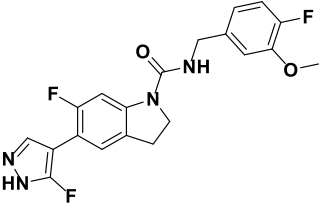
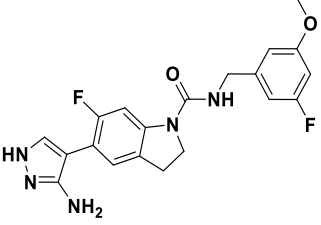
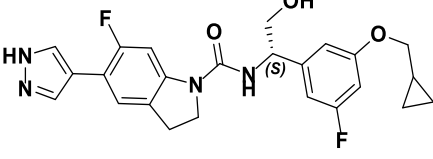
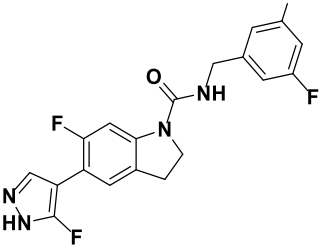
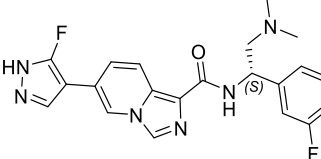
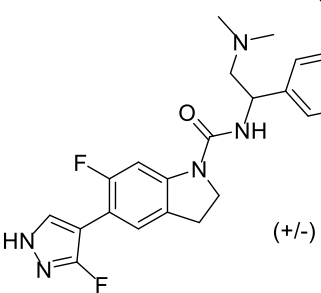
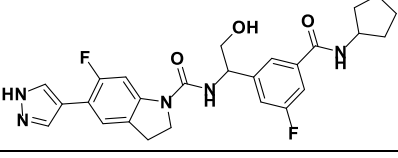
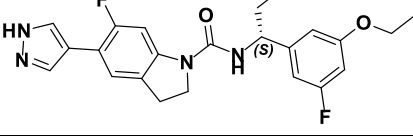
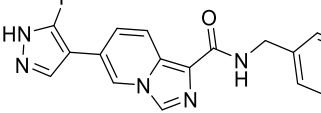
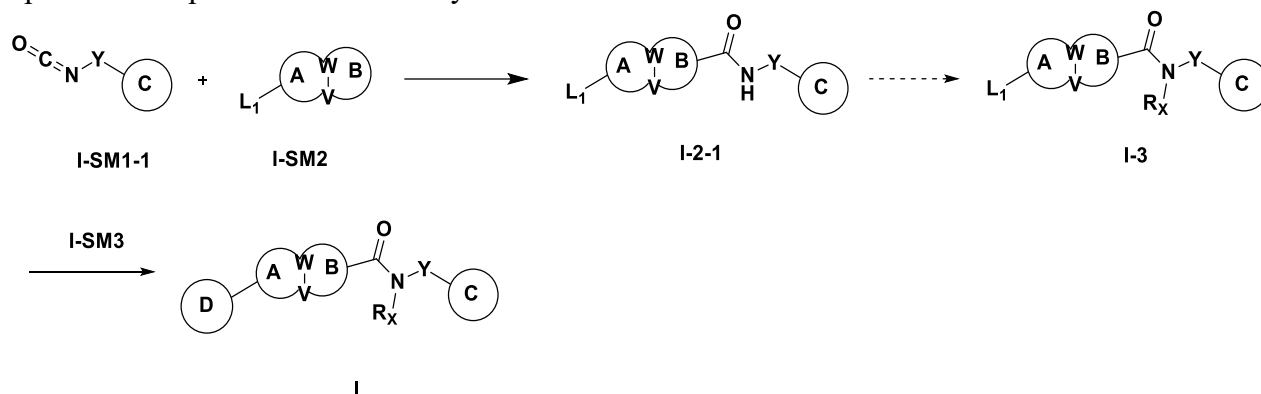


T384	
T385	
T386	
T387	
T388	
T388'	
T389	
T390	
T391	

Specific examples of scheme 1 may include scheme 1-1:



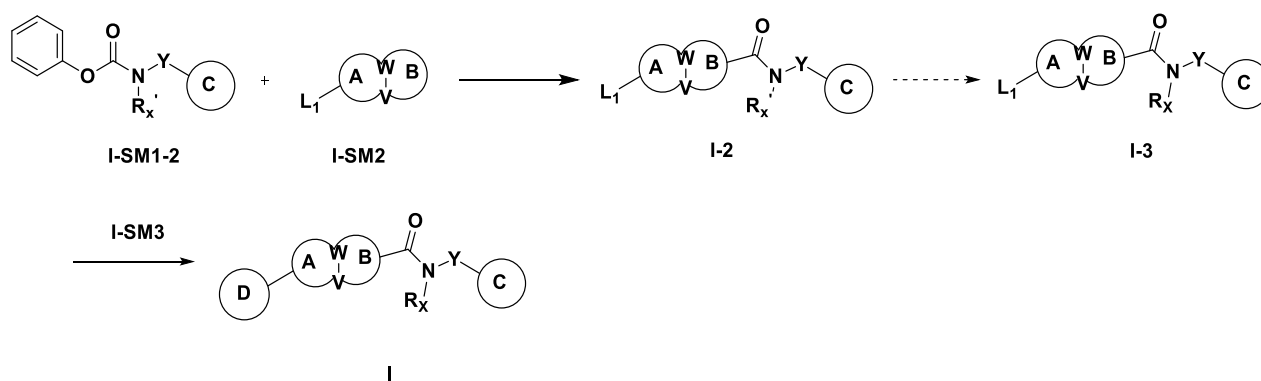
a1') reacting a compound I-SM1-1 with a compound I-SM2 under an alkaline condition to obtain a compound I-2-1;

a2) optionally, further subjecting the compound I-2-1 to derivatization treatment of R_x on amide nitrogen to obtain a compound I-3; and

a3') subjecting the compound I-2-1 or I-3 and a compound I-SM3 to Suzuki coupling reaction to obtain a compound I;

wherein, A, B, C, D, W, V, Y and R_x are defined as in the formula (I) above; R_x is not H; L_1 is selected from halogen, and the halogen may be selected from F, Cl, Br and I; the compound I-SM3 is borate containing a ring D group;

or scheme 1-2:



a1'') reacting a compound I-SM1-2 with a compound I-SM2 under an alkaline condition to obtain a compound I-2;

a2'') optionally, further subjecting the compound I-2 to derivatization treatment of R_x on amide nitrogen to obtain a compound I-3; and

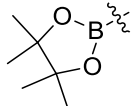
a3'') subjecting the compound I-2 or I-3 and a compound I-SM3 to Suzuki coupling reaction to

obtain a compound I;

wherein, ring A, ring B, ring C, ring D, W, V, Y and R_x are selected from the definitions in the formula (I) above; R_x' is selected from R_x and a group which may be converted to R_x by derivatization step (a2"); L_1 is selected from halogen, and the halogen may be selected from F,

5 Cl, Br and I; the compound I-SM3 is borate containing a ring D group;

A group protection or deprotection step may optionally be performed in the above schemes, and operations and conditions in the step may be conventional in the art. According to the preparation method of the present disclosure, leaving groups and amino protecting groups used
10 may be groups commonly used in the art. For example, the leaving group may be selected from

halogen (e.g., I or Cl), , and the like. The "active formate group" described in the above schemes is a group conventionally selected by one skilled in the art to provide C=O in the reaction (phenol or alcohol fragment in the formate leaves), for example, the "active formate group" in "-N(R_x')-active formate group", i.e. a group (in which the phenol or alcohol fragment is easy to leave) providing carbonyl of the amide structure -N(R_x')-C(=O)- in the product,
15 wherein the "active formate group" is preferably phenol formate (PhO(C=O)-) or a substituted phenol formate, e.g. *p*-nitrophenol formate (*p*-NO₂-PhO(C=O)-).

According to the preparation method of the present disclosure, operations and conditions in the steps may be conventional in the art. Operations and conditions in the step a1), a1'), a1"), b1)
20 or c1) may be conventional in the art, and the base used is an inorganic base or an organic base, for example, at least one selected from triethylamine (TEA), potassium carbonate, isopropylamine, diisopropylethylamine (DIEA), pyridine, lithium carbonate, cesium carbonate, potassium *tert*-butoxide, sodium *tert*-butoxide, 1,8-diazabicycloundec-7-ene, sodium methoxide, sodium ethoxide, potassium phosphate, potassium hydrogen phosphate, potassium
25 dihydrogen phosphate, sodium bicarbonate and potassium bicarbonate.

According to the preparation method of the present disclosure, for the step a1), a1'), a1"), b1) or c1), the reaction may preferably be performed in the presence of a solvent, preferably in an aprotic organic solvent, for example, one or more of tetrahydrofuran (THF), acetonitrile, DMF, dichloromethane, *n*-hexane, ethyl acetate, diethyl ether, methyl *tert*-butyl ether, toluene,

chloroform, cyclohexane, dioxane and acetone.

According to the preparation method of the present disclosure, operations and conditions in the step a2), a2'), a2''), b2) or c2) may be conventional in the art. For example, such reactions as alkylation and acylation may preferably be performed in the presence of a solvent, preferably an organic solvent, such as one or more of methanol, ethanol, isopropanol, *tert*-butanol, toluene, chloroform, cyclohexane, tetrahydrofuran (THF), dichloromethane, acetonitrile, DMF, *n*-hexane, ethyl acetate, diethyl ether, methyl *tert*-butyl ether, dioxane and acetone, preferably dichloromethane.

According to an embodiment of the present disclosure, for the coupling reaction in the step a3), a3'), a3''), b3) or c3), operations and conditions may be conventional in the art. The reaction may preferably be performed in the presence of a solvent, such as one or more of methanol, ethanol, isopropanol, *tert*-butanol, toluene, chloroform, cyclohexane, tetrahydrofuran (THF), acetonitrile, DMF, dichloromethane, *n*-hexane, ethyl acetate, diethyl ether, methyl *tert*-butyl ether, acetone, dioxane, DMF and water, preferably a mixed solution of dioxane or DMF and water.

According to an embodiment of the present disclosure, the coupling reaction in the step a3), a3'), a3''), b3) or c3) may be performed in the presence of a catalyst and a base, and the catalyst includes widely used Pd-containing catalysts, such as at least one of Pd(OAc)₂ and ligand XPhos, tetrakis(triphenylphosphine)palladium (i.e., Pd(PPh₃)₄), [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (i.e., Pd(dppf)Cl₂), and the like. For example, the reaction is performed in the presence of K₃PO₄, Pd(OAc)₂ and XPhos. The base is a conventional base in the art, and includes an inorganic base or an organic base, for example, at least one selected from triethylamine (TEA), potassium carbonate, isopropylamine, diisopropylethylamine (DIEA), pyridine, lithium carbonate, cesium carbonate, potassium *tert*-butoxide, sodium *tert*-butoxide, 1,8-diazabicycloundec-7-ene, sodium methoxide, sodium ethoxide, sodium fluoride, potassium fluoride, cesium fluoride, potassium phosphate, potassium hydrogen phosphate, potassium dihydrogen phosphate, sodium bicarbonate and potassium bicarbonate.

It will be understood by those skilled in the art that the compound of formula (I) or the racemate,

the stereoisomer, the tautomer and the nitrogen oxide thereof can be used as a starting material or an intermediate to prepare the prodrug or the pharmaceutically acceptable salt of the compound of formula (I) or the racemate, the stereoisomer, the tautomer and the nitrogen oxide thereof. Therefore, the present disclosure also provides use of the compound of formula (I) or the racemate, the stereoisomer, the tautomer or the nitrogen oxide thereof in preparing the prodrug or the pharmaceutically acceptable salt of the compound of formula (I) or the racemate, the stereoisomer, the tautomer or the nitrogen oxide thereof.

The present disclosure also provides use of at least one of the compound of formula (I) and the racemate, the stereoisomer, the tautomer, the nitrogen oxide, the isotopically labeled compound, the solvate, the polymorph, the metabolite, the ester, the pharmaceutically acceptable salt and the prodrug thereof in preparing a medicament, wherein the medicament is an inhibitor of protein kinase.

In particular, the medicament has the function of regulating Rho-kinase. The medicament can be used for preventing or treating one or more diseases caused by high expression of ROCK or excessive activation of ROCK, such as cardiovascular and cerebrovascular diseases, neurological diseases, fibrosis diseases, ocular diseases, tumors, arterial thrombotic disorders, radiation damage, respiratory diseases, and autoimmune diseases, including atherosclerosis, acute coronary syndrome, hypertension, cerebral vasospasm, cerebral ischemia, ischemic stroke, restenosis, heart disease, heart failure, cardiac hypertrophy, myocardial ischemia-reperfusion injury, diabetes, diabetic nephropathy, cancer, neuronal degeneration (peripheral or central), nerve injury diseases, spinal cord injury, erectile dysfunction, platelet aggregation, leukocyte aggregation, glaucoma, ocular hypertension, asthma, osteoporosis, pulmonary fibrosis (such as idiopathic pulmonary fibrosis), hepatic fibrosis, renal fibrosis, COPD, kidney dialysis (epithelial stability), glomerulosclerosis, neuronal degeneration inflammation, and the like.

The present disclosure also provides a pharmaceutical composition comprising a therapeutically effective amount of at least one of the compound of formula (I) and the racemate, the stereoisomer, the tautomer, the nitrogen oxide, the isotopically labeled compound,

the solvate, the polymorph, the metabolite, the ester, the pharmaceutically acceptable salt and the prodrug thereof.

Preferably, the pharmaceutical composition may optionally further comprise a pharmaceutically acceptable auxiliary material, such as a carrier or an excipient. As an example,
5 the auxiliary material may be at least one selected from: a disintegrant, a glidant, a lubricant, a diluent, a filler, an adhesive and a colorant.

The pharmaceutical composition of the present disclosure has the function of regulating Rho-kinase. The pharmaceutical composition can be used for preventing or treating one or more diseases caused by high expression of ROCK or excessive activation of ROCK, such as
10 cardiovascular and cerebrovascular diseases, neurological diseases, fibrosis diseases, ocular diseases, tumors, arterial thrombotic disorders, radiation damage, respiratory diseases, and autoimmune diseases, including atherosclerosis, acute coronary syndrome, hypertension, cerebral vasospasm, cerebral ischemia, ischemic stroke, restenosis, heart disease, heart failure, cardiac hypertrophy, myocardial ischemia-reperfusion injury, diabetes, diabetic nephropathy,
15 cancer, neuronal degeneration (peripheral or central), nerve injury diseases, spinal cord injury, erectile dysfunction, platelet aggregation, leukocyte aggregation, glaucoma, ocular hypertension, asthma, osteoporosis, pulmonary fibrosis (such as idiopathic pulmonary fibrosis), hepatic fibrosis, renal fibrosis, COPD, kidney dialysis (epithelial stability), glomerulosclerosis, neuronal degeneration inflammation, and the like.

20 The present disclosure also provides a method for regulating Rho-kinase function, which comprises administering to an individual in need thereof an effective amount of the compound of formula (I) or the racemate, the stereoisomer, the tautomer, the nitrogen oxide, the isotopically labeled compound, the solvate, the polymorph, the metabolite, the ester, the
25 pharmaceutically acceptable salt or the prodrug thereof or the pharmaceutical composition. The method can be used for preventing or treating one or more diseases caused by high expression of ROCK or excessive activation of ROCK.

The present disclosure also provides a method for preventing or treating one or more diseases caused by high expression of ROCK or excessive activation of ROCK, which comprises
30 administering to an individual in need thereof an effective amount of the compound of formula

(I) or the racemate, the stereoisomer, the tautomer, the nitrogen oxide, the isotopically labeled compound, the solvate, the polymorph, the metabolite, the ester, the pharmaceutically acceptable salt or the prodrug thereof or the pharmaceutical composition. The disease is, for example, cardiovascular and cerebrovascular diseases, neurological diseases, fibrosis diseases, ocular diseases, tumors, arterial thrombotic disorders, radiation damage, respiratory diseases, and autoimmune diseases, including atherosclerosis, acute coronary syndrome, hypertension, cerebral vasospasm, cerebral ischemia, ischemic stroke, restenosis, heart disease, heart failure, cardiac hypertrophy, myocardial ischemia-reperfusion injury, diabetes, diabetic nephropathy, cancer, neuronal degeneration (peripheral or central), nerve injury diseases, spinal cord injury, erectile dysfunction, platelet aggregation, leukocyte aggregation, glaucoma, ocular hypertension, asthma, osteoporosis, pulmonary fibrosis (such as idiopathic pulmonary fibrosis), hepatic fibrosis, renal fibrosis, COPD, kidney dialysis (epithelial stability), glomerulosclerosis, neuronal degeneration inflammation, and the like.

In another aspect, the present disclosure provides a compound of formula (I) for use in regulating Rho-kinase function, and the modulating comprises administering to an individual in need thereof an effective amount of one or more compounds disclosed herein or a pharmaceutical composition comprising the compound.

