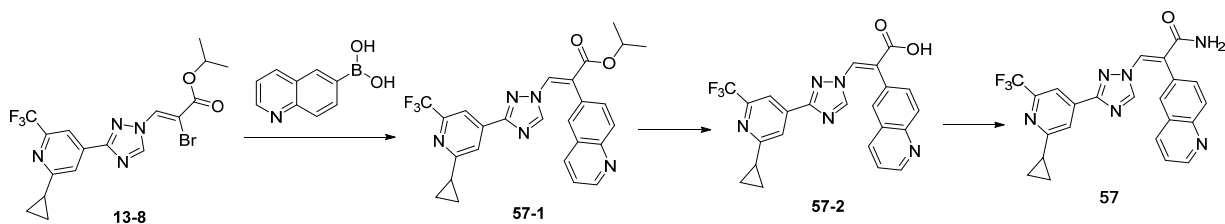
hydrate (40.8 mg) and water (4 mL) was added dropwise in an ice-water bath, and the mixture was reacted at room temperature for 4 h. The reaction solution was adjusted to pH 6-7 with hydrochloric acid, extracted with ethyl acetate (20 mL $\times$ 2), dried over anhydrous sodium sulfate, and filtered, and the filtrate was evaporated to dryness under reduced pressure to give compound **56-2**, which was directly used in the next step.

(3) Preparation of compound **56**:

Compound **56-2** (144.4 mg) was dispersed in tetrahydrofuran (5 mL), N-methylmorpholine (64.7 mg) and isobutyl chloroformate (87.4 mg) were added in an ice-water bath, and the mixture was stirred for 30 min. Ammonium hydroxide (67.2 mg) was added dropwise, and the mixture was reacted in an ice-water bath for 10 min. Water was added to quench the reaction, and the resulting mixture was extracted with ethyl acetate (20 mL $\times$ 2), dried over anhydrous sodium sulfate, concentrated until no liquid flowed out, and purified by preparative liquid chromatography to give compound **56** (60 mg). ESI-MS: $m/z = 451.26 [M+H]^+$.

^1H NMR (500 MHz, DMSO- d_6) δ 9.00 (s, 1H), 8.95 (d, $J = 4.3$ Hz, 1H), 8.54 (s, 1H), 8.13 (d, $J = 8.4$ Hz, 1H), 7.82 – 7.70 (m, 2H), 7.59 (s, 1H), 7.52 (t, $J = 7.6$ Hz, 1H), 7.42 (d, $J = 4.3$ Hz, 1H), 7.23 (s, 1H), 7.18 (s, 1H), 7.05 (s, 1H), 2.14 (tt, $J = 8.3, 4.7$ Hz, 1H), 1.06 (dd, $J = 8.1, 3.0$ Hz, 2H), 0.90 – 0.75 (m, 2H).

Example 57



(1) Preparation of compound **57-1**:

Compound **13-8** (200 mg) and quinoline-6-boronic acid (93.4 mg) were dispersed in 1,4-dioxane (5 mL), and potassium carbonate (186.57 mg), Pd(dppf)Cl₂ (14.6 mg), and water (0.5 mL) were added. The mixture was heated to 90 °C and reacted under nitrogen atmosphere. After the reaction was completed, the reaction solution was concentrated under reduced pressure and purified by column chromatography to give compound **57-1**.

(2) Preparation of compound **57-2**:

Compound **57-1** (150 mg) was dissolved in tetrahydrofuran (4 mL), a solution of lithium hydroxide

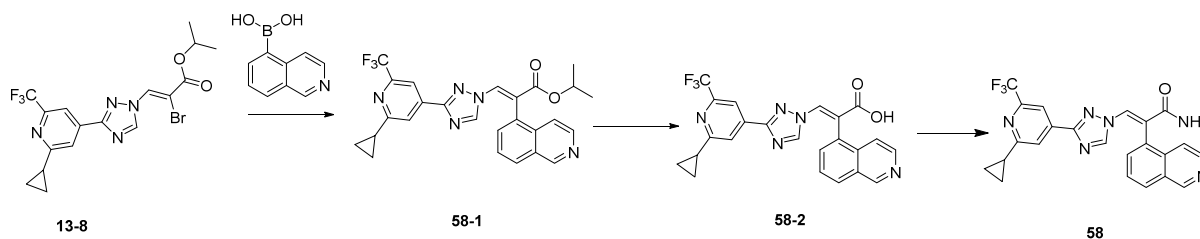
hydrate (38.3 mg) and water (4 mL) was added dropwise in an ice-water bath, and the mixture was reacted at room temperature for 4 h. The reaction solution was adjusted to pH 6-7 with hydrochloric acid, extracted with ethyl acetate (20 mL $\times$ 2), dried over anhydrous sodium sulfate, and filtered, and the filtrate was evaporated to dryness under reduced pressure to give compound **57-2**, which was directly used in the next step.

(3) Preparation of compound **57**:

Compound **57-2** (135.4 mg) was dispersed in tetrahydrofuran (5 mL), N-methylmorpholine (60.7 mg) and isobutyl chloroformate (81.9 mg) were added in an ice-water bath, and the mixture was stirred for 30 min. Ammonium hydroxide (63 mg) was added dropwise, and the mixture was reacted in an ice-water bath for 10 min. Water was added to quench the reaction, and the resulting mixture was extracted with ethyl acetate (20 mL $\times$ 2), dried over anhydrous sodium sulfate, concentrated until no liquid flowed out, and purified by preparative liquid chromatography to give compound **57** (30 mg). ESI-MS: $m/z = 451.21$ $[M+H]^+$.

^1H NMR (500 MHz, DMSO- d_6) δ 8.96 (dd, $J = 4.2, 1.7$ Hz, 1H), 8.81 (s, 1H), 8.39 (dd, $J = 8.6, 1.8$ Hz, 1H), 8.27 (s, 1H), 8.07 (d, $J = 8.6$ Hz, 1H), 7.93 (d, $J = 1.9$ Hz, 1H), 7.65 – 7.53 (m, 4H), 7.37 (d, $J = 1.3$ Hz, 1H), 7.15 (s, 1H), 2.10 (ddd, $J = 8.2, 6.5, 4.1$ Hz, 1H), 1.03 – 0.98 (m, 2H), 0.82 – 0.77 (m, 2H).

Example 58



(1) Preparation of compound **58-1**:

Compound **13-8** (200 mg) and isoquinoline-5-boronic acid (93.4 mg) were dispersed in 1,4-dioxane (5 mL), and potassium carbonate (186.57 mg), Pd(dppf)Cl₂ (14.6 mg), and water (0.5 mL) were added. The mixture was heated to 90 °C and reacted under nitrogen atmosphere. After the reaction was completed, the reaction solution was concentrated under reduced pressure and purified by column chromatography to give compound **58-1**.

(2) Preparation of compound **58-2**:

Compound **58-1** (160 mg) was dissolved in tetrahydrofuran (4 mL), a solution of lithium hydroxide

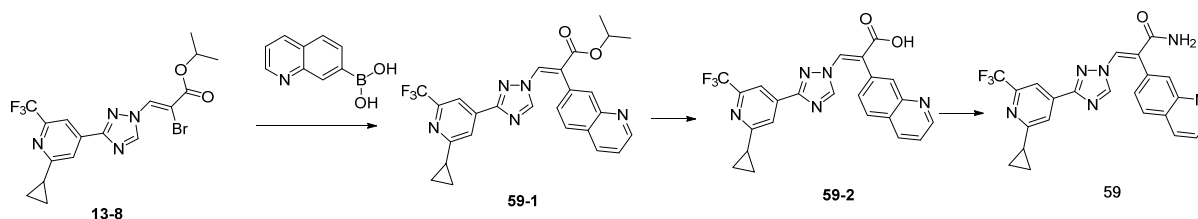
hydrate (40.8 mg) and water (4 mL) was added dropwise in an ice-water bath, and the mixture was reacted at room temperature for 4 h. The reaction solution was adjusted to pH 6-7 with hydrochloric acid, extracted with ethyl acetate (20 mL $\times$ 2), dried over anhydrous sodium sulfate, and filtered, and the filtrate was evaporated to dryness under reduced pressure to give compound **58-2**, which was directly used in the next step.

(3) Preparation of compound **58**:

Compound **58-2** (144.4 mg) was dispersed in tetrahydrofuran (5 mL), N-methylmorpholine (64.7 mg) and isobutyl chloroformate (87.4 mg) were added in an ice-water bath, and the mixture was stirred for 30 min. Ammonium hydroxide (67.2 mg) was added dropwise, and the mixture was reacted in an ice-water bath for 10 min. Water was added to quench the reaction, and the resulting mixture was extracted with ethyl acetate (20 mL $\times$ 2), dried over anhydrous sodium sulfate, concentrated until no liquid flowed out, and purified by preparative liquid chromatography to give compound **58** (40 mg). ESI-MS: $m/z = 451.20 [M+H]^+$.

^1H NMR (500 MHz, DMSO- d_6) δ 9.39 (s, 1H), 8.89 (s, 1H), 8.51 (s, 1H), 8.41 (d, $J = 5.9$ Hz, 1H), 8.23 (d, $J = 8.2$ Hz, 1H), 7.76 (dd, $J = 8.2, 7.1$ Hz, 1H), 7.66 (dd, $J = 7.0, 1.2$ Hz, 1H), 7.56 (s, 1H), 7.54 (d, $J = 5.9$ Hz, 1H), 7.37 (d, $J = 1.2$ Hz, 1H), 7.11 (s, 1H), 7.04 (d, $J = 1.2$ Hz, 1H), 2.18 (tt, $J = 8.1, 4.7$ Hz, 1H), 1.05 (dd, $J = 8.2, 2.9$ Hz, 2H), 0.85 (d, $J = 7.0$ Hz, 2H).

Example 59



(1) Preparation of compound **59-1**:

Compound **13-8** (200 mg) and quinoline-7-boronic acid (93.4 mg) were dispersed in 1,4-dioxane (5 mL), and potassium carbonate (186.57 mg), Pd(dppf)Cl₂ (14.6 mg), and water (0.5 mL) were added. The mixture was heated to 90 °C and reacted under nitrogen atmosphere. After the reaction was completed, the reaction solution was concentrated under reduced pressure and purified by column chromatography to give compound **59-1**.

