

PYRIMIDINONE COMPOUNDS AND USES THEREOF

Technical Field

5 The present invention relates to pyrimidinone compounds, pharmaceutical compositions comprising same, methods for preparing same, and uses thereof.

Background Art

10 RIPK1 (receptor-interacting protein 1 kinase), a serine/threonine protein kinase, is an important cell signal transduction molecule. RIPK1, the first member of the RIP kinase family, was initially identified by Stanger et al. in 1995 through yeast two-hybrid experiments. The C terminal domain of RIPK1 is a death domain (DD), which can interact with Fas, a member of the death receptor family so that it was designated as receptor-interacting protein (Stanger BZ. et al., Cell. 1995, 81: 513-523). The N-terminal
15 serine/threonine-specific kinase domain, mediates autophosphorylation of RIPK1 at serine/threonine residue sites; while the C-terminal death domain, interacts with other death domain-containing proteins; the intermediate domain with RIP homotypic interaction motif (RHIM), is required for the interaction of RIPK1 and RIPK3 (Grootjans S, et al., Cell Death Differ. 2017, 24(7): 1184-1195).

20 Necroptosis as a new form of programmed cell death, regulated and controlled by intracellular signal factors are critical process in the organismal development and viability. Dysfunction of this process can result in a pathological mechanism that leads to a disease state. Necrosis can be triggered by a variety of triggers, including tumor necrosis factor (TNF α), Fas, TNF-related apoptosis-inducing ligand (TRAIL), interferon
25 (IFN), lipopolysaccharide (LPS), double-stranded RNA and DNA damage, endoplasmic reticulum stress, viral infection, and anti-cancer drugs. RIPK1 as the key molecule regulates apoptosis, necroptosis and inflammatory signaling pathways, and participates in many important biological processes such as embryonic development, hematopoietic system development, and maintenance of immune homeostasis (Ofengeim D, et al., Nat
30 Rev Mol Cell Biol. 2013, 14: 727-736). As in the necroptosis caused by TNF α , once TNF α binds to TNFR1, cytoplasmic domain of trimerized TNFR1 recruits multiple molecules including RIPK1, to activate the NF- κ B signaling pathway, leading to the

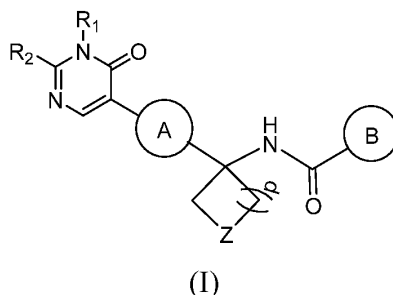
production of multiple cytokines and promoting cell survival (Kelliher MA, et al., Immunity. 1998, 8: 297-303). In the context of various cell types and microenvironments, RIPK1 recruits Fas-associated protein with death domain (FADD) and caspase 8 precursor to trigger apoptosis (Feoktistova M, et al., Mol Cell. 2011, 43: 449-463). When
5 the apoptosis pathway is inhibited, RIPK1 interacts with RIPK3 via the RHIM domain to facilitate the autophosphorylation of RIPK3. The autophosphorylated RIPK3, in turn, phosphorylates MLKL, thereby prompting MLKL to form trimers and to be translocated to the plasma membrane, causing cell membrane to swell and burst and the leakage of contents, leading to the initiation of necroptosis (Cai Z, et al., Nat Cell Biol. 2014, 16:
10 55-65). Therefore, regulating and controlling the kinase activity of RIPK1 can affect the inflammatory response triggered by apoptosis, programmed cell necrosis, and intracellular substances released after cell disruption.

Given the important roles RIPK1 plays in regulating and controlling cell death and in inflammation, RIPK1 has elicited significant interest in studying the potential
15 therapeutic benefit of selective RIPK1 inhibitors in a variety of diseases. Current studies have shown that RIPK1 inhibitors have potential therapeutic effects on a variety of diseases, such as central nervous system degenerative diseases, peripheral inflammation and autoimmune diseases. These diseases include multiple sclerosis (Ofengeim D, et al., Cell Rep. 2015, 10: 1836-1849), Huntington's disease (Zhu S, et al., Cell Death Dis. 2011,
20 2: e115-24), Alzheimer's disease (Caccamo A, et al., Nat Neurosci. 2017, 20: 1236-1246), Parkinson's disease (Lin QS, et al., Lab Invest. 2020, 100(3): 503-511), amyotrophic lateral sclerosis (Re DB, et al. Neuron. 2014, 81(5): 1001-1008), retinitis pigmentosa (Murakami Y, et al., Proc Natl Acad Sci U S A. 2012, 109(36): 14598-603), retinal degeneration (Jang KH, et al., Exp Eye Res. 2019, 180: 8-17), age-related macular
25 degeneration (AMD) (Murakami Y, et al., Cell Death Differ. 2013, 21: 270-7), inflammatory bowel disease including Crohn's disease and ulcerative colitis (Liu ZY, et al., Am J Cancer Res. 2015, 5(10): 3174-85), psoriasis (Duan X, et al., Cell Death Dis. 2020, 11(2): 134), rheumatoid arthritis (Jhun J, et al., J Transl Med. 2019, 17(1): 84), ischemia reperfusion injury of parenchymatous organs such as heart (Oerlemans MIFJ, et
30 al., Basic Res Cardiol. 2012, 107: 270), brain (Degterev A, et al., Nat. Chem. Biol. 2005, 1: 112-119) and kidney (Linkermann A, et al., Kidney Int. 2012, 81: 751-61), renal transplant rejection (Lau A, et al., Am J Transplant. 2013, 13: 2805-18), asthma (Zhang

H, et al., J Cell Physiol. 2019, 234(9): 15080-15088), chronic obstructive pulmonary disease (Mizumura K, et al., Respir Investig. 2016, 54(6): 407-412), non-alcoholic fatty liver disease (Majdi A, et al., J Hepatol. 2020, 72(4): 627-635), alcohol fatty liver disease (Wang S, et al., Oncotarget. 2016, 7: 17681-17698), arterosclerosis (Lin J, et al., Cell Rep. 2013, 3: 200-10; Karunakaran D, et al., FASEB J. 2018, 32(supplement): 38.1-38.1), sepsis/systemic inflammatory response syndrome (Duprez L, et al., Immunity. 2011, 35(6): 908-18), chemotherapy drugs induced organ injury (Xu Y, et al., J Am Soc Nephrol. 2015, 26(11): 2647-58), Gaucher's Disease (Vitter EB, et al., Nat Med. 2014, 20, 204-208), and malignancies (Wang W, et al., Cancer Cell. 2018, 34(5): 757-774; Strilic B, et al., Nature. 2016, 536(7615): 215-8). There are needs for new RIPK1 inhibitors for use in the treatment of these diseases, especially inflammatory diseases or autoimmune diseases. The present invention addresses such needs.

Summary of the Invention

Provided is a compound of formula (I):



or a pharmaceutically acceptable salt thereof, or a solvate, a racemic mixture, an enantiomer, a diastereomer or a tautomer thereof, wherein

R_1 is hydrogen, C_{1-6} alkyl, C_{1-6} haloalkyl, cyano-substituted C_{1-6} alkyl, $-(C_{1-6}$ alkylene) $_n$ - C_{3-6} cycloalkyl, $-(C_{1-6}$ alkylene) $_n$ -phenyl, $-(C_{1-6}$ alkylene) $_n$ -4-6 membered heterocyclyl or $-(C_{1-6}$ alkylene) $_n$ -5-6 membered heteroaryl; wherein the C_{3-6} cycloalkyl, phenyl, 4-6 membered heterocyclyl and 5-6 membered heteroaryl are each optionally substituted with one or more groups independently chosen from: halogen, -CN, -OH, -NH₂, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, -O(C_{1-6} alkyl), -O(C_{1-6} haloalkyl), -NH(C_{1-6} alkyl) and -N(C_{1-6} alkyl)₂;

R_2 is hydrogen, halogen, -CN, -NH₂, C_{1-6} alkyl, C_{1-6} haloalkyl, -O(C_{1-6} alkyl), -O(C_{1-6} haloalkyl), -NH(C_{1-6} alkyl) or -N(C_{1-6} alkyl)₂;

Z is O, NR₃ or CR₄R₅;

R₃ is hydrogen or C₁₋₆ alkyl;

R₄ and R₅ are each independently chosen from: hydrogen, halogen, -CN, -OH, C₁₋₆ alkyl, C₁₋₆ haloalkyl, -O(C₁₋₆ alkyl), -O(C₁₋₆ haloalkyl) and C₃₋₆ cycloalkyl;

5  is phenyl or 5-6 membered heteroaryl, each of which is optionally substituted with one or more groups independently chosen from: halogen, -CN, -OH, -NH₂, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, -O(C₁₋₆ alkyl), -O(C₁₋₆ haloalkyl), -NH(C₁₋₆ alkyl) and -N(C₁₋₆ alkyl)₂;

 is 5-12 membered heteroaryl, which is optionally substituted with one or
10 more groups independently chosen from: halogen, -CN, -OH, oxo, -NH₂, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, -O(C₁₋₆ alkyl), -O(C₁₋₆ haloalkyl), -NH(C₁₋₆ alkyl), -N(C₁₋₆ alkyl)₂, -(C₁₋₆ alkylene)_n-C₃₋₆ cycloalkyl, -(C₁₋₆ alkylene)_n-phenyl, -(C₁₋₆ alkylene)_n-4-6 membered heterocyclyl and -(C₁₋₆ alkylene)_n-5-6 membered heteroaryl;
15 wherein the phenyl, C₃₋₆ cycloalkyl, 4-6 membered heterocyclyl and 5-6 membered heteroaryl are each optionally substituted with one or more groups independently chosen from: halogen, -CN, -OH, -NH₂, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, -O(C₁₋₆ alkyl), -O(C₁₋₆ haloalkyl), -NH(C₁₋₆ alkyl), -N(C₁₋₆ alkyl)₂ and C₃₋₆ cycloalkyl;
n is 0 or 1;
and p is 0 or 1.

20 Also provided is a pharmaceutical composition, comprising the compound of formula (I) of the present invention (e.g., a compound of any of the examples as described herein) or a pharmaceutically acceptable salt thereof, and optionally comprising a pharmaceutically acceptable carrier.

Also provided is a method of *in vivo* or *in vitro* inhibiting the activity of RIPK1,
25 comprising contacting RIPK1 with an effective amount of the compound of formula (I) of the present invention (e.g., a compound of any of the examples as described herein) or a pharmaceutically acceptable salt thereof.

Also provided is a method of treating a disease partially or completely mediated by RIPK1 in a subject, comprising administering to the subject in need thereof an effective
30 amount of the compound of formula (I) of the present invention (e.g., the compound of

formula (I-1) or a compound of any of the examples as described herein) or a pharmaceutically acceptable salt thereof.

Also provided is a method of treating an autoimmune disease, an inflammatory disease, a neurodegenerative disease, or cancer in a subject, comprising administering to
5 the subject in need thereof an effective amount of the compound of formula (I) of the present invention (e.g., the compound of formula (I-1) or a compound of any of the examples as described herein) or a pharmaceutically acceptable salt thereof.

Also provided is the use of the compound of formula (I) of the present invention (e.g., the compound of formula (I-1) or a compound of any of the examples as described
10 herein) or a pharmaceutically acceptable salt thereof in the treatment of a disease partially or completely mediated by RIPK1 in a subject.

Also provided is the use of the compound of formula (I) of the present invention (e.g., the compound of formula (I-1) or a compound of any of the examples as described herein) or a pharmaceutically acceptable salt thereof in the treatment of an autoimmune
15 disease, an inflammatory disease, a neurodegenerative disease or cancer in a subject.

Also provided is the use of the compound of formula (I) of the present invention (e.g., the compound of formula (I-1) or a compound of any of the examples as described herein) or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating a disease partially or completely mediated by RIPK1 in a subject.

Also provided is the use of the compound of formula (I) of the present invention (e.g., the compound of formula (I-1) or a compound of any of the examples as described herein) or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating an autoimmune disease, an inflammatory disease, a neurodegenerative
20 disease or cancer in a subject.

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Detailed Description of the Invention

Definitions

As used in the present application, the following words, phrases and symbols are generally intended to have the meanings as set forth below, except to the extent that the
30 context in which they are used indicates otherwise.

A dash (“-”) that is not between two letters or symbols is used to indicate a point of attachment for a substituent. For example, -O(C₁₋₆ alkyl) refers to the attachment of C₁₋₆ alkyl to the rest of the molecule through an oxygen atom.

The term “alkyl” as used herein refers to a straight or branched saturated hydrocarbon radical containing 1-18 carbon atoms, preferably 1-10 carbon atoms, particularly preferably 1-6 carbon atoms, further preferably 1-4 carbon atoms. For example, “C₁₋₆ alkyl” refers to an alkyl containing 1-6 carbon atoms. Examples of alkyl include, but are not limited to, methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl, and t-butyl.

The term “alkylene” as used herein refers to a straight or branched saturated divalent hydrocarbon radical containing 1-18 carbon atoms, preferably 1-10 carbon atoms, particularly preferably 1-6 carbon atoms, further preferably 1-4 carbon atoms. For example, “C₁₋₆ alkylene” refers to a straight or branched alkylene containing 1-6 carbon atoms, for example, straight alkylene-(CH₂)_n-, wherein n is an integer from 1 to 6, such as -CH₂-, -CH₂-CH₂-, -CH₂-CH₂-CH₂- etc., or branched alkylene, such as -CH₂-CH(CH₃)-CH₂-, -CH(CH₃)-CH₂-, -CH(CH₃)- and the like.

The term “alkenyl” as used herein refers to a straight or branched unsaturated hydrocarbon radical having one or more, for example 1, 2, or 3 carbon-carbon double bonds (C=C) and 2-10 carbon atoms, preferably 2-6 carbon atoms, more preferably 2-4 carbon atoms. For example, “C₂₋₆ alkenyl” refers to an alkenyl radical containing 1, 2 or 3, preferably 1 or 2 carbon-carbon double bonds, and 2-6 carbon atoms. Examples of alkenyl include, but are not limited to, vinyl, propenyl, allyl and 2-butenyl. The point of attachment for the alkenyl can be on or not on the double bonds.

The term “alkynyl” as used herein refers to a straight or branched unsaturated hydrocarbon radical having one or more, for example 1, 2, or 3, carbon-carbon triple bonds (C≡C) and 2-10 carbon atoms, preferably 2-6 carbon atoms, more preferably 2-4 carbon atoms. For example, “C₂₋₆ alkynyl” refers to an alkynyl radical containing 1, 2 or 3, preferably 1 or 2 carbon-carbon triple bonds, and 2-6 carbon atoms. Examples of alkynyl include, but are not limited to, ethynyl, 2-propynyl and 2-butylnyl. The point of attachment for the alkynyl can be on or not on the triple bonds.

The term “halogen” or “halo” as used herein refers to fluoro, chloro, bromo, and iodo, preferably fluoro, chloro and bromo, more preferably fluoro and chloro.

The term “haloalkyl” as used herein refers to an alkyl radical, as defined herein, in which one or more, for example 1, 2, 3, 4, 5 or 6, hydrogen atoms are replaced with halogen atoms, and when more than one hydrogen atoms are replaced with halogen atoms, the halogen atoms may be the same or different from each other. C₁₋₆ haloalkyl
5 refers to an alkyl radical having 1-6 carbon atoms, in which one or more hydrogen atoms, for example 1, 2, 3, 4, 5 or 6 hydrogen atoms are replaced with halogen atoms. Examples of haloalkyl include, but are not limited to, -CF₃, -CHF₂, -CH₂CF₃, -CH(CH₃)CF₃, -CH(CF₃)₂ and the like.

The term “cyano-substituted alkyl” as used herein refers to an alkyl radical, as
10 defined herein, in which one or more hydrogen atoms, for example 1, 2 or 3 hydrogen atoms are replaced with cyano. For example, “cyano-substituted C₁₋₆ alkyl” refers to a straight or branched saturated hydrocarbon radical having 1-6 carbon atoms, in which one or more hydrogen atoms, for example 1, 2 or 3 hydrogen atoms are replaced with cyano. Examples of cyano-substituted alkyl include, but are not limited to, cyanomethyl, 1-
15 cyanoethyl, 1-cyanopropyl and the like.

The term “cycloalkyl” as used herein refers to a saturated or partially unsaturated cyclic hydrocarbon radical having 3-12, such as 3-8 or 3-6 ring carbon atoms; which may have one or more rings, such as 1, 2 or 3 rings, preferably 1 or 2 rings, most preferably 1 ring (i.e. monocyclic). The cycloalkyl includes a fused or bridged ring, or a spirocyclic
20 ring. The rings of the cycloalkyl may be saturated or have one or more, for example, one or two double bonds (i.e. partially unsaturated), but not fully conjugated, and not an aryl as defined herein. “C₃₋₁₂ cycloalkyl” refers to monocyclic or bicyclic cycloalkyl having 3-12 ring carbon atoms, more preferably saturated monocyclic or bicyclic cycloalkyl having 3-12 ring carbon atoms. “C₃₋₆ cycloalkyl” refers to monocyclic cycloalkyl having
25 3-6 ring carbon atoms, more preferably saturated monocyclic cycloalkyl having 3-6 ring carbon atoms. Examples of cycloalkyl include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, bicyclo[4.1.0]heptanyl, bicyclo[3.1.1]heptanyl, spiro[3.3]heptanyl, spiro[2.2]pentanyl, cyclopropenyl, cyclobutenyl, cyclopentenyl, cyclopentadienyl, cyclohexenyl, cycloheptenyl,
30 cyclooctenyl and bicyclo[3.1.1]hept-2-ene.

The term “heterocyclyl” or “heterocycle” as used herein refers to: saturated or partially unsaturated cyclic radicals having 3-12 ring atoms, such as 3-8 ring atoms, 4-7

ring atoms or 4-6 ring atoms, and containing one or more, for example 1, 2 or 3, preferably 1 or 2 heteroatoms independently chosen from N, O and S in the rings, with the remaining ring atoms being carbon; it may have one or more rings, for example 1, 2 or 3, preferably 1 or 2 rings. Preferably, “3-12 membered heterocyclyl” refers to
5 monocyclic or bicyclic heterocycloalkyl having 3-12 ring atoms, which is saturated or partially unsaturated, preferably saturated, has 1, 2 or 3, preferably 1 or 2 ring heteroatoms chosen from N, O and S, with the remaining ring atoms being carbon atoms; “4-6 membered heterocyclyl” refers to monocyclic heterocyclyl having 4-6 ring atoms, which is saturated or partially unsaturated, preferably saturated, and has 1, 2 or 3,
10 preferably 1 or 2 ring heteroatoms chosen from N, O and S, with the remaining ring atoms being carbon atoms. N and S in heterocyclyl may be optionally oxidized. The point of attachment of heterocyclyl can be on the N heteroatom or carbon. The heterocyclyl includes a fused or bridged ring, or a spirocyclic ring. The rings of heterocyclyl may be saturated or have one or more, for example, one or two double bonds (i.e. partially
15 unsaturated), but not fully conjugated, and not a heteroaryl as defined herein. Examples of heterocyclyl include, but are not limited to: oxiranyl, aziridinyl, oxetanyl, azetidiny, pyrrolidyl, tetrahydrofuranyl, tetrahydropyranyl, dioxolanyl, dioxanyl, morpholinyl, thiomorpholinyl, piperidyl, piperazinyl, pyrazolidinyl, and oxaspiro[3.3]heptanyl.

The term “aryl” or “aromatic ring” as used herein refers to carbocyclic hydrocarbon
20 radical of 6 to 14 carbon atoms consisting of one ring or more fused rings, wherein at least one ring is an aromatic ring. Examples of aryl include, but are not limited to: phenyl, naphthyl, 1,2,3,4-tetrahydronaphthyl, indenyl, indanyl, azulenyl, preferably phenyl and naphthyl, most preferably phenyl.

The term “heteroaryl” or “heteroaromatic ring” as used herein refers to aromatic
25 hydrocarbon radical having 5-12 ring atoms (e.g., 5-10 ring atoms, 5-9 ring atoms, 5-6 ring atoms or 6 ring atoms) (i.e., 5-12 membered heteroaryl, 5-10 membered heteroaryl, 5-9 membered heteroaryl, 5-6 membered heteroaryl or 6 membered heteroaryl), and containing one or more (e.g., 1, 2, 3 or 4, preferably 1, 2 or 3) ring heteroatoms independently chosen from N, O and S in the rings, with the remaining ring atoms being
30 carbon atoms; which may have one or more rings, such as 1, 2, or 3 rings, preferably 1 or 2 rings. Preferably, the heteroaryl is:

monocyclic aromatic hydrocarbyl having 5, 6 or 7 ring atoms (namely, 5-7 membered monocyclic heteroaryl) (preferably monocyclic aromatic hydrocarbyl having 5 or 6 ring atoms (namely, 5-6 membered monocyclic heteroaryl)), and containing one or more, for example 1, 2, 3 or 4, preferably 1, 2 or 3 ring heteroatoms independently
5 chosen from N, O and S (preferably N and O) in the ring, with the remaining ring atoms being carbon atoms; or

bicyclic aromatic hydrocarbyl having 8-12 ring atoms (namely, 8-12 membered bicyclic heteroaryl) (preferably bicyclic aromatic hydrocarbyl having 8, 9, 10 ring atoms (namely, 8-10 membered bicyclic heteroaryl), more preferably bicyclic aromatic
10 hydrocarbyl having 8 or 9 ring atoms (namely, 8-9 membered bicyclic heteroaryl)), and containing one or more, for example 1, 2, 3 or 4, preferably 2, 3 or 4 ring heteroatoms independently chosen from N, O and S (preferably N) in the ring, with the remaining ring atoms being carbon atoms, wherein at least one ring is an aromatic ring. For example, bicyclic heteroaryl includes a 5-6 membered heteroaryl ring fused with a 5-6 membered
15 cycloalkyl ring; bicyclic heteroaryl also includes a 5-6 membered heteroaryl ring fused with a 5-6 membered heterocyclyl ring.

When the total number of S and O atoms in the heteroaryl group exceeds 1, said S and O heteroatoms are not adjacent to one another.