In yet another aspect, the present disclosure provides a compound of formula (I) for use in a method for preventing or treating one or more diseases caused by high expression of ROCK or excessive activation of ROCK, and the method comprises administering to an individual in need thereof an effective amount of the compound of formula (I) or the racemate, the stereoisomer, the tautomer, the nitrogen oxide, the isotopically labeled compound, the solvate, the polymorph, the metabolite, the ester, the pharmaceutically acceptable salt or the prodrug thereof or the pharmaceutical composition. The disease is, for example, cardiovascular and cerebrovascular diseases, neurological diseases, fibrosis diseases, ocular diseases, tumors, arterial thrombotic disorders, radiation damage, respiratory diseases, and autoimmune diseases, including atherosclerosis, acute coronary syndrome, hypertension, cerebral vasospasm, cerebral ischemia, ischemic stroke, restenosis, heart disease, heart failure, cardiac hypertrophy, myocardial ischemia-reperfusion injury, diabetes, diabetic nephropathy, cancer, neuronal degeneration (peripheral or central), nerve injury diseases, spinal cord injury, erectile dysfunction, platelet

aggregation, leukocyte aggregation, glaucoma, ocular hypertension, asthma, osteoporosis, pulmonary fibrosis (such as idiopathic pulmonary fibrosis), hepatic fibrosis, renal fibrosis, COPD, kidney dialysis (epithelial stability), glomerulosclerosis, neuronal degeneration inflammation, and the like.

5

Definitions and Description

Unless otherwise stated, the definitions of groups and terms described in the specification and claims of the present application, including definitions thereof as examples, exemplary definitions, preferred definitions, definitions documented in tables, definitions of specific
10 compounds in the examples, and the like, may be arbitrarily combined and incorporated with each other. The definitions of groups and the structures of the compounds in such combinations and incorporations should fall within the scope of the present specification.

When a numerical range defined by "integer" is recited in the specification and claims of this application, it shall be construed as reciting both endpoints of the range and every integer within
15 the range. For example, "an integer of 0 to 6" shall be construed to include every integer of 0, 1, 2, 3, 4, 5 and 6. The term "more" refers to three or more.

The term "halogen" refers to F, Cl, Br and I. In other words, F, Cl, Br and I may be described as "halogen" in the specification.

The term "aliphatic hydrocarbyl" includes saturated or unsaturated, linear or branched
20 hydrocarbyl; the type of the aliphatic hydrocarbyl may be selected from alkyl, alkenyl, alkynyl and the like, and the number of carbon atoms of the aliphatic hydrocarbyl may be 1–20, may preferably be 1–12, may also be 1–10, and may further preferably be 1–6. For example, the (C₁-C₁₂) aliphatic hydrocarbyl may be selected from (C₁-C₁₂) alkyl, (C₂-C₁₂) alkenyl and (C₂-C₁₂) alkynyl, and in some embodiments, it may be selected from (C₁-C₆)alkyl, (C₂-C₆)alkenyl and
25 (C₂-C₆)alkynyl. Specifically, it may include, but is not limited to: methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, isobutyl, *tert*-butyl, *n*-pentyl, isopentyl, neopentyl, *n*-hexyl, vinyl, propenyl, butenyl, pentenyl, hexenyl, ethynyl, propynyl, butynyl, pentynyl and hexynyl; further, it may be selected from methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, isobutyl, *tert*-butyl, *n*-pentyl, isopentyl, neopentyl, *n*-hexyl, vinyl, 1-propenyl, 2-propenyl, 1-methylvinyl, 1-butenyl, 1-
30 ethylvinyl, 1-methyl-2-propenyl, 2-butenyl, 3-butenyl, 2-methyl-1-propenyl, 2-methyl-2-

propenyl, 1-pentenyl, 1-hexenyl, ethynyl, 1-propynyl, 2-propynyl, 1-butylnyl, 2-butylnyl, 1-isobutylnyl, 1-isopentynyl, 2-isopentynyl, 1-methyl-2-propynyl, 3-butylnyl, 1-pentynyl and 1-hexynyl;

the "aliphatic hydrocarbyl" may optionally comprise one, two or more heteroatoms (which may

5 be construed as optional insertion of heteroatoms into any C-C bond and C-H bond of the aliphatic hydrocarbyl). Suitable heteroatoms will be apparent to those skilled in the art and include, for example, sulfur, nitrogen, oxygen, phosphorus and silicon. The aliphatic hydrocarbyl comprising heteroatoms may be selected from the following groups: (C₁-C₁₂) aliphatic hydrocarbyloxy, (C₁-C₁₂) aliphatic hydrocarbylmercapto, (C₁-C₆) aliphatic hydrocarbyloxy, (C₁-C₆) aliphatic hydrocarbylmercapto, (C₁-C₆) aliphatic hydrocarbyloxy(C₁-C₆) aliphatic hydrocarbyl, (C₁-C₆) aliphatic hydrocarbylmercapto(C₁-C₆) aliphatic hydrocarbyl, (C₁-C₆) aliphatic hydrocarbyloxy(C₁-C₆) aliphatic hydrocarbyloxy, (C₁-C₆) aliphatic hydrocarbylmercapto(C₁-C₆) aliphatic hydrocarbylmercapto, *N*-(C₁-C₃) aliphatic hydrocarbylamino(C₁-C₆) aliphatic hydrocarbyl, and *N,N*-di-(C₁-C₃) aliphatic hydrocarbylamino(C₁-C₆) aliphatic hydrocarbyl; for example, it may be methoxy, ethoxy, propoxy, butoxy, pentoxy, methoxymethyl, ethoxymethyl, propoxymethyl, methoxyethyl, ethoxyethyl, propoxyethyl, methoxypropyl, ethoxypropyl, propoxypropyl, *N*-methylaminomethyl, *N*-methylaminoethyl, *N*-ethylaminoethyl, *N,N*-dimethylaminomethyl, *N,N*-dimethylaminoethyl, or *N,N*-diethylaminoethyl; the "aliphatic hydrocarbyl" moieties
15
20 contained in the other groups are defined as above.

The term "C₃₋₂₀ alicyclic hydrocarbyl" is to be understood as a cyclic hydrocarbyl that has aliphatic properties and contains closed carbocycle in the molecule. It may represent saturated or partially unsaturated monovalent monocyclic, bicyclic or polycyclic hydrocarbon rings, and also includes bridged or spiro rings. For example, when the alicyclic hydrocarbyl contains two
25 or more carbocycles, they may be linked in a variety of ways: two rings in the molecule may share one carbon atom, and the system is called spiro; two carbon atoms on the ring can be linked by a carbon bridge to form a bicyclic or polycyclic system, which is called a bridge ring; several rings may also be interconnected to form a cage-like structure. The alicyclic hydrocarbyl may have 3–20 carbon atoms and is preferably "C₃₋₁₂ alicyclic hydrocarbyl", and it may also be
30 "C₃₋₇ alicyclic hydrocarbyl", which may have 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17,

18, 19 or 20 carbon atoms. The alicyclic hydrocarbonyl may be "cycloalkyl", "cycloalkenyl", "cycloalkynyl", etc. (the number of carbon atoms may be selected from any one of the above integers from 3 to 20), and the alicyclic hydrocarbonyl may be monocyclic hydrocarbonyl such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclononyl or cyclodecyl, or bicyclic hydrocarbonyl such as decahydronaphthalene ring. For example, the term "C₃₋₇ cycloalkyl" refers to a saturated monovalent monocyclic or bicyclic hydrocarbon ring which may be a spiro or bridged ring, and it has 3, 4, 5, 6 or 7 carbon atoms. The C₃₋₇ cycloalkyl group may be, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, bicyclo[1.1.0]butyl, spiropentyl, spiro[2.3]hexyl, bicyclo[1.1.1]pentyl, bicyclo[2.1.0]pentyl, bicyclo[2.1.1]hexyl or bicyclo[3.1.0]hexyl.

The term "3-20 membered heterocyclyl" refers to a saturated or partially unsaturated monovalent monocyclic, bicyclic or polycyclic hydrocarbon ring, and also includes bridged or spiro rings, and it comprises 1–5 heteroatoms independently selected from N, O, B, P, Si and S. The "3-20 membered heterocyclyl" may be, for example, "3-12 membered heterocyclyl", "3-7 membered heterocyclyl" or "5-6 membered heterocyclyl". The term "3-12 membered heterocyclyl" refers to a saturated monovalent monocyclic or bicyclic hydrocarbon ring comprising 1–5, preferably 1–3, heteroatoms selected from N, O, B, P, Si and S. The heterocyclyl may be connected to the rest of the molecule through any one of the carbon atoms or the nitrogen atom (if present). Each atom of the heterocyclyl is independently optionally substituted, e.g., with 1–5 substituents, 1–3 substituents or 1 substituent, regardless of whether the heterocyclyl is modified by "substituted" or not, and suitable substituents include, but are not limited to, OH, amino, oxo, halogen, CN, nitro, C₁₋₂₀ aliphatic hydrocarbonyl, C₃₋₂₀ alicyclic hydrocarbonyl, and the like. In particular, the heterocyclyl may include, but is not limited to: 3 membered rings, such as aziridinyl, oxiranyl and thiranyl; 4 membered rings, such as azetidyl, oxetanyl and thietanyl; 5 membered rings, such as dihydrofuranyl, tetrahydrofuranyl, dioxolyl, pyrrolidinyl, imidazolidinyl, pyrazolidinyl, pyrrolinyl, dihydrothienyl, tetrahydrothienyl, dihydropyrrolyl, dioxalanyl, oxasulfuranyl, disulfuranyl, oxazolidin-2-one, triazolyl, oxadiazolyl and thiadiazolyl; or 6 membered rings such as dihydropyranyl, tetrahydropyranyl, piperidinyl, morpholinyl, dithianyl, thiomorpholinyl, dihydropyridyl, thiacyclohexyl, dithiacyclohexyl, dioxanyl, piperazinyl or trithianyl; or 7 membered ring such

as diazepanyl, azepanyl, oxepanyl and thiepanyl. Optionally, the heterocyclyl may be benzo-fused. The heterocyclyl may be bicyclic, such as but not limited to a 5,5-membered ring such as a hexahydrocyclopenta[*c*]pyrrol-2(1*H*)-yl ring, or a 5,6-membered bicyclic ring such as a hexahydropyrrolo[1,2-*a*]pyrazin-2(1*H*)-yl ring. The ring containing nitrogen atoms may be partially unsaturated, i.e., it may comprise one or more double bonds, such as but not limited to 2,5-dihydro-1*H*-pyrrolyl, 4*H*-[1,3,4]thiadiazinyl, 4,5-dihydrooxazolyl or 4*H*-[1,4]thiazinyl, or it may be benzo-fused, such as but not limited to dihydroisoquinolyl. According to the present disclosure, the heterocyclyl is non-aromatic.

The term "C₆₋₂₀ aryl" refers to an aromatic or partially aromatic monovalent monocyclic, bicyclic or tricyclic hydrocarbon ring having 6–20 carbon atoms, and is preferably "C₆₋₁₄ aryl" or "C₆₋₁₀ aryl". The term "C₆₋₁₄ aryl" preferably refers to an aromatic or partially aromatic monovalent monocyclic, bicyclic or tricyclic hydrocarbon ring having 6, 7, 8, 9, 10, 11, 12, 13 or 14 carbon atoms ("C₆₋₁₄ aryl"), in particular a ring having 6 carbon atoms ("C₆ aryl"), such as phenyl; or a biphenyl, a ring having 9 carbon atoms ("C₉ aryl") such as indanyl or indenyl, a ring having 10 carbon atoms ("C₁₀ aryl") such as tetrahydronaphthyl, dihydronaphthyl or naphthyl, a ring having 13 carbon atoms ("C₁₃ aryl") such as fluorenyl, or a ring having 14 carbon atoms ("C₁₄ aryl") such as anthracenyl.

The term "5-20 membered heteroaryl" refers to an aromatic monovalent monocyclic, bicyclic or tricyclic ring which has 5–20 ring atoms and comprises 1–5 heteroatoms independently selected from N, O and S, such as "5-14 membered heteroaryl", "5-10 membered heteroaryl" or "5-6 membered heteroaryl". The term "5-14 membered heteroaryl" refers to a monovalent aromatic monocyclic, bicyclic or tricyclic ring which has 5, 6, 7, 8, 9, 10, 11, 12, 13 or 14 ring atoms, in particular 5, 6, 9 or 10 carbon atoms, comprises 1–5, preferably 1–3 heteroatoms independently selected from N, O and S, and may be benzo-fused in each case. The term "5-6 membered heteroaryl" refers to a monovalent monocyclic aromatic ring which has 5 or 6 ring atoms, comprises 1–3 heteroatoms independently selected from N, O and S, and may be benzo-fused in each case. In particular, the heteroaryl is selected from thienyl, furanyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, isoxazolyl, isothiazolyl, oxadiazolyl, triazolyl, thiadiazolyl, thia-4*H*-pyrazolyl and the like and benzo derivatives thereof, such as benzofuranyl, benzothienyl, benzoxazolyl, benzoisoxazolyl, benzimidazolyl, benzotriazolyl,

indazolyl, indolyl, and isoindolyl; or pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl and the like and benzo derivatives thereof, such as quinolyl, quinazoliny, and isoquinolyl; or azocinyl, indoliziny, purinyl and the like and benzo derivatives thereof; or cinnoliny, phthalazinyl, quinazoliny, quinoxaliny, naphthyridiny, pteridiny, carbazolyl, acridiny, phenazinyl, phenothiaziny, phenoxazinyl, and the like.

Unless otherwise stated, the heterocyclyl, heteroaryl or heteroarylene includes all possible isomeric forms thereof, e.g., positional isomers thereof. Accordingly, for some illustrative non-limiting examples, pyridinyl or pyridinylene includes pyridin-2-yl, pyridinylene-2-yl, pyridin-3-yl, pyridinylene-3-yl, pyridin-4-yl, and pyridinylene-4-yl; thienyl or thienylene includes thien-2-yl, thien-2-ylene, thien-3-yl, and thien-3-ylene.

Unless otherwise indicated, the term "leaving group", as used herein, shall refer to a charged or uncharged atom or group that is liberated during a substitution or replacement reaction. Suitable examples include, but are not limited to, H, F, Br, Cl, I, mesylate group, tosylate group, and the like.

In any method for preparing the compound disclosed herein, it may be necessary and/or desirable to protect sensitive or reactive groups on any molecule concerned. This can be achieved by conventional protective groups, as described in textbooks or in reference books in the art. The protective group may be removed at a convenient subsequent stage using methods known in the art. Those skilled in the art will recognize that, other reagents, including but not limited to Pd/C, Pd(OH)₂, PdCl₂, Pd(OAc)₂/Et₃SiH, Raney nickel, an appropriately selected acid, an appropriately selected base, fluoride, and the like, may be used in this deprotection step depending on the particular protective group.

The target compound may be isolated according to known methods, for example by extraction, filtration or column chromatography.

According to the molecular structure, the compounds disclosed herein may be chiral and may therefore exist in various enantiomeric forms. These compounds may therefore exist in racemic or optically active form. The compounds disclosed herein or intermediates thereof may be separated into enantiomers by chemical or physical methods well known to those skilled in the art, or used in this form for synthesis. In the case of racemic amines, diastereoisomers are prepared from mixtures by reaction with optically active resolving agents. Examples of suitable

resolving agents are optically active acids such as *R*- or *S*-tartaric acid, diacetyltartaric acid, dibenzoyltartaric acid, mandelic acid, malic acid, lactic acid, suitable *N*-protected amino acids (e.g., *N*-benzoylproline or *N*-benzenesulfonylproline) or various optically active camphorsulfonic acids. Enantiomeric resolution by chromatography can be advantageously
5 performed with the aid of optically active resolving agents, such as dinitrobenzoylphenylglycine, cellulose triacetate or other carbohydrate derivatives or chirally derivatized methacrylate polymers immobilized on silica gel. Suitable eluents for this purpose are mixtures of solvent containing water or alcohol, for example, hexane/isopropanol/acetonitrile.

10 Those skilled in the art will appreciate that not all nitrogen-containing heterocycles can form N-oxides, as nitrogen needs to have available lone pairs of electrons used for oxidation to oxides; those skilled in the art will identify nitrogen-containing heterocycles capable of forming N-oxides. Those skilled in the art will also recognize that tertiary amines are capable of forming N-oxides. Synthetic methods for preparing N-oxides of heterocycles and tertiary amines are
15 well known to those skilled in the art and include oxidation by peroxy acids such as peroxyacetic acid and *m*-chloroperbenzoic acid (MCPBA), hydrogen peroxide, alkyl hydroperoxides such as *tert*-butyl hydroperoxide, sodium perborate, and dioxiranes such as dimethyldioxirane. These methods for preparing N-oxides have been widely described and reviewed in the literature.