(2) Preparation of compound **59-2**:

Compound **59-1** (145 mg) was dissolved in tetrahydrofuran (4 mL), a solution of lithium hydroxide

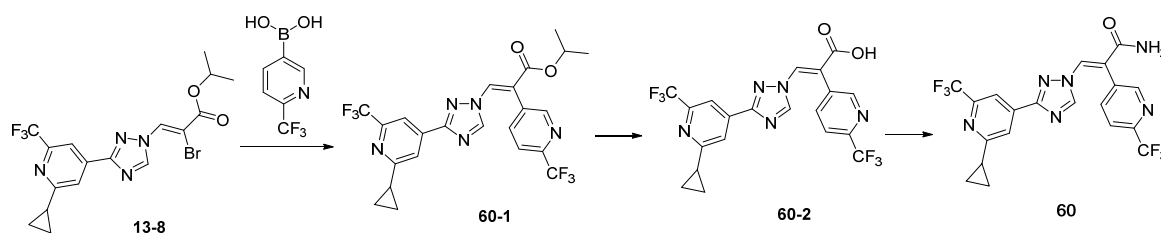
hydrate (37 mg) and water (4 mL) was added dropwise in an ice-water bath, and the mixture was reacted at room temperature for 4 h. The reaction solution was adjusted to pH 6-7 with hydrochloric acid, extracted with ethyl acetate (20 mL $\times$ 2), dried over anhydrous sodium sulfate, and filtered, and the filtrate was evaporated to dryness under reduced pressure to give compound **59-2**, which was directly used in the next step.

(3) Preparation of compound **59**:

Compound **59-2** (135.4 mg) was dispersed in tetrahydrofuran (5 mL), N-methylmorpholine (60.6 mg) and isobutyl chloroformate (81.9 mg) were added in an ice-water bath, and the mixture was stirred for 30 min. Ammonium hydroxide (63 mg) was added dropwise, and the mixture was reacted in an ice-water bath for 10 min. Water was added to quench the reaction, and the resulting mixture was extracted with ethyl acetate (20 mL $\times$ 2), dried over anhydrous sodium sulfate, concentrated until no liquid flowed out, and purified by preparative liquid chromatography to give compound **59** (40 mg). ESI-MS: $m/z = 451.22$ $[M+H]^+$.

^1H NMR (500 MHz, DMSO- d_6) δ 8.93 (dd, $J = 4.2, 1.8$ Hz, 1H), 8.83 (s, 1H), 8.44 (dd, $J = 8.4, 1.8$ Hz, 1H), 8.27 (s, 1H), 8.04 (d, $J = 8.4$ Hz, 1H), 7.93 (d, $J = 1.6$ Hz, 1H), 7.66 – 7.55 (m, 3H), 7.46 (dd, $J = 8.4, 1.7$ Hz, 1H), 7.32 (d, $J = 1.3$ Hz, 1H), 7.17 (s, 1H), 2.12 (tt, $J = 8.4, 4.7$ Hz, 1H), 1.01 (dt, $J = 8.1, 3.3$ Hz, 2H), 0.83 – 0.77 (m, 2H).

Example 60



(1) Preparation of compound **60-1**:

Compound **13-8** (200 mg) and 6-trifluoromethylpyridine-3-boronic acid (103.1 mg) were dispersed in 1,4-dioxane (5 mL), and potassium carbonate (186.57 mg), Pd(dppf)Cl₂ (14.6 mg), and water (0.5 mL) were added. The mixture was heated to 90 °C and reacted under nitrogen atmosphere. After the reaction was completed, the reaction solution was concentrated under reduced pressure and purified by column chromatography to give compound **60-1**.

(2) Preparation of compound **60-2**:

Compound **60-1** (130 mg) was dissolved in tetrahydrofuran (4 mL), a solution of lithium hydroxide

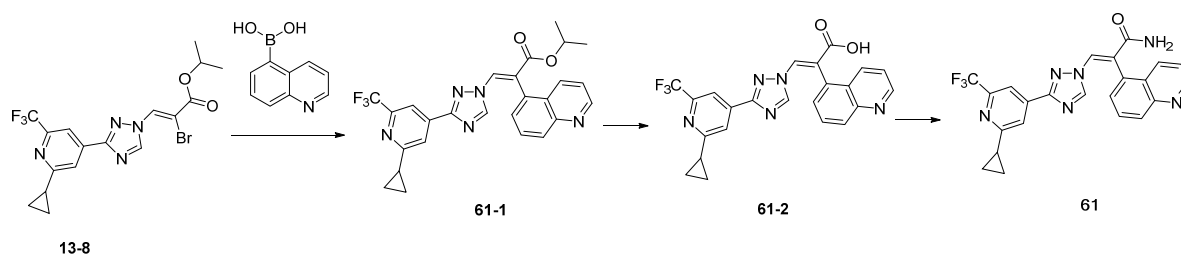
hydrate (32 mg) and water (4 mL) was added dropwise in an ice-water bath, and the mixture was reacted at room temperature for 4 h. The reaction solution was adjusted to pH 6-7 with hydrochloric acid, extracted with ethyl acetate (20 mL $\times$ 2), dried over anhydrous sodium sulfate, and filtered, and the filtrate was evaporated to dryness under reduced pressure to give compound **60-2**, which was directly used in the next step.

(3) Preparation of compound **60**:

Compound **60-2** (117.3 mg) was dispersed in tetrahydrofuran (5 mL), N-methylmorpholine (50.6 mg) and isobutyl chloroformate (68.3 mg) were added in an ice-water bath, and the mixture was stirred for 30 min. Ammonium hydroxide (52.5 mg) was added dropwise, and the mixture was reacted in an ice-water bath for 10 min. Water was added to quench the reaction, and the resulting mixture was extracted with ethyl acetate (20 mL $\times$ 2), dried over anhydrous sodium sulfate, concentrated until no liquid flowed out, and purified by preparative liquid chromatography to give compound **60** (45 mg). ESI-MS: m/z = 469.19 $[M+H]^+$.

^1H NMR (500 MHz, DMSO- d_6) δ 9.13 (s, 1H), 8.66 (d, J = 2.0 Hz, 1H), 8.41 (s, 1H), 8.04 – 7.94 (m, 2H), 7.74 (s, 1H), 7.64 (s, 1H), 7.38 (s, 1H), 7.30 (s, 1H), 2.24 (tt, J = 8.3, 4.7 Hz, 1H), 1.06 (dt, J = 8.0, 3.3 Hz, 2H), 0.99 – 0.86 (m, 2H).

Example 61



(1) Preparation of compound **61-1**:

Compound **13-8** (200 mg) and quinoline-5-boronic acid (93.4 mg) were dispersed in 1,4-dioxane (5 mL), and potassium carbonate (186.57 mg), Pd(dppf)Cl₂ (14.6 mg), and water (0.5 mL) were added. The mixture was heated to 90 °C and reacted under nitrogen atmosphere. After the reaction was completed, the reaction solution was concentrated under reduced pressure and purified by column chromatography to give compound **61-1**.

(2) Preparation of compound **61-2**:

Compound **61-1** (220 mg) was dissolved in tetrahydrofuran (4 mL), a solution of lithium hydroxide

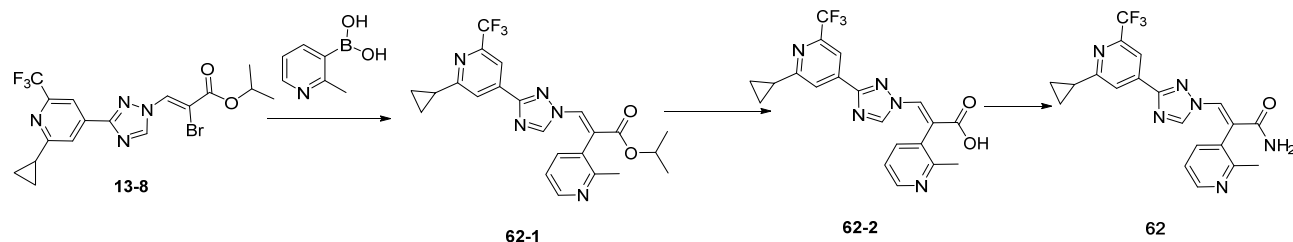
hydrate (56.6 mg) and water (4 mL) was added dropwise in an ice-water bath, and the mixture was reacted at room temperature for 4 h. The reaction solution was adjusted to pH 6-7 with hydrochloric acid, extracted with ethyl acetate (20 mL $\times$ 2), dried over anhydrous sodium sulfate, and filtered, and the filtrate was evaporated to dryness under reduced pressure to give compound **61-2**, which was directly used in the next step.

(3) Preparation of compound 61:

Compound **61-2** (203.1 mg) was dispersed in tetrahydrofuran (5 mL), N-methylmorpholine (91 mg) and isobutyl chloroformate (123 mg) were added in an ice-water bath, and the mixture was stirred for 30 min. Ammonium hydroxide (94 mg) was added dropwise, and the mixture was reacted in an ice-water bath for 10 min. Water was added to quench the reaction, and the resulting mixture was extracted with ethyl acetate (20 mL $\times$ 2), dried over anhydrous sodium sulfate, concentrated until no liquid flowed out, and purified by preparative liquid chromatography to give compound **61** (70 mg). ESI-MS: $m/z = 451.21 [M+H]^+$.

^1H NMR (500 MHz, DMSO- d_6) δ 8.89 (dd, $J = 4.1, 1.7$ Hz, 1H), 8.83 (s, 1H), 8.51 (s, 1H), 8.18 – 8.08 (m, 2H), 7.84 (dd, $J = 8.5, 7.1$ Hz, 1H), 7.57 (s, 1H), 7.50 (dd, $J = 7.0, 1.2$ Hz, 1H), 7.45 (dd, $J = 8.5, 4.1$ Hz, 1H), 7.32 (d, $J = 1.3$ Hz, 1H), 7.17 (d, $J = 1.4$ Hz, 1H), 7.09 (s, 1H), 2.16 (tt, $J = 8.0, 4.7$ Hz, 1H), 1.06 (dd, $J = 8.2, 2.8$ Hz, 2H), 0.85 (q, $J = 4.2$ Hz, 2H).

Example 62



(1) Preparation of compound 62-1:

Compound **13-8** (200 mg) and 2-methylpyridine-3-boronic acid (73.95 mg) were dispersed in 1,4-dioxane (5 mL), and potassium carbonate (186.6 mg), Pd(dppf)Cl₂ (14.6 mg), and water (0.5 mL) were added. The mixture was heated to 90 °C and reacted under nitrogen atmosphere. After the reaction was completed, the reaction solution was concentrated under reduced pressure and purified by column chromatography to give compound **62-1**.

(2) Preparation of compound 62-2:

Compound **62-1** (140 mg) was dissolved in tetrahydrofuran (5 mL), a solution of lithium hydroxide

hydrate (38.5 mg) and water (5 mL) was added dropwise in an ice-water bath, and the mixture was reacted at room temperature for 2 h. The reaction solution was adjusted to pH 6-7 with hydrochloric acid, extracted with ethyl acetate (20 mL $\times$ 2), dried over anhydrous sodium sulfate, and filtered, and the filtrate was evaporated to dryness under reduced pressure to give compound **62-2**, which was directly used in the next step.

(3) Preparation of compound **62**:

Compound **62-2** (124.6 mg) was dispersed in tetrahydrofuran (5 mL), N-methylmorpholine (60.7 mg) and isobutyl chloroformate (81.9 mg) were added in an ice-water bath, and the mixture was stirred for 30 min. Ammonium hydroxide (63 mg) was added dropwise, and the mixture was reacted in an ice-water bath for 10 min. Water was added to quench the reaction, and the resulting mixture was extracted with ethyl acetate (20 mL $\times$ 2), dried over anhydrous sodium sulfate, concentrated until no liquid flowed out, and purified by preparative liquid chromatography to give compound **62** (72 mg). ESI-MS: $m/z = 415.27$ $[M+H]^+$.