Examples of monocyclic heteroaryl include, but are not limited to, pyridyl, N-oxide
20 pyridyl, pyrazinyl, pyrimidyl, triazinyl (e.g., 1,3,5-triazinyl), pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, oxadiazolyl (e.g., 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl and 1,3,4-oxadiazolyl), thiazolyl, isothiazolyl, thiadiazolyl, tetrazolyl, triazolyl (e.g., 1,2,3-triazolyl and 1,2,4-triazolyl), thienyl, furanyl, pyranyl, pyrrolyl, and pyridazinyl. Examples of bicyclic heteroaryl include, but are not limited to, benzodioxolyl, benzoxazolyl,
25 benzoisoxazolyl, benzothienyl, benzothiazolyl, benzoisothiazolyl, imidazopyridyl (e.g., imidazo[1,2-a]pyridyl), imidazopyridazinyl (e.g., imidazo[1,2-b]pyridazinyl), pyrrolopyridyl (e.g., 1H-pyrrolo[2,3-b]pyridyl), pyrrolopyrimidyl (e.g., pyrrolo[3,4-d]pyrimidyl), pyrrolotriazolyl (e.g., pyrrolo[1,2-b][1,2,4]triazolyl), dihydropyrrolotriazolyl (e.g., 6,7-dihydro-5H-pyrrolo[1,2-b][1,2,4]triazolyl),
30 pyrazolopyridyl (e.g., 1H-pyrazolo[3,4-b]pyridyl and pyrazolo[4,3-c]pyridyl), pyrazolopyrimidyl (e.g., pyrazolo[3,4-d]pyrimidyl and pyrazolo[1,5-a]pyrimidyl), triazolopyridyl (e.g., [1,2,4]triazolo[4,3-a]pyridyl and [1,2,4]triazolo[1,5-a]pyridyl),

tetrazolopyridyl (e.g., tetrazolo[1,5-a]pyridyl), benzofuranyl, benzoimidazoliny, indolyl, indazolyl, purinyl, quinoliny, isoquinoliny, and quinazoliny.

The term “hydroxyl” as used herein refers to -OH group.

The term “oxo” as used herein refers to =O group.

5 The term “cyano” as used herein refers to -CN group.

When a structural formula herein contains an asterisk “*”, it means that the chiral center at the “*” mark in the compound is a single configuration of (R) configuration or (S) configuration; wherein the content of the single-configuration compound marked with “*” is at least 90% (e.g., 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5%,
10 99.9%, 100%, or any value between these listed values).

When a structural formula herein contains “(RS)”, it means that the chiral center at the “(RS)” mark in the compound contains two configurations (R) and (S), that is, the compound is a mixture of the two configurations.

The term “optional” or “optionally” as used herein means that the subsequently
15 described event or circumstance may or may not occur, and the description includes instances wherein the event or circumstance occur and instances in which it does not occur. For example, “optionally substituted alkyl” includes “unsubstituted alkyl” and “substituted alkyl” defined herein. It will be understood by the POSITA, with respect to any group containing one or more substituents, that such groups are not intended to
20 introduce any substitution or substitution patterns that are sterically impractical, chemically incorrect, synthetically non-feasible and/or inherently unstable.

The term “substituted” or “substituted with...”, as used herein, means that one or more hydrogen atoms on the designated atom or group are replaced with one or more substituents chosen from the indicated group of substituents, provided that the designated
25 atom's normal valence is not exceeded. When a substituent is oxo (i.e., =O), then two hydrogens on a single atom are replaced by the oxo. Combinations of substituents and/or variables are permitted only when they result in chemically correct and stable compounds. A chemically correct and stable compound is meant to imply a compound that is sufficiently robust to survive sufficient isolation from a reaction mixture, and then can be
30 formulated into a formulation having at least practical utility.

Unless otherwise specified, substituents are named into the core structure. For example, it is to be understood that when (cycloalkyl)alkyl is listed as a possible

substituent, the point of attachment of this substituent to the core structure is in the alkyl portion.

The term “substituted with one or more groups” as used herein means that one or more hydrogens on the designated atom or group are independently replaced with one or more substituents chosen from indicated group. In some embodiments, “substituted with one or more groups” means the designated atom or group is replaced with 1, 2, 3, 4, 5 or 6, preferably 1, 2, 3 or 4 substituents independently chosen from designated group.

It will be understood by the POSITA that some of the compounds of formula (I) may contain one or more chiral centers and therefore exist in two or more stereoisomeric forms. The racemates of these isomers, the individual isomers and mixtures enriched in one enantiomer, as well as diastereomers when there are two chiral centers, and mixtures enriched with specific diastereomers are within the scope of the present invention. It will be further understood by the POSITA that the present invention includes all the individual stereoisomers (e.g. enantiomers), racemic mixtures or partially resolved mixtures of the compounds of formula (I) and, where appropriate, the individual tautomeric forms thereof.

The term “stereoisomers” as used herein refers to compounds that have the same chemical constitution but differ in the arrangement of atoms or groups in space.

Stereoisomers include enantiomers, diastereomers and the like.

The terms “enantiomers” and “enantiomeric forms” as used herein can be used interchangeably and refer to two stereoisomers of a compound that are non-superimposable mirror images of each other.

The terms “diastereomers” and “diastereomeric forms” as used herein can be used interchangeably and refer to stereoisomers that have two or more chiral centers and whose molecules are not mirror images of each other. Diastereomers have different physical properties, such as melting points, boiling points, spectral properties, or biological activities. A mixture of diastereomers can be separated by high-resolution analytical methods such as electrophoresis and chromatography such as HPLC.

Stereochemical definitions and conventions can follow: S. P. Parker edit, McGraw-Hill Dictionary of Chemical Terms (1984) McGraw-Hill Book Company, New York; and Eliel, E. and Wilen, S., “Stereochemistry of Organic Compounds”, John Wiley & Sons, Inc., New York, 1994. Many organic compounds exist in optically active forms, that is,

they have the ability to rotate the plane of plane-polarized light. When describing optically active compounds, the prefixes D and L or R and S are used to indicate the absolute configuration of the molecule with respect to its chiral center. The prefixes d and l or (+) and (-) are used to denote the symbols for the rotation of plane-polarized light of the compound, where (-) or l indicates that the compound is levorotatory. The compound prefixed with (+) or d is dextrorotatory. For a given chemical structure, these stereoisomers are the same except that they are mirror images of each other. Specific stereoisomers can also be referred to as enantiomers, and a mixture of such isomers are usually called an enantiomeric mixture. A mixture of enantiomers at 50 : 50 is called a racemic mixture or racemate, which can occur in situations where there is no stereoselectivity or stereospecificity in a chemical reaction or method. The terms “racemic mixture” and “racemate” refer to an equimolar mixture of two enantiomers that are not optically active.

In some embodiments, the present invention provides compounds of various stereoisomeric purities, that is, enantiomeric or diastereomeric purity expressed in different “ee” or “de” values. In some embodiments, the compound of formula (I) described herein has an enantiomeric purity of at least 60% ee (e.g., 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5%, 99.9% ee, or any value between these listed values). In some embodiments, the compound of formula (I) described herein has an enantiomeric purity of greater than 99.9% ee. In some embodiments, the compound of formula (I) described herein has a diastereomeric purity of at least 60% de (e.g., 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5%, 99.9% de, or any value between these listed values). In some embodiments, the compound of formula (I) described herein has a diastereomeric purity of greater than 99.9% de.

The term “enantiomeric excess” or “ee” refers to the amount of one enantiomer relative to the other. For a mixture of R and S enantiomers, the percentage of enantiomeric excess is defined as $|R - S| * 100$, where R and S are the mole or weight fractions of the respective enantiomers in the mixture, $R + S = 1$. If the optical rotation of a chiral substance is known, the percentage of enantiomeric excess is defined as $([a]_{\text{obs}}/[a]_{\text{max}})*100$, wherein $[a]_{\text{obs}}$ is the optical rotation of the enantiomeric mixture, and $[a]_{\text{max}}$ is the optical rotation of the pure enantiomer.

The term “diastereomeric excess” or “de” refers to the amount of one diastereomer relative to the other, and is defined by analogy based on the enantiomeric excess.

Therefore, for a mixture of diastereomers D1 and D2, the percentage of diastereomeric excess is defined as $|D1 - D2| * 100$, wherein D1 and D2 are the mole or weight

5 fractions of the respective diastereomers in the mixture, $D1 + D2 = 1$.

The diastereomeric excess and enantiomeric excess can be measured by a number of analytical techniques (including nuclear magnetic resonance spectroscopy, chiral column chromatography and/or optical polarimetry) according to conventional protocols well known to a person skilled in the art.

10 The racemates can be used as such or can be resolved into their individual isomers. The resolution can afford stereochemically pure compounds or mixtures enriched in one or more isomers. Methods for separation of isomers are well known (cf. Allinger N. L. and Eliel E. L. in “*Topics in Stereochemistry*”, Vol. 6, Wiley Interscience, 1971) and include physical methods such as chromatography using a chiral adsorbent. Individual
15 isomers can be prepared in chiral form from chiral precursors. Alternatively, individual isomers can be separated chemically through the following process: forming diastereomeric salts with a mixture and a chiral acid (e.g., the individual enantiomers of 10-camphorsulfonic acid, camphoric acid, alpha-bromocamphoric acid, tartaric acid, diacetyltartaric acid, malic acid, pyrrolidone-5-carboxylic acid, and the like), fractionally
20 crystallizing the salts, and then freeing one or both of the resolved bases, optionally repeating the process, so as obtain either or both substantially free of the other; i.e., in a form having an optical purity of > 95%. Alternatively, the racemates can be covalently linked to a chiral compound (auxiliary) to produce diastereomers which can be separated by chromatography or by fractional crystallization after which time the chiral auxiliary is
25 chemically removed to afford the pure enantiomers.

The term “tautomer” as used herein refers to constitutional isomers of compounds generated by rapid movement of an atom in two positions in a molecule. Tautomers readily interconvert into each other, e.g., enol form and ketone form are typical tautomers.

A “pharmaceutically acceptable salt” is intended to mean a salt of a free acid or base
30 of a compound of formula (I) that is non-toxic, biologically tolerable, or otherwise biologically suitable for administration to the subject. For example, the pharmaceutically acceptable salt is an acid addition salt including such as a salt derived from an inorganic

acid and an organic acid. Said inorganic acid includes such as hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, phosphoric acid, and nitric acid; said organic acid includes such as p-toluenesulfonic acid, salicylic acid, methanesulfonic acid, oxalic acid, succinic acid, citric acid, malic acid, lactic acid, fumaric acid, and the like.

- 5 For examples, see, generally, S. M. Berge et. al., "Pharmaceutical Salts", J. Pharm. Sci., 1977, 66:1-19, and Handbook of Pharmaceutical Salts, Properties, Selection, and Use, edited by Stahl and Wermuth, Wiley-VCH and VHCA, Zurich, 2002.

In addition, if a compound of the present invention herein is obtained as an acid addition salt, the free base can be obtained by basifying a solution of the acid addition salt. Conversely, if the product is a free base, an acid addition salt, particularly a pharmaceutically acceptable acid addition salt, may be produced by dissolving the free base in a suitable solvent and treating the solution with an acid, in accordance with conventional procedures for preparing acid addition salts from base compounds. The POSITA will recognize various synthetic methodologies that may be used without undue experimentation to prepare non-toxic pharmaceutically acceptable acid addition salts or base addition salts.

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The term "solvates" means solvent addition forms that contain either stoichiometric or non-stoichiometric amounts of solvent. Some compounds have a tendency to trap a fixed molar ratio of solvent molecules in the solid state, thus forming a solvate. When the solvent is water, the formed solvate is a hydrate, and when the solvent is alcohol, the formed solvate is an alcoholate. Hydrates are formed by the combination of one or more molecules of water, with one molecule of the substances in which the water retains its molecular state as H₂O, such combination being able to form one or more hydrates, for example, hemihydrate, monohydrate, and dihydrate.

20

The term "deuterate" means the compound formed by replacing one or more, for example, 1, 2 or 3 hydrogen atoms in a compound with its isotope deuterium, wherein at the substitution position, the abundance of isotope deuterium (i.e., the deuteration degree) of the element deuterium is at least greater than the natural abundance. In some embodiments, the deuterate in the compound of formula (I) or in the compound of its sub-formula (I-1) has a deuteration degree of at least 50% (e.g., 50%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5%, 99.9%, or any value therebetween). In some embodiments, the compound of formula (I)

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or the compound of its sub-formula (I-1) has a deuteration degree of greater than 99.9% or up to 100%.

As used herein, the terms “group(s)” and “radical(s)” are synonymous and are intended to indicate functional groups or fragments of molecules attachable to other
5 fragments of molecules.

The term “active ingredient” is used herein to refer to a chemical substance with biological activity, such as the compound of formula (I) of the present invention (e.g., a compound of any of the examples as described herein) or a pharmaceutically acceptable salt thereof. In some embodiments, the “active ingredient” is a chemical substance having
10 pharmaceutical use, and its pharmaceutical activity can be determined by appropriate *in vitro* or *in vivo* trials (for example, preclinical or clinical trials).

The terms “treating” or “treatment” of a disease or disorder, in the context of achieving therapeutic benefit, refer to administering one or more pharmaceutical substances, especially the compound of formula (I) described herein or a
15 pharmaceutically acceptable salt thereof to a subject that has the disease or disorder, or has a symptom of a disease or disorder, or has a predisposition toward a disease or disorder, with the purpose to cure, alleviate, relieve, alter, remedy, ameliorate, improve, or affect the disease or disorder, the symptoms of the disease or disorder, or the predisposition toward the disease or disorder. Therefore, the “treatment” described herein
20 includes preventive treatment, curative treatment and palliative treatment. In some embodiment, the disease or disorder is an autoimmune disease or inflammatory disease.

The terms “treating”, “contacting” and “reacting”, in the context of a chemical reaction, mean adding or mixing two or more reagents under appropriate conditions to produce the indicated and/or the desired product. It should be appreciated that the
25 reaction which produces the indicated and/or the desired product may not necessarily result directly from the combination of two reagents which were initially added, i.e., there may be one or more intermediates which are produced in the mixture which ultimately lead to the formation of the indicated and/or the desired product.

The term “effective amount” as used herein refers to an amount of the RIPK1
30 inhibitor sufficient to generally bring about a therapeutic benefit in patients in need of treatment for a disease or disorder mediated partially or completely by RIPK1 activity. Effective amounts or doses of the active ingredient of the present disclosure may be

ascertained by methods such as modeling, dose escalation studies or clinical trials, and by taking into consideration factors, e.g., the route of administration, the pharmacokinetics of the agent, the severity of the disease or disorder, the subject's previous or ongoing therapy, the subject's health status and response to drugs, and the judgment of the
5 attending physician.

An exemplary dose is in the range of from about 0.0001 to about 200 mg of active ingredient/kg body weight/day, for example from about 0.001 to 100 mg/kg body weight/day, or about 0.01 to 35 mg/kg body weight/day, or about 0.1 to 10 mg/kg body weight/day, daily in single or divided dosage units (e.g., BID, TID, QID). For a 70 kg
10 person, a suitable dose is from about 0.05 to about 7 g/day, or from about 0.2 to about 5 g/day.

The term “inhibition” or “inhibiting” refers to a decrease in the baseline activity of a biological activity. The term “inhibition of RIPK1 activity” refers to a decrease in the activity of RIPK1 as a direct or indirect response to the presence of the compound of
15 formula (I) and/or a pharmaceutically acceptable salt thereof, relative to the activity of RIPK1 in the absence of the compound of formula (I) and/or a pharmaceutically acceptable salt thereof described herein. The decrease in activity may be due to the direct interaction of the compound of formula (I) and/or a pharmaceutically acceptable salt thereof described herein with RIPK1, or due to the interaction of the compound of
20 formula (I) and/or a pharmaceutically acceptable salt thereof described herein, with one or more other factors that in turn affect the RIPK1 activity. For example, the presence of the compound of formula (I) and/or a pharmaceutically acceptable salt thereof described herein may decrease the RIPK1 activity by directly binding to the RIPK1, by directly or indirectly influencing another factor, or by directly or indirectly decreasing the amount of
25 RIPK1 present in the cell or organism.

The term “subject” as used herein means mammals and non-mammals. Mammals means any member of the mammalia class including, but not limited to, humans; non-human primates such as chimpanzees and other apes and monkey species; farm animals such as cattle, horses, sheep, goats, and swine; domestic animals such as rabbits, dogs,
30 and cats; laboratory animals including rodents, such as rats, mice, and guinea pigs; and the like. Examples of non-mammals include, but are not limited to, birds, and the like.

The term “subject” does not denote a particular age or sex. In some embodiments, the subject is a human.

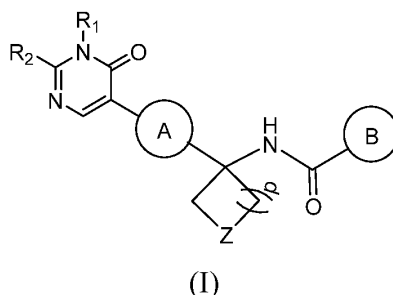
The term “pharmaceutically acceptable” refers to that the substances defined following the term can be used to prepare a pharmaceutical composition, which are generally safe, non-toxic, and have no undesirable biological or other properties, especially for human pharmaceutical use.

The term “about” as used herein means approximately, in the region of, roughly, or around. When the term “about” is used in conjunction with a numerical range, it adjusts the range by extending the limit above or below the numerical value given. In general, the term “about” is used herein to modify a numerical value above or below the stated value by a variance of 20%.

Technical and scientific terms used herein and not specifically defined have the meaning commonly understood by the POSITA to which the present disclosure pertains.

15 Detailed Description of Embodiments

Embodiment 1. A compound of formula (I):



or a pharmaceutically acceptable salt thereof, or a solvate, a racemic mixture, an enantiomer, a diastereomer or a tautomer thereof, wherein

R_1 is hydrogen, C_{1-6} alkyl, C_{1-6} haloalkyl, cyano-substituted C_{1-6} alkyl, $-(C_{1-6} \text{ alkylene})_n-C_{3-6}$ cycloalkyl, $-(C_{1-6} \text{ alkylene})_n$ -phenyl, $-(C_{1-6} \text{ alkylene})_n$ -4-6 membered heterocyclyl or $-(C_{1-6} \text{ alkylene})_n$ -5-6 membered heteroaryl; wherein the C_{3-6} cycloalkyl, phenyl, 4-6 membered heterocyclyl and 5-6 membered heteroaryl are each optionally substituted with one or more groups independently chosen from: halogen, -CN, -OH, -NH₂, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, $-O(C_{1-6} \text{ alkyl})$, $-O(C_{1-6} \text{ haloalkyl})$, $-NH(C_{1-6} \text{ alkyl})$ and $-N(C_{1-6} \text{ alkyl})_2$;

R₂ is hydrogen, halogen, -CN, -NH₂, C₁₋₆ alkyl, C₁₋₆ haloalkyl, -O(C₁₋₆ alkyl), -O(C₁₋₆ haloalkyl), -NH(C₁₋₆ alkyl) or -N(C₁₋₆ alkyl)₂;

Z is O, NR₃ or CR₄R₅;

R₃ is hydrogen or C₁₋₆ alkyl;

- 5 R₄ and R₅ are each independently chosen from: hydrogen, halogen, -CN, -OH, C₁₋₆ alkyl, C₁₋₆ haloalkyl, -O(C₁₋₆ alkyl), -O(C₁₋₆ haloalkyl) and C₃₋₆ cycloalkyl;

- 10  is phenyl or 5-6 membered heteroaryl, each of which is optionally substituted with one or more groups independently chosen from: halogen, -CN, -OH, -NH₂, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, -O(C₁₋₆ alkyl), -O(C₁₋₆ haloalkyl), -NH(C₁₋₆ alkyl) and -N(C₁₋₆ alkyl)₂;

- 15  is 5-12 membered heteroaryl, which is optionally substituted with one or more groups independently chosen from: halogen, -CN, -OH, oxo, -NH₂, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, -O(C₁₋₆ alkyl), -O(C₁₋₆ haloalkyl), -NH(C₁₋₆ alkyl), -N(C₁₋₆ alkyl)₂, -(C₁₋₆ alkylene)_n-C₃₋₆ cycloalkyl, -(C₁₋₆ alkylene)_n-phenyl, -(C₁₋₆ alkylene)_n-4-6 membered heterocyclyl and -(C₁₋₆ alkylene)_n-5-6 membered heteroaryl; wherein the phenyl, C₃₋₆ cycloalkyl, 4-6 membered heterocyclyl and 5-6 membered heteroaryl are each optionally substituted with one or more groups independently chosen from: halogen, -CN, -OH, -NH₂, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, -O(C₁₋₆ alkyl), -O(C₁₋₆ haloalkyl), -NH(C₁₋₆ alkyl), -N(C₁₋₆ alkyl)₂ and C₃₋₆ cycloalkyl;
- 20 n is 0 or 1;
and p is 0 or 1.

- Embodiment 2. The compound of formula (I), or a pharmaceutically acceptable salt thereof, or a solvate, a racemic mixture, an enantiomer, a diastereomer or a tautomer thereof according to embodiment 1, wherein R₁ is C₁₋₆ alkyl, C₁₋₆ haloalkyl, cyano-
- 25 substituted C₁₋₆ alkyl, -(C₁₋₆ alkylene)_n-C₃₋₆ cycloalkyl or -(C₁₋₆ alkylene)_n-4-6 membered heterocyclyl; and wherein the C₃₋₆ cycloalkyl and 4-6 membered heterocyclyl are each optionally substituted with one or more groups independently chosen from: halogen, -CN, -OH, -NH₂, C₁₋₆ alkyl, C₁₋₆ haloalkyl, -O(C₁₋₆ alkyl), -O(C₁₋₆ haloalkyl), -NH(C₁₋₆ alkyl) and -N(C₁₋₆ alkyl)₂.

Embodiment 3. The compound of formula (I), or a pharmaceutically acceptable salt thereof, or a solvate, a racemic mixture, an enantiomer, a diastereomer or a tautomer thereof according to embodiment 2, wherein R_1 is C_{1-6} alkyl, C_{1-6} haloalkyl, cyano-substituted C_{1-6} alkyl, $-(C_{1-6} \text{ alkylene})_n-C_{3-6}$ cycloalkyl or $-(C_{1-6} \text{ alkylene})_n$ -4-6 membered heterocyclyl; wherein the C_{3-6} cycloalkyl and 4-6 membered heterocyclyl are each optionally substituted with one or more groups independently chosen from: halogen and C_{1-6} alkyl.

Embodiment 4. The compound of formula (I), or a pharmaceutically acceptable salt thereof, or a solvate, a racemic mixture, an enantiomer, a diastereomer or a tautomer thereof according to embodiment 3, wherein R_1 is C_{1-6} alkyl, and preferably, R_1 is methyl or i-propyl.

Embodiment 5. The compound of formula (I), or a pharmaceutically acceptable salt thereof, or a solvate, a racemic mixture, an enantiomer, a diastereomer or a tautomer thereof according to embodiment 3, wherein R_1 is C_{1-6} haloalkyl, $-(C_{1-6} \text{ alkylene})_n-C_{3-6}$ cycloalkyl or $-(C_{1-6} \text{ alkylene})_n$ -4-6 membered heterocyclyl; wherein the C_{3-6} cycloalkyl is optionally substituted with one or more groups independently chosen from: halogen and C_{1-6} alkyl;

preferably, R_1 is $-(C_{1-6} \text{ alkylene})_n-C_{3-6}$ cycloalkyl, wherein the C_{3-6} cycloalkyl is optionally substituted with one or more halogen, and n is 0 or 1; or R_1 is 4-6 membered heterocyclyl, wherein the 4-6 membered heterocyclyl is oxetanyl, tetrahydrofuranyl or tetrahydropyranyl.