20 A pharmaceutically acceptable salt may be, for example, acid addition salts of the compounds disclosed herein having a nitrogen atom in the chain or ring with sufficient basicity, for example, acid addition salts formed with the following inorganic acids: hydrochloric acid, hydrofluoric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, pyrosulfuric acid, phosphoric acid or nitric acid; hydrosulfates; or acid addition salts with the following organic acids: formic acid,
25 acetic acid, acetoacetic acid, pyruvic acid, trifluoroacetic acid, propionic acid, butyric acid, hexanoic acid, heptanoic acid, undecanoic acid, lauric acid, benzoic acid, salicylic acid, 2-(4-hydroxybenzoyl)benzoic acid, camphoric acid, cinnamic acid, cyclopentanepropionic acid, digluconic acid, 3-hydroxy-2-naphthoic acid, nicotinic acid, pamoic acid, pectinic acid, peroxosulfuric acid, 3-phenylpropionic acid, picric acid, pivalic acid, 2-hydroxyethanesulfonic
30 acid, itaconic acid, sulfamic acid, trifluoromethanesulfonic acid, dodecylsulfuric acid,

ethanesulfonic acid, benzenesulfonic acid, *p*-toluenesulfonic acid, methanesulfonic acid, 2-naphthalenesulfonic acid, naphthalenedisulfonic acid, camphorsulfonic acid, citric acid, tartaric acid, stearic acid, lactic acid, oxalic acid, malonic acid, succinic acid, malic acid, adipic acid, alginic acid, maleic acid, fumaric acid, *D*-gluconic acid, mandelic acid, ascorbic acid, glucoheptonic acid, glycerophosphoric acid, aspartic acid, sulfosalicylic acid, hemisulfuric acid, or thiocyanic acid.

In addition, another suitable pharmaceutically acceptable salt of the compounds disclosed herein having sufficient acidity is an alkali metal salt (e.g., sodium salt or potassium salt), an alkaline earth metal salt (e.g., calcium salt or magnesium salt), an ammonium salt, or a salt formed with an organic base which provides a physiologically acceptable cation, for example, a salt formed with: a sodium ion, a potassium ion, *N*-methylglucamine, dimethylglucamine, ethylglucamine, lysine, dicyclohexylamine, 1,6-hexanediamine, ethanolamine, glucosamine, meglumine, sarcosine, serinol, trihydroxymethylaminomethane, aminopropanediol, or 1-amino-2,3,4-butanetriol. As an example, the pharmaceutically acceptable salts include salts formed from the group -COOH with the following: a sodium ion, a potassium ion, a calcium ion, a magnesium ion, *N*-methylglucamine, dimethylglucamine, ethylglucamine, lysine, dicyclohexylamine, 1,6-hexanediamine, ethanolamine, glucosamine, meglumine, sarcosine, serinol, trihydroxymethylaminomethane, aminopropanediol, or 1-amino-2,3,4-butanetriol.

In addition, the basic nitrogen-containing groups may be quaternized with the following agents: lower alkyl halides such as methyl, ethyl, propyl and butyl chlorides, bromides and iodides; dialkyl sulfates such as dimethyl sulfate, diethyl sulfate, dibutyl sulfate, and dipentyl sulfate; long chain halides such as decyl, lauryl, myristyl and stearyl chlorides, bromides and iodides; and aralkyl halides such as benzyl and phenethyl bromides. As an example, pharmaceutically acceptable salts include hydrochloride, sulfate, nitrate, bisulfate, hydrobromide, acetate, oxalate, citrate, mesylate, formate, meglumine, and the like.

Since the compounds disclosed herein may have a plurality of salt-forming sites, the "pharmaceutically acceptable salt" includes not only a salt formed at 1 salt-forming site of the compounds disclosed herein but also salts formed at 2, 3 or all of the salt-forming sites thereof. For this purpose, the molar ratio of the compound of formula I to a radical ion (anion) of an acid or a cation of a base required for salt formation may vary within a wide range, and may be,

for example, 4:1 to 1:4, such as 3:1, 2:1, 1:1, 1:2, and 1:3.

According to the present disclosure, the pharmaceutically acceptable anions include anions selected from those generated by the ionization of inorganic or organic acids. The "inorganic acid" includes, but is not limited to, hydrochloric acid, hydrofluoric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, pyrosulfuric acid, phosphoric acid, or nitric acid. The "organic

acid" includes, but is not limited to, formic acid, acetic acid, acetoacetic acid, pyruvic acid, trifluoroacetic acid, propionic acid, butyric acid, hexanoic acid, heptanoic acid, undecanoic acid, lauric acid, benzoic acid, salicylic acid, 2-(4-hydroxybenzoyl)benzoic acid, camphoric acid, cinnamic acid, cyclopentanepropionic acid, digluconic acid, 3-hydroxy-2-naphthoic acid, nicotinic acid, pamoic acid, pectinic acid, peroxosulfuric acid, 3-phenylpropionic acid, picric acid, pivalic acid, 2-hydroxyethanesulfonic acid, itaconic acid, sulfamic acid, trifluoromethanesulfonic acid, dodecylsulfuric acid, ethanesulfonic acid, benzenesulfonic acid, *p*-toluenesulfonic acid, methanesulfonic acid, 2-naphthalenesulfonic acid, naphthalenedisulfonic acid, camphorsulfonic acid, citric acid, tartaric acid, stearic acid, lactic acid, oxalic acid, malonic acid, succinic acid, malic acid, adipic acid, alginic acid, maleic acid, fumaric acid, *D*-gluconic acid, mandelic acid, ascorbic acid, glucoheptonic acid, glycerophosphoric acid, aspartic acid, sulfosalicylic acid, hemisulfuric acid, or thiocyanic acid.

The term "tautomer" refers to functional isomers resulting from the rapid movement of an atom in a molecule between two positions. The compounds disclosed herein may exhibit the tautomerism. Tautomeric compounds may exist in two or more interconvertible forms. Prototropic tautomers result from the migration of a covalently bonded hydrogen atom between two atoms. Tautomers generally exist in an equilibrium form. Trying to separate a single tautomer usually lead to a mixture, the physicochemical properties of which are consistent with the mixture of the compound. The position of the equilibrium depends on the chemical properties of the molecule. For example, in many aliphatic aldehydes and ketones such as acetaldehyde, the keto form predominates; whereas in phenols, the enol form predominates. The present disclosure comprises all tautomeric forms of the compound.

The term "effective amount" or "therapeutically effective amount" refers to an amount of the compounds disclosed herein sufficient to effect the intended use, including but not limited to the treatment of a disease as defined below. The therapeutically effective amount may vary

depending on the following factors: the intended use (*in vitro* or *in vivo*), or the subject and diseases or conditions being treated, such as weight and age of the subject, severity of the diseases or conditions and mode of administration, which can be readily determined by one of ordinary skill in the art. The specific dosage will vary depending on the following factors: the selected particular compound, the dosage regimen to be followed, whether to administer in combination with other compounds, the schedule of administration, the tissue to be administered and the physical delivery system carried.

The term "auxiliary material" refers to a pharmaceutically acceptable inert ingredient. Examples of types of excipients include, without limitation, adhesives, disintegrants, lubricants, glidants, stabilizers, fillers, diluents, and the like. Excipients are capable of enhancing the handling characteristics of the pharmaceutical formulation, i.e., making the formulation more amenable to direct compression by increasing flowability and/or adhesiveness. Examples of typical pharmaceutically acceptable carriers suitable for use in the above formulations include: saccharides, such as lactose, sucrose, mannitol, and sorbitol; starches, such as corn starch, tapioca starch and potato starch; cellulose and its derivatives, such as sodium carboxymethylcellulose, ethyl cellulose and methyl cellulose; calcium phosphates, such as dicalcium phosphate and tricalcium phosphate; sodium sulfate; calcium sulfate; polyvinylpyrrolidone; polyvinyl alcohol; stearic acid; alkaline earth metal stearate, such as magnesium stearate and calcium stearate; vegetable oils such as peanut oil, cottonseed oil, sesame oil, olive oil and corn oil; nonionic, cationic and anionic surfactants; a glycol polymer; fatty alcohols; and grain hydrolysis solids and other nontoxic compatible auxiliary materials commonly available in pharmaceutical formulations, such as fillers, adhesives, disintegrants, buffers, preservatives, antioxidants, lubricants, and colorants.

Part of the abbreviations in the text are defined as follows: HATU: 2-(7-benzotriazole oxide)--*N,N,N',N'*-tetramethyluronium hexafluorophosphate; Pd(dppf)Cl₂: [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II); EA: ethyl acetate; Boc: *tert*-butoxycarbonyl.

Beneficial effects of the present disclosure:

The compound provided herein has excellent ROCK inhibitory activity. In addition, the

compound of the present disclosure has good safety and metabolic stability and high bioavailability. Further, the compound of the present disclosure has a low risk of potential hepatotoxicity. Finally, the compound of the present disclosure is simple in preparation and easy to purify, and therefore has good application prospects.

5

DETAILED DESCRIPTION

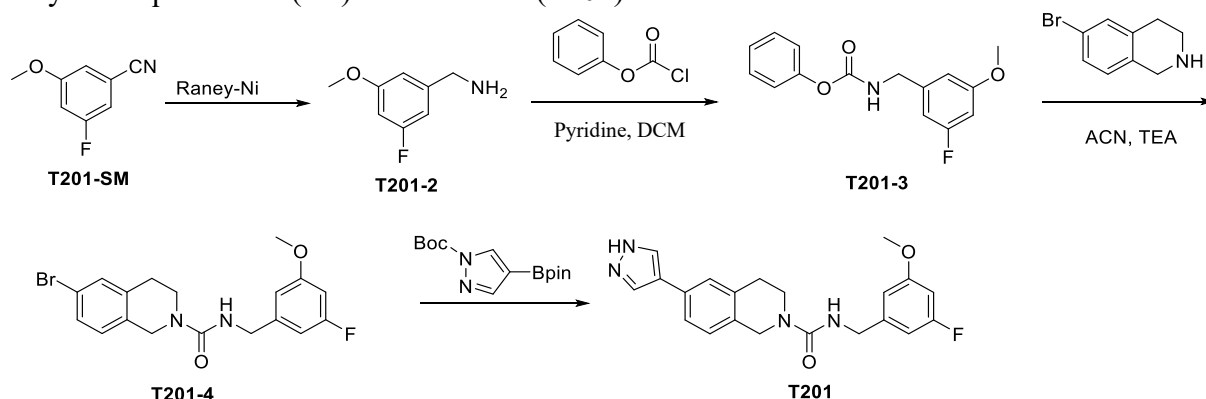
The compounds of the general formulas disclosed herein and the preparation method and use thereof will be described in detail with reference to the following examples. The following examples are merely exemplary illustration and explanation of the present disclosure, and should not be construed as limiting the protection scope of the present disclosure. All techniques implemented based on the aforementioned content of the present disclosure are encompassed within the protection scope of the present disclosure.

Unless otherwise stated, the starting materials and reagents used in the following examples are all commercially available products or can be prepared by known methods.

15

<Preparation Examples>

Example 1: Preparation of Compound *N*-(3-fluoro-5-methoxybenzyl)-6-(1*H*-pyrazol-4-yl)-3,4-dihydroisoquinoline-2(1*H*)-carboxamide (T201)



20

1.1 Preparation of compound (3-fluoro-5-methoxyphenyl)methanamine (T201-2)

Raney Ni (100 mg) and aqueous ammonia (0.2 mL) were added to a solution of compound T201-SM (500 mg) in methanol, and the mixture was stirred overnight at room temperature under hydrogen atmosphere. The reaction solution was filtered and concentrated under reduced pressure, and the residue was purified by column chromatography to give the title product (300

25

mg).

LCMS: $[M+H]^+ = 156.3$.

1.2 Preparation of compound phenyl-3-fluoro-5-methoxybenzyl carbamate (T201-3)

Compound T201-2 (50mg) and pyridine (76 mg) were dissolved in dichloromethane (5 mL), and phenyl chloroformate (75 mg) was added dropwise at 0 °C. After the addition was completed, the mixture was stirred at room temperature for 4 h. The reaction solution was extracted with water and dichloromethane, and the organic phase was washed with saturated brine and dried over anhydrous sodium sulfate. The organic phase was then concentrated under reduced pressure to give the title product.

LCMS: $[M+H]^+ = 276.1$.

1.3 Preparation of compound 6-bromo-*N*-(3-fluoro-5-methoxybenzyl)-3,4-dihydroisoquinoline-2(1*H*)-carboxamide (T201-4)

Compound T201-3 (30 mg), 6-bromo-1,2,3,4-tetrahydroisoquinoline (CAS: 226942-29-6, 23 mg), and triethylamine (22 mg) were dissolved in acetonitrile (3 mL). The mixture was stirred overnight at 80 °C, and then the reaction was completed. The reaction solution was concentrated under reduced pressure and the residue was purified by column chromatography to give the title product (30 mg).

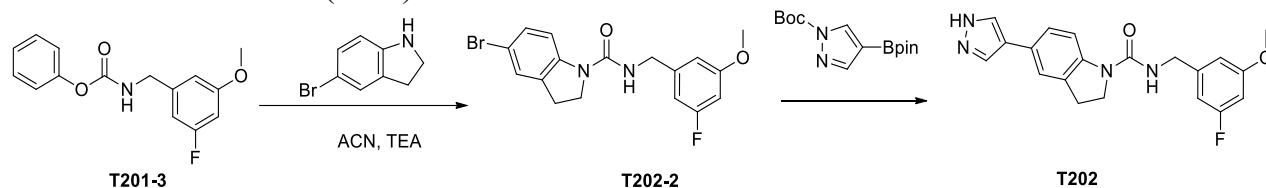
LCMS: $[M+H]^+ = 395.0$.

1.4 Preparation of compound *N*-(3-fluoro-5-methoxybenzyl)-6-(1*H*-pyrazol-4-yl)-3,4-dihydroisoquinoline-2(1*H*)-carboxamide (T201)

Compound T201-4 (30 mg), 1-Boc-pyrazole-4-boronic acid pinacol ester (CAS: 552846-17-0; 24 mg), sodium carbonate (16.2 mg), potassium acetate (15 mg) and Pd(PPh₃)₄ (8.8 mg) were dissolved in dioxane/H₂O (10 mL/2 mL). the mixture was stirred overnight at 90 °C under nitrogen atmosphere, and then the reaction was completed. The reaction solution was filtered and concentrated, and the residue was purified by preparative high performance liquid chromatography, and lyophilized to give the target product (5 mg).

¹H NMR (400 MHz, DMSO-d₆) δ = 12.90 (s, 1H), 8.14 (s, 1H), 7.90 (s, 1H), 7.42-7.41 (m, 2H), 7.19-7.16 (m, 1H), 7.12-7.10 (m, 1H), 6.68-6.64 (m, 3H), 4.51 (s, 2H), 4.24 (d, J = 5.6 Hz, 2H), 3.72 (s, 3H), 3.60 (t, J = 6.0 Hz, 2H), 2.81 (t, J = 5.6 Hz, 2H); LCMS: $[M+H]^+ = 381.1$.

Example 2: Preparation of Compound *N*-(3-fluoro-5-methoxybenzyl)-5-(1*H*-pyrazol-4-yl)indoline-1-carboxamide (T202)



2.1 Preparation of compound 5-bromo-*N*-(3-fluoro-5-methoxybenzyl)-2,3-indoline-1-carboxamide (T202-2)

Compound T201-3 (300 mg), 5-bromoindoline (CAS: 22190-33-6, 215 mg) and triethylamine (219 mg) were dissolved in acetonitrile (10 mL). The mixture was stirred overnight at 80 °C, and then the reaction was completed. The reaction solution was concentrated under reduced pressure and the residue was purified by column chromatography to give the title compound (549 mg).

LCMS: $[M+H]^+ = 381.3$.

2.2 Preparation of compound *N*-(3-fluoro-5-methoxybenzyl)-5-(1*H*-pyrazol-4-yl)indoline-1-carboxamide (T202)

Compound T202-2 (200 mg), 1-Boc-pyrazole-4-boronic acid pinacol ester (171 mg), sodium carbonate (112 mg), potassium acetate (103 mg) and $Pd(PPh_3)_4$ (61 mg) were dissolved in dioxane/ H_2O (10 mL/2 mL). The mixture was stirred overnight at 90 °C under nitrogen atmosphere, and then the reaction was completed. The reaction solution was filtered and concentrated, and the residue was purified by preparative high performance liquid chromatography, and lyophilized to give the target product (100 mg).

^1H NMR (400 MHz, $DMSO-d_6$) δ = 12.80 (s, 1H), 8.05 (s, 1H), 7.82-7.77 (m, 2H), 7.40 (s, 1H), 7.32-7.30 (m, 1H), 7.25-7.22 (m, 1H), 6.75-6.66 (m, 3H), 4.30 (d, J = 6.0 Hz, 2H), 3.97 (d, J = 8.8 Hz, 2H), 3.76 (s, 3H), 3.16 (t, J = 8.4 Hz, 2H). LCMS: $[M+H]^+ = 367.1$.