^1H NMR (500 MHz, DMSO- d_6) δ 8.95 (s, 1H), 8.52 (dd, $J = 4.9, 1.8$ Hz, 1H), 8.31 (s, 1H), 7.66 (d, $J = 1.3$ Hz, 1H), 7.57 – 7.52 (m, 1H), 7.50 (dt, $J = 4.4, 2.4$ Hz, 2H), 7.29 (dd, $J = 7.6, 4.9$ Hz, 1H), 7.14 (s, 1H), 2.28 (s, 3H), 2.27 – 2.23 (m, 1H), 1.09 (dt, $J = 8.3, 3.2$ Hz, 2H), 0.96 – 0.90 (m, 2H).

Test Example 1. Inhibitory Activity on *In Vitro* Cell Proliferation

1.1 Assay for inhibitory activity on Jurkat cell proliferation

Jurkat cells in a good growth state were collected into a centrifuge tube, adjusted to a cell density of 5×10^4 cells/mL, and seeded in a 96-well plate (100 μL /well). The cells were incubated overnight in a cell incubator. Compounds were added using a nanoliter pipettor such that the final concentrations of the compounds were 1000 nM-0.46 nM (the addition was performed in duplicate). Meanwhile, a control was set. After another 72 h of incubation in the cell incubator, the assay reagent CCK-8 (manufacturer: Dojindo Laboratories, Beijing; 10 μL /well) was added. After 2 h of incubation in the cell incubator, absorbance was measured at 450 nm on an Envision microplate reader. A four-parameter analysis was performed, a dose-response curve was fit, and IC_{50} was calculated.

1.2 Assay for inhibitory activity on OCI-LY10 cell proliferation

OCI-LY10 cells in a good growth state were collected into a centrifuge tube, adjusted to a cell density of 9×10^4 cells/mL, and seeded in a 96-well plate (100 μL /well). The cells were incubated overnight in a cell incubator. Compounds were added using a nanoliter pipettor such that the final

concentrations of the compounds were 1000 nM-0.46 nM (the addition was performed in duplicate). Meanwhile, a control was set. After another 72 h of incubation in the cell incubator, the assay reagent CCK-8 (manufacturer: Dojindo Laboratories, Beijing; 10 μ L/well) was added. After 2 h of incubation in the cell incubator, absorbance was measured at 450 nm on an Envision microplate reader. A four-parameter analysis was performed, a dose-response curve was fit, and IC₅₀ was calculated.

1.3 Assay for inhibitory activity on RPMI-8226 cell proliferation

RPMI-8226 cells in a good growth state were collected into a centrifuge tube. The cell density was adjusted, and the cells were seeded in a 96-well plate and incubated overnight in a cell incubator. Compounds were added using a nanoliter pipettor, and a control was set. The plate was placed in the cell incubator for further incubation, and the assay reagent was added. After the cells were incubated in the cell incubator for a period of time, absorbance was measured on an Envision microplate reader. A four-parameter analysis was performed, a dose-response curve was fit, and IC₅₀ was calculated.

The specific results are shown in Table 1. For the inhibitory activity on Jurkat cell proliferation, A represents IC₅₀ $\leq$ 20 nM; For the inhibitory activity on OCI-LY10 cell proliferation, + represents IC₅₀ $\leq$ 40 nM.

Table 1. Activity assay results for compounds

Compound No.	Inhibitory activity on Jurkat cell proliferation (IC ₅₀ , nM)	Inhibitory activity on OCI-LY10 cell proliferation (IC ₅₀ , nM)
1	A	+
2	A	+
3	A	+
4	A	+
5	A	+
10	A	+
11	A	+
13	A	+
14	A	+
15	A	+
16	A	+
17	A	+
25	A	+
26	A	+
30	A	+
32	A	+
33	A	+
36	A	+

37	A	+
38	A	+
39	A	+
40	A	+
41	A	+
43	A	+
46	A	+
53	A	+
54	A	+
57	A	+
59	A	+
60	A	+

The compounds of the present application showed good results in the *in vitro* cell proliferation inhibitory activity assay.

Test Example 2. *In Vitro* Liver Microsomal Stability

Liver microsome incubation samples were prepared by mixing a PBS buffer (pH = 7.4), a liver microsome solution (0.5 mg/mL), a test compound, and an NADPH + MgCl₂ solution, and incubated at 37 °C and 300 rpm for 1 h. Zero-hour samples were prepared by mixing a PBS buffer (pH = 7.4), a liver microsome solution (0.5 mg/mL), and a test compound. An acetonitrile solution containing an internal standard was added to the samples, and supernatants were prepared by protein precipitation, diluted, and then assayed by LC/MS/MS. The assay results are shown in Table 2.

Table 2. *In vitro* metabolic stability of related compounds in liver microsomes of various species

Compound No.	Mouse liver microsome	Human liver microsome
	Residuals at 60 min (%)	
1	97.97%	101.38%
2	87.82%	92.23%
3	94.26%	95.65%
4	93.27%	100.33%
5	99.03%	97.64%
8	98.98%	101.7%
10	93.99%	95.75%
11	89.63%	86.18%
13	91.15%	93.23%
14	83.14%	80.48%
15	88.38%	87.55%
16	90.60%	88.75%
17	95.11%	93.92%
21	99.28%	94.26%
25	94.66%	110.48%
26	90.27%	96.64%
27	94.24%	102.54%

30	89.94%	98.75%
32	95.08%	100.32%
33	98.21%	104.79%
34	87.79%	101.21%
38	83.25%	102.40%
39	89.18%	106.91%

The compounds of the present application showed good properties in the liver microsomal stability assay.

Test Example 3. *In Vivo* Pharmacokinetics

3.1 Mouse pharmacokinetics

ICR mice weighing 18-22 g were randomized into groups of 9 mice per group after 3-5 days of acclimatization and then administered intragastrically at a dose of 3 mg/kg.

Plasma samples to be tested were prepared by taking blood from the orbit at time points of 15 min, 30 min, 1 h, 2 h, 4 h, 6 h, 8 h, 10 h, and 24 h.

20 μ L of each plasma sample to be tested and a standard curve sample were taken, and an acetonitrile solution containing an internal standard was added. A supernatant was obtained by protein precipitation, diluted, and then assayed by LC/MS/MS.

Pharmacokinetic parameters were fitted using a non-compartmental model. The assay results are shown in Table 3.

Table 3

Compound No.	Mice administered by single intravenous injection 1 mpk				Mice administered intragastrically 3 mpk					
	AUC (0-24) (h*ng/mL)	AUC (0- ∞) h*ng/mL	t _{1/2} (h)	CL (L/h/kg)	AUC (0-24) (h*ng/mL)	AUC (0- ∞) (h*ng/mL)	T _{max} (h)	t _{1/2} (h)	C _{max} (ng/mL)	Absolute bioavailability F (%)
2	874	879	1.26	1.14	2726	2731	3.0	2.57	483	103.93%
3	1544	1574	1.66	0.635	5277	5296	3.0	2.80	681	113.9%
15	1619	1629	1.34	0.614	4604	4654	3.0	3.48	599	94.77%
21	1629	1633	3.02	0.61	4754	4759	1.0	2.35	871	97.31%
38	1037	1044	1.41	0.958	3485	3804	1.0	2.55	874	112.06%

The compounds of the present application showed good properties in the pharmacokinetic assay, including but not limited to, good bioavailability, AUC, and the like.

3.2 Mouse brain distribution

ICR mice weighing 20-26 g were randomized into groups of 3 mice per group after 3-5 days of acclimatization and then administered intragastrically at a dose of 5 mg/kg.

Plasma samples to be tested were prepared by taking blood from the orbit at a time point of 3 h.

Meanwhile, brain tissue at each time point was collected, and the homogenate was weighed.

20 μ L of each plasma to be tested and tissue homogenate sample and a standard curve sample were taken, and an acetonitrile solution was added. A supernatant was obtained by protein precipitation, diluted, and then assayed by LC/MS/MS. The brain-to-blood ratio was calculated.

The brain-to-blood ratios of the compounds of the present application were less than 1, showing a low brain uptake amount.

Test Example 4. *In Vivo* Pharmacodynamics

Efficacy evaluation in OCI-LY10 human diffuse large B-cell lymphoma NOD-SCID mouse subcutaneous xenograft tumor model

(1) SPF female NOD-SCID mice (source: Jiangsu Huachuang Xinnuo Pharmaceutical Technology Co., Ltd.) were inoculated subcutaneously at the right side armpit with OCI-LY10 human diffuse large B-cell lymphoma cells at 1×10^7 cells/mouse. When the mean tumor volume reached about 200 mm^3 , the animals were divided into a control group (vehicle control group) and treatment groups (compound groups).

The administration dose included 1 mg/kg, 2 mg/kg, and 4 mg/kg, and the administration frequency was once daily. The day of grouping was defined as day 0, and intragastric administration was started on day 0 for 21 consecutive days.

Alternatively, the administration dose was 4 mg/kg, and the administration frequency was 5 times per week. The day of grouping was defined as day 0, and intragastric administration was started on day 0 five times per week for two consecutive weeks.

The tumor volume was measured once every 3 days, and meanwhile, the mice were weighed and the data were recorded; the general behavior of the mice was observed and recorded every day. After the experiment was completed, the tumors were removed, weighed, and photographed.

The detection index and the calculation formula are as follows:

Tumor volume $\text{TV} (\text{mm}^3) = 1/2 \times (a \times b^2)$, wherein a is the long diameter of the tumor, and b is the short diameter of the tumor;

Relative tumor volume $\text{RTV} = \text{TV}_t/\text{TV}_0$, wherein TV_0 is the tumor volume on day 0, and TV_t is the tumor volume at each measurement;

Relative tumor proliferation rate $\text{T/C} (\%) = (\text{T}_{\text{RTV}}/\text{C}_{\text{RTV}}) \times 100\%$, wherein T_{RTV} is RTV of the treatment group, and C_{RTV} is RTV of the vehicle control group;

Tumor growth inhibition rate TGI (%) = $(1 - TW/TW_0) \times 100\%$; wherein TW is the tumor weight of the treatment group, and TW_0 is the tumor weight of the vehicle control group;

Weight change rate WCR (%) = $(W_t - W_{t_0})/W_{t_0} \times 100\%$, wherein W_{t_0} is the body weight of the mouse on day 0, and W_t is the body weight of the mouse at each measurement.

The specific assay results are shown in Table 4 and Table 5.