Embodiment 6. The compound of formula (I), or a pharmaceutically acceptable salt thereof, or a solvate, a racemic mixture, an enantiomer, a diastereomer or a tautomer thereof according to any one of embodiments 1-5, wherein R_2 is hydrogen, $-NH_2$, C_{1-6} alkyl, $-NH(C_{1-6} \text{ alkyl})$ or $-N(C_{1-6} \text{ alkyl})_2$; preferably, R_2 is hydrogen, $-NH_2$ or C_{1-6} alkyl; and more preferably, R_2 is hydrogen.

Embodiment 7. The compound of formula (I), or a pharmaceutically acceptable salt thereof, or a solvate, a racemic mixture, an enantiomer, a diastereomer or a tautomer thereof according to any one of embodiments 1-6, wherein p is 0, and Z is CR_4R_5 ; more preferably, p is 0, and Z is CH_2 .

Embodiment 8. The compound of formula (I), or a pharmaceutically acceptable salt thereof, or a solvate, a racemic mixture, an enantiomer, a diastereomer or a tautomer

thereof according to any one of embodiments 1-7, wherein $\textcircled{\text{A}}$ is phenyl or 5-6 membered heteroaryl, each of which is optionally substituted with one or more groups independently chosen from: halogen, C_{1-6} alkyl and C_{1-6} haloalkyl;

preferably, $\textcircled{\text{A}}$ is phenyl or pyridyl, each of which is optionally substituted with one or more groups independently chosen from: halogen, C_{1-6} alkyl and C_{1-6} haloalkyl;

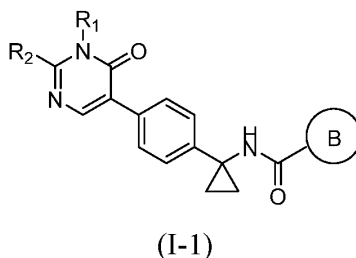
more preferably, $\textcircled{\text{A}}$ is phenyl, which is optionally substituted with one or more

groups independently chosen from: halogen, C_{1-6} alkyl or C_{1-6} haloalkyl; or $\textcircled{\text{A}}$ is pyridyl.

Embodiment 9. The compound of formula (I), or a pharmaceutically acceptable salt thereof, or a solvate, a racemic mixture, an enantiomer, a diastereomer or a tautomer

thereof according to any one of embodiments 1-8, wherein $\textcircled{\text{B}}$ is 5-12 membered heteroaryl, preferably 5-10 membered heteroaryl, more preferably 5-9 membered heteroaryl, which is optionally substituted with one or more groups independently chosen from: halogen, C_{1-6} alkyl, $-(\text{C}_{1-6} \text{ alkylene})_n\text{-C}_{3-6}$ cycloalkyl, $-(\text{C}_{1-6} \text{ alkylene})_n\text{-phenyl}$, $-(\text{C}_{1-6} \text{ alkylene})_n\text{-4-6 membered heterocyclyl}$ and $-(\text{C}_{1-6} \text{ alkylene})_n\text{-5-6 membered heteroaryl}$; and wherein the phenyl, C_{3-6} cycloalkyl, 4-6 membered heterocyclyl and 5-6 membered heteroaryl are each optionally substituted with one or more halogen.

Embodiment 10. The compound of formula (I), or a pharmaceutically acceptable salt thereof, or a solvate, a racemic mixture, an enantiomer, a diastereomer or a tautomer thereof according to embodiment 1, wherein the compound of formula (I) is the compound of formula (I-1):



wherein

- R₁ is C₁₋₆ alkyl, C₁₋₆ haloalkyl, cyano-substituted C₁₋₆ alkyl, -(C₁₋₆ alkylene)_n-C₃₋₆ cycloalkyl or -(C₁₋₆ alkylene)_n-4-6 membered heterocyclyl; wherein the C₃₋₆ cycloalkyl and 4-6 membered heterocyclyl are each optionally substituted with one or more groups independently chosen from: halogen and C₁₋₆ alkyl; preferably, R₁ is C₁₋₆ alkyl, C₁₋₆ haloalkyl, -(C₁₋₆ alkylene)_n-C₃₋₆ cycloalkyl or -(C₁₋₆ alkylene)_n-4-6 membered heterocyclyl; wherein the C₃₋₆ cycloalkyl is optionally substituted with one or more groups independently chosen from: halogen and C₁₋₆ alkyl;
- R₂ is hydrogen, -NH₂, C₁₋₆ alkyl, -NH(C₁₋₆ alkyl) or -N(C₁₋₆ alkyl)₂; preferably, R₂ is hydrogen, -NH₂ or C₁₋₆ alkyl; and more preferably, R₂ is hydrogen;

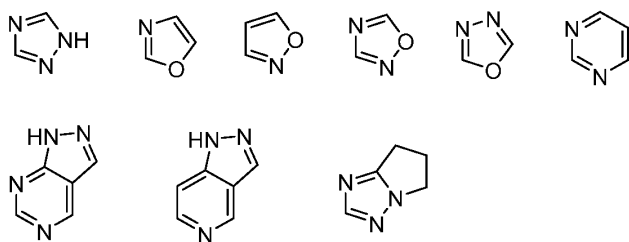
- 10  is 5-12 membered heteroaryl, preferably 5-10 membered heteroaryl, more preferably 5-9 membered heteroaryl, which is optionally substituted with one or more groups independently chosen from: halogen, C₁₋₆ alkyl, -(C₁₋₆ alkylene)_n-C₃₋₆ cycloalkyl, -(C₁₋₆ alkylene)_n-phenyl, -(C₁₋₆ alkylene)_n-4-6 membered heterocyclyl and -(C₁₋₆ alkylene)_n-5-6 membered heteroaryl; wherein the phenyl, C₃₋₆ cycloalkyl, 4-6 membered heterocyclyl and 5-6 membered heteroaryl are each optionally substituted with one or more halogen;
- 15 and n is 0 or 1.

Embodiment 11. The compound of formula (I), or a pharmaceutically acceptable salt thereof, or a solvate, a racemic mixture, an enantiomer, a diastereomer or a tautomer

- 20 thereof according to any one of embodiments 1-10, wherein  is triazolyl, oxazolyl, isoxazolyl, oxadiazolyl, pyrimidyl, pyrazolopyrimidyl, pyrazolopyridyl or dihydropyrrolotriazolyl, each of which is optionally substituted with one or more groups independently chosen from: halogen, C₁₋₆ alkyl, -(C₁₋₆ alkylene)_n-C₃₋₆ cycloalkyl, -(C₁₋₆ alkylene)_n-phenyl, -(C₁₋₆ alkylene)_n-4-6 membered heterocyclyl and -(C₁₋₆ alkylene)_n-5-6 membered heteroaryl; and wherein the phenyl, C₃₋₆ cycloalkyl, 4-6 membered heterocyclyl and 5-6 membered heteroaryl are each optionally substituted with one or more halogen.

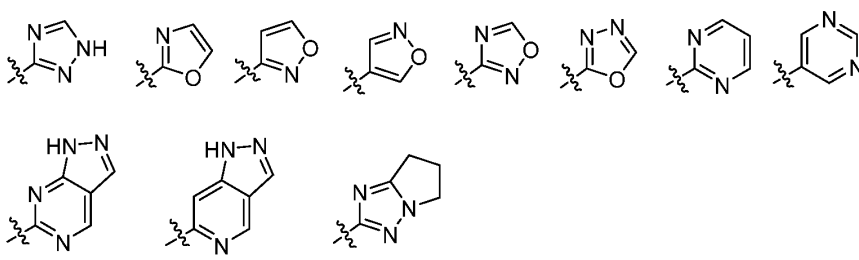
- Embodiment 12. The compound of formula (I), or a pharmaceutically acceptable salt thereof, or a solvate, a racemic mixture, an enantiomer, a diastereomer or a tautomer
- 30 thereof according to embodiment 11, wherein

B is chosen from



each of which is optionally substituted with one or more groups independently chosen from: halogen, C₁₋₆ alkyl, -(C₁₋₆ alkylene)_n-C₃₋₆ cycloalkyl, -(C₁₋₆ alkylene)_n-phenyl, -(C₁₋₆ alkylene)_n-4-6 membered heterocyclyl and -(C₁₋₆ alkylene)_n-5-6 membered heteroaryl; wherein the phenyl, C₃₋₆ cycloalkyl, 4-6 membered heterocyclyl and 5-6 membered heteroaryl are each optionally substituted with one or more halogen;

preferably,  is chosen from



10 each of which is optionally substituted with one or more groups independently chosen from: halogen, C₁₋₆ alkyl, -(C₁₋₆ alkylene)_n-C₃₋₆ cycloalkyl, -(C₁₋₆ alkylene)_n-phenyl, -(C₁₋₆ alkylene)_n-4-6 membered heterocyclyl and -(C₁₋₆ alkylene)_n-5-6 membered heteroaryl; wherein the phenyl, C₃₋₆ cycloalkyl, 4-6 membered heterocyclyl and 5-6 membered heteroaryl are each optionally substituted with one or more halogen.

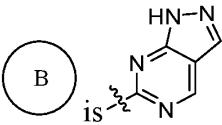
Embodiment 13. The compound of formula (I), or a pharmaceutically acceptable salt thereof, or a solvate, a racemic mixture, an enantiomer, a diastereomer or a tautomer

thereof according to embodiment 12, wherein  is , which is optionally substituted with one or more groups independently chosen from: C₁₋₆ alkyl, -(C₁₋₆ alkylene)_n-C₃₋₆ cycloalkyl, -(C₁₋₆ alkylene)_n-phenyl, -(C₁₋₆ alkylene)_n-4-6 membered heterocyclyl and -(C₁₋₆ alkylene)_n-5-6 membered heteroaryl; and wherein the C₃₋₆

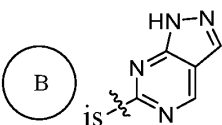
cycloalkyl, 4-6 membered heterocyclyl and 5-6 membered heteroaryl are each optionally substituted with one or more halogen, and n is 0 or 1.

Embodiment 14. The compound of formula (I), or a pharmaceutically acceptable salt thereof, or a solvate, a racemic mixture, an enantiomer, a diastereomer or a tautomer

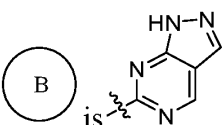
5 thereof according to embodiment 13, wherein

 is B , which is optionally substituted with one or more groups independently chosen from: C_{1-6} alkyl;

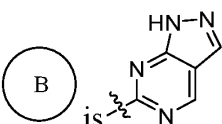
or

 is B , which is optionally substituted with one or more groups independently chosen from: $-(\text{C}_{1-6} \text{ alkylene})_n-\text{C}_{3-6} \text{ cycloalkyl}$, wherein n is 0 or 1; wherein the C_{3-6} cycloalkyl is optionally substituted with one or more halogen;

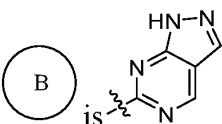
or

 is B , which is optionally substituted with one or more groups independently chosen from: $-(\text{C}_{1-6} \text{ alkylene})_n\text{-phenyl}$, wherein n is 0 or 1;

15 or

 is B , which is optionally substituted with one or more groups independently chosen from: 4-6 membered heterocyclyl; wherein the 4-6 membered heterocyclyl is oxetanyl;

or

 is B , which is optionally substituted with one or more groups independently chosen from: 5-6 membered heteroaryl; wherein the 5-6 membered heteroaryl is pyridyl.

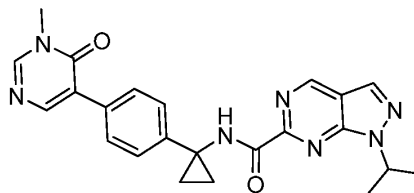
Embodiment 15. The compound of formula (I), or a pharmaceutically acceptable salt thereof according to embodiment 1, wherein the compound of formula (I) is chosen from compounds 1-19, 22-48 and 53-95:

Compound

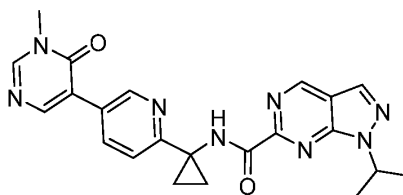
Structure

No.

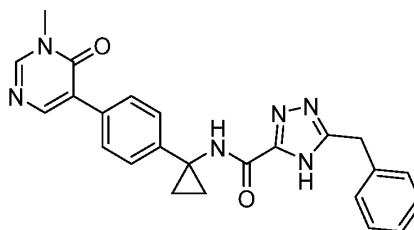
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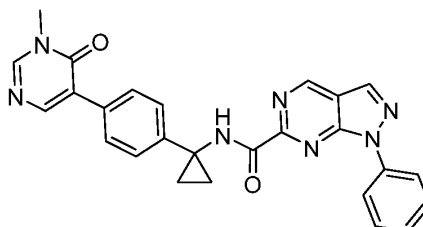
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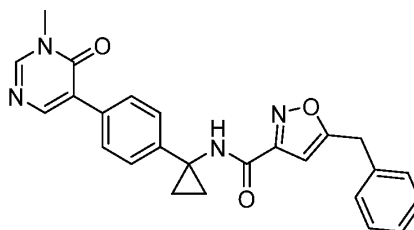
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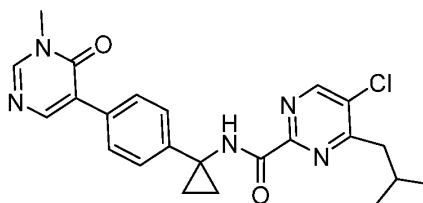
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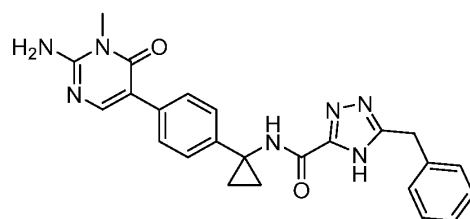
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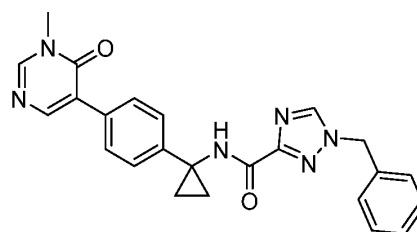
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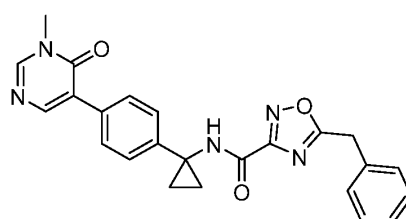
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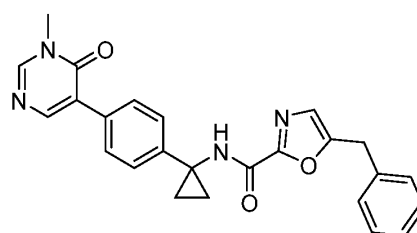
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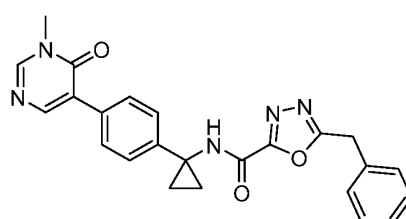
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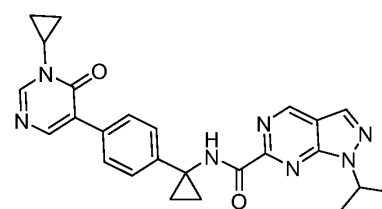
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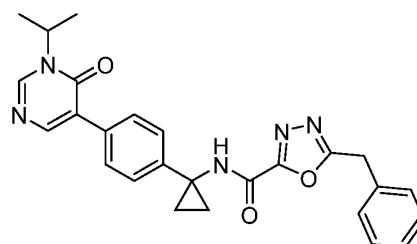
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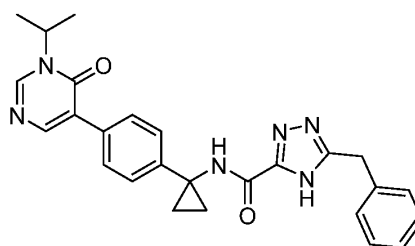
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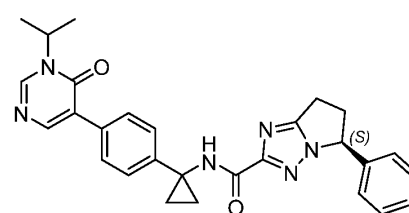
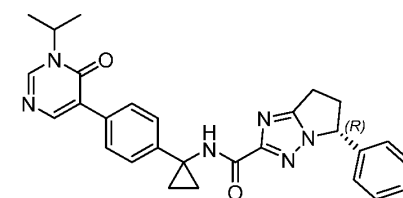


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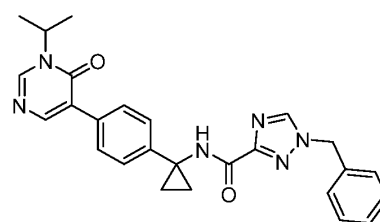


15 and 16

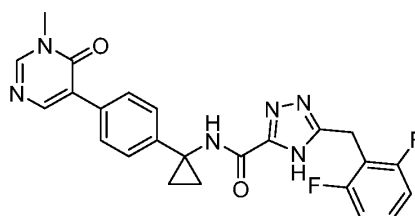
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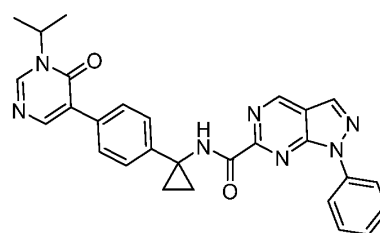
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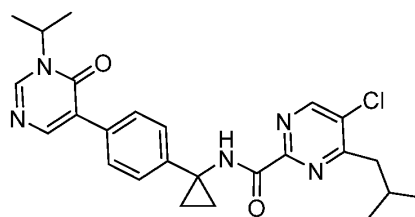
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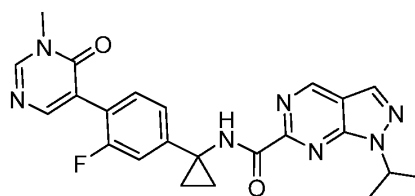
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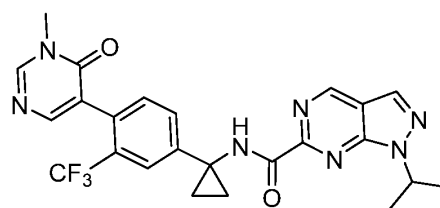
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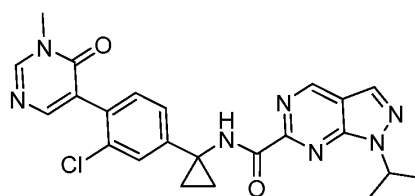
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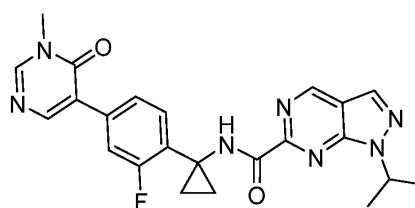
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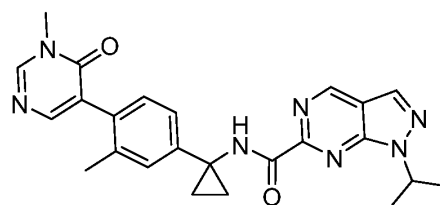
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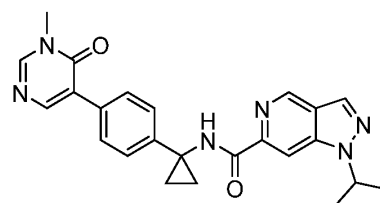
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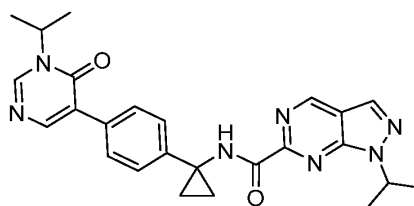
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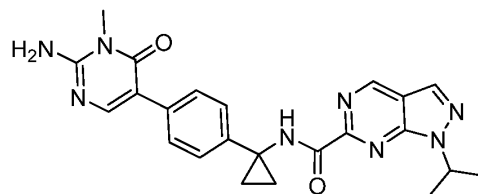
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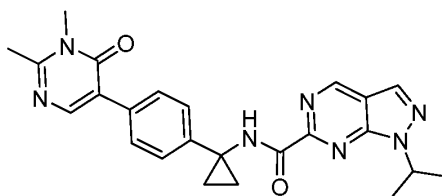
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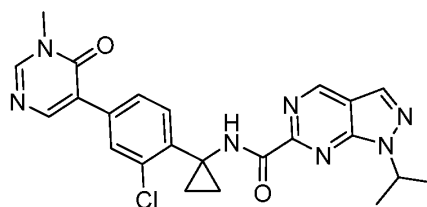
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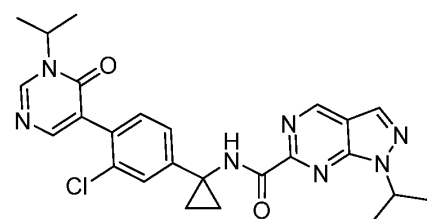
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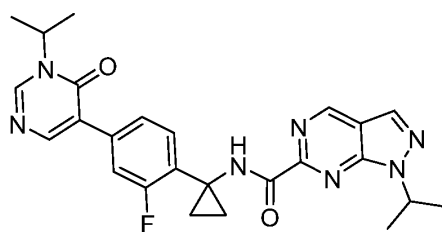
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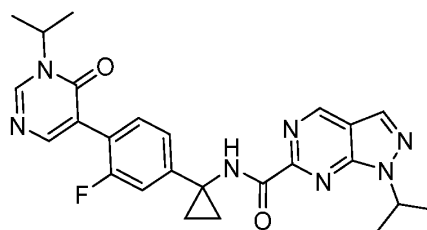
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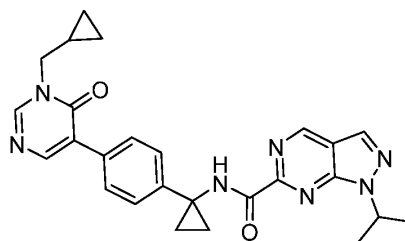
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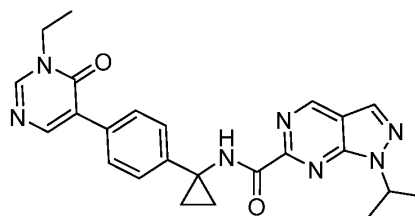
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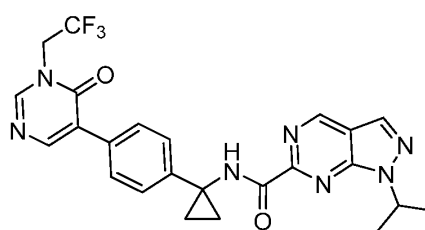
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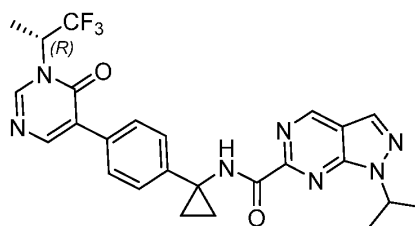
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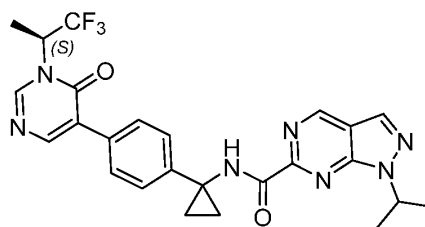
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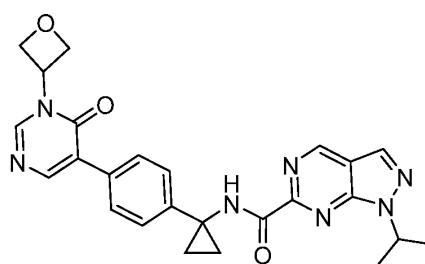
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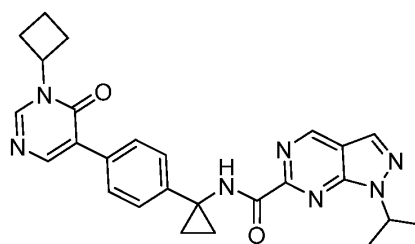
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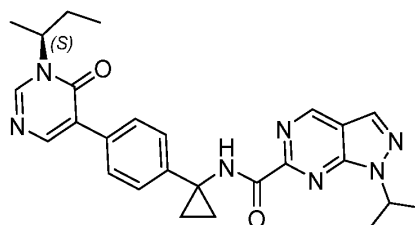
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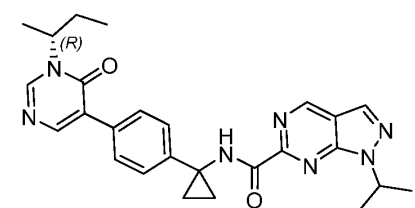
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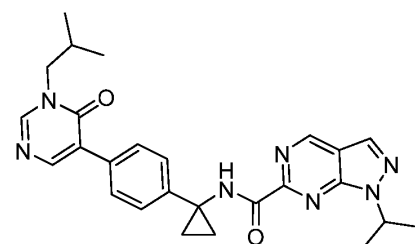
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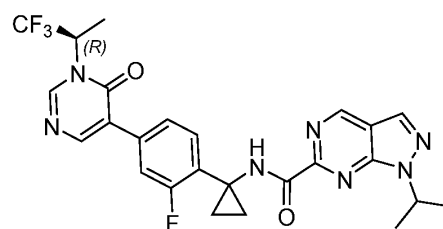
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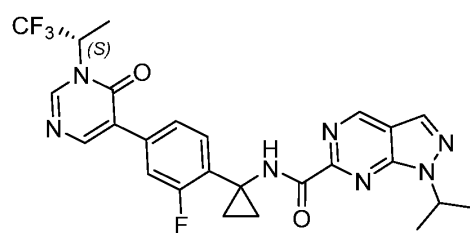
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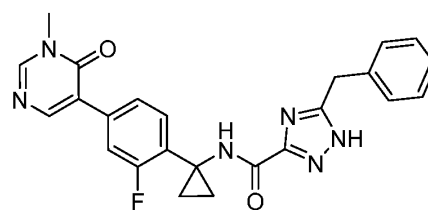
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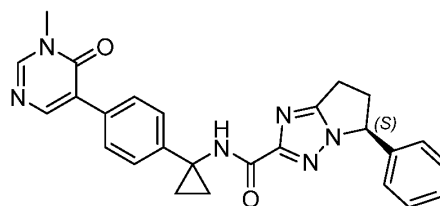