Example 3: Preparation of compound 1-methyl-6-(1*H*-pyrazol-4-yl)-1*H*-indole-3-carboxylic acid-3-fluoro-5-methoxy-benzoylamide (T203)

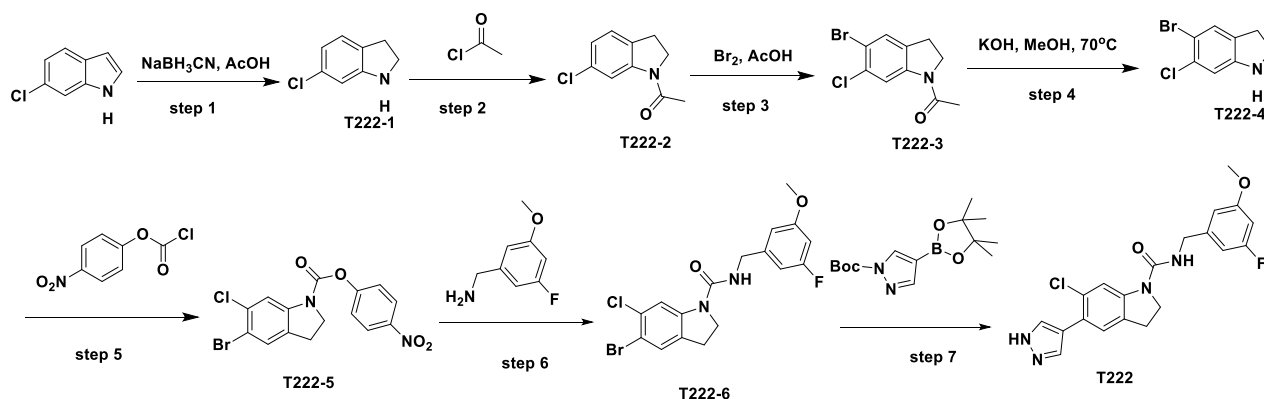
carboxamide (T221-3)

(3-fluoro-5-methoxyphenyl)methylamine (1333 mg) was added directly to the reaction solution obtained in the previous step, and the mixture was stirred overnight under reflux. The reaction solution was concentrated by rotary evaporation, and the residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate = 2:1) to give a pale yellow oily liquid (700 mg, 85% purity, 68% yield). LC-MS [M+H]⁺: 412.6.

7 Preparation of compound 7-chloro-*N*-(3-fluoro-5-methoxybenzyl)-5-(1*H*-pyrazol-4-yl)indoline-1-carboxamide (T221)

Compound T221-3 (500 mg), 1-Boc-pyrazole-4-boronic acid pinacol ester (714 mg), potassium carbonate (500 mg) and [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (89 mg) were dissolved in anhydrous dioxane (15 mL) and water (3 mL) under nitrogen atmosphere, and the mixture was reacted at 90 °C for 12 h. The reaction solution was cooled to room temperature, diluted with water (20 mL) and extracted with ethyl acetate (15 mL × 2). The organic phases were combined, washed with saturated brine (15 mL), dried over anhydrous sodium sulfate, filtered and concentrated, and the resulting crude product was purified by silica gel column chromatography (petroleum ether/ethyl acetate = 0–100%) and then purified by preparative chromatography to give a white solid (40 mg, 8.7% yield). LC-MS [M+H]⁺: 400.9. ¹H NMR (400 MHz, DMSO) δ 12.91(bris, 1H), 8.05 (bris, 2H), 7.66 (t, J = 6.0 Hz, 1H), 7.46 (s, 1H), 7.44 (s, 1H), 6.78 – 6.67 (m, 3H), 4.30 (d, J = 5.8 Hz, 2H), 4.03 (t, J = 7.9 Hz, 2H), 3.77 (s, 3H), 3.09 (t, J = 7.9 Hz, 2H).

Example 16: Preparation of 7-chloro-*N*-(3-fluoro-5-methoxybenzyl)-5-(1*H*-pyrazol-4-yl)indoline-1-carboxamide (T222)



1. Preparation of compound 6-chloroindoline (T222-1)

6-chloroindole (2.0 g) was dissolved in acetic acid (20 mL), and in an ice water bath, sodium cyanoborocyanide (1.0 g) was slowly added at 0 °C. After the addition was completed, the mixture was warmed to room temperature and stirred for 12 h. After the reaction was completed, the reaction solution was placed in an ice bath, the pH was adjusted to be alkaline with NaOH solution (1 N), and dichloromethane was added for extraction. The organic phase was dried over anhydrous sodium sulfate and concentrated by rotary evaporation to give a crude product in the form of a white solid (2.2 g). LC-MS $[M+H]^+$: 153.9.

2 Preparation of compound 1-(6-chloroindoline-1-yl)ethan-1-one (T222-2)

Compound T222-1 (2.2 g) and pyridine (1.3 g) were dissolved in tetrahydrofuran (50 mL), and in an ice water bath, acetyl chloride (1.1 g) was slowly added dropwise at 0 °C. The mixture was warmed to room temperature and stirred overnight. Water (50 mL) was added to quench the reaction, and ethyl acetate (60 mL $\times$ 3) was added for extraction. The organic phases were combined, washed with saturated brine (40 mL $\times$ 2), dried over anhydrous sodium sulfate, filtered and concentrated by rotary evaporation. The resulting crude product was purified by silica gel column chromatography (petroleum ether:ethyl acetate = 10:1) to give a white solid (2.5 g, 97% two-step yield). LC-MS $[M+H]^+$: 239.8.

3 Preparation of compound 1-(5-bromo-6-chloroindoline-1-yl)ethan-1-one (T222-3)

Compound T222-2 (2.3 g) was dissolved in acetic acid (30 mL), and in an ice water bath, bromine (2.1 g) was slowly added dropwise. The mixture was warmed to room temperature and reacted for 4 h. Solid was precipitated out during the reaction, and after the reaction was completed, the mixture was filtered under vacuum. The filter cake was washed once with ethyl acetate to give a white solid (2.5 g, 77% yield). LC-MS $[M+H]^+$: 273.8.

4. Preparation of compound 5-bromo-6-chloroindoline (T222-4)

Compound T222-3 (2.5 g) and KOH (5.1 g) were dissolved in methanol/water (1:1, 30 mL), and the mixture was warmed to 70 °C and stirred overnight. The reaction solution was then cooled to room temperature and concentrated by rotary evaporation to give a crude product, which was purified by silica gel column chromatography (petroleum ether:ethyl acetate = 2:1) to give the product in the form of a white solid (1.6 g, 75.6% yield). LC-MS $[M+H]^+$: 231.8.

5 Preparation of compound *p*-nitrophenyl 5-bromo-6-chloroindoline-1-carboxylate (T222-5)

Compound T222-4 (1.6 g) and pyridine (1.6 g) were dissolved in tetrahydrofuran (30 mL), and *p*-nitrophenyl chloroformate (1.7 g) was added. The mixture was stirred for 4 h. After the reaction was completed, the reaction solution was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate = 2/1) to give a crude product in the form of a yellow solid (2 g). LC-MS $[M+Na]^+$: 418.5.

6 Preparation of compound 5-bromo-6-chloro-*N*-(3-fluoro-5-methoxybenzyl) indoline-1-carboxamide (T222-6)

Compound T222-5 (2 g, crude product) was dissolved in DMF (20 mL), and (3-fluoro-5-methoxyphenyl)carboxamide (3.2 g) and triethylamine (2.08 g) were added. The mixture was warmed to 130 °C and stirred overnight. The reaction solution was diluted with water and extracted with ethyl acetate (50 mL × 3). The organic phases were combined, washed with saturated brine (50 mL), dried over anhydrous sodium sulfate, filtered and concentrated by rotary evaporation, and the residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate = 2:1) to give a yellow solid (2 g, 70.3% two-step yield). LC-MS $[M+H]^+$: 412.6.

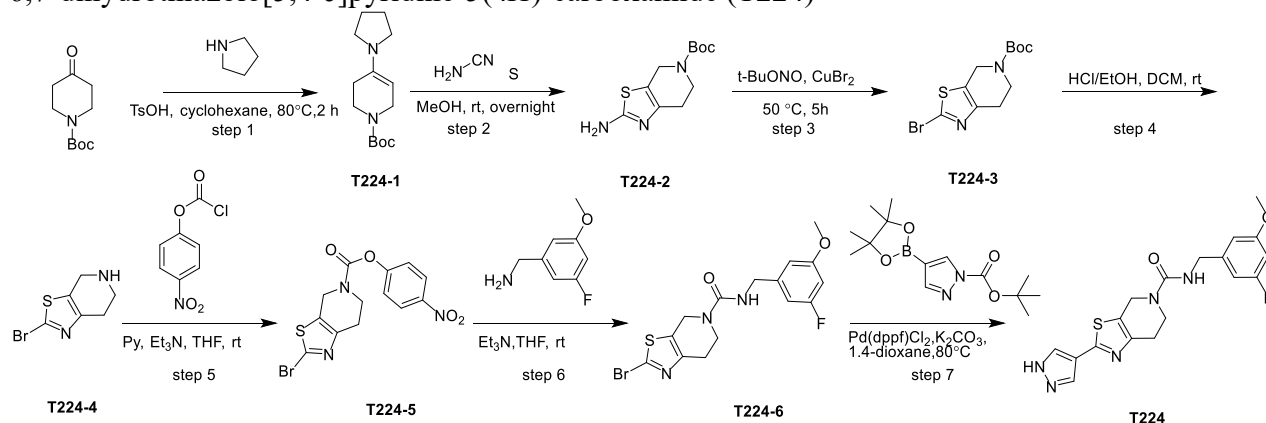
7 Preparation of compound 6-chloro-*N*-(3-fluoro-5-methoxybenzyl)-5-(1*H*-pyrazol-4-yl)indoline-1-carboxamide (T222)

Under nitrogen atmosphere, compound T222-6(400 mg), 1-*tert*-butoxycarbonylpyrazole-4-boronic acid pinacol ester (570 mg), potassium carbonate (400 mg) and [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (71 mg) were dissolved in anhydrous dioxane (30 mL) and water (3 mL), and the mixture was reacted at 90 °C for 12h. The reaction solution was cooled to room temperature, diluted with water (20 mL) and extracted with ethyl acetate (15 mL × 2), and the organic phases were combined, washed with saturated brine (15 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate = 0–100%) and then purified by preparative chromatography to give a white solid (102.6 mg, 26.3% yield). LC-MS $[M+H]^+$: 400.9.

¹H NMR (400 MHz, DMSO) δ 12.97 (s, 1H), 8.06 (s, 1H), 7.90 (s, 1H), 7.81 (s, 1H), 7.42 – 7.34 (m, 2H), 6.76 – 6.67 (m, 3H), 4.31 (d, *J* = 5.8 Hz, 2H), 4.01 (t, *J* = 8.7 Hz, 2H), 3.76 (s,

3H), 3.16 (t, J = 8.6 Hz, 2H).

Example 17: Preparation of Compound *N*-(3-fluoro-5-methoxybenzyl)-2-(1*H*-pyrazol-4-yl)-6,7-dihydrothiazolo[5,4-*c*]pyridine-5(4*H*)-carboxamide (T224)



1 Preparation of compound *tert*-butyl 4-(pyrrolidin-1-yl)-3,6-dihydropyridine-1(2*H*)-carboxylate (T224-1)

Tert-butyl 4-carboxypiperidine-1-carboxylate (2.00 g), tetrahydropyrrole (0.75 g) and *p*-toluenesulfonic acid monohydrate (10 mg) were dissolved in cyclohexane (20 mL), and the mixture was reacted at 80 °C for 2 h in a reaction apparatus provided with a reflux water separator. The reaction solution was cooled to room temperature and filtered, and the filtrate was concentrated by rotary evaporation to give a crude product in the form of a yellow solid (2.37 g), which was directly used in the next step.

2 Preparation of compound *tert*-butyl 2-amino-6,7-dihydrothiazolo[5,4-*c*]pyridine-5(4*H*)-carboxylate (T224-2)

Compound T224-1 (2.00 g) and elemental sulfur powder (0.25 g) were dissolved in methanol (15 mL). The mixture was cooled to 0 °C, and a solution of cyanamide (0.34 g) in methanol (5 mL) was added dropwise. After the addition was completed, the mixture was stirred overnight at room temperature. After the reaction was completed, the reaction solution was filtered, and the filter cake was washed with ethyl acetate (30 mL). The filter cake was collected and dried to give a crude product in the form of a pale yellow solid (2.20 g). LC-MS $[M+H]^+$: 255.8.

3 Preparation of compound *tert*-butyl 2-bromo-6,7-dihydrothiazolo[5,4-*c*]pyridine-5(4*H*)-carboxylate (T224-3)

Compound T224-2 (2.00 g), *tert*-butyl nitrite (1.22 g) and cuprous bromide (2.13 g) were

dissolved in *N,N*-dimethylformamide (50 mL), and the mixture was reacted at 50 °C for 5 h under nitrogen atmosphere. The reaction solution was cooled to room temperature, and water (50 mL) was added to quench the reaction. The reaction solution was filtered, and the filtrate was extracted with ethyl acetate (40 mL × 3). The organic phases were combined, washed with saturated brine (50 mL × 3), dried over anhydrous sodium sulfate, filtered and concentrated, and the resulting crude product was purified by silica gel column chromatography (petroleum ether:ethyl acetate = 4:1) to give the product in the form of a white solid (300 mg, 10% yield). LC-MS $[M+H]^+$: 318.7.

4 Preparation of compound 2-bromo-4,5,6,7-tetrahydrothiazolo[5,4-*c*]pyridine (T224-4)

Compound T224-3 (300 mg) was dissolved in dichloromethane (2 mL), and a solution of hydrogen chloride in ethanol (33%, 1 mL) was added. The mixture was stirred overnight at room temperature. After the reaction was completed, the reaction solution was concentrated by rotary evaporation, and dichloromethane (30 mL) was added. The mixture was washed with saturated sodium bicarbonate solution (20 mL) and saturated brine (20 mL), dried over anhydrous sodium sulfate, filtered and concentrated, and the resulting crude product was purified by silica gel column chromatography (dichloromethane:ethyl acetate = 10:1) to give a white solid (250 mg, 91%). LC-MS $[M+H]^+$: 218.7.

5 Preparation of compound *p*-nitrophenyl 2-bromo-6,7-dihydrothiazolo[5,4-*c*]pyridine-5(4*H*)-carboxylate (T224-5)

Compound T224-4 (150 mg) was dissolved in tetrahydrofuran (4 mL), and *p*-nitrophenyl chloroformate (215 mg), pyridine (170 mg) and triethylamine (358 mg) were added. The mixture was stirred overnight at room temperature under nitrogen atmosphere. After the reaction was completed, the reaction solution was directly used in the next step. LC-MS $[M+H]^+$: 383.5.

6 Preparation of compound 2-bromo-*N*-(3-fluoro-5-methoxybenzyl)-6,7-dihydrothiazolo[5,4-*c*]pyridine-5(4*H*)-carboxamide (T224-6)

(3-fluoro-5-methoxyphenyl)methylamine (400 mg) and triethylamine (303 mg) were added to the reaction solution obtained in the previous step, and the mixture was stirred at room temperature for 4 h. Water (20 mL) was added to quench the reaction, and ethyl acetate (15 mL × 3) was added for extraction. The organic phases were combined, washed with a saturated

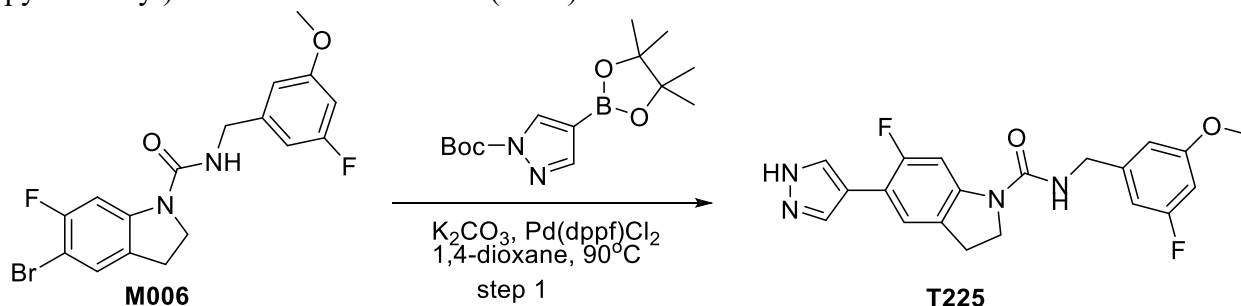
saline brine (20 mL), dried over anhydrous sodium sulfate and filtered, and the filtrate was concentrated by rotary evaporation. The resulting crude product was purified by silica gel column chromatography (4 g, petroleum ether:ethyl acetate = 10:1) to give a white solid (120 mg, 41.88%). LC-MS $[M+H]^+$: 399.6.