Table 4. Effect on OCI-LY10 cell (NOD-SCID) mouse subcutaneous xenograft tumor

Compound	Dose	Day 21 of assay			Day 23 of assay	
		TV(mm ³) (mean±SD)	RTV (mean±SD)	T/C(%)	Weight change rate (%) (mean ± SD)	TGI(%)
Control group	N/A	2260±850	10.8±4.3	----	9.9±4.7	----
Compound 21	2mg/kg	520±178	2.4±0.4	22.2%	-2.0±6.5	89.3%*
Compound 25	4mg/kg	360±105	1.8±0.6	16.7%	1.7±5.3	91.1%*

Note: comparison with the control group, where * denotes $p < 0.05$ and ** denotes $p < 0.01$.

Table 5. Effect on OCI-LY10 cell (NOD-SCID) mouse subcutaneous xenograft tumor

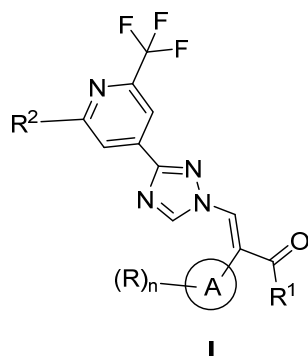
Group	Dose	Day 18 of assay			Day 21 of assay	
		TV(mm ³) (mean±SD)	RTV (mean±SD)	T/C(%)	Weight change rate (%) (mean ± SD)	TGI(%)
Control group	N/A	1525±586	7.8±3.5	----	7.9±1.0	----
Compound 11	4mg/kg	326±52	1.7±0.2	21.8%	0.6±8.1	89.7%**

Note: comparison with the control group, where ** denotes $p < 0.01$.

The compounds of the present application had no significant toxicity in the assay, and the results showed that the compounds had good tumor growth inhibition rates.

CLAIMS

1. A compound of formula I, a pharmaceutically acceptable salt thereof, or a stereoisomer thereof:



wherein,

R^1 is selected from the group consisting of $-NH_2$, C_{1-6} alkyl-O-, C_{1-6} alkyl-NH-, and $(C_{1-6}$ alkyl) $_2$ N-;

ring A is selected from the group consisting of a C_{6-10} aromatic ring group and a 5- to 10-membered heteroaromatic ring group;

R is selected from the group consisting of halogen, CN, OH, NH_2 , C_{1-6} alkyl, C_{1-6} alkyl-O-, C_{1-6} alkyl-S-, C_{1-6} haloalkyl-O-, C_{1-6} haloalkyl-S-, C_{1-6} haloalkyl, C_{1-6} alkyl substituted with 3- to 10-membered heterocycloalkyl, R^aNH -, and $(R^a)_2N$ -;

R^a is selected from the group consisting of C_{1-6} alkyl, C_{3-10} cycloalkyl, and 3- to 10-membered heterocycloalkyl, and R^a is optionally substituted with one or more groups selected from the group consisting of halogen, CN, OH, NH_2 , C_{1-6} alkyl, C_{1-6} alkyl-O-, and 5- to 6-membered heterocycloalkyl;

n is selected from the group consisting of 0, 1, 2, 3, and 4;

R^2 is selected from the group consisting of cyclopropyl and trifluoromethyl.

2. The compound of formula I, the pharmaceutically acceptable salt thereof, or the stereoisomer thereof according to claim 1, wherein R^1 is selected from the group consisting of $-NH_2$, C_{1-4} alkyl-O-, C_{1-4} alkyl-NH-, and $(C_{1-4}$ alkyl) $_2$ N-;

alternatively, R^1 is selected from the group consisting of $-NH_2$, C_{1-3} alkyl-O-, C_{1-3} alkyl-NH-, and $(C_{1-3}$ alkyl) $_2$ N-;

alternatively, R^1 is selected from the group consisting of $-NH_2$, isopropyl-O-, and methyl-NH-;

alternatively, R^1 is selected from the group consisting of $-NH_2$ and isopropyl-O-;

alternatively, R^1 is selected from $-NH_2$.

3. The compound of formula I, the pharmaceutically acceptable salt thereof, or the stereoisomer thereof according to claim 1 or 2, wherein ring A is selected from the group consisting of phenyl and a 5- to 10-membered heteroaromatic ring group;

alternatively, ring A is selected from the group consisting of 5-, 6-, 7-, 8-, 9-, and 10-membered

heteroaromatic ring groups;

alternatively, ring A is selected from the group consisting of 5- to 6-membered and 9- to 10-membered heteroaromatic ring groups;

alternatively, ring A is selected from a 10-membered heteroaromatic ring group;

alternatively, ring A is selected from the group consisting of 5- to 6-membered heteroaromatic ring groups;

alternatively, ring A is selected from a 6-membered heteroaromatic ring group;

alternatively, ring A is selected from the group consisting of pyrimidinyl, pyridinyl, pyrazolyl, isoxazolyl, oxazolyl, quinolyl, indazolyl, pyridazinyl, thiazolyl, furanyl, pyranyl, thienyl, pyrrolyl, pyrazinyl, isothiazolyl, oxazolyl, indolyl, naphthyridinyl, isoquinolyl, quinazolinyl, and benzofuranyl;

alternatively, ring A is selected from the group consisting of pyrimidinyl, pyridinyl, pyrazolyl, isoxazolyl, quinolyl, indazolyl, naphthyridinyl, and isoquinolyl;

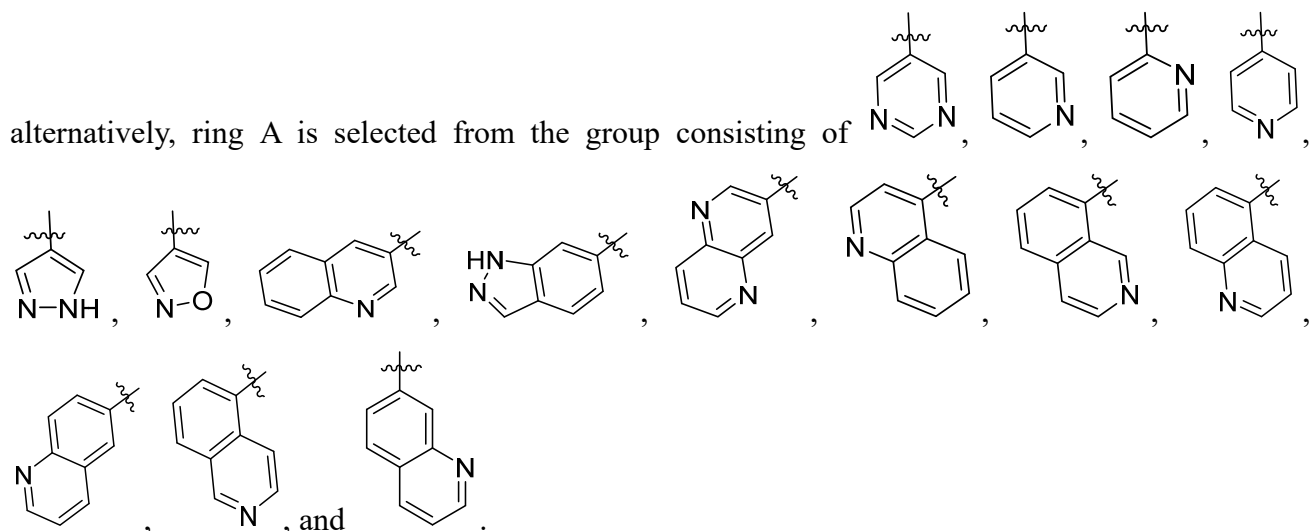
alternatively, ring A is selected from the group consisting of pyrimidinyl and pyridinyl;

alternatively, ring A is selected from pyrimidinyl;

alternatively, ring A is selected from pyridinyl;

alternatively, ring A is selected from the group consisting of pyrazolyl and isoxazolyl;

alternatively, ring A is selected from the group consisting of quinolyl, indazolyl, naphthyridinyl, and isoquinolyl;



4. The compound of formula I, the pharmaceutically acceptable salt thereof, or the stereoisomer thereof according to any one of claims 1-3, wherein R is selected from the group consisting of halogen, CN, OH, NH₂, C₁₋₄ alkyl, C₁₋₄ alkyl-O-, C₁₋₄ alkyl-S-, C₁₋₄ haloalkyl-O-, C₁₋₄ haloalkyl-S-, C₁₋₄ haloalkyl, R^aNH-, and (R^a)₂N-;

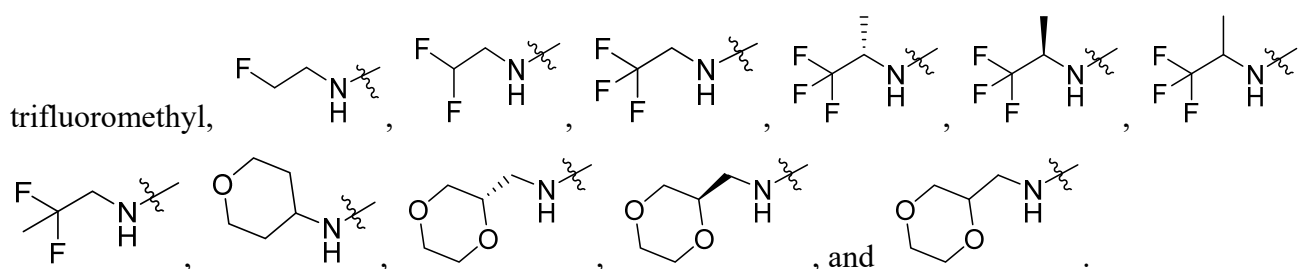
alternatively, R is selected from the group consisting of halogen, CN, OH, NH₂, C₁₋₃ alkyl, C₁₋₃

alkyl-O-, C₁₋₃ alkyl-S-, C₁₋₃ haloalkyl-O-, C₁₋₃ haloalkyl-S-, C₁₋₃ haloalkyl, R^aNH-, and (R^a)₂N-;

alternatively, R is selected from the group consisting of fluorine, chlorine, CN, OH, NH₂, C₁₋₃ alkyl, C₁₋₃ alkyl-O-, C₁₋₃ haloalkyl, and R^aNH-;

alternatively, R is selected from the group consisting of fluorine, CN, NH₂, methyl, methoxy, trifluoromethyl, and R^aNH-;

alternatively, R is selected from the group consisting of fluorine, CN, NH₂, methyl, methoxy,



5. The compound of formula I, the pharmaceutically acceptable salt thereof, or the stereoisomer thereof according to any one of claims 1-4, wherein R^a is selected from the group consisting of C₁₋₄ alkyl, C₃₋₆ cycloalkyl, and 3- to 6-membered heterocycloalkyl, and R^a is optionally substituted with one or more groups selected from the group consisting of halogen, CN, OH, NH₂, and 5- to 6-membered heterocycloalkyl;

alternatively, R^a is selected from the group consisting of C₁₋₃ alkyl, C₅₋₆ cycloalkyl, and 5- to 6-membered heterocycloalkyl, and R^a is optionally substituted with one or more groups selected from the group consisting of halogen, CN, OH, NH₂, and 5- to 6-membered heterocycloalkyl;

alternatively, R^a is selected from the group consisting of C₁₋₃ alkyl and 5- to 6-membered heterocycloalkyl, and R^a is optionally substituted with one or more groups selected from the group consisting of halogen, CN, OH, NH₂, and 5- to 6-membered heterocycloalkyl;

alternatively, R^a is selected from the group consisting of C₁₋₃ alkyl and 6-membered heterocycloalkyl, and R^a is optionally substituted with one or more groups selected from the group consisting of fluorine, chlorine, bromine, CN, OH, NH₂, and 6-membered heterocycloalkyl;

alternatively, R^a is selected from the group consisting of methyl, ethyl, propyl, and tetrahydropyranyl, and R^a is optionally substituted with one or more fluorine or dioxane;

alternatively, R^a is selected from the group consisting of FCH₂CH₂-, F₂CHCH₂-, F₃CCH₂-, CF₃CH(CH₃)-, CH₃CF₂CH₂-, tetrahydropyranyl, and dioxane-CH₂-.