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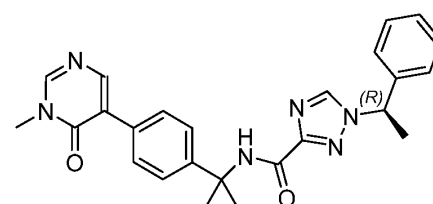
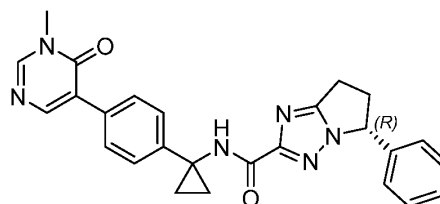
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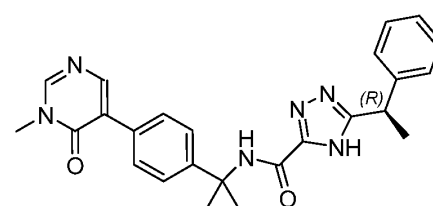
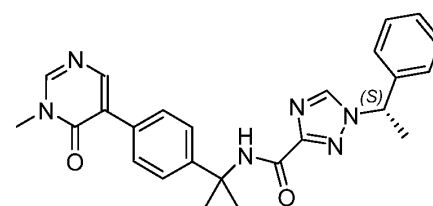
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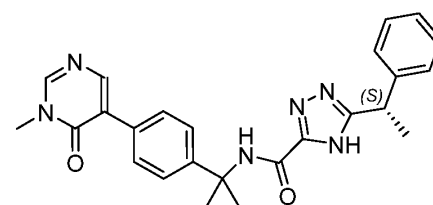
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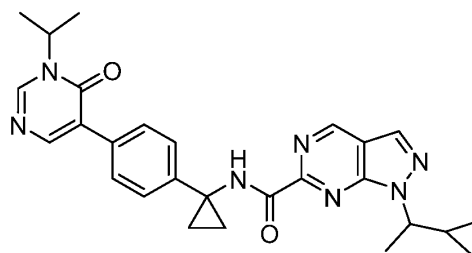


57 and 58

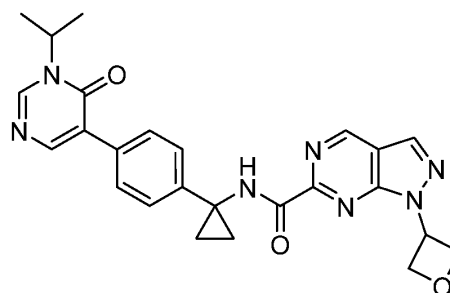
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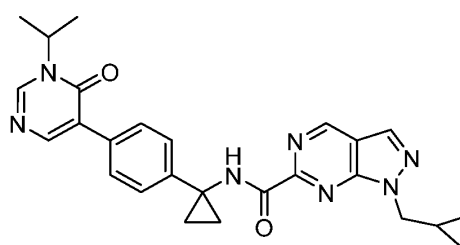
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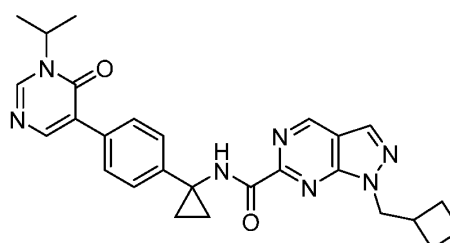
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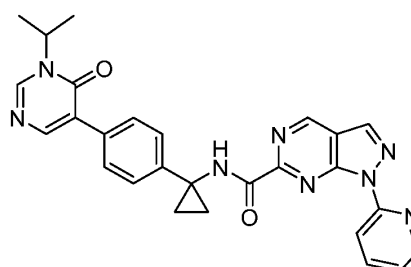
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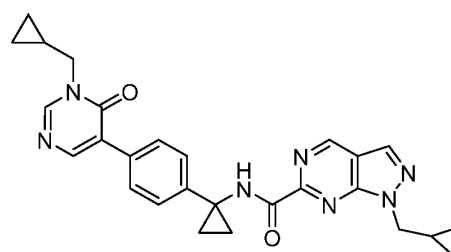
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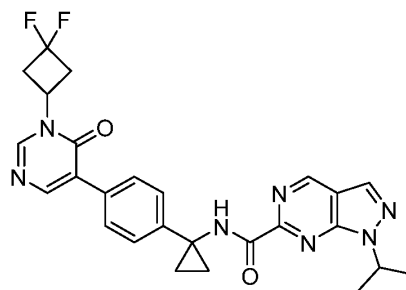
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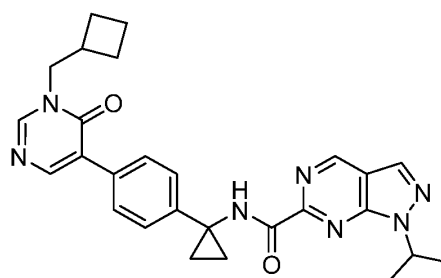
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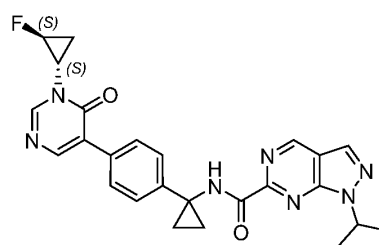
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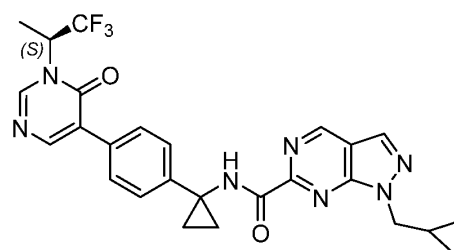
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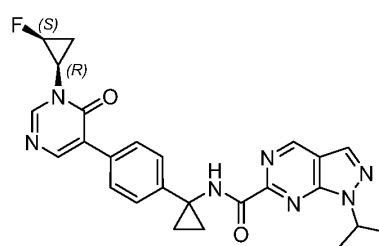
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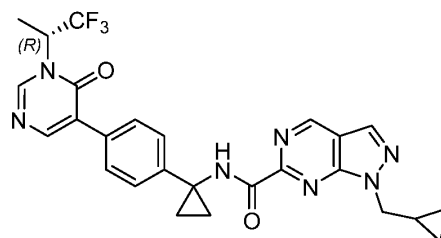
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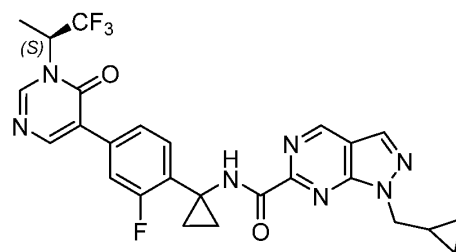
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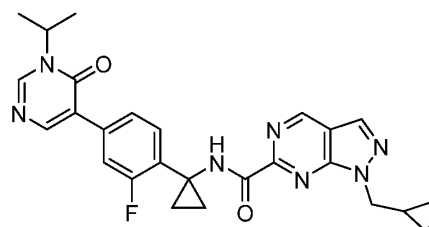
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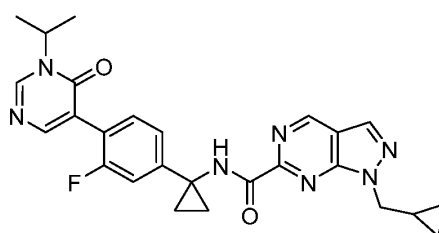
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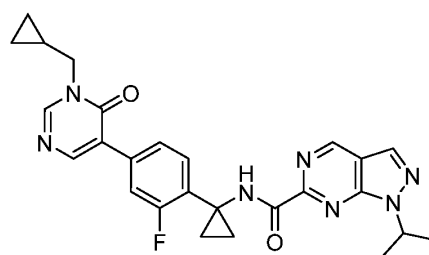
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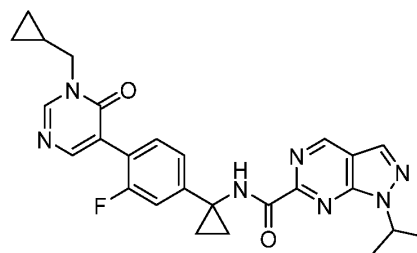
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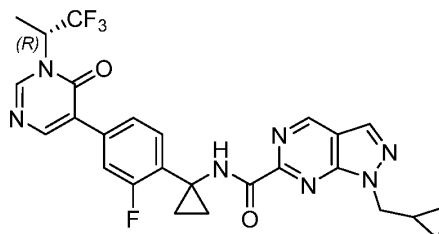
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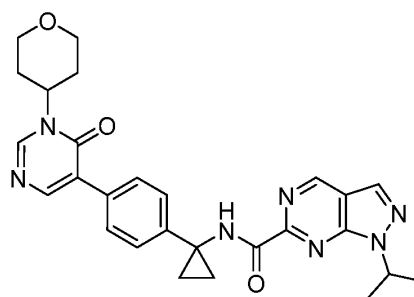
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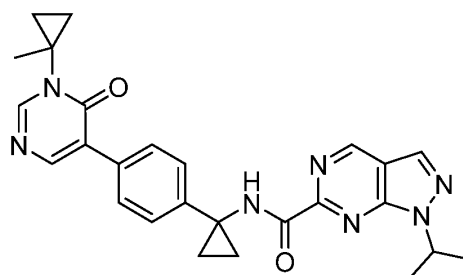
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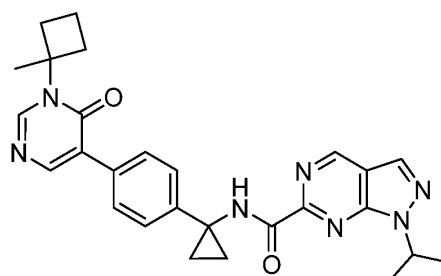
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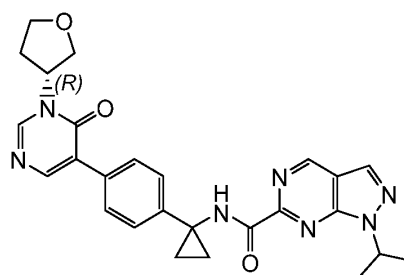


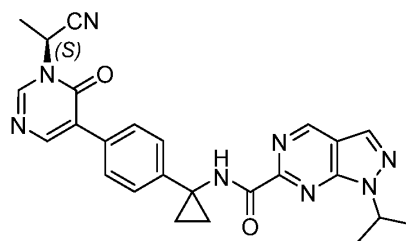
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80 and 81

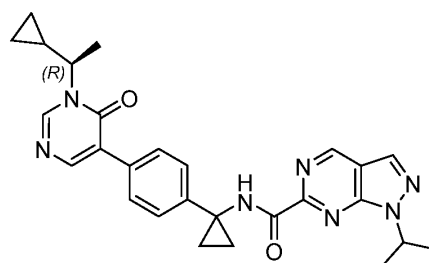
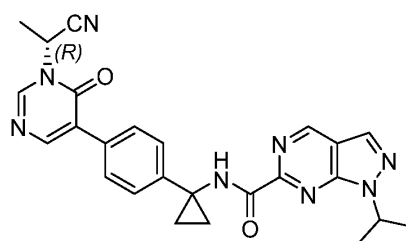
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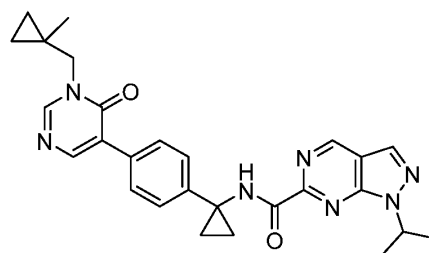
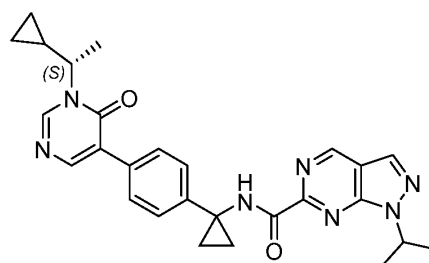
82 and 83

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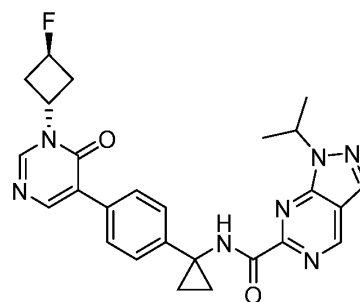


84 and 85

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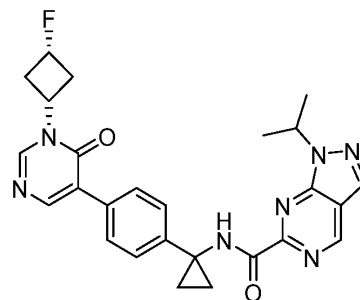


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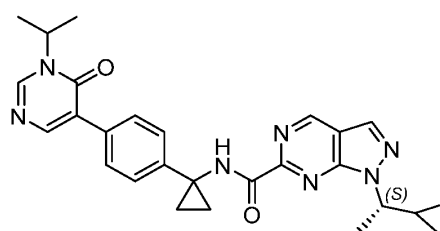
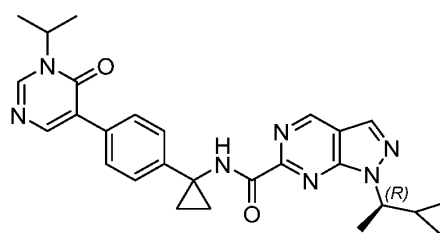
87 and 88

and



89 and 90

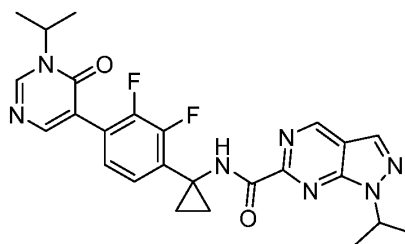
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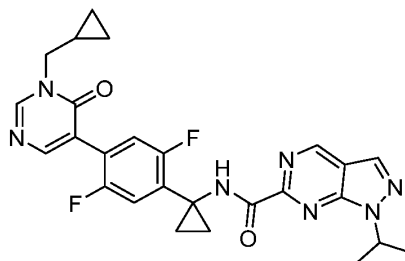
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92

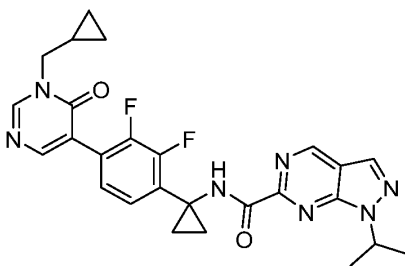
93



94



95



Embodiment 16. A pharmaceutical composition, comprising the compound or a pharmaceutically acceptable salt thereof according to any one of embodiments 1-15, and optionally comprising a pharmaceutically acceptable carrier.

Embodiment 17. A method of *in vivo* or *in vitro* inhibiting the activity of RIPK1, comprising contacting RIPK1 with an effective amount of the compound or a pharmaceutically acceptable salt thereof according to any one of embodiments 1-15.

Embodiment 18. A method of treating a disease partially or completely mediated by RIPK1 in a subject, comprising administering to the subject an effective amount of the compound or a pharmaceutically acceptable salt thereof according to any one of embodiments 1-15.

Embodiment 19. The method according to embodiment 18, wherein the disease is chosen from an autoimmune disease, an inflammatory disease, a neurodegenerative disease and cancer.

Embodiment 20. The compound or a pharmaceutically acceptable salt thereof according to any one of embodiments 1-15, for use as a medicament.

Embodiment 21. The compound or a pharmaceutically acceptable salt thereof according to any one of embodiments 1-15, for use in the treatment of a disease partially or completely mediated by RIPK1 in a subject.

Embodiment 22. The compound or a pharmaceutically acceptable salt thereof
5 according to embodiment 21, wherein the disease is chosen from an autoimmune disease, an inflammatory disease, a neurodegenerative disease and cancer.

Embodiment 23. Use of the compound or a pharmaceutically acceptable salt thereof according to any one of embodiments 1-15 in the manufacture of a medicament for treating a disease partially or completely mediated by RIPK1 in a subject.

10 Embodiment 24. The use according to embodiment 23, wherein the disease is chosen from an autoimmune disease, an inflammatory disease, a neurodegenerative disease and cancer.

Embodiment 25. A pharmaceutical combination, comprising the compound or a pharmaceutically acceptable salt thereof according to any one of embodiments 1-15, and
15 at least one additional therapeutic agent.

Embodiment 26. The pharmaceutical combination according to embodiment 25, wherein the therapeutic agent is an anti-inflammatory agent or an anti-neoplastic agent; preferably, the anti-neoplastic agent is chosen from a radiotherapeutic agent, a chemotherapeutic agent, an immunotherapeutic agent and a targeted therapeutic agent.

20 The diseases partially or completely mediated by RIPK1 described herein can be more specifically selected from multiple sclerosis, systemic scleroderma, inflammatory bowel diseases (including Crohn's disease, ulcerative colitis), psoriasis, atopic dermatitis, asthma, chronic obstructive pulmonary disease, Behcet's disease, rheumatoid arthritis, spinal arthritis, osteoarthritis, systemic juvenile idiopathic arthritis (SoJIA), retinitis
25 pigmentosa, retinal degeneration, age-related macular degeneration, pancreatitis, ischemia reperfusion injury of parenchymatous organs, organ-graft rejection, septicemia, systemic inflammatory response syndrome, chemotherapy drugs induced organ injury, non-alcoholic fatty liver disease, alcohol fatty liver disease, atherosclerosis, Gaucher's Disease, Huntington's disease, Alzheimer's disease, Parkinson's disease, amyotrophic
30 lateral sclerosis (ALS) and spinal muscular atrophy (SMA).

The autoimmune disease or inflammatory disease described herein can be more specifically chosen from multiple sclerosis, systemic scleroderma, inflammatory bowel

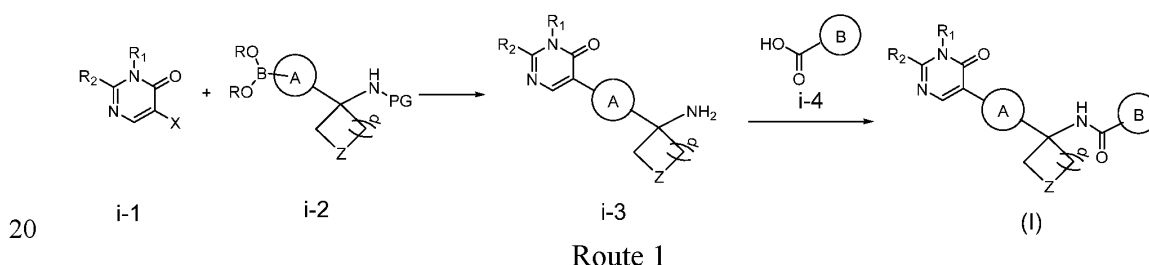
diseases (including Crohn's disease, ulcerative colitis), psoriasis, atopic dermatitis, asthma, chronic obstructive pulmonary disease, Behcet's disease, rheumatoid arthritis, spinal arthritis, osteoarthritis, systemic juvenile idiopathic arthritis (SoJIA), ischemia reperfusion injury of parenchymatous organs, organ-graft rejection, septicemia, systemic inflammatory response syndrome, systemic lupus erythematosus and autoimmune nephritis.

The neurodegenerative diseases described herein can be more specifically chosen from Parkinson's disease (PD), multiple system atrophy (MSA), Alzheimer's disease (AD), frontotemporal lobar dementia, Huntington's disease (HD), corticobasal degeneration, spinocerebellar ataxia (SCA), amyotrophic lateral sclerosis (ALS), spinal muscular atrophy (SMA), hereditary motor and sensory neuropathy (CMT), etc.

The cancer described herein can be solid tumor or hematologic malignancy (e.g., leukemia, lymphoma or myeloma).