5 7 Preparation of compound *N*-(3-fluoro-5-methoxybenzyl)-2-(1*H*-pyrazol-4-yl)-6,7-dihydrothiazolo [5,4-*c*]pyridine-5(4*H*)-carboxamide (T224)

Compound T224-6 (100 mg), *tert*-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole-1-carboxylate (106 mg), [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (35 mg) and potassium carbonate (99 mg) were dissolved in a mixed solution of 1,4-dioxane (8 mL) and water (2 mL), and the mixture was stirred overnight at 80 °C. The reaction solution was filtered, and the filtrate was concentrated by rotary evaporation. The residue was purified by silica gel column chromatography (4 g, dichloromethane:ethyl acetate = 5:1), purified by preparative chromatography (chromatographic column: -Gemini-C18, 150 × 21.2 mm, 5μm; mobile phase: ACN-H₂O (0.05% NH₃); gradient: 25–40) and then lyophilized to give a white solid (14.3 mg). LC-MS $[M+H]^+$: 388.2.

¹H NMR (400 MHz, DMSO) δ 13.26 (brs, 1H), 8.31 (s, 1H), 7.92 (s, 1H), 7.37 (t, J = 5.8 Hz, 1H), 6.69 – 6.62 (m, 3H), 4.62 (s, 2H), 4.24 (d, J = 5.6 Hz, 2H), 3.75 – 3.70 (m, 5H), 2.81 – 2.75 (m, 2H).

Example 18: Preparation of Compound 6-fluoro-*N*-(3-fluoro-5-methoxybenzyl)-5-(1*H*-pyrazol-4-yl)indoline-1-carboxamide (T225)

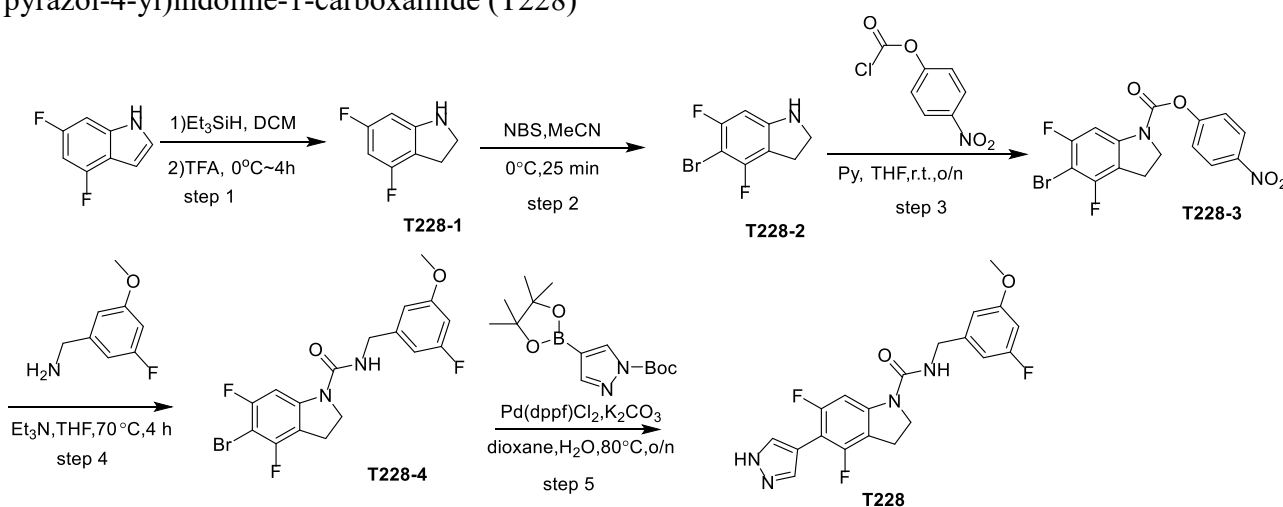


Compound M006 (2.90 g) was dissolved in 1,4-dioxane (20 mL) and water (5 mL), and *tert*-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole-1-carboxylate (2.58 g), potassium carbonate (4.09 g) and [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II)

(534 mg) were added under nitrogen atmosphere. The mixture was reacted at 90 °C for 3 h, and then the reaction solution was cooled to room temperature. Water (20mL) was added, and ethyl acetate (50 mL × 3) was added for extraction. The organic phases were combined, washed with saturated brine (50 mL), dried over anhydrous sodium sulfate, filtered and concentrated by rotary evaporation. The resulting crude product was purified by high pressure liquid chromatography to give compound T225 in the form of a white solid (1.1 g, 28.9% yield). MS $[M+H]^+ = 385.0$.

^1H NMR (300 MHz, CD₃OD) δ 7.91 (s, 2H), 7.63 (d, $J = 12.9$ Hz, 1H), 7.43 (d, $J = 7.7$ Hz, 1H), 6.74 (s, 1H), 6.67 (d, $J = 8.9$ Hz, 1H), 6.57 - 6.53 (m, 1H), 4.40 (s, 2H), 4.03 (t, $J = 8.6$ Hz, 2H), 3.79 (s, 3H), 3.21 (t, $J = 8.7$ Hz, 2H).

Example 19: Preparation of Compound 4,6-difluoro-*N*-(3-fluoro-5-methoxybenzyl)-5-(1*H*-pyrazol-4-yl)indoline-1-carboxamide (T228)



1 Preparation of compound 4,6-difluoroindoline (T228-1)

4, 6-difluoro-1*H*-indole (1.68 g) was dissolved in anhydrous dichloromethane (36 mL), and triethylsilane (3.55 g, 30.56) was added. The mixture was cooled to 0 °C, and trifluoroacetic acid (18 mL) was added dropwise. After the dropwise addition was completed, the resulting mixture was warmed to room temperature and reacted for 4 h. After the reaction was completed, saturated aqueous sodium carbonate solution was added to adjust the pH to 10, and dichloromethane (30 mL × 3) was added for extraction. The organic phases were combined, washed with saturated brine (30 mL), dried over anhydrous sodium sulfate, filtered and concentrated by rotary evaporation, and the resulting crude product was purified by silica gel

column chromatography (12 g, petroleum ether:ethyl acetate = 10:1) to give the product T228-1 (900 mg, 52.6% yield). LC-MS $[M+H]^+$: 156.0.

2 Preparation of compound 5-bromo-4,6-difluoroindoline (T228-2)

Compound T228-1 (800 mg) was dissolved in anhydrous acetonitrile (8 mL), and the mixture was cooled to 0 °C and a solution of *N*-bromosuccinimide (551 mg) in anhydrous acetonitrile (5 mL) was added dropwise. After the dropwise addition was completed, the mixture was controlled to be 0 °C and reacted for 25 min. After the reaction was completed, saturated sodium bicarbonate solution (20 mL) was added to quench the reaction, and ethyl acetate (20 mL × 3) was added for extraction. The organic phases were combined, washed with saturated brine (30 mL), dried over anhydrous sodium sulfate, filtered and concentrated by rotary evaporation, and the residue was purified by silica gel column chromatography (4 g, petroleum ether:ethyl acetate = 15:1) to give compound T228-2 (400 mg, 29.8% yield). LC-MS $[M+H]^+$: 233.9.

3 Preparation of compound *p*-nitrophenyl 5-bromo-4,6-difluoroindoline-1-carboxylate (T228-3)

p-nitrophenyl chloroformate (388 mg) was dissolved in anhydrous tetrahydrofuran (5 mL) under nitrogen atmosphere, and a solution of compound T228-2 (300 mg) and pyridine (304 mg) in tetrahydrofuran (5 mL) was added dropwise. The mixture was stirred overnight at room temperature. The reaction solution was directly used in the next step without treatment. LC-MS $[M+H]^+$: 398.9.

4 Preparation of compound 5-bromo-4,6-difluoro-*N*-(3-fluoro-5-methoxybenzyl)indoline-1-carboxamide (T228-4)

(3-fluoro-5-methoxyphenyl)methylamine (398 mg) and triethylamine (388 mg) were added to the reaction solution obtained in the previous step, and the mixture was heated under reflux for 4 h. After the reaction was completed, water (30 mL) was added to quench the reaction, and ethyl acetate (20 mL × 3) was added for extraction. The organic phases were combined, washed with saturated brine (30 mL), dried over sodium sulfate, filtered and concentrated by rotary evaporation, and the residue was purified by silica gel column chromatography (4 g, dichloromethane:ethyl acetate = 5:1) to give the product T228-4 (210 mg, 35.5%). LC-MS $[M+H]^+$: 414.8.

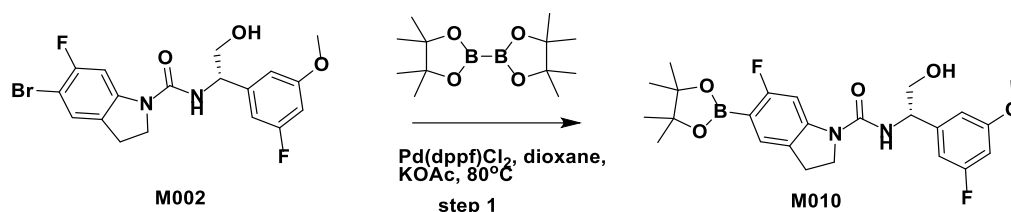
5 Preparation of compound 4,6-difluoro-*N*-(3-fluoro-5-methoxybenzyl)-5-(1*H*-pyrazol-4-yl)indoline-1-carboxamide (T228)

Compound T228-4 (210 mg), *tert*-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole-1-carboxylate (223 mg), [1,1'-

5 bis(diphenylphosphino)ferrocene]dichloropalladium(II) (75 mg) and potassium carbonate (211 mg) were dissolved in a mixed solution of 1,4-dioxane (5 mL) and water (1 mL) under nitrogen atmosphere, and the mixture was stirred overnight at 80 °C. The reaction solution was filtered, and the filtrate was concentrated by rotary evaporation. The residue was purified by silica gel column chromatography (4 g, dichloromethane:ethyl acetate = 1:1), purified by preparative
10 chromatography (chromatographic column: -Gemini-C18, 150 × 21.2 mm, 5μm; mobile phase: ACN-H₂O (0.05% NH₃); gradient: 20–70) and then lyophilized to give the pure product (21.2 mg, 7.3% yield). LC-MS [M+H]⁺: 403.1.

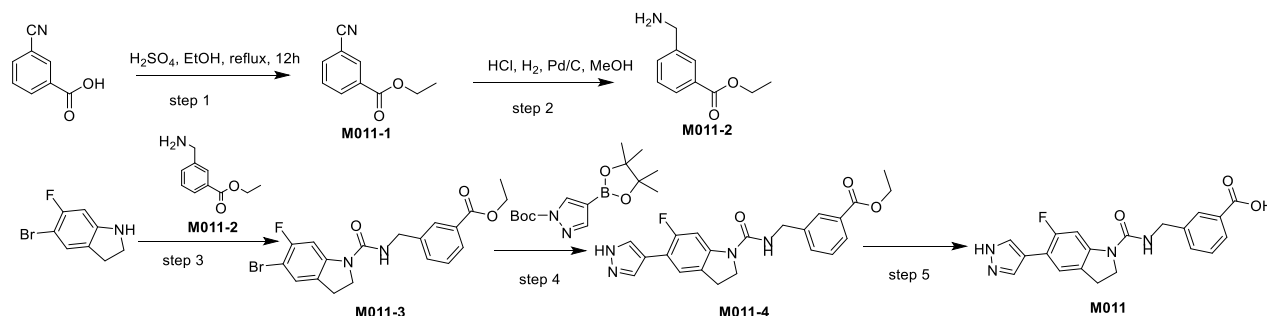
¹H NMR (301 MHz, CDCl₃) δ 8.07 (s, 2H), 7.67 (d, J = 12.4 Hz, 1H), 6.69 (s, 1H), 6.67 (d, J = 11.0 Hz, 1H), 6.55 (d, J = 10.5 Hz, 1H), 4.91 (t, J = 4.5 Hz, 1H), 4.49 (d, J = 5.4 Hz, 2H),
15 4.03 (t, J = 8.6 Hz, 2H), 3.81 (s, 3H), 3.26 (t, J = 8.5 Hz, 1H).

For Example 20, reference was made to the preparation method of Example 19 above to obtain the following compounds:



A solution of compound M002 (200 mg), 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (238 mg) and potassium acetate (138 mg) were dissolved in dioxane (4 mL) under nitrogen atmosphere, and [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (34 mg) was added. The mixture was reacted at 80 °C for 6 h. The reaction solution was concentrated under reduced pressure to give the compound (crude product), MS (M+H)⁺ = 475.3.

10 Example 32: Preparation of Intermediate 11, Compound 3-((6-fluoro-5-(1*H*-pyrazol-4-yl)indoline-1-carboxamido<oxalylamino>methyl)benzoic acid (M011)



(1) Preparation of compound ethyl 3-cyanobenzoate (M011-1)

3-cyanobenzoic acid (3.0 g) was dissolved in ethanol (30 mL), and concentrated sulfuric acid (3 mL) was added. The mixture was stirred under reflux for 12 h. The reaction solution was concentrated under reduced pressure, diluted with water (50 mL) and extracted with ethyl acetate (30 mL × 2). The organic phases were combined, washed with saturated brine (30 mL), dried over anhydrous sodium sulfate, filtered and concentrated, and the residue was purified by silica gel column chromatography (PE/EA = 10/1) to give a yellow oily liquid (2.0 g, 57% yield). LC-MS [M+H]⁺: 176.0.

(2) Preparation of compound ethyl 3-(aminomethyl)benzoate (M011-2)

Compound M011-1 (2.0 g) was dissolved in methanol (20 mL), and 5% Pd/C (500 mg) and concentrated hydrochloric acid (1 mL) were added. The mixture was stirred overnight at room

temperature under hydrogen atmosphere. The reaction solution was filtered and concentrated by rotary evaporation, and the resulting solid was dissolved in dichloromethane (50 mL), followed by addition of sodium carbonate solution (20 mL, 2 N). The mixture was stirred at room temperature for 30 min, washed with water (20mL $\times$ 3), dried over anhydrous sodium sulfate and concentrated to give a yellow oily liquid (2.0 g, crude product). LC-MS $[M+H]^+$: 180.0.

(3) Preparation of compound ethyl 3-((5-bromo-6-fluoroindoline-1-carboxamido<oxalylamino>)methyl)benzoate (M011-3)

5-bromo-6-fluoroindoline (1000 mg) was dissolved in tetrahydrofuran (15 mL), and 4-nitrophenyl chlorate (1400 mg) and pyridine (1098 mg) were added. The mixture was reacted overnight at room temperature. Compound M011-2 (1244 mg) and DIEA (1791 mg) were added to the reaction solution, and the resulting mixture was reacted at 70 °C for 12 h. Water (30 mL) was added to quench the reaction, and ethyl acetate (30 mL $\times$ 3) was added for extraction. The organic phases were combined, washed with saturated brine (30 mL), dried over anhydrous sodium sulfate, filtered and concentrated, and the residue was separated by silica gel column chromatography (PE/EA = 3/1) to give a yellow solid (800 mg, 41% yield). LC-MS $[M+H]^+$: 422.9.

(4) Preparation of compound ethyl 3-((6-fluoro-5-(1H-pyrazol-4-yl)indoline-1-carboxamido<oxalylamino>)methyl)benzoate (M011-4)

Compound M011-3 (800 mg) was dissolved in 1,4-dioxane (10 mL) and water (2 mL) under nitrogen atmosphere, and *tert*-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole-1-carboxylate (840 mg), Pd(dppf)Cl₂ (118 mg) and potassium carbonate (788 mg) were added. The mixture was reacted overnight at 90 °C. The reaction solution was diluted with water (25 mL) and extracted with ethyl acetate (30mL $\times$ 3). The organic phases were combined, washed with saturated brine (30 mL), dried over anhydrous sodium sulfate, filtered and concentrated, and the residue was separated by column chromatography (PE/EA = 3/1) to give a white solid (500 mg, 64% yield), MS $[M/2 + H]^+ = 408.8$.

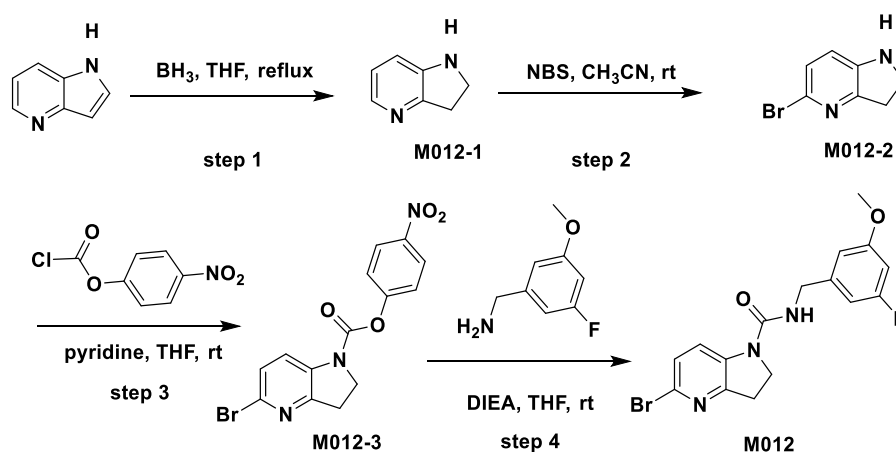
(5) Preparation of compound 3-((6-fluoro-5-(1H-pyrazol-4-yl)indoline-1-carboxamido<oxalylamino>)methyl)benzoic acid (M011)

Compound M011-4 (500 mg) was dissolved in tetrahydrofuran/methanol (1/1 = 8 mL), and

sodium hydroxide solution (2 N, 3 mL) was added. The mixture was stirred overnight at room temperature. The pH was adjusted to 5–6 with concentrated hydrochloric acid, and the reaction solution was directly concentrated under reduced pressure to give a white liquid (650 mg, crude product). LC-MS $[M+H]^+$: 481.0.