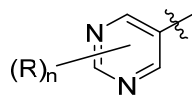
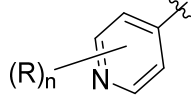
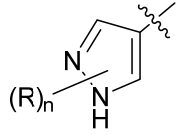
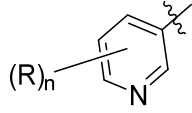
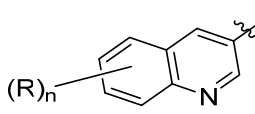
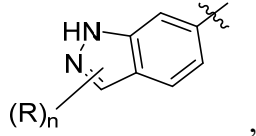
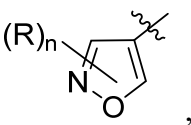
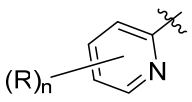
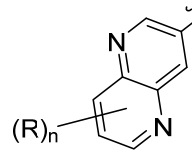
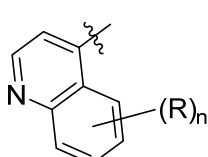
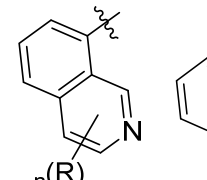
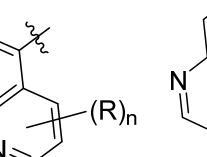
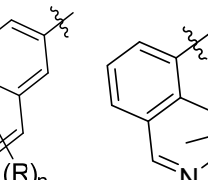
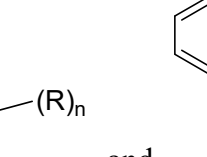
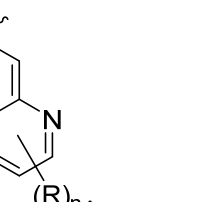
6. The compound of formula I, the pharmaceutically acceptable salt thereof, or the stereoisomer thereof according to any one of claims 1-5, wherein n is selected from the group consisting of 0, 1, 2, and 3;

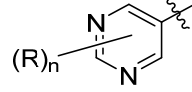
alternatively, n is selected from the group consisting of 0, 1, and 2;

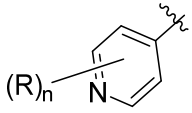
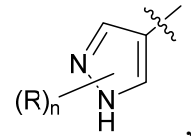
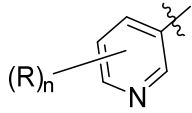
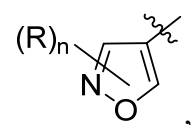
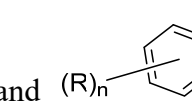
alternatively, n is selected from the group consisting of 0 and 1.

7. The compound of formula I, the pharmaceutically acceptable salt thereof, or the stereoisomer thereof according to any one of claims 1-6, wherein R^2 is selected from cyclopropyl.

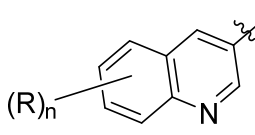
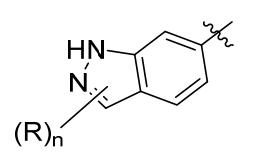
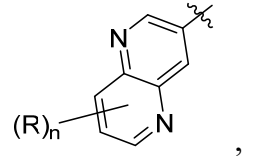
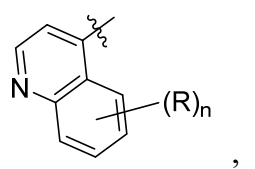
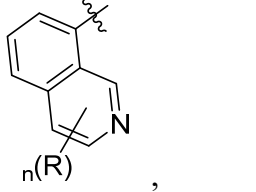
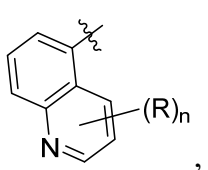
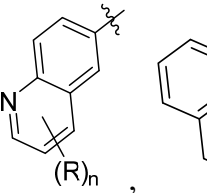
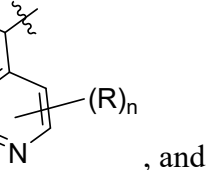
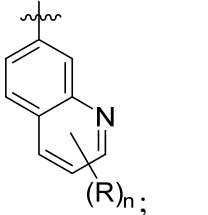
8. The compound of formula I, the pharmaceutically acceptable salt thereof, or the stereoisomer thereof according to any one of claims 1-7, wherein structural unit $(R)_n$ - is selected from the

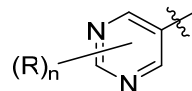
group consisting of , , , ,
, , , , ,
, , , , , and ;

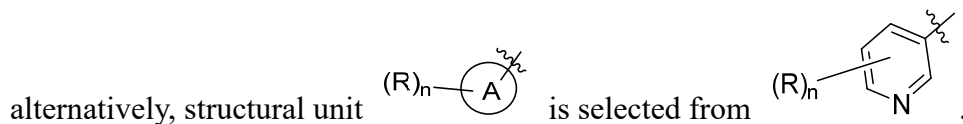
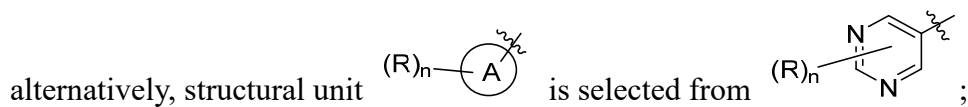
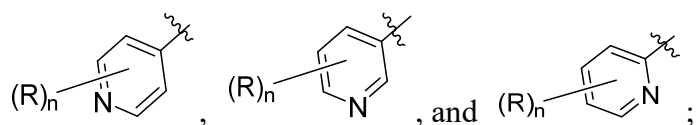
alternatively, structural unit $(R)_n$ - is selected from the group consisting of ,

, , , , and ;

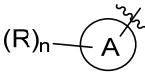
alternatively, structural unit $(R)_n$ - is selected from the group consisting of

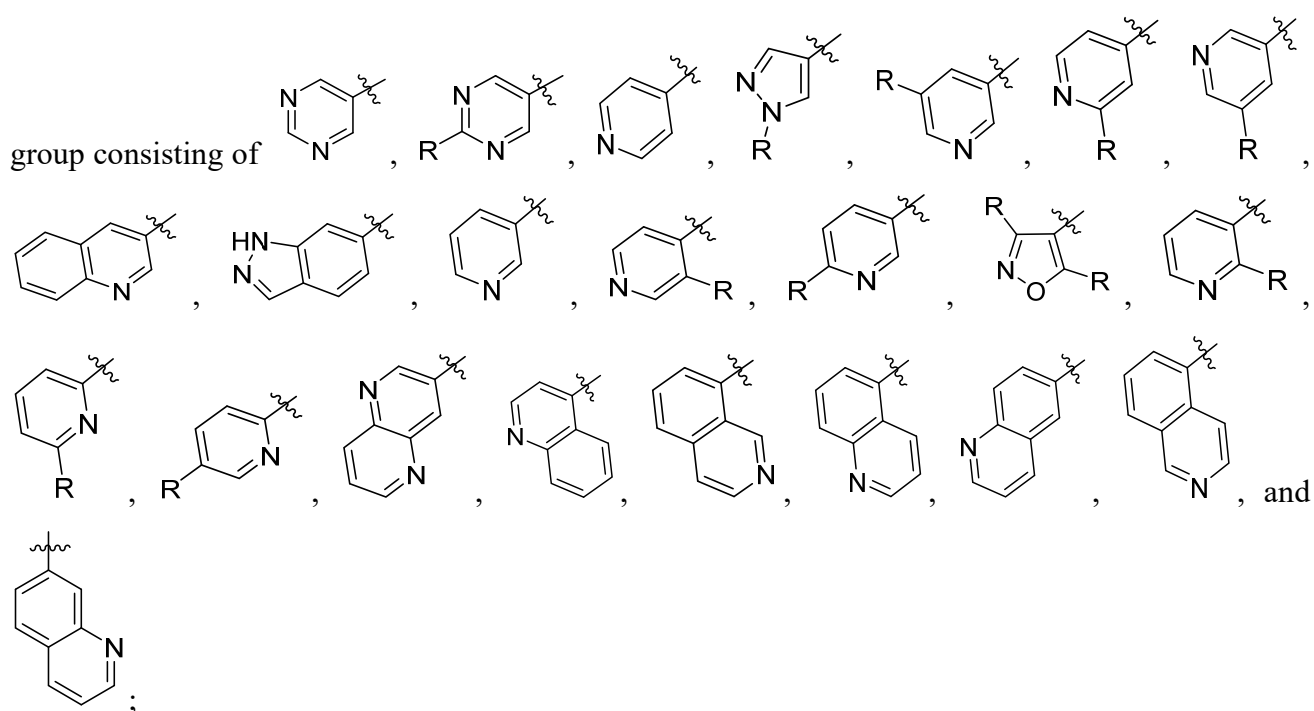
, , , , ,
, , , and ;

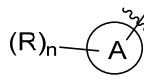
alternatively, structural unit $(R)_n$ - is selected from the group consisting of ,