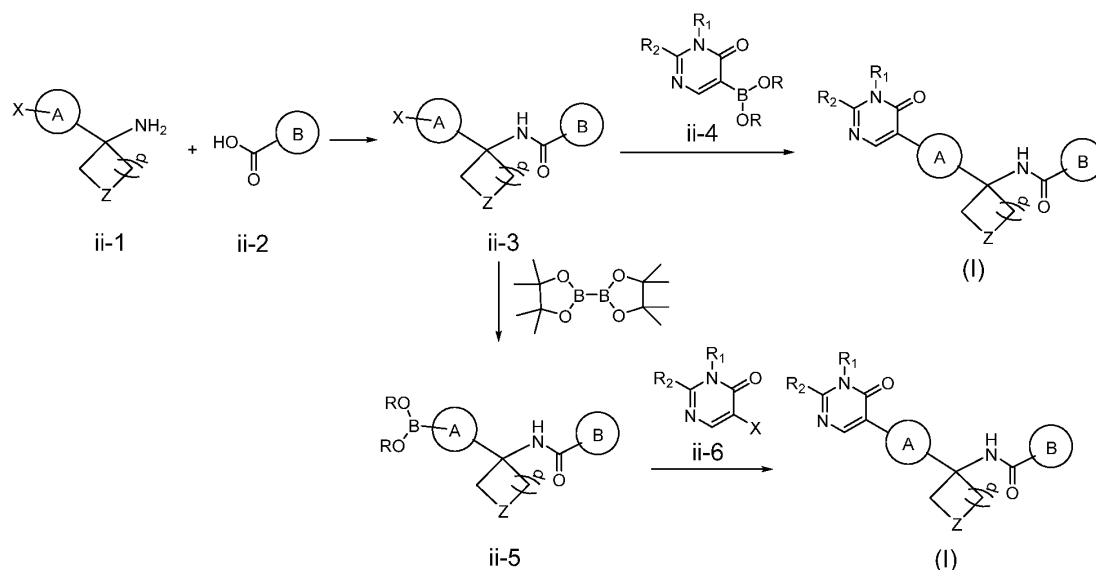
General synthetic methods

The compound of formula (I) or a pharmaceutically acceptable salt thereof described herein can be synthesized using commercially available materials, by methods known in the art, or methods disclosed in the application. The synthetic methods shown in routes 1 and 2 illustrate the general synthetic methods for preparing the compounds of the present invention.



As shown in route 1, a compound of formula i-1 is subjected to coupling reaction and deprotection reaction with a compound of formula i-2 to give an amino compound of formula i-3, which is subjected to condensation reaction with a carboxylic acid

25 compound of formula i-4 to give a compound of formula (I), wherein R_1 , R_2 , Z , p , $\textcircled{A}$, $\textcircled{B}$ are as defined above; X is halogen; PG is a protecting group; $B(OR)_2$ is boronic acid or borate.



As shown in route 2, a compound of formula **ii-1** is subjected to condensation
 5 reaction with a compound of formula **ii-2** to give a compound of formula **ii-3**, then which
 is subjected to coupling reaction with boronic acid or borate of formula **ii-4** to give the
 compound of formula (I); or the compound of formula **ii-3** is reacted with
 bis(pinacolato)diboron to give a compound of formula **ii-5**, then which is subjected to
 coupling reaction with a halogenated compound of formula **ii-6** to give the compound of
 10 formula (I), wherein R_1 , R_2 , Z, p, $\textcircled{A}$, $\textcircled{B}$ are as defined above; X is halogen; $B(OR)_2$
 is boronic acid or borate.

The substituents of the compounds thus obtained can be further modified to provide
 other desired compounds. Synthetic chemistry transformations are described, for example,
 in R. Larock, *Comprehensive Organic Transformations*, VCH Publishers (1989); L.
 15 Fieser and M. Fieser, *Fieser and Fieser's Reagents for Organic Synthesis*, John Wiley
 and Sons (1994); *Encyclopedia of Reagents for Organic Synthesis*, edited by L. Paquette,
 John Wiley and Sons (1995) and subsequent editions thereof.

Before use, the compound of formula (I) or a pharmaceutically acceptable salt
 thereof described herein can be purified by column chromatography, high performance
 20 liquid chromatography, crystallization or other suitable methods.

Pharmaceutical Compositions and Utility

A composition comprising the compound of formula (I) or a pharmaceutically acceptable salt thereof described herein can be administered in various known manners, such as orally, parenterally, by inhalation spray, or via an implanted reservoir. The term
5 “parenteral” as used herein includes subcutaneous, intracutaneous, intravenous, intramuscular, intraarticular, intraarterial, intrasynovial, intrasternal, intrathecal, intralesional and intracranial injection or infusion techniques.

An oral composition can be any orally acceptable dosage form including, but not limited to, tablets, capsules, pills, powder, emulsions, and aqueous suspensions,
10 dispersions and solutions. Commonly used carriers for tablets include lactose and corn starch. Lubricating agents, such as magnesium stearate, are also typically added to tablets. For oral administration in a capsule form, useful diluents include lactose and dried corn starch. When aqueous suspensions or emulsions are administered orally, the active ingredient can be suspended or dissolved in an oily phase combined with emulsifying or
15 suspending agents. If desired, certain sweetening, flavoring, or coloring agents can be added.

A sterile injectable composition (e.g., aqueous or oleaginous suspension) can be formulated according to techniques known in the art using suitable dispersing or wetting agents (e.g., Tween 80) and suspending agents. The sterile injectable composition can
20 also be a sterile injectable solution or suspension in a non-toxic parenterally acceptable diluent or solvent, for example, as a solution in 1,3-butanediol. Among the pharmaceutically acceptable vehicles and solvents that can be employed are mannitol, water, Ringer’s solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium (e.g., synthetic
25 mono- or di-glycerides). Fatty acids, such as oleic acid and its glyceride derivatives, and natural pharmaceutically acceptable oils, such as olive oil or castor oil, especially in their polyoxyethylated versions, are often used in the preparation of an injectable composition. These oil solutions or suspensions can also contain a long-chain alcohol diluent or dispersant or carboxymethyl cellulose or similar dispersing agents.

30 An inhalation composition can be prepared according to techniques well known in the art of pharmaceutical formulation and can be prepared as solutions in saline, employing benzyl alcohol or other suitable preservatives, absorption promoters to

enhance bioavailability, fluorocarbons, and/or other solubilizing or dispersing agents known in the art.

A topical composition can be formulated in form of oil, cream, lotion, ointment, and the like. Suitable carriers for the composition include vegetable or mineral oils, white petrolatum (white soft paraffin), branched chain fats or oils, animal fats and high molecular weight alcohols (greater than C12). In some embodiments, the pharmaceutically acceptable carrier is one in which the active ingredient is soluble. Emulsifiers, stabilizers, humectants and antioxidants may also be included as well as agents imparting color or fragrance, if desired. Additionally, transdermal penetration enhancers may be employed in those topical formulations. Examples of such enhancers can be found in U.S. Patent Nos. 3,989,816 and 4,444,762.

Creams may be formulated from a mixture of mineral oil, self-emulsifying beeswax and water in which mixture the active ingredient, dissolved in a small amount of an oil, such as almond oil, is admixed. An example of such a cream is one which includes, by weight, about 40 parts water, about 20 parts beeswax, about 40 parts mineral oil and about 1 part almond oil. Ointments may be formulated by mixing a solution of the active ingredient in a vegetable oil, such as almond oil, with warm soft paraffin and allowing the mixture to cool. An example of such an ointment is one which includes about 30% by weight almond oil and about 70% by weight white soft paraffin.

A pharmaceutically acceptable carrier refers to a carrier that is compatible with active ingredients of the composition (and in some embodiments, capable of stabilizing the active ingredients) and not deleterious to the subject to be treated. For example, solubilizing agents, such as cyclodextrins (which form specific, more soluble complexes with the compound of formula (I) or a pharmaceutically acceptable salt thereof described herein), can be utilized as pharmaceutical excipients for delivery of the active ingredients. Examples of other carriers include colloidal silicon dioxide, magnesium stearate, cellulose, sodium lauryl sulfate, and pigments such as D&C Yellow # 10.

In some embodiments, the compound of formula (I) or a pharmaceutically acceptable salt thereof can be present in an amount of 1, 5, 10, 15, 20, 25, 50, 75, 80, 85, 90, 95, 100, 125, 150, 200, 250, 300, 400 and 500 mg in a tablet. In some embodiments, the compound of formula (I) or a pharmaceutically acceptable salt thereof can be present

in an amount of 1, 5, 10, 15, 20, 25, 50, 75, 80, 85, 90, 95, 100, 125, 150, 200, 250, 300, 400 and 500 mg in a capsule.

Suitable *in vitro* assays can be used to evaluate the practical utility of the compound of formula (I) or a pharmaceutically acceptable salt thereof described herein in inhibiting the activity of RIPK1. The compound of formula (I) or a pharmaceutically acceptable salt thereof described herein can further be examined for the utility in treating autoimmune diseases, inflammatory diseases, neurodegenerative diseases or cancers by *in vivo* assays. For example, the compound of formula (I) or a pharmaceutically acceptable salt thereof described herein can be administered to an animal (e.g., a mouse model) having an autoimmune disease or an inflammatory disease and its therapeutic effects can be accessed. If the pre-clinical results are successful, the dosage range and administration route for animals, such as humans, can be projected.

The compound of formula (I) or a pharmaceutically acceptable salt thereof described herein can be used to achieve a beneficial therapeutic or prophylactic effect, for example, in subjects with an autoimmune disease or inflammatory disease.

The term “autoimmune disease” refers to a disease or disorder arising from or directed against an individual's own tissues or organs, or a co-segregate or manifestation thereof, or resulting condition therefrom. Examples of autoimmune diseases include, but are not limited to: chronic obstructive pulmonary disease (COPD), allergic rhinitis, lupus erythematosus, myasthenia gravis, multiple sclerosis (MS), rheumatoid arthritis (RA), collagen-induced arthritis, psoriasis, inflammatory bowel disease (IBD), asthma, idiopathic thrombocytopenic purpura (ITP), and myeloproliferative disease, such as myelofibrosis, post-polycythemia vera/essential thrombocythosis myelofibrosis (post-PV/ET myelofibrosis).

The term “inflammatory disease” or “inflammatory disorder” refers to a pathological state that leads to inflammation, especially due to neutrophil chemotaxis. Non-limiting examples of inflammatory diseases include systemic inflammation and local inflammation, inflammation associated with immunosuppression, organ-graft rejection, allergic disease, inflammatory skin disease (including psoriasis and atopic dermatitis); systemic scleroderma and sclerosis; reactions associated with inflammatory bowel diseases (IBD, such as Crohn's disease and ulcerative colitis); ischemia reperfusion injury, including reperfusion injury of tissue caused by surgery, myocardial ischemia,

such as myocardial infarction, cardiac arrest, reperfusion after heart operation and abnormal contractile response of coronary vessel after percutaneous transluminal coronary angioplasty, surgical tissue reperfusion injury of stroke and abdominal aortic aneurysm; cerebral edema secondary to stroke; cranial trauma, and hemorrhagic shock;

5 asphyxia; adult respiratory distress syndrome; acute lung injury; Behcet's disease; dermatomyositis; polymyositis; multiple sclerosis (MS); dermatitis; meningitis; encephalitis; uveitis; osteoarthritis; lupus nephritis; autoimmune disease such as rheumatoid arthritis (RA), Sjorgen's syndrome, and vasculitis; diseases involving leukopedesis; central nervous system (CNS) inflammatory disease and multiple organ

10 injury syndrome secondary to septicemia or trauma; alcoholic hepatitis; bacterial pneumonia; antigen-antibody complex mediated disease, including glomerulonephritis; pyaemia; sarcoidosis; immunopathologic responses to tissue/organ transplantation; lung inflammation, including pleurisy, alveolitis, vasculitis, pneumonia, chronic bronchitis, bronchiectasia, diffuse panthogenic bronchiolitis, hypersensitivity pneumonitis, idiopathic

15 pulmonary fibrosis (IPF), cystic fibrosis, etc. Preferably indications include, but are not limited to, chronic inflammation, autoimmune diabetes, rheumatoid arthritis (RA), rheumatoid spondylitis, gouty arthritis and other arthrosis conditions, multiple sclerosis (MS), asthma, systemic lupus erythematosus, adult respiratory distress syndrome, Behcet's disease, psoriasis, chronic pulmonary inflammatory disease, graft versus host

20 reaction, Crohn's disease, ulcerative colitis, inflammatory bowel disease (IBD), Alzheimer's disease and pyresis, and any diseases associated with inflammation and related conditions.

In some embodiments, the autoimmune disease or inflammatory disease is chosen from multiple sclerosis, systemic scleroderma, inflammatory bowel diseases, Crohn's

25 disease, ulcerative colitis, psoriasis, atopic dermatitis, asthma, chronic obstructive pulmonary disease, Behcet's disease, rheumatoid arthritis, spinal arthritis, osteoarthritis, systemic juvenile idiopathic arthritis (SoJIA), ischemia reperfusion injury of parenchymatous organs, organ-graft rejection, septicemia, systemic inflammatory response syndrome, systemic lupus erythematosus and autoimmune nephritis.

30 The compound of formula (I) or a pharmaceutically acceptable salt thereof described herein can be used to achieve a beneficial therapeutic or prophylactic effect, for example, in subjects with neurodegenerative disease.

The term “neurodegenerative diseases” refers to degenerative diseases or disorders of the nervous system caused by neuronal degeneration and apoptosis. Examples of neurodegenerative diseases include, but are not limited to: Parkinson's disease (PD), multiple system atrophy, Alzheimer's disease (AD), frontotemporal lobar dementia, Huntington's disease (HD), corticobasal degeneration, spinocerebellar ataxia, amyotrophic lateral sclerosis (ALS), spinal muscular atrophy (SMA), hereditary motor and sensory neuropathy (CMT), etc.

The compound of formula (I) or a pharmaceutically acceptable salt thereof described herein can be used to achieve a beneficial therapeutic or prophylactic effect, for example, in subjects with cancer.

As used herein, the term “cancer” refers to a cellular disorder characterized by uncontrolled or dysregulated cell proliferation, decreased cellular differentiation, inappropriate ability to invade surrounding tissue, and/or ability to establish new growth at ectopic sites. The term “cancer” includes, but is not limited to, solid tumors and hematologic malignancies. The term “cancer” encompasses diseases of skin, tissues, organs, bone, cartilage, blood, and vessels. The term “cancer” encompasses primary cancer, and further metastatic cancer.

Non-limiting examples of solid tumors include pancreatic cancer; bladder cancer; colorectal cancer; breast cancer, including metastatic breast cancer; prostate cancer, including androgen-dependent and androgen-independent prostate cancer; testicular cancer; renal cancer, including, e.g., metastatic renal cell carcinoma; urothelial carcinoma; liver cancer; hepatocellular cancer; lung cancer, including, e.g., non-small cell lung cancer (NSCLC), bronchioloalveolar carcinoma (BAC), and adenocarcinoma of the lung; ovarian cancer, including, e.g., progressive epithelial or primary peritoneal cancer; cervical cancer; endometrial cancer; gastric cancer; esophageal cancer; head and neck cancer, including, e.g., squamous cell carcinoma of the head and neck; skin cancer, including, e.g., melanoma and basal carcinoma; neuroendocrine cancer, including metastatic neuroendocrine tumors; brain tumors, including, e.g., glioma, anaplastic oligodendroglioma, adult glioblastoma multiforme, and adult anaplastic astrocytoma; bone cancer; sarcoma, including, e.g., Kaposi's sarcoma; adrenal carcinoma; mesothelial carcinoma; choriocarcinoma; muscle carcinoma; connective tissue carcinoma; and thyroid carcinoma.

Non-limiting examples of hematologic malignancies include acute myelogenous leukemia (AML); chronic myelogenous leukemia (CML), including accelerated phase CML and CML blastic phase (CML-BP); acute lymphocytic leukemia (ALL); chronic lymphocytic leukemia (CLL); Hodgkin's lymphoma; non-Hodgkin's lymphoma (NHL);
5 follicular lymphoma; mantle cell lymphoma (MCL); B-cell lymphoma; T-cell lymphoma; diffuse large B-cell lymphoma (DLBCL); multiple myeloma (MM); Waldenstrom's macroglobulinemia; myelodysplastic syndrome (MDS), including refractory anemia (RA), refractory anemia with ringed siderblast (RARS), refractory anemia with excess blast (RAEB) and refractory anemia with excess blast in transformation (RAEB-T); and
10 myeloproliferative syndrome.

In addition, the compound of formula (I) (e.g., the compound of formula (I-1) or a compound of any of the examples as described herein) or a pharmaceutically acceptable salt thereof described herein can be administered in combination with additional therapeutic agents, for treating the autoimmune disease, inflammatory disease or cancer.
15 The additional therapeutic agents may be administered separately with the compound of formula (I) or a pharmaceutically acceptable salt thereof described herein or included with such an ingredient in a pharmaceutical composition according to the disclosure, such as a fixed-dose combination drug product. In some embodiments, the additional therapeutic agents are those that are known or discovered to be effective in the treatment
20 of a disease partially or completely mediated by RIPK1, such as another RIPK1 inhibitor or a compound active against another target associated with the particular disease. The combination may serve to increase efficacy (e.g., by including in the combination a compound potentiating the potency or effectiveness of the compound of formula (I) or a pharmaceutically acceptable salt thereof described herein), decrease one or more side
25 effects, or decrease the required dose of the compound of formula (I) or a pharmaceutically acceptable salt thereof described herein.

In some embodiments, the compound of formula (I) (e.g., the compound of formula (I-1) or a compound of any of the examples as described herein) or a pharmaceutically acceptable salt thereof described herein can be administered in combination with anti-
30 inflammatory agents.

Examples of anti-inflammatory agent include, but are not limited to, adrenocortical hormones (such as fluticasone propionate, beclometasone dipropionate, mometasone

furoate, triamcinolone acetonide or budesonide), disease modifying agents (such as antimalarial drugs, methotrexate, sulfasalazine, masalazine, azathioprine, 6-mercaptopurine, metronidazole, D-penicillamine), non-steroidal anti-inflammatory drugs (such as acetaminophen, aspirin, sodium salicylate, cromoglycate sodium, magnesium salicylate, choline magnesium trisalicylate, salsalate, ibuprofen, naproxen, diclofenac, diflunisal, etodolac, fenoprofen calcium, flurbiprofen, piroxicam, indomethacin, ketoprofen, ketorolac tromethamine, meclofenamic acid, meclofenamate sodium, mefenamic acid, nabumetone, oxaprozin, phenyl butyl nitron (PBN), sulindac or tolmetin), COX-2 inhibitors, cytokine synthesis/release inhibitors (such as anti-cytokine antibody, anti-cytokine receptor antibody, etc.).

In some embodiments, the compound of formula (I) (e.g., the compound of formula (I-1) or a compound of any of the examples as described herein) or a pharmaceutically acceptable salt thereof described herein can be administered in combination with anti-neoplastic agents. The term “anti-neoplastic agent” as used herein refers to any agent that is administered to a subject suffering from cancer for the purposes of treating the cancer, includes, but is not limited to a radiotherapeutic agent, a chemotherapeutic agent, an immunotherapeutic agent, a targeted therapeutic agent, and the like.

Non-limiting examples of chemotherapeutic agents include topoisomerase I inhibitors (e.g., irinotecan, topotecan, camptothecin and analogs or metabolites thereof, and doxorubicin); topoisomerase II inhibitors (e.g., etoposide, teniposide, mitoxantrone, idarubicin, and daunorubicin); alkylating agents (e.g., melphalan, chlorambucil, busulfan, thiotepa, ifosfamide, carmustine, lomustine, semustine, streptozocin, decarbazine, methotrexate, mitomycin C, and cyclophosphamide); DNA intercalators (e.g., cisplatin, oxaliplatin, and carboplatin); DNA intercalators and free radical generators such as bleomycin; nucleoside mimetics (e.g., 5-fluorouracil, capecitabine, gemcitabine, fludarabine, cytarabine, azacitidine, mercaptopurine, thioguanine, pentostatin, and hydroxyurea); paclitaxel, docetaxel, and related analogs; vincristine, vinblastin, and related analogs; thalidomide and related analogs (e.g., CC-5013 and CC-4047).

Non-limiting examples of the immunotherapeutic agents or the targeted therapeutic agents include MEK inhibitor, RAF inhibitor, mTOR inhibitor, PAK inhibitor, CDK inhibitor, VEGFR inhibitor, PARP inhibitor, ERBB inhibitor, PI3K inhibitor, AKT inhibitor, IDO inhibitor, A2AR inhibitor, autophagy inhibitor, immune checkpoint

inhibitor, such as PD-1 inhibitor, PD-L1 inhibitor, etc. For example, Trametinib, Cobimetinib, Vemurafenib, Dabrafenib, Rapamycin, Temsirolimus, Everolimus, Palbociclib, Ribociclib, Fruquintinib, Olaparib, Niraparib, Neratinib, Chloroquine, Hydroxychloroquine, LXH254, Selumetinib, LY3214996, Abemaciclib, P1446A-05
5 (Voruciclib), LGX818 (Encorafenib), ARRY-162 (Binimetinib), Gefitinib, Imatinib mesylate, Cetuximab, Trastuzumab, Rituximab, Panitumumab, BYL719 (Alpelisib), Bevacizumab, Pembrolizumab, Atezolizumab, PDR001 (Spartalizumab), Durvalumab, Nivolumab, Avelumab, Libtayo (Cemiplimab), Tislelizumab, JS001, Sintilimab, Camrelizumab and the like.

10

Examples

The examples below are intended to be purely exemplary and should not be considered to be limiting in any way. Efforts have been made to ensure the accuracy with respect to numbers used (e.g., amounts, temperature, etc.), but the POSITA should
15 understand that some experimental errors and deviations should be accounted for. Unless indicated otherwise, parts are parts by weight, temperature is in degrees Centigrade, and pressure is at or near atmospheric. All MS data were determined by Agilent 6120 or Agilent 1100. All NMR data were generated using a Varian 400 MR machine. All reagents, except intermediates, used in this invention are commercially available. All
20 compound names except the reagents are generated by Chemdraw 18.2.

If there is any atom with empty valence(s) in any one of the structures disclosed herein, the empty balance(s) is (are) the hydrogen atom(s) which is (are) omitted for convenience purpose.

In the present application, in the case of inconsistency of the name and structure of a
25 compound, when the two of which are both given for the compound, it is subject to the structure of the compound, unless the context shows that the structure of the compound is incorrect and the name is correct.