5

Example 33: Preparation of Intermediate 12, Compound 5-bromo-*N*-(3-fluoro-5-methoxybenzyl)-2,3-dihydro-1*H*-pyrrolo(3,2-*b*)pyridine-1-carboxamide (M012)



(1) Preparation of compound 2,3-dihydro-1*H*-pyrrolo(3,2-*b*)pyridine (M012-1)

10 1*H*-pyrrolo(3,2-*b*)pyridine (2.00 g) was dissolved in anhydrous tetrahydrofuran (50 mL), and a solution of borane in tetrahydrofuran (51 mL, 1 M) was added under nitrogen atmosphere. The mixture was heated under reflux and stirred for 4 h. The reaction solution was cooled to room temperature, and in an ice water bath, methanol was slowly added dropwise to quench the reaction. Then the reaction solution was concentrated under reduced pressure. The residue was dissolved in methanol (50 mL), and the mixture was refluxed overnight. The reaction solution was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (DCM:MeOH = 20:1) to give a yellow solid (1.00 g, 49% yield). MS $(M+H)^+$ = 121.1.

(2) Preparation of compound 5-bromo-2,3-dihydro-1*H*-pyrrolo(3,2-*b*)pyridine (M012-2)

20 Compound M012-1 (1.00 g) was dissolved in anhydrous acetonitrile (30 mL), and a solution of *N*-bromosuccinimide (1.63 g) in acetonitrile (10 mL) was slowly added dropwise. The mixture was stirred at room temperature for 3 h. Water (30 mL) was added, and ethyl acetate (20 mL × 3) was added for extraction. The organic phases were combined, washed with saturated brine (20 mL), dried over anhydrous sodium sulfate, filtered and concentrated, and the resulting crude

product was purified by silica gel column chromatography (PE:EA = 2:1) to give a greyish-green solid (0.81 g, 48% yield). MS (M+H)⁺ = 199.1.

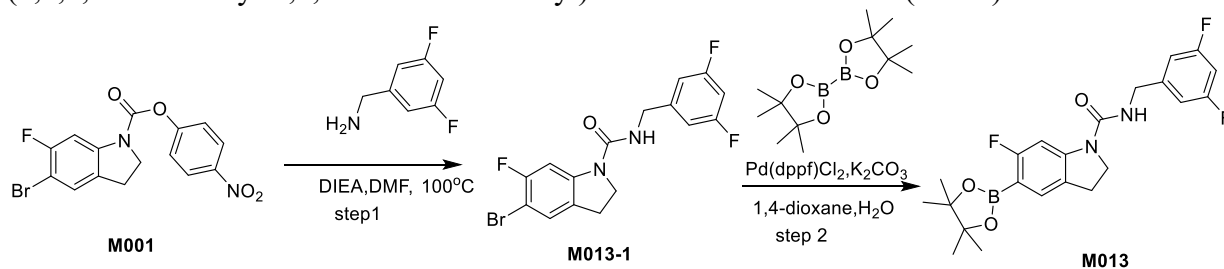
(3) Preparation of compound 4-nitrophenyl-5-bromo-2,3-dihydro-1*H*-pyrrolo(3,2-*b*)pyridine-1-carboxylic acid (M012-3)

5 4-nitrophenyl chloroformate (607 mg) was dissolved in THF (8 mL), and then a solution of compound M012-2 (500 mg) and pyridine (596 mg) in THF (2 mL) was added dropwise under nitrogen atmosphere. The mixture was stirred overnight at room temperature. After the reaction was complete as detected by LCMS, the reaction solution was directly used in the next step without treatment. MS (M+H)⁺ = 364.0.

10 (4) Preparation of compound 5-bromo-*N*-(3-fluoro-5-methoxybenzyl)-2,3-dihydro-1*H*-pyrrolo(3,2-*b*)pyridine-1-carboxamide (M012)

N,N-diisopropylethylamine (1616 mg) and (3-fluoro-5-methoxyphenyl)methylamine (621 mg) were added to the reaction solution obtained in the previous step, and the mixture was stirred overnight at room temperature. The reaction solution was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (PE:EA = 3:1) to give a yellow solid (950 mg, 98% two-step yield). MS (M+H)⁺ = 380.0.

Example 34: Preparation of Intermediate 13, Compound *N*-(3,5-difluorobenzyl)-6-fluoro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)indoline-1-carboxamide (M013)



(1) Preparation of compound 5-bromo-*N*-(3,5-difluorobenzyl)-6-fluoroindoline-1-carboxamide (M013-1)

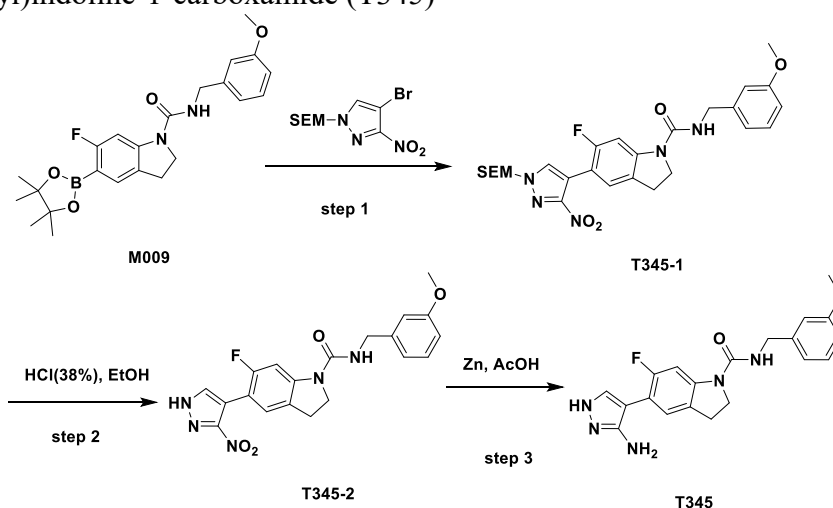
Compound M001 (1000 mg) and (3,5-difluorophenyl)methylamine (450 mg) were dissolved in dimethylformamide (10 mL), and the mixture was mixed well by stirring, followed by addition of diisopropylethylamine (1693 mg). The resulting mixture was stirred at 100 °C for 1 h. The reaction solution was diluted with water (50 mL) and extracted with ethyl acetate (20 mL × 3). The organic phases were combined, washed with saturated brine (20 mL), dried over anhydrous

sodium sulfate and concentrated under reduced pressure, and the resulting crude product was purified by column chromatography (petroleum ether:ethyl acetate = 5:1) to give compound M013-1 in the form of a white solid (860 mg, 80.96% yield). MS (M+H)⁺ = 382.2.

(2) Preparation of compound *N*-(3,5-difluorobenzyl)-6-fluoro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)indoline-1-carboxamide (M013)

Compound M013-1 (860 mg) was dissolved in anhydrous 1,4-dioxane (15 mL) under nitrogen atmosphere, and 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (1698.85 mg), potassium acetate (875.409 mg) and [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (244.754 mg) were added. The mixture was reacted at 90 °C for 4 h. After the reaction was completed, the reaction solution was filtered and concentrated by rotary evaporation, and the resulting crude product was purified by column chromatography (petroleum ether:dichloromethane = 15:1) to give compound M013 in the form of a brown oil (350 mg, 34.49% yield). MS (M+H)⁺ = 433.3.

Example 35: Preparation of Compound 5-(3-amino-1*H*-pyrazol-4-yl)-6-fluoro-*N*-(3-methoxybenzyl)indoline-1-carboxamide (T345)



Preparation of compound 6-fluoro-*N*-(3-methoxybenzyl)-5-(3-nitro-1-(((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazol-4-yl)indoline-1-carboxamide (T345-1)

Compound M009 (800 mg), 4-bromo-3-nitro-1-(((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazole (544 mg), anhydrous potassium carbonate (1040 mg) and [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (137 mg) were added to 1,4-dioxane/water (20:1, 10 mL) under nitrogen atmosphere. The mixture was stirred at 80 °C for

2 h in an oil bath. After the reaction was completed, the reaction solution was diluted with water (50 mL) and extracted with ethyl acetate (30 mL $\times$ 3). The organic phases were combined, washed with saturated brine (20 mL), dried over anhydrous sodium sulfate, filtered and concentrated, and the residue was purified by silica gel column chromatography (petroleum ether:ethyl acetate = 20:1) to give a yellow oil (650 mg, 63.9% yield), MS (M+H)⁺ = 542.1.

2 Preparation of compound 6-fluoro-*N*-(3-methoxybenzyl)-5-(3-nitro-1*H*-pyrazol-4-yl)indoline-1-carboxamide (T345-2)

Compound T345-1 (650 mg) was dissolved in ethanol (10 mL), and concentrated hydrochloric acid (1 mL) was added. The mixture was stirred under reflux in an oil bath for 5 h, and after the reaction was completed as detected by liquid mass spectrometry, the reaction solution was directly used in the next step without treatment. MS (M+H)⁺ = 412.1.

3 Preparation of compound 5-(3-amino-1*H*-pyrazol-4-yl)-6-fluoro-*N*-(3-methoxybenzyl)indoline-1-carboxamide (T345)

Activated zinc powder (798 mg) was added to the reaction solution obtained in the previous step in an ice bath, and then acetic acid (3 mL) was added. The mixture was warmed to room temperature and stirred for 2 h. The reaction solution was concentrated under reduced pressure, and then saturated sodium bicarbonate (10 mL) was added and ethyl acetate (5 mL $\times$ 3) was added for extraction. The organic phases were combined, dried over anhydrous sodium sulfate, filtered and concentrated, and the resulting crude product was purified by silica gel column chromatography (dichloromethane:methanol = 20:1) to give a white solid (98 mg, 21.4% two-step yield), MS (M+H)⁺ = 382.2.

¹H NMR (400 MHz, DMSO) δ 11.69 (s, 1H), 7.61 (d, *J* = 12.9 Hz, 1H), 7.46 (s, 1H), 7.31 (dd, *J* = 11.5, 6.1 Hz, 2H), 7.24 (t, *J* = 8.0 Hz, 1H), 6.93 – 6.87 (m, 2H), 6.80 (dd, *J* = 7.3, 1.9 Hz, 1H), 4.59 (s, 2H), 4.31 (d, *J* = 5.8 Hz, 2H), 3.99 (t, *J* = 8.7 Hz, 2H), 3.74 (s, 3H), 3.12 (t, *J* = 8.5 Hz, 2H).

Example 36: Preparation of Compound 6-fluoro-*N*-(1-(3-fluoro-5-methoxyphenyl)ethyl)-5-(1*H*-pyrazol-4-yl)indoline-1-carboxamide (T341)

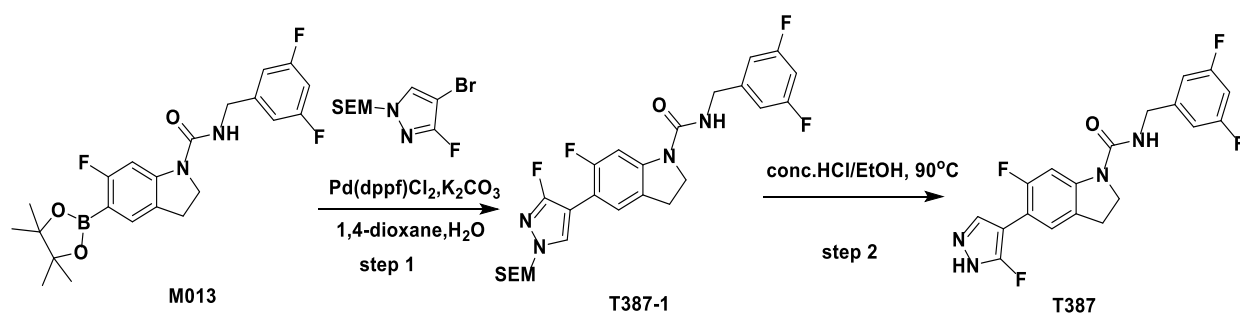
1,4-dioxane (3 mL) and water (0.5 mL) under nitrogen atmosphere, and compound T380-3 (500 mg), potassium carbonate (296 mg) and [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (78 mg) were added. The mixture was reacted at 80 °C for 3 h. The reaction solution was cooled to room temperature, water (30 mL) was added, and then ethyl acetate (30 mL × 3) was added for extraction. The organic phases were combined, washed with saturated brine (30 mL × 2), dried over anhydrous sodium sulfate, filtered and concentrated by rotary evaporation, and the resulting crude product was purified by silica gel column chromatography (eluent: petroleum ether:ethyl acetate = 2:1) to give compound T380-4 (200 mg, 33.00% yield). MS $[M+H]^+ = 555.3$.

5 Preparation of compound *N*-(3-(cyclopropylmethoxy)benzyl)-6-fluoro-5-(3-fluoro-1*H*-pyrazol-4-yl)indoline-1-carboxamide (T380)

Compound T380-4 (210 mg) was dissolved in dichloromethane (5 mL), and trifluoroacetic acid (2 mL) was added. The mixture was reacted at room temperature for 5 h. After the reaction was completed, the reaction solution was directly concentrated by rotary evaporation, and the resulting crude product was purified by high pressure liquid phase chromatography to give compound T380 in the form of a white solid (14.4 mg, 8.92% yield). MS $[M+H]^+ = 425.1$.

¹H NMR (400 MHz, DMSO) δ 12.61 (s, 1H), 7.90 (s, 1H), 7.65 (d, *J* = 12.9 Hz, 1H), 7.37 (t, *J* = 5.9 Hz, 1H), 7.31 (d, *J* = 7.7 Hz, 1H), 7.21 (t, *J* = 8.1 Hz, 1H), 6.91 – 6.84 (m, 2H), 6.78 (dd, *J* = 8.2, 1.5 Hz, 1H), 4.30 (d, *J* = 5.8 Hz, 2H), 4.01 (t, *J* = 8.7 Hz, 2H), 3.79 (d, *J* = 7.0 Hz, 2H), 3.15 (t, *J* = 8.6 Hz, 2H), 1.25 – 1.18 (m, 1H), 0.60 – 0.51 (m, 2H), 0.36 – 0.27 (m, 2H).

Example 51: Preparation of Compound *N*-(3,5-difluorobenzyl)-6-fluoro-5-(5-fluoro-1*H*-pyrazol-4-yl)indoline-1-carboxamide (T387)



1 Preparation of compound *N*-(3,5-difluorobenzyl)-6-fluoro-5-((3-fluoro-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazol-4-yl)indoline-1-carboxamide (T387-1)

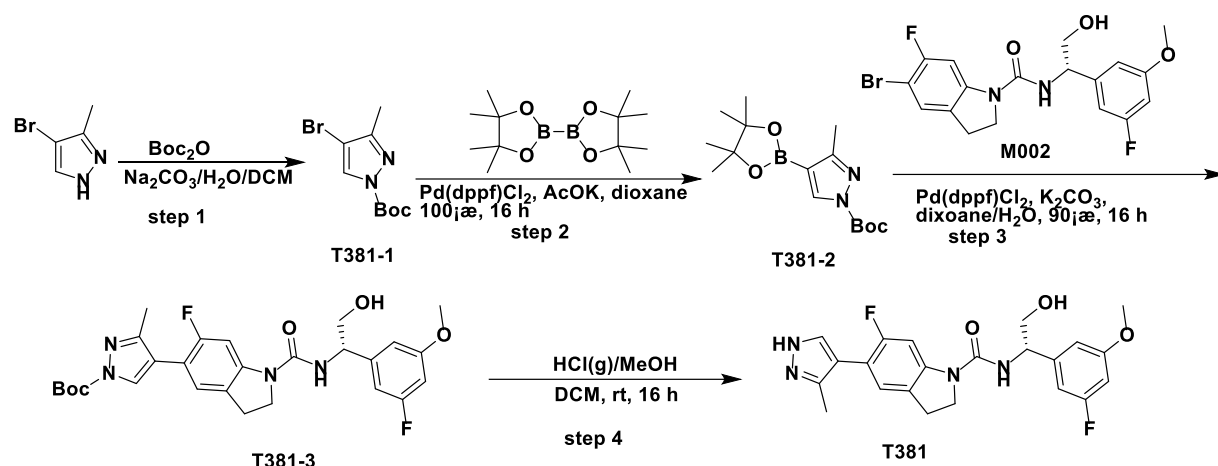
4-bromo-3-fluoro-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazole (172 mg) was dissolved in 1,4-dioxane (3 mL) and water (0.5 mL) under nitrogen atmosphere, and compound M013 (250
5 mg), potassium carbonate (240 mg) and [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (42 mg) were added. The mixture was reacted at 80 °C for 3 h. The reaction solution was cooled to room temperature, water (30 mL) was added, and then ethyl acetate (30 mL × 3) was added for extraction. The organic phases were combined, washed with saturated brine (30 mL × 2), dried over anhydrous sodium sulfate,
10 filtered and concentrated by rotary evaporation, and the resulting crude product was purified by silica gel column chromatography (eluent: petroleum ether:ethyl acetate = 2:1) to give compound T387-1 in the form of a yellow oil (100 mg, 32.40% yield). MS $[M+Na]^+ = 543.0$.