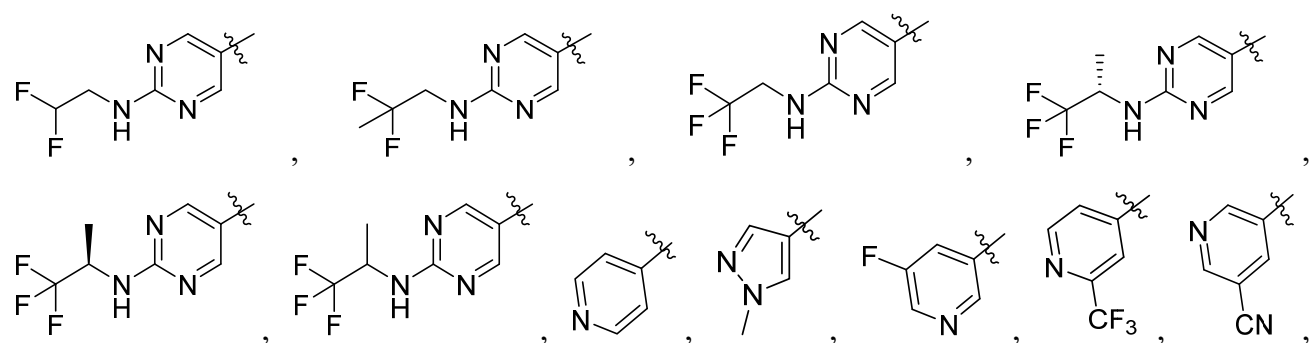


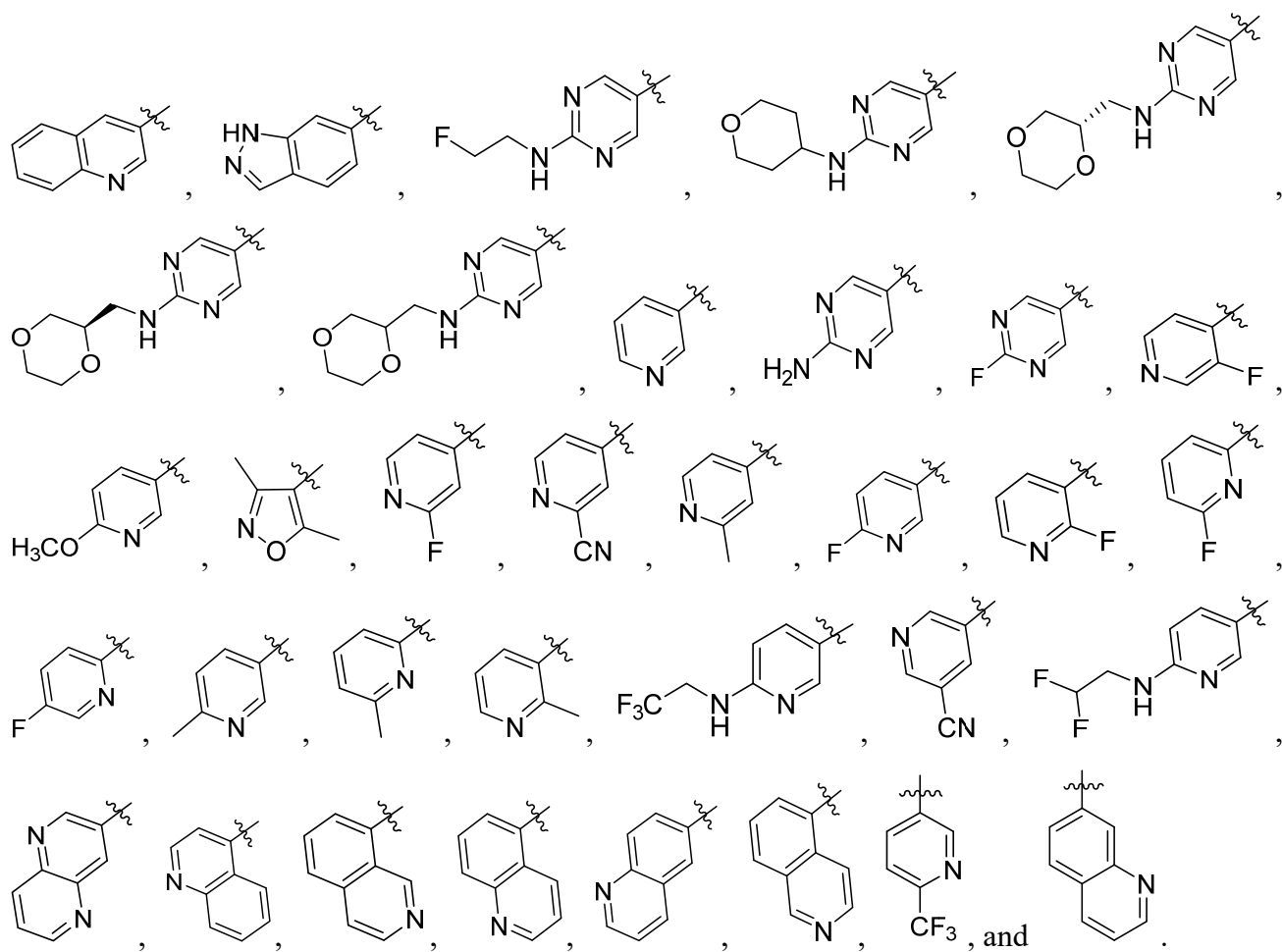
9. The compound of formula I, the pharmaceutically acceptable salt thereof, or the stereoisomer

thereof according to any one of claims 1-8, wherein structural unit $(R)_n$ - is selected from the

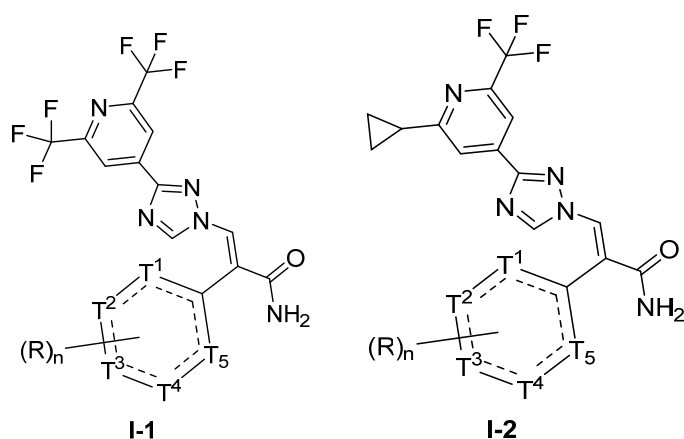


optionally, structural unit $(R)_n$ - is selected from the group consisting of





10. The compound of formula I, the pharmaceutically acceptable salt thereof, or the stereoisomer thereof according to any one of claims 1-9, being selected from the group consisting of a compound of formula I-1 and a compound of formula I-2, a pharmaceutically acceptable salt thereof, or a stereoisomer thereof,



wherein T¹, T², T³, T⁴, and T⁵ are each independently selected from the group consisting of a bond, O, S, N, and CH, no more than one of which is selected from a bond and at least one of which is selected from N;

$\diagup$ represents a single bond or a double bond;

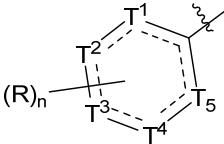
optionally, T^1 , T^2 , T^3 , T^4 , and T^5 are each independently selected from the group consisting of N and CH, at least one of which is selected from N;

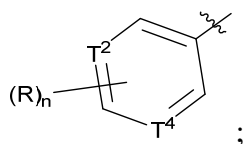
alternatively, T^2 and T^4 are selected from N, and T^1 , T^3 , and T^5 are selected from CH;

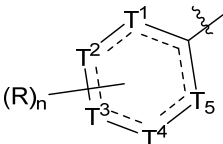
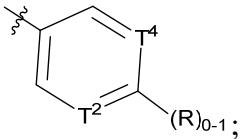
alternatively, T^3 is selected from N, and T^1 , T^2 , T^4 , and T^5 are selected from CH;

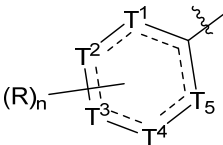
alternatively, T^2 is selected from N, and T^1 , T^3 , T^4 , and T^5 are selected from CH.

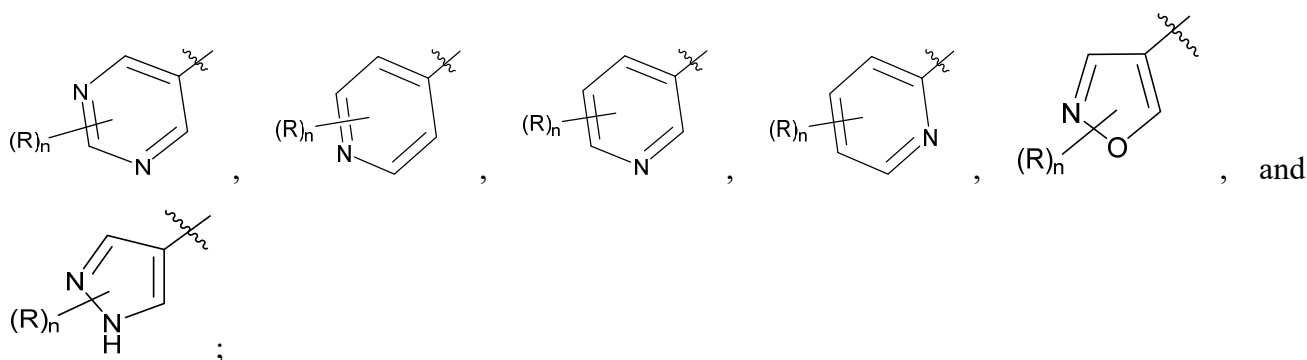
11. The compound of formula I, the pharmaceutically acceptable salt thereof, or the stereoisomer

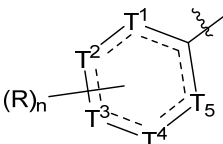
thereof according to claim 10, wherein structural unit  is selected from

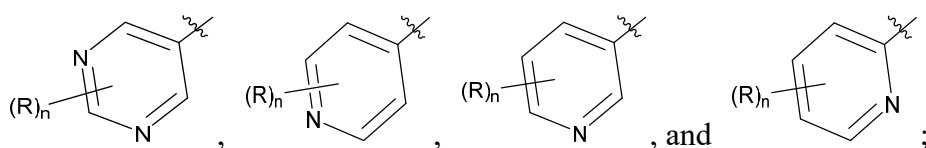


alternatively, structural unit  is selected from 

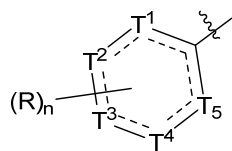
alternatively, structural unit  is selected from the group consisting of



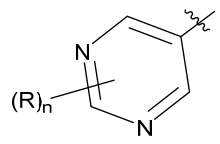
alternatively, structural unit  is selected from the group consisting of