In the following examples, the abbreviations are used:

AcOH	Acetic acid
AgNO ₃	Silver nitrate
BF ₃ OEt ₂	Boron trifluoride diethyl etherate
CDCl ₃	Deuterated chloroform

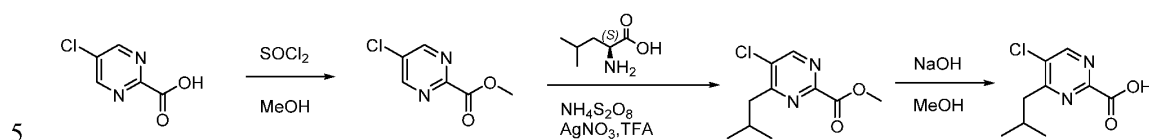
Cs ₂ CO ₃	Cesium carbonate
Cu(OAc) ₂	Copper acetate
DBU	1,8-diazabicyclo-undec-7-ene
DCM or CH ₂ Cl ₂	Dichloromethane
DCE	1,2-dichloroethane
DIEA	<i>N,N</i> -diisopropylethylamine
DIAD	Diisopropyl azodicarboxylate
DEA	Diethylamine
DMF	<i>N,N</i> -dimethylformamide
DMSO	Dimethyl sulfoxide
EA	Ethyl acetate
EtOH	Ethanol
HATU	<i>O</i> -(7-azabenzotriazole-1-yl)- <i>N,N,N',N'</i> -tetramethyluronium hexafluorophosphate
IPA	Isopropanol
K ₂ CO ₃	Potassium carbonate
KOAc	Potassium acetate
LiOH	Lithium hydroxide
MeOH	Methanol
MeCN	Acetonitrile
MeI	Iodomethane
MeONa	Sodium methoxide
NaOH	Sodium hydroxide
NCS	<i>N</i> -chlorosuccinimide
NH ₂ NH ₂	Hydrazine
NH ₄ SO ₂ O ₈	Ammonium persulphate
NMP	<i>N</i> -methylpyrrolidone
Pd(dppf)Cl ₂	[1,1'-bis(diphenylphosphino) ferrocene]palladium dichloride
Pd(PPh ₃) ₄	Tetra(triphenylphosphine)palladium
PPh ₃	Triphenylphosphine
PE	Petroleum ether

POCl ₃	Phosphorus oxychloride
Pyridine	Pyridine
SOCl ₂	Thionyl chloride
Ti(i-PrO) ₄	Titanium tetraisopropoxide
THF	Tetrahydrofuran
TEA	Triethylamine
TFA	Trifluoroacetic acid
Tol	Toluene
TLC	Thin-layer chromatography
p-TLC	Preparative thin-layer chromatography
Zn(CN) ₂	Zinc cyanide

Example 1. Preparation of intermediates and compounds

Intermediate 1

5-chloro-4-isobutylpyrimidine-2-carboxylic acid



(A) methyl 5-chloropyrimidine-2-carboxylate

Methyl 5-chloropyrimidine-2-carboxylate (500 mg, 3.15 mmol) was dissolved in MeOH (20 mL), then SOCl₂ (0.5 mL) was added slowly. The solution was warmed to 80°C and reacted overnight. TLC (PE : EA = 5 : 1) showed that the reaction was completed. After cooling, the reaction solution was concentrated under reduced pressure and the residue was purified by flash column chromatography (eluting with gradient MeOH/H₂O = 0% - 100%) to give 500 mg of the product.

(B) methyl 5-chloro-4-isobutylpyrimidine-2-carboxylate

15 Methyl 5-chloropyrimidine-2-carboxylate (500 mg, 2.90 mmol), L-leucine (760 mg, 5.80 mmol) and NH₄S₂O₈ (3.04 g, 14.49 mmol) were dissolved in a mixed solvent of DCE (10 mL) and H₂O (9 mL), then TFA (218 uL, 2.9 mmol) was added. The mixture was stirred at room temperature for about 1 minute. A solution of 2 mol/L AgNO₃ in H₂O (1.45 mL, 2.90 mmol) was added in one portion. The mixture was warmed to 80°C and 20 reacted for 24 hours. After the reaction was completed, the reaction solution was cooled

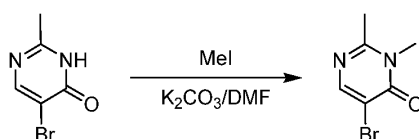
and concentrated under reduced pressure, and the residue was purified by flash column chromatography (eluting with gradient MeOH/H₂O = 0% - 100%) to give 80 mg of product. MS (m/z) = 229 [M+H]⁺.

(C) 5-chloro-4-isobutylpyrimidine-2-carboxylic acid

- 5 Methyl 5-chloro-4-isobutylpyrimidine-2-carboxylate (80 mg, 0.35 mmol) was dissolved in MeOH (5 mL), 2 mol/L NaOH in H₂O (1.0 mL, 2.0 mmol) was added. The solution was reacted at room temperature for 2 hours. After the reaction was completed, 2 mol/L HCl aqueous solution was added until pH was about 7. The mixed solution was concentrated under reduced pressure, and the residue was purified by flash column chromatography (eluting with gradient MeOH/H₂O = 0% - 100%) to give 70 mg of the product. MS (m/z) = 215 [M+H]⁺.

Intermediate 2

5-bromo-2,3-dimethylpyrimidin-4(3H)-one

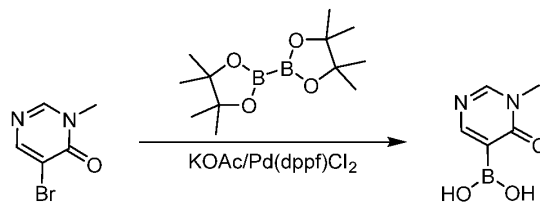


- 15 The mixture of 5-bromo-2-methylpyrimidin-4(3H)-one (756 mg, 4 mmol), iodomethane (568 mg, 4 mmol), and potassium carbonate (828 mg, 6 mmol) in DMF (5 mL) was stirred at room temperature under nitrogen atmosphere for 2 hours. After the reaction was completed, water (10 mL) was added to the reaction system, and the mixture was extracted with ethyl acetate (10 mL x 3). The organic layer was washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified by column chromatography (eluting with gradient PE/EA = 10% - 50%) to obtain 500 mg of the product as pale yellow solid. MS (m/z) = 203 [M+H]⁺.

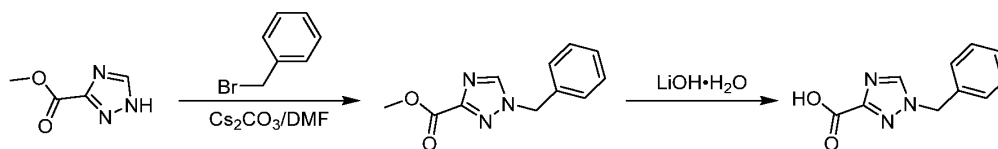
- The following intermediates were prepared according to the procedure of Intermediate 2 using the corresponding materials and reagents under appropriate conditions that will be recognized by one skilled in the art.

Intermediate No.	Structural formula	MS (M+H) ⁺	Intermediate No.	Structural formula	MS (M+H) ⁺
3		216.9	4		229, 231 [M+2H] ⁺

5		203.9	36		227.8, 229.8 [M+2H] ⁺
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Intermediate 6**(1-methyl-6-oxo-1,6-dihydropyrimidin-5-yl)boronic acid**

- 5 The mixture of 5-bromo-3-methylpyrimidin-4(3H)-one (1 g, 5.29 mmol), bis(pinacolato)diboron (2.02 g, 7.94 mmol), KOAc (1.56 g, 15.87 mmol), and Pd(dppf)Cl₂ (194 mg, 0.26 mmol) in dioxane (30 mL) was stirred at 120°C under nitrogen atmosphere for 2 hours. The solvent was removed. The residue was purified by flash column chromatography (eluting with gradient MeOH/H₂O (+ 0.1% HCOOH)=
- 10 10% - 80%) to give 525 mg of the product as white solid. MS (m/z) = 155 [M+H]⁺.

Intermediate 7**1-benzyl-1H-1,2,4-triazole-3-carboxylic acid**

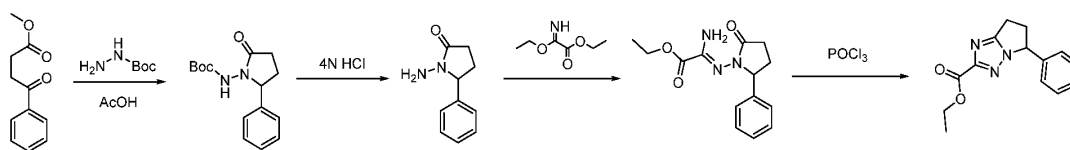
- (A) methyl 1-benzyl-1H-1,2,4-triazole-3-carboxylate
- 15 The mixture of methyl 1H-1,2,4-triazole-3-carboxylate (2 g, 15.7 mmol), (bromomethyl)benzene (2 g, 15.7 mmol), and Cs₂CO₃ (7.68 g, 15.7 mmol) in DMF (100 mL) was stirred at room temperature under nitrogen atmosphere for 5 hours. After the reaction was completed, water (20 mL) was added to the reaction system, and the mixture was extracted with ethyl acetate (20 mL x 3). The organic layer was washed with brine,
- 20 dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified by column chromatography (eluting with gradient PE/EA = 10% - 80%) to obtain 0.8 g of product as white solid. MS (m/z) = 218 [M+H]⁺.
- (B) 1-benzyl-1H-1,2,4-triazole-3-carboxylic acid

Methyl 1-benzyl-1*H*-1,2,4-triazole-3-carboxylate (0.8 g, 3.68 mmol) was dissolved in THF (20 mL), then a solution of LiOH (0.46 g, 11.04 mmol) in water (5 mL) was added. The mixture was stirred at room temperature for 1 hour and then THF was removed. 2N HCl was added to adjust pH = 6. Then the solid was collected by filtration.

- 5 The solid was washed with ice water 3 times. The filter cake was dried to afford 0.5 g of the product. MS (*m/z*) = 204 [*M*+H]⁺.

Intermediate 8

ethyl 5-phenyl-6,7-dihydro-5*H*-pyrrolo[1,2-*b*][1,2,4]triazole-2-carboxylate



- 10 (A) tert-butyl (2-oxo-5-phenylpyrrolidin-1-yl)carbamate

To a solution of methyl 4-oxo-4-phenylbutanoate (5 g, 26.03 mmol) in AcOH (15 mL) was added tert-butyl hydrazinecarboxylate (5.15 g, 39.04 mmol) at room temperature. The reaction mixture was reacted at 40°C overnight, then sodium cyanoborohydride (2.45 g, 39.04 mmol) was added, and the mixture was reacted at the

15 temperature for 4 hours. After the reaction was completed, the mixture was cooled to room temperature and concentrated under reduced pressure. The residue was purified by flash column chromatography (eluting with gradient MeOH/H₂O = 0%- 100%) to give 4.2 g of target product. MS (*m/z*) = 221 [*M*-56]⁺.

(B) 1-amino-5-phenylpyrrolidin-2-one

- 20 To a solution of tert-butyl (2-oxo-5-phenylpyrrolidin-1-yl)carbamate (4.2 g, 15.20 mmol) in MeOH (10 mL) was added 4N HCl (11.4 mL, 45.61 mmol) at room temperature. The reaction mixture was reacted at 50°C for 2 hours. After the reaction was completed, the mixture was cooled to room temperature and concentrated under reduced pressure to give 3.1 g of the target product. MS (*m/z*) = 177 [*M*+H]⁺.

- 25 (C) ethyl (Z)-2-amino-2-((2-oxo-5-phenylpyrrolidin-1-yl)imino)acetate

To a solution of 1-amino-5-phenylpyrrolidin-2-one (2.5 g, 14.20 mmol) in EtOH (10 mL) was added ethyl 2-ethoxy-2-iminoacetate (6.17 g, 42.6 mmol) at room temperature. The reaction mixture was heated to reflux and reacted for 8 hours. After the reaction was completed, the mixture was cooled to room temperature and concentrated under reduced

30 pressure. The residue was purified by flash column chromatography (eluting with

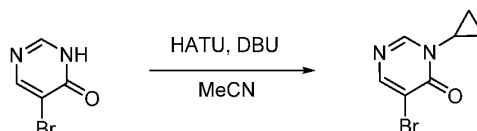
gradient MeOH/H₂O = 0% - 100%) to give 3.2 g of the target product. MS (m/z) = 276 [M+H]⁺.

(D) ethyl 5-phenyl-6,7-dihydro-5*H*-pyrrolo[1,2-*b*][1,2,4]triazole-2-carboxylate

To a solution of ethyl (Z)-2-amino-2-((2-oxo-5-phenylpyrrolidin-1-yl)imino)acetate (3.2 g, 11.63 mmol) in DCE (10 mL) was added POCl₃ (3 mL) at room temperature. The reaction mixture was heated to 100°C and reacted for 8 hours. After the reaction was completed, the mixture was cooled to room temperature and concentrated under reduced pressure. The residue was purified by flash column chromatography (eluting with gradient MeOH/H₂O = 0% - 100%) to give 1.8 g of the target product. MS (m/z) = 258 [M+H]⁺.

Intermediate 9

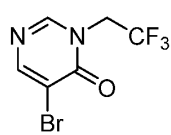
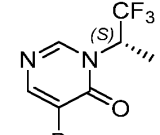
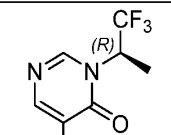
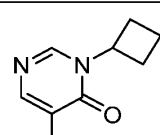
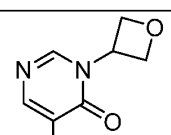
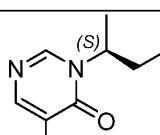
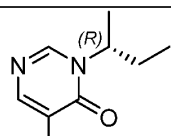
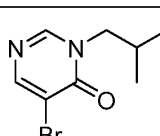
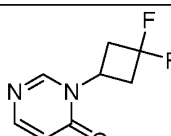
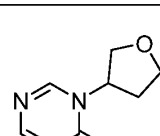
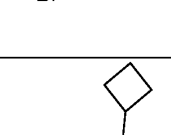
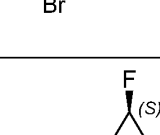
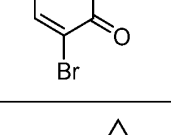
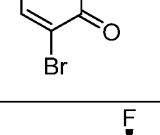
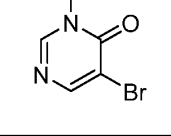
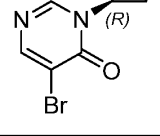
5-bromo-3-cyclopropylpyrimidin-4(3*H*)-one



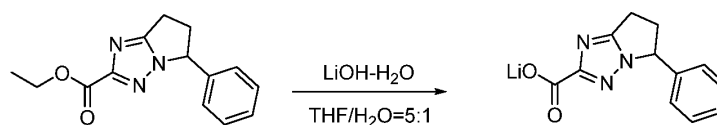
To a solution of 5-bromopyrimidin-4(3*H*)-one (500 mg, 2.86 mmol), cyclopropanamine (136 mg, 2.38 mmol), and DBU (534 mg, 3.57 mmol) in MeCN (10 mL) was added HATU (1.2 g, 3.09 mmol). The reaction mixture was heated to 45°C and reacted for 20 hours. After concentration under reduced pressure, the residue was purified by flash column chromatography (eluting with gradient MeOH/H₂O = 0% - 100%) to give 200 mg of the target product. MS (m/z) = 216 [M+H]⁺.

The following intermediates were prepared according to the procedure of Intermediate 9 using the corresponding materials and reagents under appropriate conditions that will be recognized by one skilled in the art.

Intermediate No.	Structural formula	MS (M+H) ⁺	Intermediate No.	Structural formula	MS (M+H) ⁺
10		217.0	11		202.9

12		256.9	13		270.9
14		270.9	15		230.9
16		231.0	17		231.0
18		231.0	19		230.9
44		264.9, 266.9 [M+2H] ⁺	45		246.0, 248.0 [M+2H] ⁺
46		243.0, 245.0 [M+2H] ⁺	47		233.0, 235.0 [M+2H] ⁺
48		229, 231 [M+2H] ⁺	49		233.0, 235.0 [M+2H] ⁺
50		243.2, 245.2 [M+2H] ⁺	51		259.0, 261.0 [M+2H] ⁺

52		228.9, 230.9 [M+2H] ⁺	53		243.0, 245.0 [M+2H] ⁺
54		243.0, 245.0 [M+2H] ⁺	55		247.0, 249.0 [M+2H] ⁺

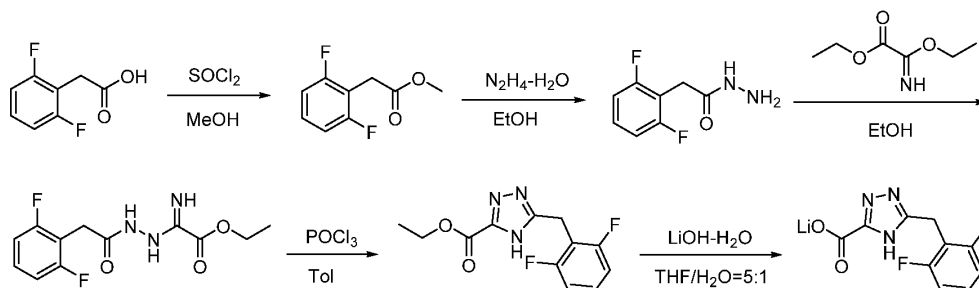
Intermediate 20**lithium 5-phenyl-6,7-dihydro-5H-pyrrolo[1,2-b][1,2,4]triazole-2-carboxylate**

To a solution of ethyl 5-phenyl-6,7-dihydro-5H-pyrrolo[1,2-b][1,2,4]triazole-2-carboxylate (100 mg, 0.39 mmol) in THF (4 mL) was added the solution of lithium hydroxide monohydrate (49 mg, 1.17 mmol) in water (0.8 mL). The reaction mixture was reacted at room temperature for 2 hours. After concentration under reduced pressure, the residue was purified by flash column chromatography (eluting with gradient MeOH/H₂O = 0% - 100%) to give 92 mg of the target product. MS (m/z) = 230 [M-Li+2H]⁺.

The following intermediate was prepared according to the procedure of Intermediate 20 using Intermediate 7(A) as the raw material under appropriate conditions that will be recognized by one skilled in the art.

Intermediate	Structural formula	MS (M+H)⁺
21		204.0 [M-Li+2H] ⁺

Intermediate 22**lithium 5-(2,6-difluorobenzyl)-4H-1,2,4-triazole-3-carboxylate**



(A) methyl 2-(2,6-difluorophenyl)acetate

To a solution of 2-(2,6-difluorophenyl)acetic acid (1.0 g, 5.81 mmol) in methanol (15 mL) was added SOCl₂ (2 mL). The reaction mixture was heated to 50°C and reacted for 2 hours, then concentrated under reduced pressure to give 1.08 g of the crude product. MS (m/z) = 187 [M+H]⁺.

(B) 2-(2,6-difluorophenyl)acetohydrazide

The mixture of methyl 2-(2,6-difluorophenyl)acetate (1.08 g, 5.81 mmol) and hydrazine hydrate (2 mL) in EtOH (10 mL) was heated to 70°C and reacted for 4 hours, then cooled to room temperature. The precipitated solid was filtered and dried to give 700 mg of the target product. MS (m/z) = 187 [M+H]⁺.

(C) ethyl 2-(2-(2-(2,6-difluorophenyl)acetyl)hydrazineyl)-2-iminoacetate

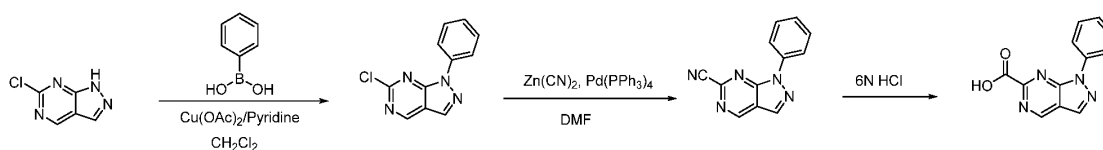
The mixture of 2-(2,6-difluorophenyl)acetohydrazide (500 mg, 2.69 mmol) and ethyl 2-ethoxy-2-iminoacetate (390 mg, 2.69 mmol) in EtOH (10 mL) was heated to 70°C and reacted for 4 hours, then cooled to room temperature. The precipitated solid was filtered and dried to give 730 mg of the target product. MS (m/z) = 286 [M+H]⁺.

(D) ethyl 5-(2,6-difluorobenzyl)-4H-1,2,4-triazole-3-carboxylate

To a solution of ethyl 2-(2-(2-(2,6-difluorophenyl)acetyl)hydrazineyl)-2-iminoacetate (315 mg, 1.10 mmol) in toluene (5 mL) was added POCl₃ (2 mL) dropwise. The reaction mixture was refluxed overnight. After concentration under reduced pressure, the residue was purified by flash column chromatography (eluting with gradient MeOH/H₂O = 0% - 100%) to give 235 mg of the target product. MS (m/z) = 268 [M+H]⁺.

(E) lithium 5-(2,6-difluorobenzyl)-4H-1,2,4-triazole-3-carboxylate

The target product was prepared according to the procedure of Intermediate 20 using ethyl 5-(2,6-difluorobenzyl)-4H-1,2,4-triazole-3-carboxylate as the raw material. MS (m/z) = 240 [M-Li+2H]⁺.

Intermediate 23**1-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidine-6-carboxylic acid****5 (A) 6-chloro-1-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidine**

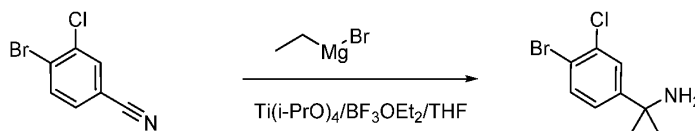
The mixture of 6-chloro-1*H*-pyrazolo[3,4-*d*]pyrimidine (1.6 g, 10.1 mmol), phenylboronic acid (2.5 g, 20.2 mmol), Cu(OAc)₂ (2.7 g, 15.2 mmol), and pyridine (1.6 g, 20.2 mmol) in DCE (15 mL) was heated to 80°C and reacted overnight. After concentration under reduced pressure, the residue was purified by flash column chromatography (eluting with gradient MeOH/H₂O = 0% - 100%) to give 377 mg of the target product. MS (m/z) = 231 [M+H]⁺.

(B) 1-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidine-6-carbonitrile

The mixture of 6-chloro-1-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidine (377 mg, 1.63 mmol), Zn(CN)₂ (125 mg, 1.06 mmol), and Pd(PPh₃)₄ (94 mg, 0.082 mmol) in DMF (5 mL) was heated to 100°C and reacted overnight. After concentration under reduced pressure, the residue was purified by flash column chromatography (eluting with gradient PE/EA = 100% - 0%) to give 335 mg of target product. MS (m/z) = 222 [M+H]⁺.

(C) 1-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidine-6-carboxylic acid

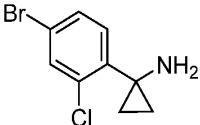
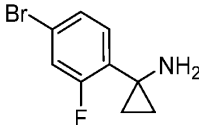
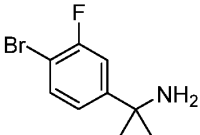
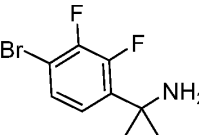
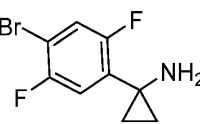
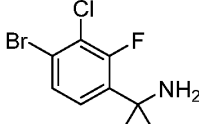
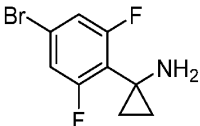
The mixture of 1-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidine-6-carbonitrile (335 mg, 1.52 mmol) in 6N HCl (2 mL) was heated to 100°C and reacted for 4 hours. After concentration under reduced pressure, the residue was purified by flash column chromatography (eluting with gradient MeOH/H₂O = 0% - 100%) to give 36 mg of the target product. MS (m/z) = 241 [M+H]⁺.