2 Preparation of compound *N*-(3,5-difluorobenzyl)-6-fluoro-5-(5-fluoro-1*H*-pyrazol-4-yl)indoline-1-carboxamide (T387)

15 Compound T387-1 (100 mg) was dissolved in ethanol (5 mL), and concentrated hydrochloric acid (1 mL) was added. The mixture was reacted at 90 °C for 1 h. After the reaction was completed, the reaction solution was directly concentrated by rotary evaporation, and the resulting crude product was dissolved in dichloromethane, basified with triethylamine and purified by preparative plate (petroleum ether:ethyl acetate = 1:1) to give compound T387 in
20 the form of a white solid (21.76 mg, 29.05% yield). MS $[M+H]^+ = 493.4$.

¹H NMR (400 MHz, DMSO) δ 12.61 (s, 1H), 7.90 (d, *J* = 1.6 Hz, 1H), 7.65 (d, *J* = 12.8 Hz, 1H), 7.46 (t, *J* = 5.9 Hz, 1H), 7.32 (d, *J* = 7.7 Hz, 1H), 7.13 – 7.02 (m, 3H), 4.35 (d, *J* = 5.8 Hz, 2H), 4.04 (t, *J* = 8.7 Hz, 2H), 3.16 (t, *J* = 8.6 Hz, 2H).

25 Example 52: Preparation of Compound *N*-(3-(difluoromethoxy)-5-fluorobenzyl)-6-fluoro-5-(1*H*-pyrazol-4-yl)indoline-1-carboxamide (T375)



1 Preparation of compound *tert*-butyl 4-bromo-3-methyl-1*H*-pyrazole-1-carboxylate (T381-1)

4-bromo-3-methylpyrazole (3.00 g) was dissolved in dichloromethane (30 mL), and sodium carbonate (10.32 g) and 4-dimethylaminopyridine (2.93 g) were added, and then di-*tert*-butyl dicarbonate (4.87 g) was added at room temperature. The mixture was reacted at room temperature for 16 h. Dichloromethane (50 mL) was added, and the mixture was washed with water (50 mL) and saturated brine (30 mL), dried over anhydrous sodium sulfate, filtered and concentrated to give a crude product in the form of a colorless oil (6 g). MS $[M+Na]^+ = 282.9/285.0$.

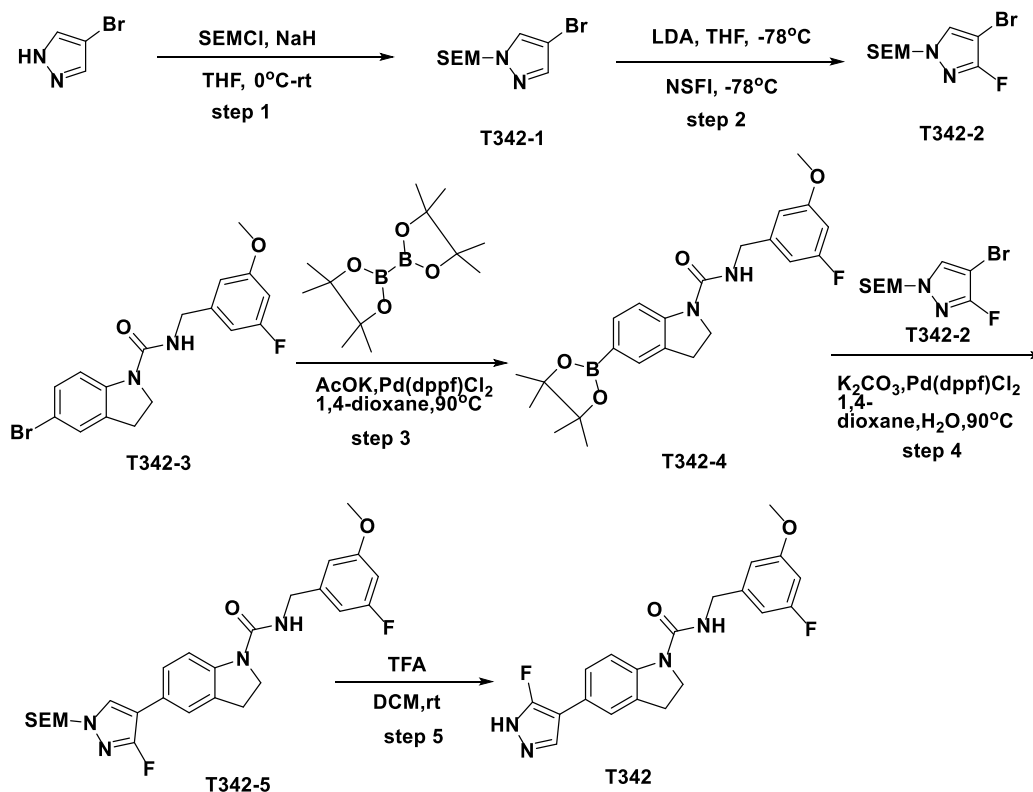
2 Preparation of compound *tert*-butyl 3-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole-1-carboxylate (T381-2)

Compound T381-1 (6.00 g), potassium acetate (2.69 g), bis(pinacolato)diboron (5.58 g) and [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (1.07 g) were added in a 250 mL single-necked flask, followed by addition of 1,4-dioxane (60 mL). The mixture was heated to 100 °C and reacted for 16 h under nitrogen atmosphere. The reaction solution was filtered and concentrated, and the resulting crude product was separated by silica gel column chromatography (petroleum ether:dichloromethane = 10:1) to give a colorless oil (3.50 g, 30% two-step yield). MS $[M-55]^-$: 252.9.

3 Preparation of compound *tert*-butyl (*S*)-4-(6-fluoro-1-((1-(3-fluoro-5-methoxyphenyl)-2-hydroxyethyl)carbamoyl)indolin-5-yl)-5-methyl-1*H*-pyrazole-1-carboxylate (T381-3)

Compound M002 (150 mg) and compound T381-2 (130 mg) were dissolved in dioxane (3 mL), and a solution of potassium carbonate (121 mg) in water (0.3 mL) and [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (26 mg) were added. The mixture was reacted at 90 °C for 16 h under nitrogen atmosphere. The reaction solution was extracted with

Example 73: Preparation of Compound 5-(5-fluoro-1*H*-pyrazol-4-yl)-*N*-(3-fluoro-5-methoxybenzyl)indoline-1-carboxamide (T342)



- 5 1 Preparation of compound 4-bromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazole (T342-1)

4-bromo-1*H*-pyrazole (10.0 g) was dissolved in anhydrous tetrahydrofuran (100 mL) under nitrogen atmosphere, and sodium hydride (60%, 4.1 g) was added at 0 °C. The mixture was reacted at 0 °C for 30 min, and then 2-(trimethylsilyl)ethoxymethyl chloride (12.0 g) was added.

- 10 The resulting mixture was reacted at room temperature for 16 h. After the reaction was completed, ice water (100 mL) was added to quench the reaction, and ethyl acetate (100 mL × 3) was added for extraction. The organic phases were combined, washed with saturated brine (100 mL × 2), dried over anhydrous sodium sulfate, filtered and concentrated by rotary evaporation to give compound T342-1 in the form of a yellow oil (13 g, crude product).

- 15 ¹H NMR (301 MHz, CDCl₃) δ 7.59 (s, 1H), 7.49 (s, 1H), 5.37 (s, 2H), 3.57 – 3.48 (m, 2H), 0.92 – 0.85 (m, 2H), 0.03 (s, 9H).

- 2 Preparation of compound 4-bromo-3-fluoro-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazole (T342-2)

Compound T342-1 (10.0 g) was dissolved in anhydrous tetrahydrofuran (50 mL), and lithium diisopropylamide (2 M, in tetrahydrofuran, 36 mL) was added dropwise at -78 °C under nitrogen atmosphere. After the dropwise addition was completed, the mixture was reacted at -78 °C for 1 h, and then *N*-fluorobisbenzenesulfonamide (22.7 g, dissolved in 50 mL of anhydrous tetrahydrofuran) was added dropwise. After the dropwise addition was completed, the resulting mixture was reacted at -78 °C for 1 h. Saturated ammonium chloride (60 mL) was added to quench the reaction, and ethyl acetate (100 mL × 3) was added for extraction. The organic phases were combined, washed with saturated brine (100 mL × 2), dried over anhydrous sodium sulfate, filtered and concentrated by rotary evaporation. The resulting crude product was purified by silica gel column chromatography (25 g; eluent: petroleum ether:ethyl acetate = 80:1) to give compound T342-2 in the form of a yellow oil (1.0 g, 9.4% yield).

¹H NMR (301 MHz, CDCl₃) δ 7.40 (d, *J* = 2.4 Hz, 1H), 5.36 (s, 2H), 3.65 – 3.58 (m, 2H), 0.97 – 0.85 (m, 2H), 0.01 (s, 9H).

3 Preparation of compound *N*-(3-fluoro-5-methoxybenzyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)indoline-1-carboxamide (T342-4)

Compound T342-3 (170 mg) was dissolved in anhydrous 1,4-dioxane (2 mL) under nitrogen atmosphere, and 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (144 mg), potassium acetate (90 mg) and [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (17 mg) were added. The mixture was reacted at 90 °C for 3 h. The reaction solution was cooled to room temperature, filtered and concentrated by rotary evaporation to give compound T342-3 in the form of a yellow oil (200 mg, crude product).

MS [*M* + *H*]⁺ = 427.1.

4 Preparation of compound 5-(5-fluoro-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazol-4-yl)-*N*-(3-fluoro-5-methoxybenzyl)indoline-1-carboxamide (T342-5)

Compound T342-2 (150 mg) was dissolved in 1,4-dioxane (3 mL) and water (0.5 mL) under nitrogen atmosphere, and compound T342-4 (260 mg), potassium carbonate (140 mg) and [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (37.2 mg) were added. The mixture was reacted at 90 °C for 3 h. The reaction solution was cooled to room temperature, water (30 mL) was added, and then ethyl acetate (20 mL × 3) was added for extraction. The organic phases were combined, washed with saturated brine (20 mL × 2), dried over anhydrous sodium sulfate,

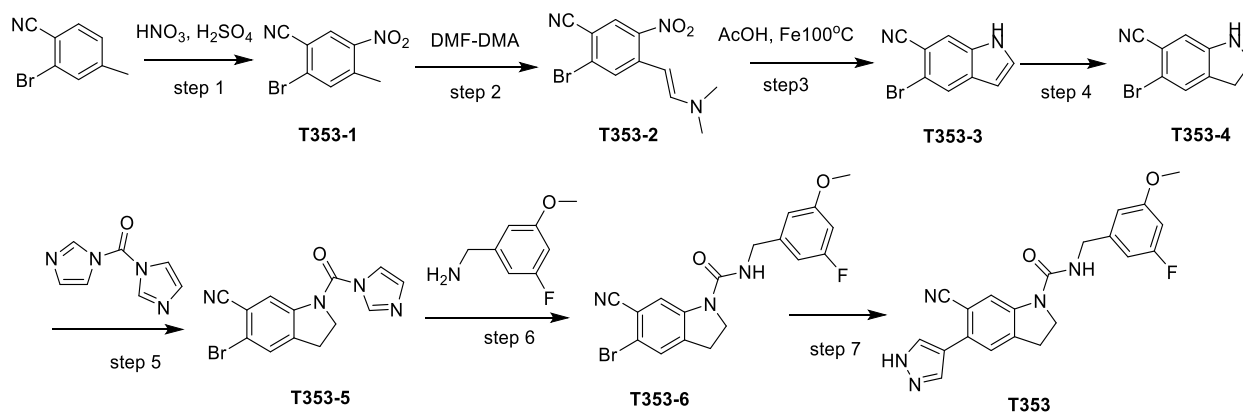
filtered and concentrated by rotary evaporation, and the resulting crude product was purified by silica gel column chromatography (eluent: petroleum ether:ethyl acetate = 2:1) to give compound T342-4 in the form of a yellow oil (100 mg, 38.24% yield). MS $[M+H]^+ = 457.1$.

5 Preparation of compound 5-(5-fluoro-1*H*-pyrazol-4-yl)-*N*-(3-fluoro-5-methoxybenzyl)indoline-1-carboxamide (T342)

Compound T342-5(100 mg) was dissolved in dichloromethane (2 mL), and trifluoroacetic acid (0.5 mL) was added. The mixture was reacted at room temperature for 2 h. After the reaction was completed, the reaction solution was directly concentrated by rotary evaporation, and the resulting crude product was purified by high pressure liquid phase chromatography to give
10 compound T342 in the form of a white solid (3.5 mg, 4.7% yield). MS $[M+H]^+ = 385.0$.

^1H NMR (400 MHz, MeOD) δ 7.86 - 7.83 (m, 2H), 7.41 (s, 1H), 7.34 (d, $J = 8.4$ Hz, 1H), 6.77 (s, 1H), 6.70 (d, $J = 9.4$ Hz, 1H), 6.58 (dt, $J = 10.8, 2.3$ Hz, 1H), 4.43 (s, 2H), 4.03 (t, $J = 8.7$ Hz, 2H), 3.81 (s, 3H), 3.25 (t, $J = 8.6$ Hz, 2H).

15 Example 74: Preparation of Compound 6-cyano-*N*-(3-fluoro-5-methoxybenzyl)-5-(1*H*-pyrazol-4-yl)indoline-1-carboxamide (T353)



1 Preparation of compound 2-bromo-4-methyl-5-nitrobenzonitrile (T353-1)

2-bromo-4-methylbenzonitrile (10.00 g) was dissolved in concentrated sulfuric acid (60 mL),
20 and concentrated nitric acid (20 mL) was added dropwise in an ice water bath. The mixture was stirred at room temperature for 2 h. After the reaction was completed, the reaction solution was poured into ice water (150 mL). The mixture was filtered and washed with water, and the precipitate was collected. The resulting crude product was separated by silica gel column chromatography (petroleum ether/ethyl acetate = 20:1) to give a white solid (9.50 g, 70% yield).

LC-MS $[M+H]^+ = 241.2$.

2 Preparation of compound (*E*)-2-bromo-4-(2-(dimethylamino)vinyl)-5-nitrobenzonitrile (T353-2)

Compound T353-1 (9.00 g) was dissolved in *N,N*-dimethylformamide (80 mL), and *N,N*-dimethylformamide dimethyl acetal (11.11g) was added. The mixture was stirred at 100 °C for 2 h under nitrogen atmosphere. After the reaction was completed, the reaction solution was concentrated to give a tan solid (13.40 g, with a product content of about 80%). and the crude product was directly used in the next step. LC-MS $[M + H]^+ = 296.1$.

3 Preparation of compound 5-bromo-1*H*-indole-6-carbonitrile (T353-3)

Compound T353-2 (11.00 g) was dissolved in acetic acid (50 mL), and iron powder (34.24 g) was added. The mixture was stirred at 100 °C for 12 h under nitrogen atmosphere. After the reaction was completed, the reaction solution was filtered to remove the iron powder and concentrated under reduced pressure. Saturated sodium carbonate solution (30 mL) was added, and ethyl acetate (50 mL × 2) was added for extraction. The organic phases were combined, washed with saturated brine (50 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The resulting crude product was separated by silica gel column chromatography (PE/EA = 8:1) to give a white solid (1.40 g, 17% yield). LC-MS $[M+H]^+ = 220.6$.

4 Preparation of compound 5-bromoindoline-6-carbonitrile (T353-4)

Compound T353-3 (1.40 g) was dissolved in dichloromethane (15 mL), and triethylsilane (3.66 g) and trifluoroacetic acid (7.5 mL) were added. The mixture was stirred at 45 °C for 4 h. The reaction solution was concentrated under reduced pressure, saturated sodium carbonate solution (25 mL) was added, and ethyl acetate (20 mL × 4) was added for extraction. The organic phases were combined, washed with saturated brine (20 mL × 2), dried over anhydrous sodium sulfate, filtered and concentrated. The resulting crude product was separated by silica gel column chromatography (petroleum ether:ethyl acetate = 8:1) to give a white solid (0.80 g, 51% yield). LC-MS $[M + H]^+ = 223.1$.

5 Preparation of compound 5-bromo-1-(1*H*-imidazole-1-carbonyl)indoline-6-carbonitrile (T353-5)

Compound T353-4 (300 mg) was dissolved in acetonitrile (3 mL), and 1-[(imidazol-1-yl)carbonyl]imidazole (326 mg) and 4-dimethylaminopyridine (327 mg) were added. The

mixture was stirred at 90 °C for 12 h under nitrogen atmosphere. After the reaction was completed, the reaction solution was concentrated under reduced pressure to give a brown solid (1.10 g). LC-MS $[M+H]^+ = 317.0$.