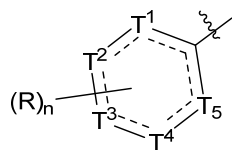
alternatively, structural unit



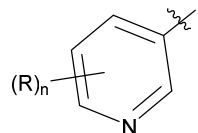
is selected from



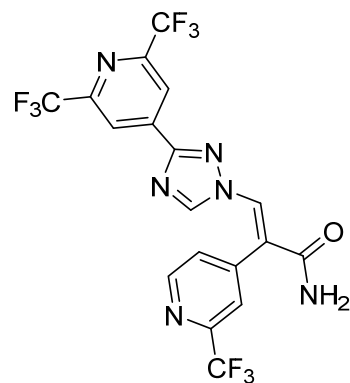
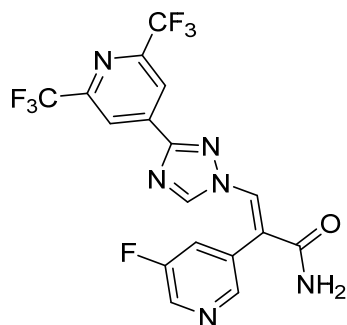
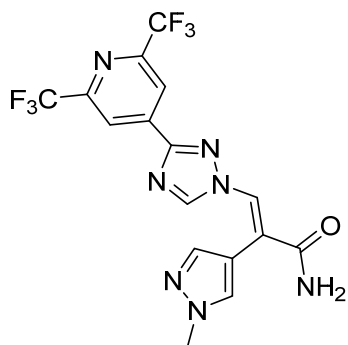
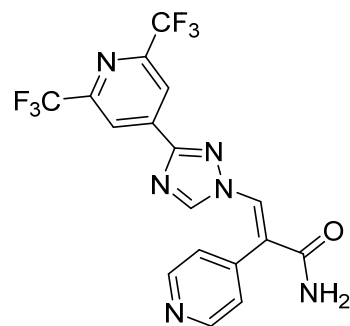
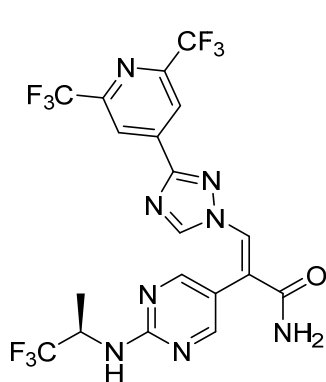
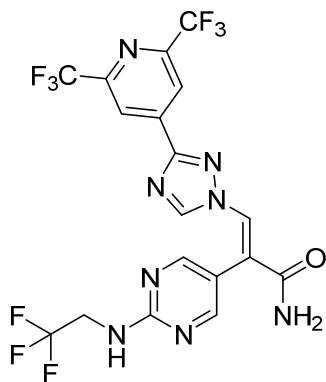
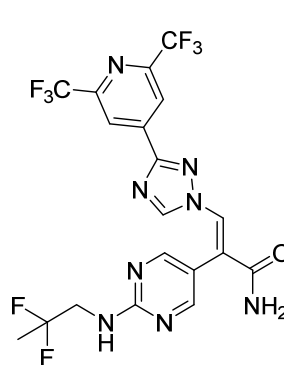
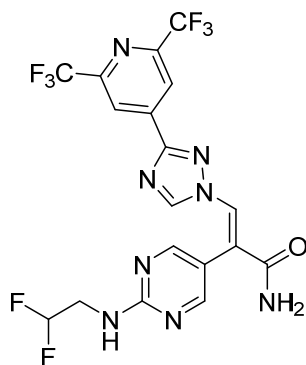
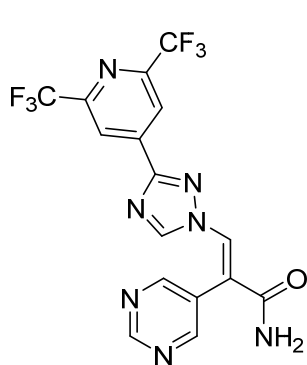
alternatively, structural unit

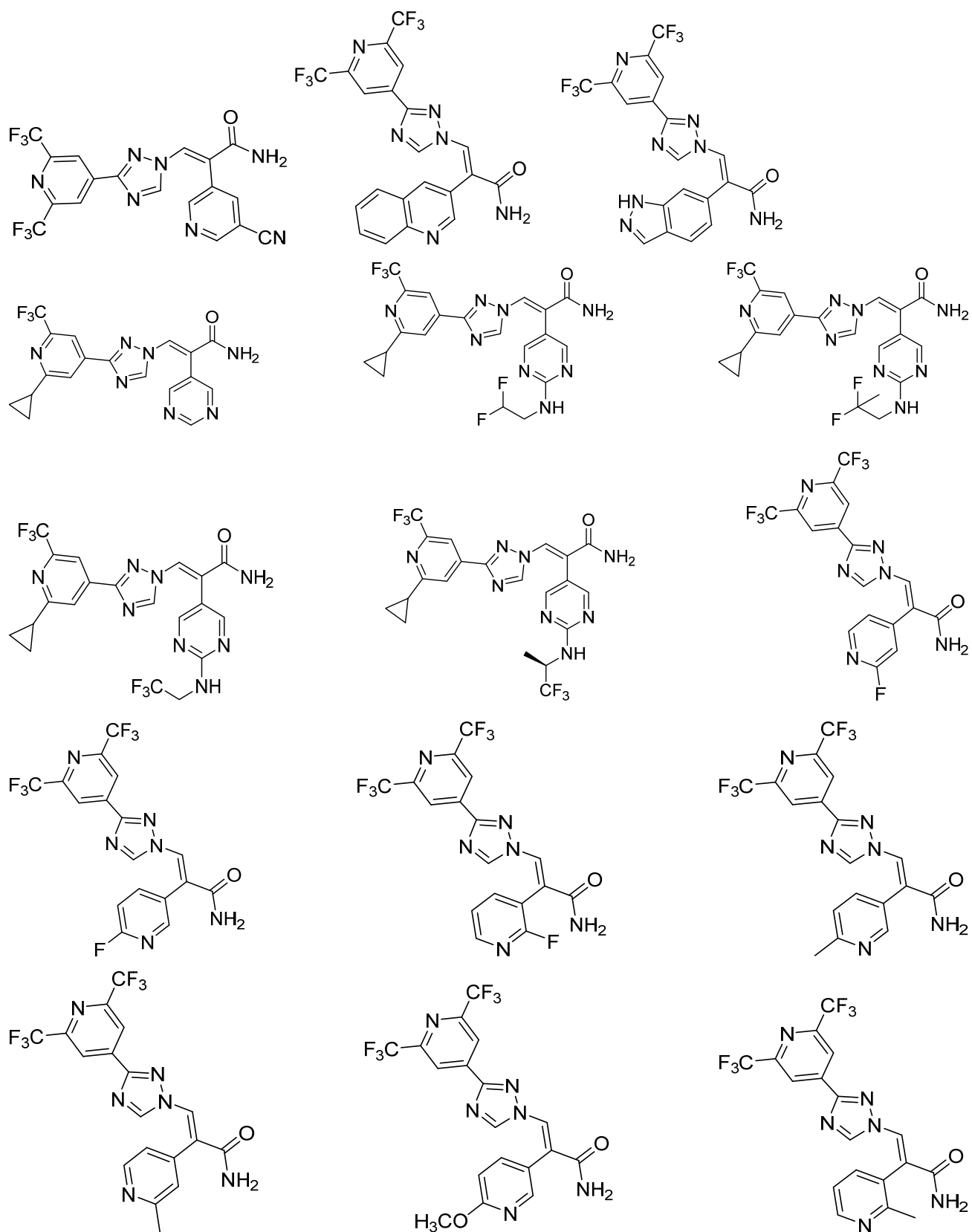


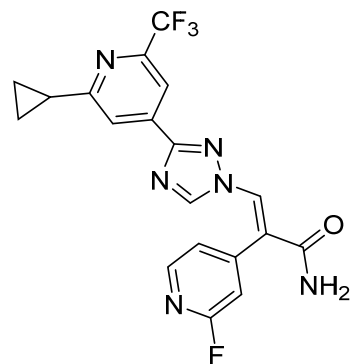
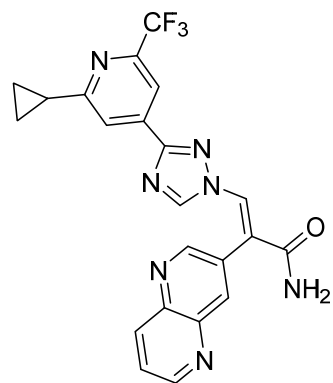
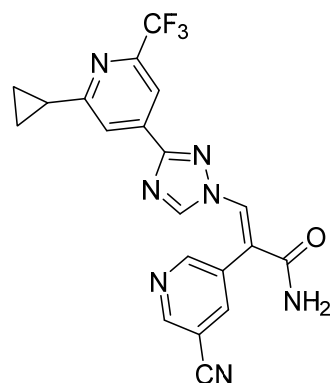
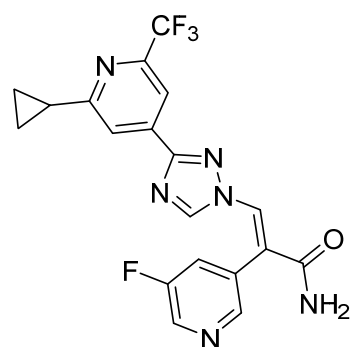
is selected from

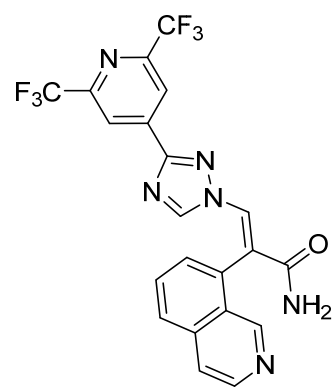
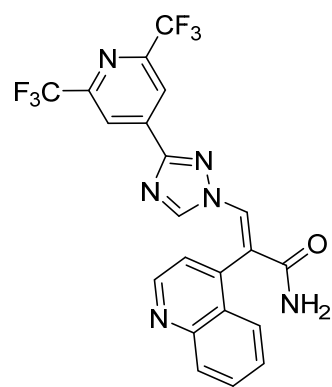
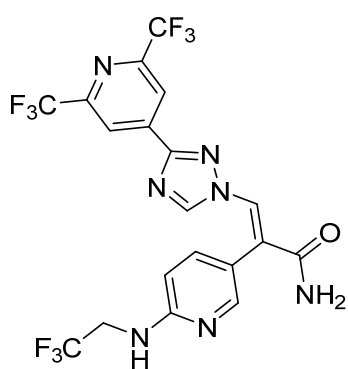
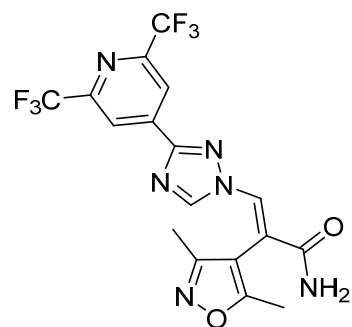
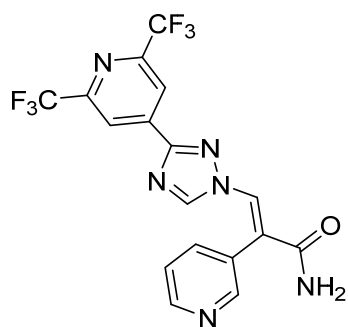
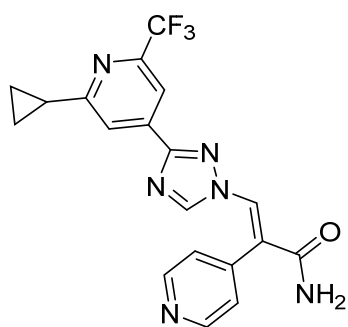
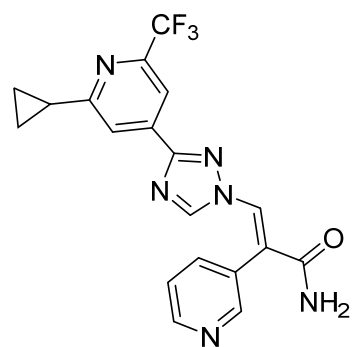
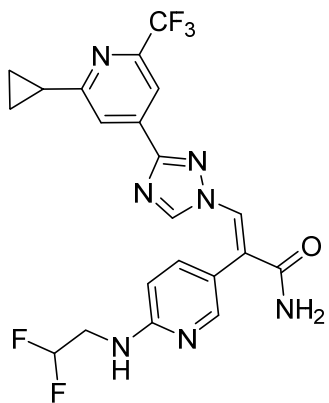
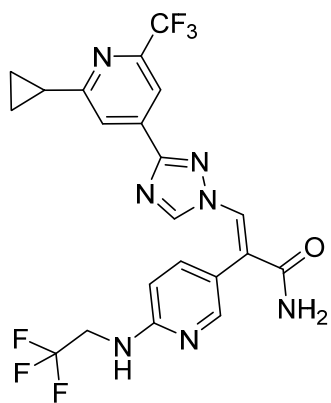
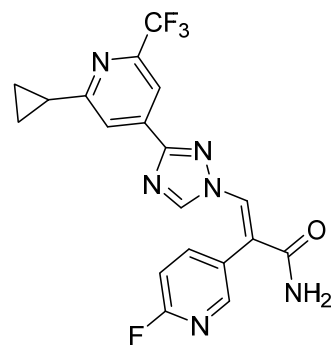
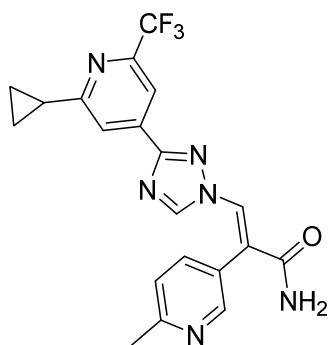
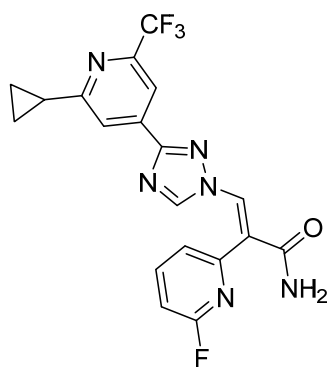