Intermediate 26**1-(4-bromo-3-chlorophenyl)cyclopropan-1-amine**

A solution of 4-bromo-3-chlorobenzonitrile (2 g, 9.3 mmol) and Titanium tetraisopropoxide (3.9 g, 13.95 mmol) in THF (40 mL) was stirred at room temperature under nitrogen atmosphere for 10 minutes. Ethylmagnesium bromide (6.2 mL, 18.6 mmol)

was added at 0°C, and the mixture was stirred at 0°C for 30 minutes, and then stirred at room temperature for 1 hour. A boron trifluoride diethyl etherate solution (2.64 g, 18.6 mmol) was added and stirred for 30 minutes, then diluted HCl (3 mL, 3 mmol) was added and stirred for 30 minutes. Then NaOH solution (10 mL, 20 mmol) was added, the mixture was extracted with ethyl acetate (50 mL x 3). The organic phase was combined, washed with saturated brine (50 mL), concentrated under reduced pressure, and the residue was purified by flash column chromatography (eluting with gradient MeOH/H₂O (+ 0.5% HCOOH)= 0% - 100%) to give 400 mg of the title product. MS (m/z) = 246 [M+H]⁺, 248 [M+2H]⁺.

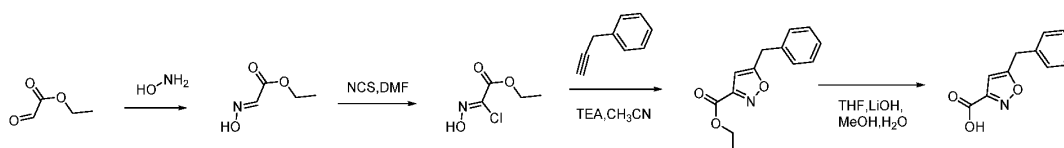
The following intermediates were prepared according to the procedure of Intermediate 26 using the corresponding materials and reagents under appropriate conditions that will be recognized by one skilled in the art.

Intermediate No.	Structural formula	MS (M+H) ⁺	Intermediate No.	Structural formula	MS (M+H) ⁺
27		246, 248 [M+2H] ⁺	28		230, 232 [M+2H] ⁺
29		230, 232 [M+2H] ⁺	56		248, 250 [M+2H] ⁺
57		248, 250 [M+2H] ⁺	58		264, 266 [M+2H] ⁺
59		248, 250 [M+2H] ⁺			

Intermediate 30

5-benzylisoxazole-3-carboxylic acid

15



(A) ethyl (*E*)-2-(hydroxyimino)acetate

To a solution of ethyl 2-oxoacetate (30 mL, 587.7 mmol) in EtOH (100 mL) was added hydroxylamine (77.5 g, 1175.4 mmol, 50% in Tol) at 0°C and then the mixture was reacted at room temperature for 2 hours. LC-MS showed that the reaction was completed. The mixture was quenched with water and the aqueous phase was extracted with ethyl acetate (150 mL x 2). The organic phase was combined, washed with brine solution, dried over anhydrous sodium sulfate and concentrated under reduced pressure to give 20.62 g of the crude product. MS (*m/z*) = 118 [M+H]⁺.

(B) ethyl (*Z*)-2-chloro-2-(hydroxyimino)acetate

To a solution of ethyl (*E*)-2-(hydroxyimino)acetate (20.62 g, 176.3 mmol) in DMF (20 mL) was added NCS (27 g, 176.3 mmol) at 0°C and then stirred at room temperature for 16 hours. The mixture was quenched with water and the aqueous phase was extracted with ethyl acetate (150 mL x 2). The organic layer was combined, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by flash column chromatography (eluting with gradient PE/EA = 100% - 0%) to give 16.8 g of the title product. MS (*m/z*) = 152 [M+H]⁺.

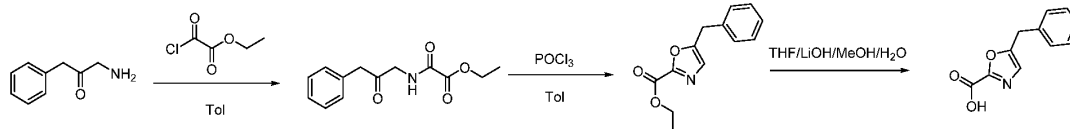
(C) ethyl 5-benzylisoxazole-3-carboxylate

To a solution of ethyl (*Z*)-2-chloro-2-(hydroxyimino)acetate (1.5 g, 9.9 mmol) in MeCN (20 mL) was added prop-2-yn-1-ylbenzene (576 mg, 4.96 mmol) and TEA (1.2 g, 11.88 mmol) at room temperature and then reacted at 90°C under nitrogen atmosphere for 6 hours. The mixture was concentrated under reduced pressure and the residue was purified by flash column chromatography (eluting with gradient PE/EA = 100% - 0%) to give 100 mg of the title product. MS (*m/z*) = 232 [M+H]⁺.

(D) 5-benzylisoxazole-3-carboxylic acid

To a solution of ethyl 5-benzylisoxazole-3-carboxylate (100 mg, 0.432 mmol) in THF (2 mL), MeOH (0.5 mL) and water (0.5 mL) was added lithium hydroxide monohydrate (54 mg, 1.296 mmol). The mixture was stirred at room temperature for 1 hour. LC-MS showed that the reaction was completed. Then the mixture was concentrated under reduced pressure, adjusted pH to 7 with 1N diluted HCl, and the solid was precipitated, and filtered to give 40 mg of the product. MS (*m/z*) = 204 [M+H]⁺.

Intermediate 31**5-benzylisoxazole-2-carboxylic acid**



(A) ethyl 2-oxo-2-((2-oxo-3-phenylpropyl)amino)acetate

To a solution of 1-amino-3-phenylpropan-2-one (500 mg, 3.35 mmol) in toluene (20 mL) was added ethyl 2-chloro-2-oxoacetate (905 mg, 6.70 mmol) at room temperature and then the mixture was reacted at 90°C under nitrogen atmosphere for 2 hours. The mixture was quenched with ice water and the aqueous phase was extracted with ethyl acetate (20 mL x 2). The organic layer was combined, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by flash column chromatography (eluting with gradient PE/EA = 100% - 0%) to give 650 mg of the title product. MS (m/z) = 250 [M+H]⁺.

(B) Ethyl 5-benzyloxazole-2-carboxylate

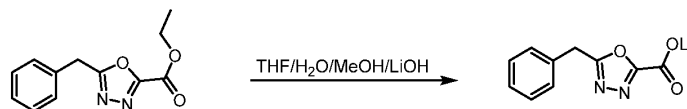
To a solution of ethyl 2-oxo-2-((2-oxo-3-phenylpropyl)amino)acetate (650 mg, 2.6 mmol) in toluene (20 mL) was added POCl₃ (2000 mg, 13 mmol) and the mixture was reacted at 120°C for 5 hours. The mixture was quenched with ice water and the aqueous phase was extracted with ethyl acetate (20 mL x 2). The organic layer was combined, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by flash column chromatography (eluting with gradient PE/EA = 100% - 0%) to give 530 mg of the title product. MS (m/z) = 232 [M+H]⁺.

(C) 5-benzyloxazole-2-carboxylic acid

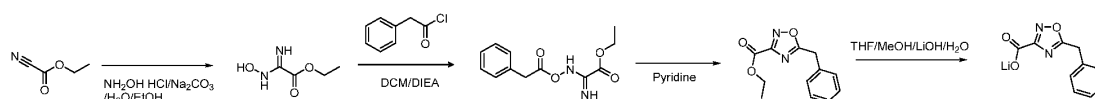
The product was prepared according to the procedure of Intermediate 30 (D) using ethyl 5-benzyloxazole-2-carboxylate as the raw material. MS (m/z) = 204 [M+H]⁺.

Intermediate 32

lithium 5-benzyl-1,3,4-oxadiazole-2-carboxylate



To a solution of ethyl 5-benzyl-1,3,4-oxadiazole-2-carboxylate (70 mg, 0.301 mmol) in THF (2 mL), MeOH (0.5 mL) and H₂O (0.5 mL) was added lithium hydroxide monohydrate (50 mg, 1.206 mmol). The mixture was reacted at 60°C for 1 hour. Then the mixture was concentrated under reduced pressure and used for next step reaction without further purification. MS (m/z) = 205 [M+H]⁺.

Intermediate 33**lithium 5-benzyl-1,2,4-oxadiazole-3-carboxylate**

5 (A) ethyl 2-(hydroxyamino)-2-iminoacetate

To a solution of ethyl carbonocyanide (2 g, 20 mmol) in EtOH (20 mL) was added hydroxylamine hydrochloride (2 g, 30 mmol) and sodium carbonate (1.63 g, 15.4 mmol), and the mixture was reacted at room temperature for 2 hours. The mixture was quenched with ice water and the aqueous phase was extracted with DCM (50 mL x 2). The organic layer was combined, washed with brine solution, dried over anhydrous sodium sulfate and concentrated under reduced pressure to give 2.3 g of the title product. MS (m/z) = 133 [M+H]⁺.

(B) ethyl 2-imino-2-((2-phenylacetoxymethyl)amino)acetate

To a solution of ethyl 2-(hydroxyamino)-2-iminoacetate (2.3 g, 18 mmol) in DCM (20 mL) was added DIEA (4.6 g, 36 mmol) and 2-phenylacetyl chloride (2.7 g, 18 mmol) at -15°C. The reaction mixture was reacted at room temperature overnight and then quenched with ice water. The solid was precipitated, filtered and dried to give 1.68 g of the title product. MS (m/z) = 251 [M+H]⁺.

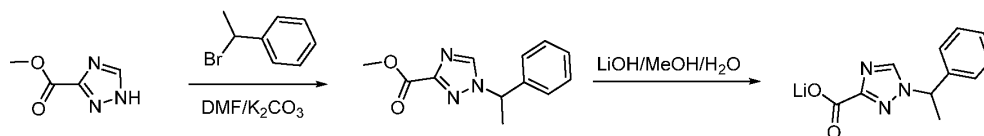
(C) Ethyl 5-benzyl-1,2,4-oxadiazole-3-carboxylate

A solution of ethyl 2-imino-2-((2-phenylacetoxymethyl)amino)acetate (800 mg, 3.2 mmol) in pyridine (10 mL) was reacted at 80°C under nitrogen atmosphere for 6 hours. The mixture was concentrated under reduced pressure and the residue was purified by flash column chromatography (eluting with gradient PE/EA= 100% - 0%) to give 600 mg of the title product. MS (m/z) = 233 [M+H]⁺.

25 (D) lithium 5-benzyl-1,2,4-oxadiazole-3-carboxylate

To a solution of ethyl 5-benzyl-1,2,4-oxadiazole-3-carboxylate (600 mg, 2.58 mmol) in THF (10 mL), MeOH (2 mL) and water (2 mL) was added lithium hydroxide monohydrate (325 mg, 7.74 mmol). The mixture was reacted at room temperature for 1 hour. Then the mixture was concentrated under reduced pressure and the residue (500 mg) was used for next step reaction without further purification. MS (m/z) = 205 [M+H]⁺.

Intermediate 34**lithium 1-(1-phenylethyl)-1H-1,2,4-triazole-3-carboxylate**



(A) methyl 1-(1-phenylethyl)-1*H*-1,2,4-triazole-3-carboxylate

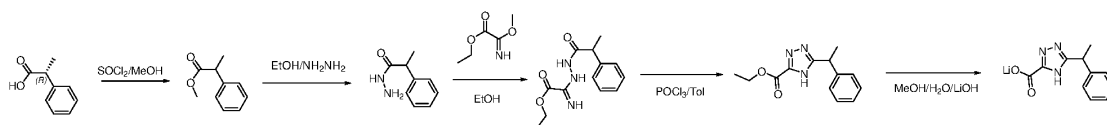
To a solution of methyl 1*H*-1,2,4-triazole-3-carboxylate (1 g, 7.87 mmol) in DMF (10 mL) was added (1-bromoethyl)benzene (1737 mg, 9.44 mmol) and potassium carbonate (2.17 g, 15.74 mmol). The mixture was reacted at room temperature for 16 hours. The mixture was concentrated under reduced pressure and the residue was purified by flash column chromatography (eluting with gradient MeOH/H₂O (+0.5% HCOOH) = 0% - 100%) to give 1.5 g of the title product. MS (*m/z*) = 232 [*M*+*H*]⁺.

(B) lithium 1-(1-phenylethyl)-1*H*-1,2,4-triazole-3-carboxylate

To a solution of methyl 1-(1-phenylethyl)-1*H*-1,2,4-triazole-3-carboxylate (1.5 g, 6.493 mmol) in MeOH (10 mL) and water (2 mL) was added lithium hydroxide monohydrate (817 mg, 19.47 mmol). The mixture was reacted at room temperature for 1 hour. The mixture was concentrated under reduced pressure and the residue was purified by flash column chromatography (eluting with gradient MeOH/H₂O = 0% - 100%) to give 1.22 g of the title product. MS (*m/z*) = 218 [*M*+*H*]⁺.

Intermediate 35

lithium 5-(1-phenylethyl)-4*H*-1,2,4-triazole-3-carboxylate



(A) methyl 2-phenylpropanoate

To a solution of (R)-2-phenylpropanoic acid (1.95 g, 12.98 mmol) in MeOH (20 mL) was added SOCl₂ (2 mL) at 0°C. The mixture was reacted at room temperature for 2 hours. Then the mixture was concentrated under reduced pressure and the residue (2.18 g) was used for next step reaction without further purification. MS (*m/z*) = 165 [*M*+*H*]⁺.

(B) 2-phenylpropanehydrazide

To a solution of methyl 2-phenylpropanoate (2.18 g, 12.98 mmol) in EtOH (20 mL) was added hydrazine hydrate (5 mL) at 0°C. The mixture was reacted at 80°C for 2 hours. The mixture was concentrated under reduced pressure and the residue was purified by

flash column chromatography (eluting with gradient MeOH/H₂O = 0% - 100%) to give 1.96 g of the title product. MS (m/z) = 165 [M+H]⁺.

(C) ethyl 2-imino-2-(2-(2-phenylpropanoyl)hydrazineyl)acetate

A mixture of 2-phenylpropanehydrazide (900 mg, 5.48 mmol) and ethyl 2-imino-2-methoxyacetate (1435 mg, 10.96 mmol) in EtOH (20 mL) was reacted at 80°C under nitrogen atmosphere for 2 hours. The mixture was cooled to room temperature, and the solid was precipitated, filtered and dried to give 1.4 g of the product. MS (m/z) = 264 [M+H]⁺.

(D) ethyl 5-(1-phenylethyl)-4*H*-1,2,4-triazole-3-carboxylate

To a solution of ethyl 2-imino-2-(2-(2-phenylpropanoyl)hydrazineyl)acetate (1.4 g, 5.32 mmol) in toluene (20 mL) was added POCl₃ (10 mL). The mixture was reacted at 120°C for 24 hours. The mixture was concentrated under reduced pressure and the residue was purified by flash column chromatography (eluting with gradient MeOH/H₂O (+0.5% HCOOH) = 0% - 100%) to give 563 mg of the title product. MS (m/z) = 246 [M+H]⁺.

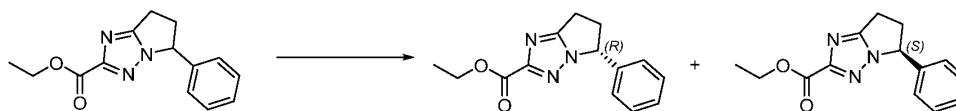
(E) lithium 5-(1-phenylethyl)-4*H*-1,2,4-triazole-3-carboxylate

The title product was prepared according to the procedure of Intermediate 34 (B) using ethyl 5-(1-phenylethyl)-4*H*-1,2,4-triazole-3-carboxylate as the raw material. MS (m/z) = 218 [M+H]⁺.

Intermediate 37 and Intermediate 38

(R)-ethyl 5-phenyl-6,7-dihydro-5*H*-pyrrolo[1,2-*b*][1,2,4]triazole-2-carboxylate
and

(S)-ethyl 5-phenyl-6,7-dihydro-5*H*-pyrrolo[1,2-*b*][1,2,4]triazole-2-carboxylate



The racemic compound was resolved by chiral HPLC to provide the optically pure enantiomers Intermediate 37 and Intermediate 38 (HPLC conditions: column: AD-H 4.6 x 150 mm; mobile phase: n-hexane/EtOH = 70/30; flow rate = 0.5 mL/min; detector: UV 254 nm). The first eluent (Intermediate 37, R_f = 3.651 min) was 100% ee, MS (m/z): 258 [M+H]⁺. The second eluent (Intermediate 38, R_f = 4.350 min) was 99.98% ee, MS (m/z): 258 [M+H]⁺.

Intermediate 39

1-(1-cyclopropylethyl)-1*H*-pyrazolo[3,4-*d*]pyrimidine-6-carboxylic acid5 (A) 6-chloro-1-(1-cyclopropylethyl)-1*H*-pyrazolo[3,4-*d*]pyrimidine

6-chloro-1*H*-pyrazolo[3,4-*d*]pyrimidine (800 mg, 5.2 mmol), 1-cyclopropylethanol (1.3 g, 15.6 mmol) and triphenylphosphine (2.0 g, 7.8 mmol) were dissolved in tetrahydrofuran (10 mL), then DIAD (1.6 mL) was slowly added, then the mixture was warmed to 60°C and reacted overnight. The reaction solution was concentrated under reduced pressure and the residue was purified by flash column chromatography (eluting with gradient PE/EA = 100%- 0%) to give 420 mg of the title product. MS (*m/z*) = 223 [M+H]⁺.

(B) 1-(1-cyclopropylethyl)-1*H*-pyrazolo[3,4-*d*]pyrimidine-6-carbonitrile

A mixture of 6-chloro-1-(1-cyclopropylethyl)-1*H*-pyrazolo[3,4-*d*]pyrimidine (420 mg, 1.88 mmol), zinc cyanide (120 mg, 1.13 mmol) and Pd(PPh₃)₄ (220 mg, 0.188 mmol) in DMF (5 mL) was heated to 110°C and reacted for 1.5 hours. The mixture was concentrated under reduced pressure and the residue was purified by flash column chromatography (eluting with gradient PE/EA= 100% - 0%) to give 310 mg of the product. MS (*m/z*) = 214 [M+H]⁺.

20 (C) 1-(1-cyclopropylethyl)-1*H*-pyrazolo[3,4-*d*]pyrimidine-6-carboxylic acid

A mixture of 1-(1-cyclopropylethyl)-1*H*-pyrazolo[3,4-*d*]pyrimidine-6-carbonitrile (310 mg, 1.45 mmol) in 1N sodium hydroxide (7 mL) was heated to 110°C and reacted for 1.5 hours. The reaction solution was cooled, and the pH was adjusted to 4 with 1N hydrochloric acid. After concentration under reduced pressure, the residue was purified by flash column chromatography (eluting with gradient MeOH/H₂O = 0% - 100%) to give 377 mg of the target product. MS (*m/z*) = 233 [M+H]⁺.

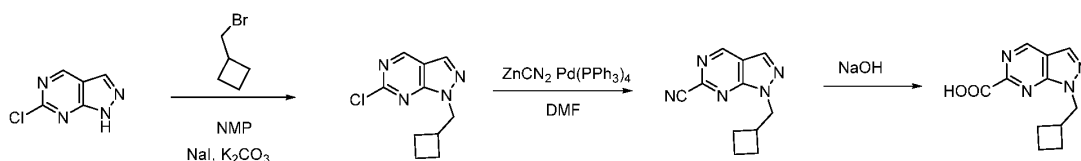
The following intermediates were prepared according to the procedure of Intermediate 39 using the corresponding materials and reagents under appropriate conditions that will be recognized by one skilled in the art.

30

Intermediate No.	Structural formula	MS (M+H) ⁺	Intermediate No.	Structural formula	MS (M+H) ⁺
40		221	41		219

Intermediate 42

1-(cyclobutylmethyl)-1H-pyrazolo[3,4-d]pyrimidine-6-carboxylic acid



5 (A) 6-chloro-1-(cyclobutylmethyl)-1H-pyrazolo[3,4-d]pyrimidine

6-chloro-1H-pyrazolo[3,4-d]pyrimidine (500 mg, 3.23 mmol), (bromo methyl)cyclobutane (965 mg, 6.46 mmol), potassium carbonate (890 mg, 6.46 mmol) and sodium iodide (970 mg, 6.46 mmol) were dissolved in NMP (5 mL), the mixture was heated to 60°C and reacted overnight. The reaction solution was cooled, to which water was added, and extracted with ethyl acetate, then the ethyl acetate extract was concentrated in vacuum, the residue was purified by flash column chromatography (eluting with gradient PE/EA = 100% - 0%), to give 310 mg of the product. MS (m/z) = 223 [M+H]⁺.

(B) 1-(cyclobutylmethyl)-1H-pyrazolo[3,4-d]pyrimidine-6-carbonitrile

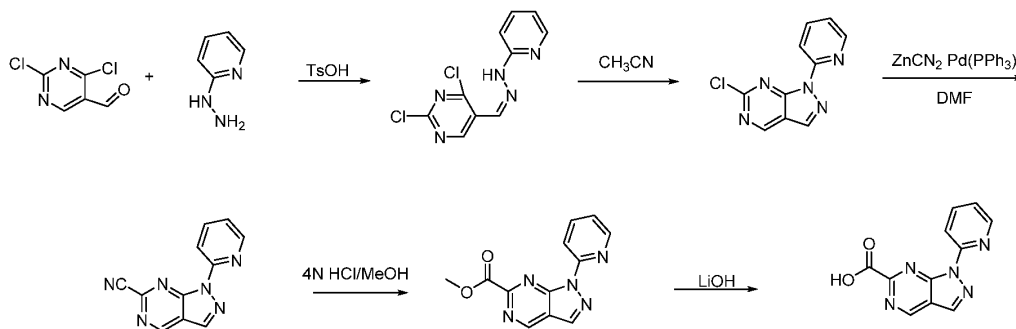
The title product was prepared according to the procedure of intermediate 39(B) using 6-chloro-1-(cyclobutylmethyl)-1H-pyrazolo[3,4-d]pyrimidine as the raw material. MS (m/z) = 214 [M+H]⁺.

(C) 1-(cyclobutylmethyl)-1H-pyrazolo[3,4-d]pyrimidine-6-carboxylic acid

The title product was prepared according to the procedure of intermediate 39(C) using 1-(cyclobutylmethyl)-1H-pyrazolo[3,4-d]pyrimidine-6-carbonitrile as the raw material. MS (m/z) = 233 [M+H]⁺.