6 Preparation of compound 5-bromo-6-cyano-*N*-(3-fluoro-5-methoxybenzyl)indoline-1-carboxamide (T353-6)

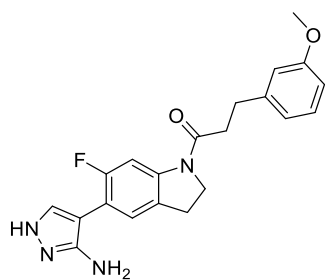
T353-5 (1.10 g, crude product) was dissolved in anhydrous *N,N*-dimethylformamide (5 mL), and (3-fluoro-5-methoxyphenyl)methylamine (0.42 g) and triethylamine (0.48 g) were added. The mixture was stirred at 90 °C for 12 h under nitrogen atmosphere. Water (30 mL) was added to quench the reaction, and ethyl acetate (20 mL × 3) was added for extraction. The organic phases were combined, washed with saturated brine (20 mL × 2), dried over anhydrous sodium sulfate, filtered and concentrated. The resulting crude product was separated by silica gel column chromatography (PE/EA = 1:1) to give a white solid (130 mg, 22% yield). LC-MS $[M+H]^+ = 404.2$.

7 Preparation of compound 6-cyano-*N*-(3-fluoro-5-methoxybenzyl)-5-(1*H*-pyrazol-4-yl)indoline-1-carboxamide (T353)

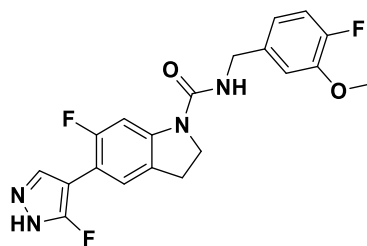
Compound T353-6 (100 mg) was dissolved in 1,4 dioxane and water (5/1, 7.2 mL), and *tert*-butyl [4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazol-1-yl]carboxylate (148 mg), potassium carbonate (104 mg) and [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (18 mg) were added. The mixture was stirred at 90 °C for 12 h under nitrogen atmosphere. The reaction solution was diluted with water (20 mL) and extracted with ethyl acetate (10 mL × 3). The organic phases were combined, washed with saturated brine (10 mL × 2), dried over anhydrous sodium sulfate, filtered and concentrated. The resulting crude product was separated by silica gel column chromatography (DCM/MeOH = 50/1) to give a white solid (23 mg, 26% yield). LC-MS $[M+H]^+ = 319.1$.

¹H NMR (400 MHz, DMSO) δ 13.09 (s, 1H), 8.15 (s, 1H), 8.06 (s, 1H), 7.95 (s, 1H), 7.55 (s, 1H), 7.48 (t, *J* = 5.8 Hz, 1H), 6.81 – 6.56 (m, 3H), 4.31 (d, *J* = 5.4 Hz, 2H), 4.03 (t, *J* = 8.6 Hz, 2H), 3.76 (s, 3H), 3.26 (t, *J* = 8.5 Hz, 2H).

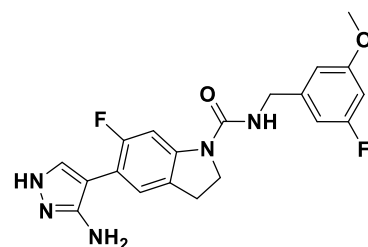
Example 75: Preparation of Compound *N*-(3-((cyclopropylmethyl)carbamoyl)-5-fluorobenzyl)-6-fluoro-5-(1*H*-pyrazol-4-yl)indoline-1-carboxamide (T378)



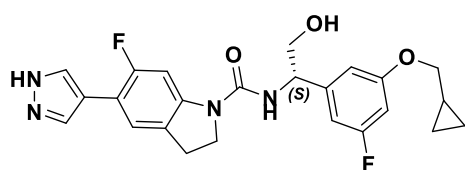
T383



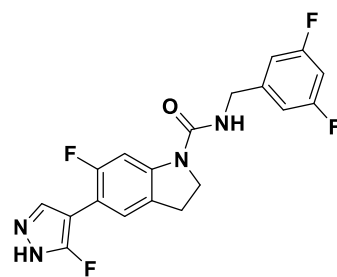
T384



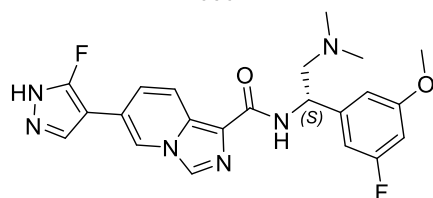
T385



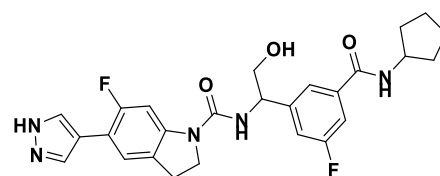
T386



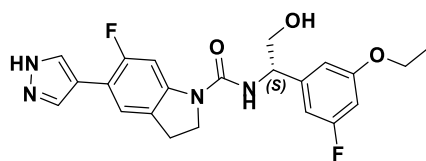
T387



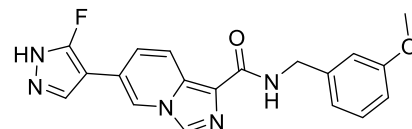
T388



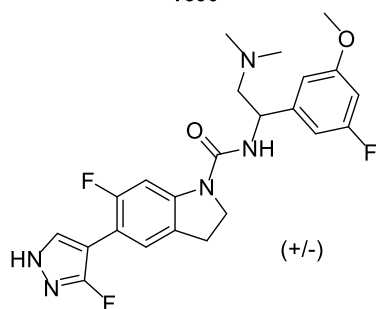
T389



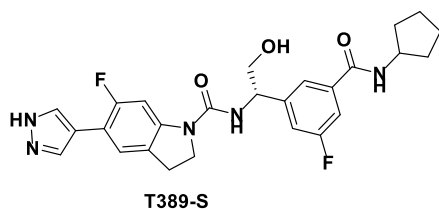
T390



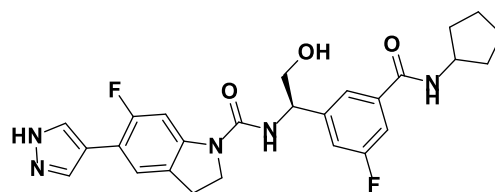
T391



T388'



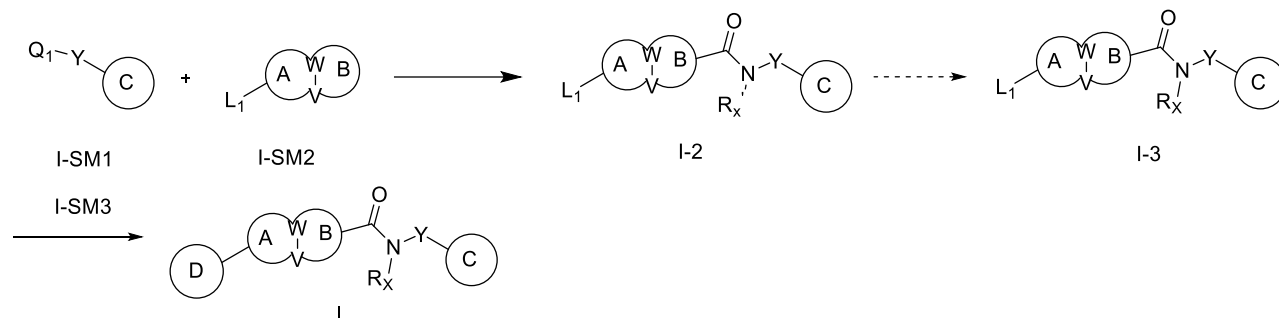
T389-S



T389-R

7. A method for preparing the compound of formula (I) or the racemate, the stereoisomer, the tautomer, the nitrogen oxide, the isotopically labeled compound, the solvate, the polymorph, the metabolite, the ester, the pharmaceutically acceptable salt or the prodrug thereof according to any one of claims 1–5, comprising at least one of the following schemes:

5 scheme 1:



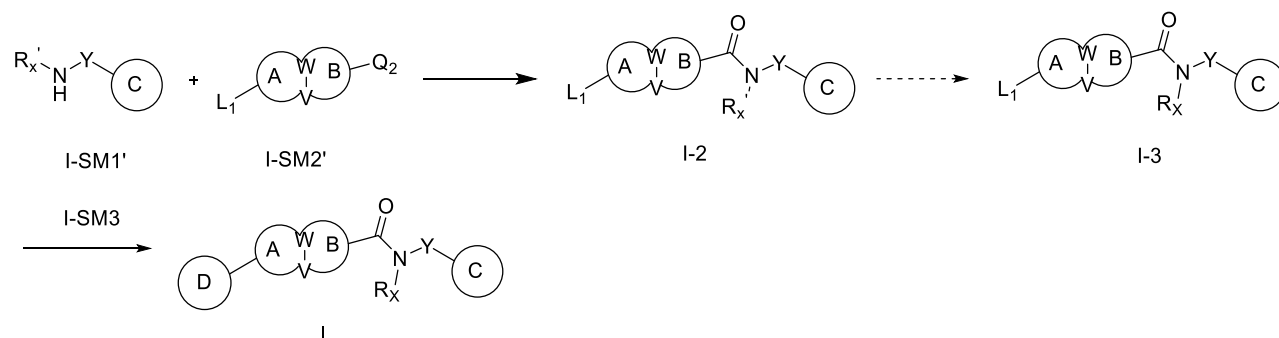
a1) reacting a compound I-SM1 with a compound I-SM2 under an alkaline condition to obtain a compound I-2;

a2) optionally, further subjecting the compound I-2 to derivatization treatment of R_x' on amide nitrogen to obtain a compound I-3; and

a3) subjecting the compound I-2 or I-3 and a compound I-SM3 to Suzuki coupling reaction to obtain a compound I;

wherein, ring A, ring B, ring C, ring D, W, V, Y and R_x are defined as in the formula (I) above; R_x' is selected from R_x and a group which can be converted to R_x by derivatization step (a2); L₁ is selected from halogen, and the halogen can be selected from F, Cl, Br and I; the group Q₁ is an isocyanate group or -N(R_x')-active formate group; the compound I-SM3 is borate containing a ring D group;

scheme 2:



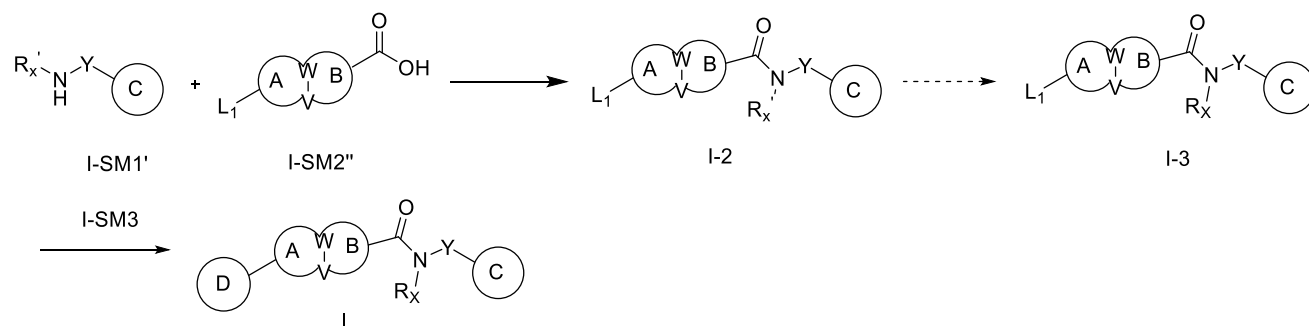
b1) reacting a compound I-SM1' with a compound I-SM2' under an alkaline condition to obtain a compound I-2;

b2) optionally, further subjecting the compound I-2 to derivatization treatment of R_x' on amide nitrogen to obtain a compound I-3; and

b3) subjecting the compound I-2 or I-3 and a compound I-SM3 to Suzuki coupling reaction to obtain a compound I;

- 5 wherein, ring A, ring B, ring C, ring D, W, V, Y and R_x are defined as in the formula (I) above; R_x' is selected from R_x and a group which can be converted to R_x by derivatization step (b2); L_1 is selected from halogen, and the halogen can be selected from F, Cl, Br and I; the group Q2 is an active formate group; the compound I-SM3 is borate containing a ring D group;

10 or scheme 3:



c1) reacting a compound I-SM1' with a compound I-SM2'' under an alkaline condition to obtain a compound I-2;

c2) optionally, further subjecting the compound I-2 to derivatization treatment of R_x' on amide nitrogen to obtain a compound I-3; and

c3) subjecting the compound I-2 or I-3 and a compound I-SM3 to Suzuki coupling reaction to obtain a compound I;

wherein, ring A, ring B, ring C, ring D, W, V, Y and R_x are selected from the definitions in the formula (I) above; R_x' is selected from R_x and a group which can be converted to R_x by derivatization step (c2); L_1 is selected from halogen, and the halogen can be selected from F, Cl, Br and I; the compound I-SM3 is borate containing a ring D group.

8. Use of at least one of the compound of formula (I) and the racemate, the stereoisomer, the tautomer, the nitrogen oxide, the isotopically labeled compound, the solvate, the polymorph, the metabolite, the ester, the pharmaceutically acceptable salt and the prodrug thereof according

to any one of claims 1–6 in preparing a medicament, wherein the medicament is an inhibitor of protein kinase.

9. The use according to claim 8, wherein the medicament is used for preventing or treating one
5 or more diseases caused by high expression of ROCK or excessive activation of ROCK;
preferably, the medicament is used for preventing or treating the following diseases:
cardiovascular and cerebrovascular diseases, neurological diseases, fibrosis diseases, ocular
diseases, tumors, arterial thrombotic disorders, radiation damage, respiratory diseases, and
autoimmune diseases, including atherosclerosis, acute coronary syndrome, hypertension,
10 cerebral vasospasm, cerebral ischemia, ischemic stroke, restenosis, heart disease, heart failure,
cardiac hypertrophy, myocardial ischemia-reperfusion injury, diabetes, diabetic nephropathy,
cancer, neuronal degeneration, nerve injury diseases, spinal cord injury, erectile dysfunction,
platelet aggregation, leukocyte aggregation, glaucoma, ocular hypertension, asthma,
osteoporosis, pulmonary fibrosis (such as idiopathic pulmonary fibrosis), hepatic fibrosis, renal
15 fibrosis, COPD, kidney dialysis, glomerulosclerosis, and neuronal degeneration inflammation.

10. A pharmaceutical composition, comprising a therapeutically effective amount of at least one
of the compound of formula (I) and the racemate, the stereoisomer, the tautomer, the nitrogen
oxide, the isotopically labeled compound, the solvate, the polymorph, the metabolite, the ester,
20 the pharmaceutically acceptable salt and the prodrug thereof according to any one of claims 1–
6, wherein

preferably, the pharmaceutical composition further comprises a pharmaceutically acceptable
auxiliary material; preferably, the auxiliary material is selected from at least one of the
following: a disintegrant, a glidant, a lubricant, a diluent, a filler, an adhesive and a colorant.

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11. A method for regulating Rho-kinase function, which comprises administering to an
individual in need thereof an effective amount of the compound of formula (I) or the racemate,
the stereoisomer, the tautomer, the nitrogen oxide, the isotopically labeled compound, the
solvate, the polymorph, the metabolite, the ester, the pharmaceutically acceptable salt or the

prodrug thereof according to claim 1.

12. A method for preventing or treating one or more diseases caused by high expression of ROCK or excessive activation of ROCK, which comprises administering to an individual in need thereof an effective amount of the compound of formula (I) or the racemate, the stereoisomer, the tautomer, the nitrogen oxide, the isotopically labeled compound, the solvate, the polymorph, the metabolite, the ester, the pharmaceutically acceptable salt or the prodrug thereof according to claim 1.

13. The method according to claim 12, wherein the disease is, for example, cardiovascular and cerebrovascular diseases, neurological diseases, fibrosis diseases, ocular diseases, tumors, arterial thrombotic disorders, radiation damage, respiratory diseases, and autoimmune diseases, including atherosclerosis, acute coronary syndrome, hypertension, cerebral vasospasm, cerebral ischemia, ischemic stroke, restenosis, heart disease, heart failure, cardiac hypertrophy, myocardial ischemia-reperfusion injury, diabetes, diabetic nephropathy, cancer, neuronal degeneration (peripheral or central), nerve injury diseases, spinal cord injury, erectile dysfunction, platelet aggregation, leukocyte aggregation, glaucoma, ocular hypertension, asthma, osteoporosis, pulmonary fibrosis (such as idiopathic pulmonary fibrosis), hepatic fibrosis, renal fibrosis, COPD, kidney dialysis (epithelial stability), glomerulosclerosis, neuronal degeneration inflammation, and the like.