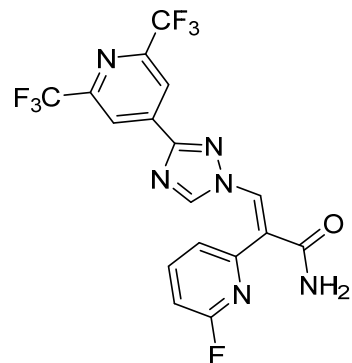
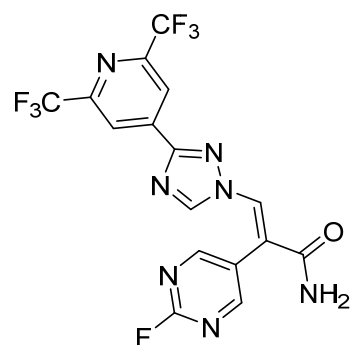
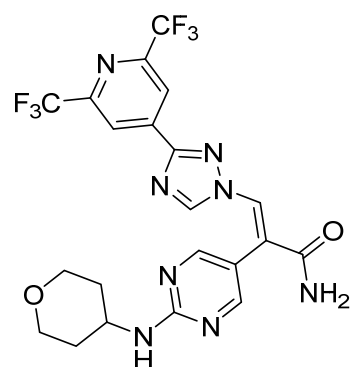
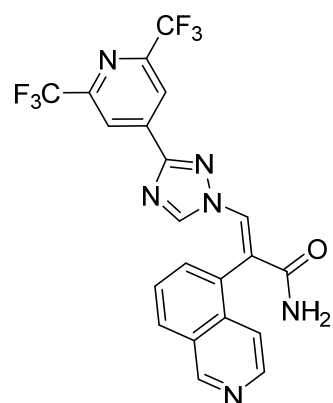
12. Compounds, pharmaceutically acceptable salts thereof, or stereoisomers thereof as follows:

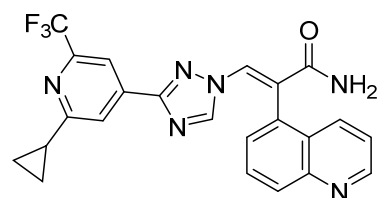
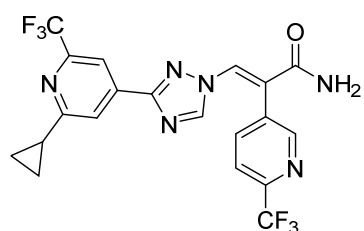
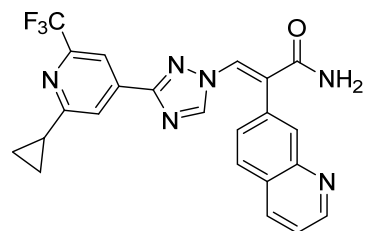
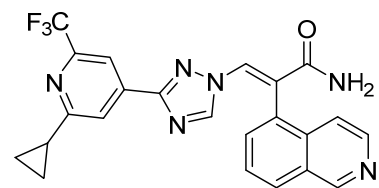
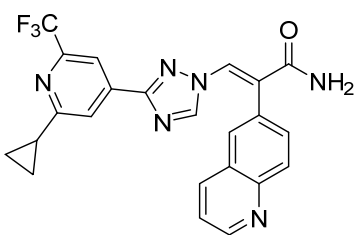
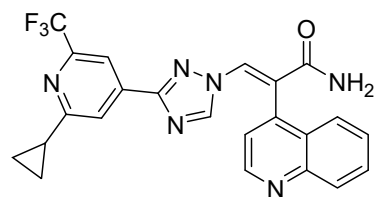
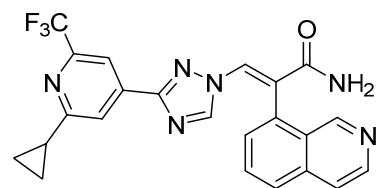
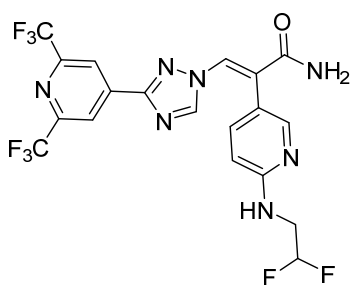
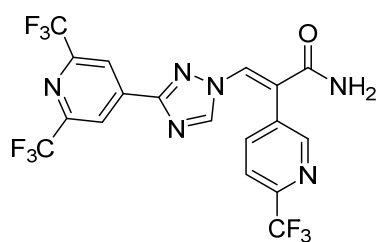
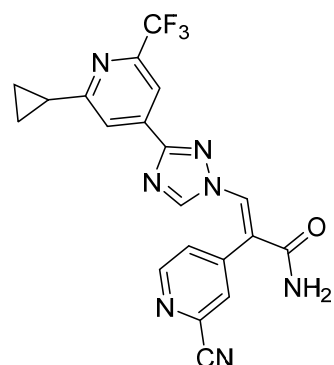
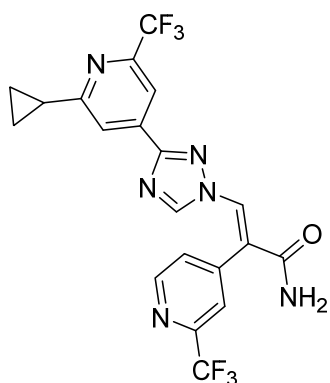
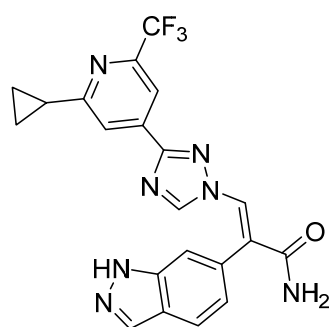
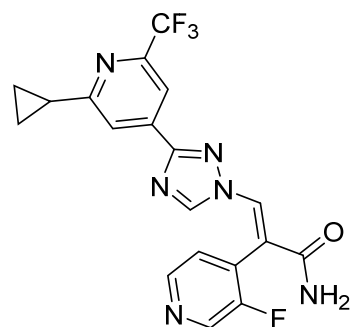
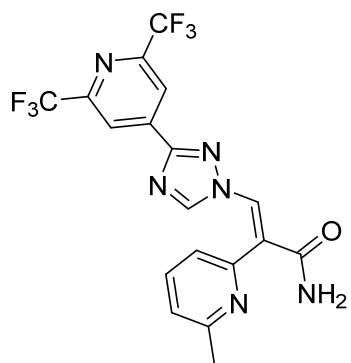
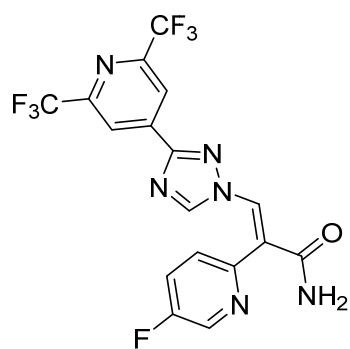


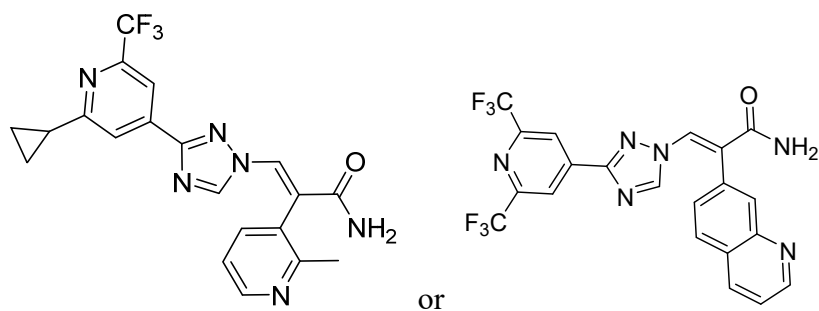












13. A pharmaceutical composition, comprising the compound, the pharmaceutically acceptable salt thereof, or the stereoisomer thereof according to any one of claims 1-12.

14. Use of the compound, the pharmaceutically acceptable salt thereof, or the stereoisomer thereof according to any one of claims 1-12 or the pharmaceutical composition according to claim 13 in the preparation of a medicament for treating various XPO-1-related diseases;

optionally, the various XPO-1-related diseases are selected from the group consisting of tumors;

alternatively, the various XPO-1-related diseases are selected from the group consisting of leukemia and lymphoma.

15. Use of the compound, the pharmaceutically acceptable salt thereof, or the stereoisomer thereof according to any one of claims 1-12 or the pharmaceutical composition according to claim 13 for treating various XPO-1-related diseases;

optionally, the various XPO-1-related diseases are selected from the group consisting of tumors;

alternatively, the various XPO-1-related diseases are selected from the group consisting of leukemia and lymphoma.