Intermediate 43

1-(pyridin-2-yl)-1H-pyrazolo[3,4-d]pyrimidine-6-carboxylic acid



(A) (Z)-2,4-dichloro-5-((2-(pyridin-2-yl)hydrazineylidene)methyl)pyrimidine

2,4-dichloropyrimidine-5-formaldehyde (500 mg, 2.8 mmol), 2-hydrazinopyridine (310 mg, 2.8 mmol) and p-toluenesulfonic acid (540 mg, 2.8 mmol) were dissolved in DMF (5 mL), the mixture was reacted at room temperature for 2 hours, then water (20 mL) and saturated sodium bicarbonate solution (10 mL) were added. The mixture was filtered to give 610 mg of product, which was directly used in the next step. MS (m/z) = 268 [M+H]⁺.

(B) 6-chloro-1-(pyridin-2-yl)-1H-pyrazolo[3,4-d]pyrimidine

(Z)-2,4-dichloro-5-((2-(pyridin-2-yl)hydrazineylidene)methyl)pyrimidine (1.4 g, 5.2 mmol) was dissolved in acetonitrile (30 mL), the mixture was heated to 140°C and reacted under microwave for 3 hours. After concentration under reduced pressure, the residue was purified by flash column chromatography (eluting with gradient MeOH/H₂O = 0% - 100%) to give 125 mg of product. MS (m/z) = 232 [M+H]⁺.

(C) 1-(pyridin-2-yl)-1H-pyrazolo[3,4-d]pyrimidine-6-carbonitrile

A mixture of 6-chloro-1-(pyridin-2-yl)-1H-pyrazolo[3,4-d]pyrimidine (125 mg, 0.54 mmol), zinc cyanide (35 mg, 0.32 mmol) and Pd(PPh₃)₄ (65 mg, 0.054 mmol) in DMF (5 mL) was heated to 110°C and reacted for 1.5 hours. After concentration under reduced pressure, the residue was purified by flash column chromatography (eluting with gradient PE/EA = 100% - 0%) to give 121 mg of the product. MS (m/z) = 223 [M+H]⁺.

(D) methyl 1-(pyridin-2-yl)-1H-pyrazolo[3,4-d]pyrimidine-6-carboxylate

1-(pyridin-2-yl)-1H-pyrazolo[3,4-d]pyrimidine-6-carbonitrile (121 mg, 0.5 mmol) was dissolved in MeOH (5 mL), 4N hydrochloric acid in methanol solution (2.5 mL) was added. The mixture was reacted at 20°C for 20 hours, and then reacted at 50°C for 3 hours. After cooling and concentration under reduced pressure, the residue was purified

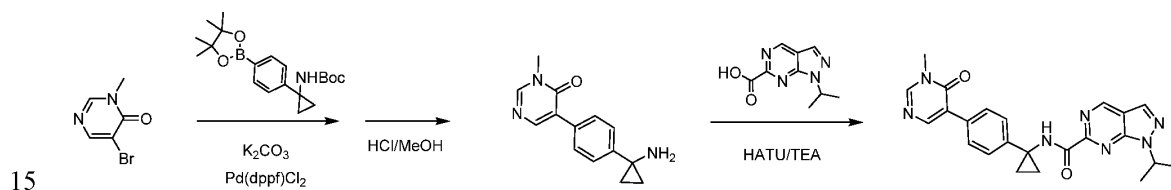
by flash column chromatography (eluting with gradient MeOH/H₂O = 0% - 100%) to give 50 mg of the product. MS (m/z) = 256 [M+H]⁺.

(E) 1-(pyridin-2-yl)-1*H*-pyrazolo[3,4-*d*]pyrimidine-6-carboxylic acid

Methyl 1-(pyridin-2-yl)-1*H*-pyrazolo[3,4-*d*]pyrimidine-6-carboxylate (50 mg, 0.22 mmol) was dissolved in tetrahydrofuran/water (5 mL/1 mL), LiOH·H₂O (50 mg, 1.10 mmol) was added, and the mixture was reacted at 25°C for 2 hours. After concentration under reduced pressure, the pH of the reaction solution was adjusted to 4 by adding 2N hydrochloric acid solution, and same was extracted with ethyl acetate (3 × 10 mL). The ethyl acetate layer was concentrated, and the residue was purified by flash column chromatography (eluting with gradient MeOH/H₂O = 0% - 100%) to give 45 mg of the product. MS (m/z) = 242 [M+H]⁺.

Compound 1

1-isopropyl-*N*-(1-(4-(1-methyl-6-oxo-1,6-dihydropyrimidin-5-yl)phenyl)cyclopropyl)-1*H*-pyrazolo[3,4-*d*]pyrimidine-6-carboxamide



(A) 5-(4-(1-aminocyclopropyl)phenyl)-3-methylpyrimidin-4(3*H*)-one

The mixture of 5-bromo-3-methylpyrimidin-4(3*H*)-one (63 mg, 0.33 mmol), tert-butyl (1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)cyclopropyl)carbamate (143 mg, 0.40 mmol), K₂CO₃ (137 mg, 0.99 mmol), and Pd(dppf)Cl₂ (12 mg, 0.02 mmol) in 10 mL of dioxane and water (3 : 1) was stirred at 120°C for 5 hours. The solvent was removed, and the residue was purified by flash column chromatography (eluting with gradient MeOH/H₂O (+0.1% HCOOH) = 10% - 80%) to give the crude product. To the crude product was added 2N HCl in MeOH (10 mL) at room temperature. The mixture was stirred for 2 hours. Then the solvent was removed to obtain 65 mg of the product as pale yellow solid. MS (m/z) = 242 [M+H]⁺.

(B) 1-isopropyl-*N*-(1-(4-(1-methyl-6-oxo-1,6-dihydropyrimidin-5-yl)phenyl)cyclopropyl)-1*H*-pyrazolo[3,4-*d*]pyrimidine-6-carboxamide

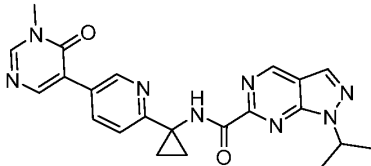
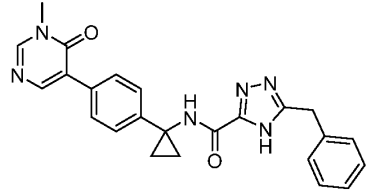
The mixture of 5-(4-(1-aminocyclopropyl)phenyl)-3-methylpyrimidin-4(3*H*)-one (65 mg, 0.27 mmol), 1-isopropyl-1*H*-pyrazolo[3,4-*d*]pyrimidine-6-carboxylic acid (56

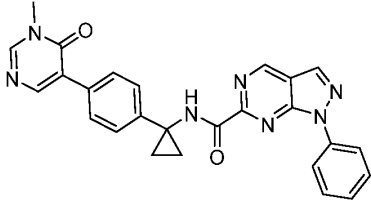
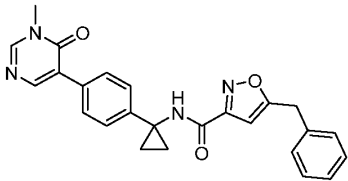
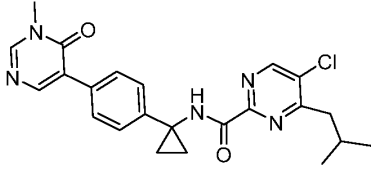
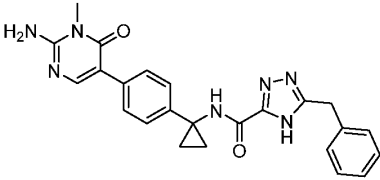
mg, 0.27 mmol), HATU (123 mg, 0.32 mmol), and TEA (82 mg, 0.81 mmol) in DCM (5 mL) was stirred at room temperature under nitrogen atmosphere for 2 hours. The solvent was removed. The residue was purified by flash column chromatography (eluting with gradient MeOH/H₂O (+0.1% HCOOH) = 10% - 80%) to obtain 90 mg of the product as

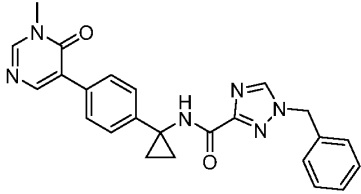
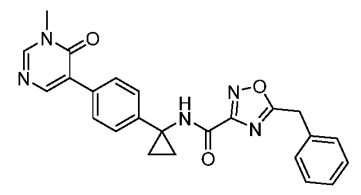
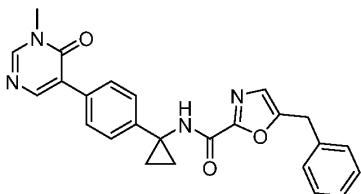
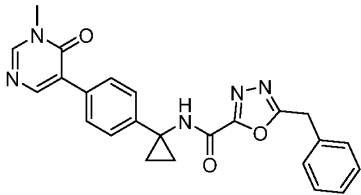
5 white solid. MS (m/z) = 430 [M+H]⁺.

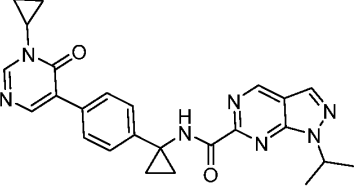
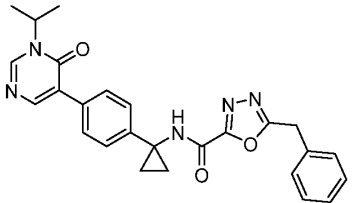
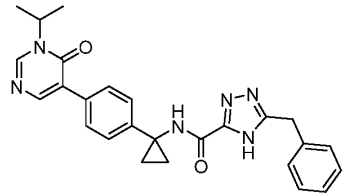
¹H NMR (400 MHz, DMSO) δ 9.71 (s, 1H), 9.41 (s, 1H), 8.47 (d, *J* = 0.4 Hz, 1H), 8.44 (s, 1H), 8.07 (s, 1H), 7.61 - 7.56 (m, 2H), 7.28 - 7.24 (m, 2H), 5.34 - 5.24 (m, 1H), 3.44 (s, 3H), 1.50 (d, *J* = 6.7 Hz, 6H), 1.36 - 1.28 (m, 4H).

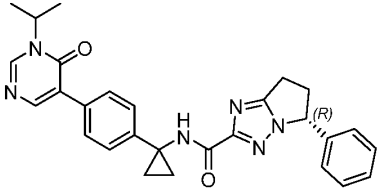
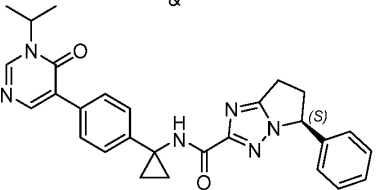
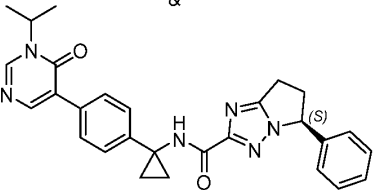
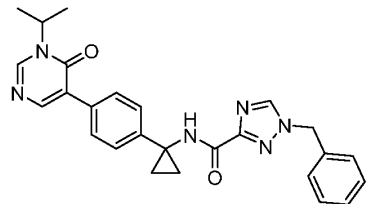
The following compounds were prepared according to the procedure of Compound 1
10 using the corresponding intermediates and reagents under appropriate conditions that will be recognized by one skilled in the art.

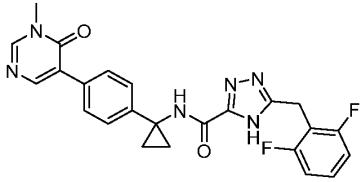
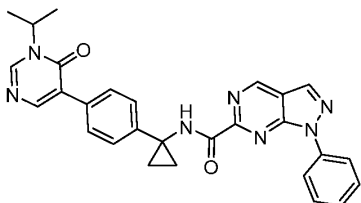
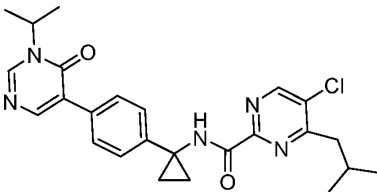
Compound	Structure	¹ H-NMR	MS	Intermediates used
2		¹ H NMR (400 MHz, DMSO) δ 9.80 (s, 1H), 9.45 (s, 1H), 8.76 - 8.71 (m, 1H), 8.49 (s, 2H), 8.19 (s, 1H), 8.02 - 7.93 (m, 1H), 7.46 - 7.38 (m, 1H), 5.40 - 5.23 (m, 1H), 3.47 (s, 3H), 1.62 - 1.58 (m, 2H), 1.52 (d, <i>J</i> = 6.7 Hz, 6H), 1.38 - 1.33 (m, 2H).	431	
3		¹ H NMR (400 MHz, DMSO) δ 9.13 (s, 1H), 8.44 (s, 1H), 8.06 (s, 1H), 7.60 - 7.53 (m, 2H), 7.31 - 7.23 (m, 4H), 7.22 - 7.16 (m, 3H), 4.05 (s, 2H), 3.45 (s, 3H), 1.29 - 1.20 (m, 4H).	427	

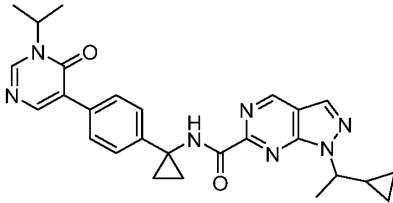
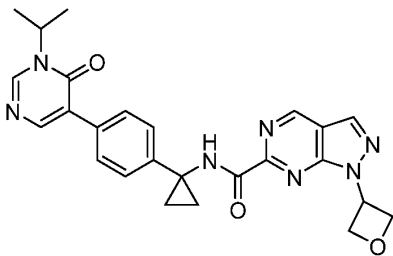
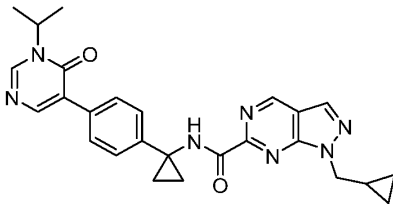
4		¹ H NMR (400 MHz, DMSO) δ 9.73 (s, 1H), 9.58 (s, 1H), 8.76 (s, 1H), 8.45 (s, 1H), 8.28 (d, J = 7.7 Hz, 2H), 8.09 (s, 1H), 7.68 - 7.57 (m, 4H), 7.43 (t, J = 7.5 Hz, 1H), 7.30 (d, J = 8.4 Hz, 2H), 3.46 (s, 3H), 1.50 - 1.28 (m, 4H).	464	23
5		¹ H NMR (400 MHz, DMSO) δ 9.46 (s, 1H), 8.44 (s, 1H), 8.07 (s, 1H), 7.60 - 7.55 (m, 2H), 7.36 - 7.24 (m, 5H), 7.22 - 7.17 (m, 2H), 6.53 (s, 1H), 4.19 (s, 2H), 3.45 (s, 3H), 1.25 (s, 4H).	427	30
6		¹ H NMR (400 MHz, CD ₃ OD) δ 8.84 (s, 1H), 8.37 (s, 1H), 8.06 (s, 1H), 7.64 - 7.54 (m, 2H), 7.41 - 7.28 (m, 2H), 3.57 (s, 3H), 2.91 (d, J = 7.3 Hz, 2H), 2.40 - 2.25 (m, 1H), 1.61 - 1.37 (m, 5H), 0.99 (d, J = 6.7 Hz, 6H).	438	1
7		¹ H NMR (400 MHz, DMSO) δ 9.21 (s, 1H), 7.75 (s, 1H), 7.46 (d, J = 8.4 Hz, 2H), 7.33 - 7.15 (m, 7H), 7.12 (d, J = 8.4 Hz, 2H), 4.07 (s, 2H), 3.30 (s, 3H), 1.25 - 1.16 (m, 4H).	442	5

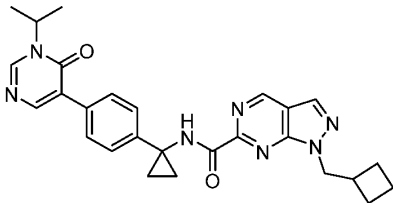
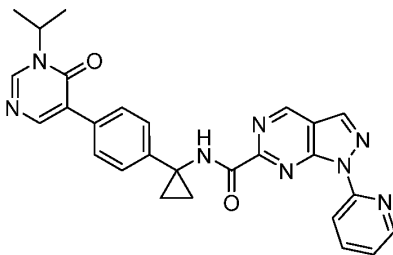
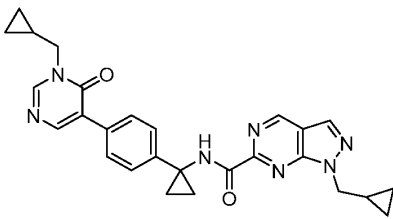
8		¹ H NMR (400 MHz, DMSO) δ 9.24 (s, 1H), 8.79 (s, 1H), 8.43 (s, 1H), 8.06 (s, 1H), 7.69 - 7.47 (m, 2H), 7.47 - 7.24 (m, 5H), 7.24 - 7.07 (m, 2H), 5.46 (s, 2H), 3.45 (s, 3H), 1.36 - 1.10 (m, 4H).	427	21
9		¹ H NMR (400 MHz, DMSO) δ 9.77 (s, 1H), 8.44 (s, 1H), 8.08 (s, 1H), 7.69 - 7.48 (m, 2H), 7.48 - 7.26 (m, 5H), 7.25 - 7.12 (m, 2H), 4.42 (s, 2H), 3.45 (s, 3H), 1.35 - 1.17 (m, 4H).	428	33
10		¹ H NMR (400 MHz, DMSO) δ 9.61 (s, 1H), 8.44 (s, 1H), 8.07 (s, 1H), 7.57 (d, J = 8.1 Hz, 2H), 7.39 - 7.21 (m, 5H), 7.18 (d, J = 8.2 Hz, 2H), 7.13 (d, J = 0.8 Hz, 1H), 4.11 (s, 2H), 3.45 (s, 3H), 1.29 - 1.21 (m, 4H).	427	31
11		¹ H NMR (400 MHz, DMSO) δ 10.04 (s, 1H), 8.45 (s, 1H), 8.08 (s, 1H), 7.58 (d, J = 8.1 Hz, 2H), 7.43 - 7.25 (m, 5H), 7.21 (d, J = 8.1 Hz, 2H), 4.35 (s, 2H), 3.45 (s, 3H), 1.33 - 1.23 (m, 4H).	428	32

12		¹ H NMR (400 MHz, CDCl ₃) δ 9.19 (s, 1H), 8.84 (s, 1H), 8.23 (s, 1H), 8.12 (s, 1H), 7.98 (s, 1H), 7.60 (d, J = 8.3 Hz, 2H), 7.44 (d, J = 8.3 Hz, 2H), 5.52 - 5.40 (m, 1H), 3.32 - 3.20 (m, 1H), 1.59 (d, J = 6.7 Hz, 6H), 1.50 - 1.42 (m, 4H), 1.23 - 1.18 (m, 2H), 0.96 - 0.90 (m, 2H).	456	9
13		¹ H NMR (400 MHz, CDCl ₃) δ 8.15 (s, 1H), 7.98 (s, 1H), 7.77 (s, 1H), 7.62 - 7.56 (m, 2H), 7.39 - 7.35 (m, 2H), 7.35 - 7.26 (m, 5H), 5.21 - 5.07 (m, 1H), 4.25 (s, 2H), 1.48 (d, J = 6.9 Hz, 6H), 1.42 - 1.37 (m, 4H).	456	10, 32
14		¹ H NMR (400 MHz, CDCl ₃) δ 8.15 (s, 1H), 7.98 - 7.90 (m, 2H), 7.54 (d, J = 8.3 Hz, 2H), 7.32 (d, J = 8.3 Hz, 2H), 7.26 - 7.20 (m, 5H), 5.23 - 5.08 (m, 1H), 4.16 (s, 2H), 1.47 (d, J = 6.9 Hz, 6H), 1.41 - 1.32 (m, 4H).	457	10

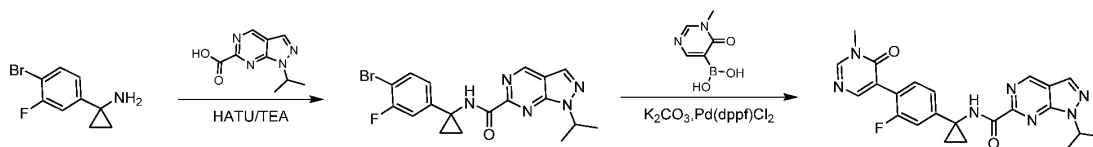
15	  &	¹ H NMR (400 MHz, CDCl ₃) δ 8.13 (s, 1H), 7.97 (s, 1H), 7.71 (s, 1H), 7.60 - 7.53 (m, 2H), 7.39 - 7.33 (m, 5H), 7.14 - 7.09 (m, 2H), 5.48 - 5.40 (m, 1H), 5.21 - 5.10 (m, 1H), 3.28 - 2.97 (m, 3H), 2.73 - 2.62 (m, 1H), 1.47 (d, J = 6.8 Hz, 6H), 1.43 - 1.34 (m, 4H).	481	10, 37 or 38
16		¹ H NMR (400 MHz, CDCl ₃) δ 8.14 (s, 1H), 7.98 (s, 1H), 7.70 (s, 1H), 7.59 - 7.54 (m, 2H), 7.39 - 7.33 (m, 5H), 7.14 - 7.09 (m, 2H), 5.50 - 5.39 (m, 1H), 5.23 - 5.09 (m, 1H), 3.29 - 2.97 (m, 3H), 2.74 - 2.60 (m, 1H), 1.47 (d, J = 6.9 Hz, 6H), 1.44 - 1.35 (m, 4H).	481	10, 37 or 38
17		¹ H NMR (400 MHz, CDCl ₃) δ 8.14 (s, 1H), 7.99 (s, 2H), 7.76 (s, 1H), 7.57 (d, J = 8.2 Hz, 2H), 7.42 - 7.36 (m, 5H), 7.34 - 7.26 (m, 2H), 5.38 (s, 2H), 5.21 - 5.10 (m, 1H), 1.47 (d, J = 6.9 Hz, 6H), 1.46 - 1.35 (m, 4H).	455	10, 21

18		¹ H NMR (400 MHz, CD ₃ OD) δ 8.37 (s, 1H), 8.05 (s, 1H), 7.59 - 7.54 (m, 2H), 7.37 - 7.28 (m, 3H), 7.05 - 6.95 (m, 2H), 4.20 (s, 2H), 3.56 (s, 3H), 1.39 - 1.33 (m, 4H).	463	22
19		¹ H NMR (400 MHz, CDCl ₃) δ 9.32 (s, 1H), 8.79 (s, 1H), 8.41 (s, 1H), 8.27 (d, J = 7.8 Hz, 2H), 8.13 (s, 1H), 7.98 (s, 1H), 7.61 - 7.54 (m, 4H), 7.45 (d, J = 8.4 Hz, 2H), 7.39 (t, J = 7.4 Hz, 1H), 5.20 - 5.10 (m, 1H), 1.49 - 1.45 (m, 10H).	492	10, 23
22		¹ H NMR (400 MHz, CDCl ₃) δ 8.70 (s, 1H), 8.50 (s, 1H), 8.13 (s, 1H), 7.98 (s, 1H), 7.58 (d, J = 8.4 Hz, 2H), 7.40 (d, J = 8.4 Hz, 2H), 5.22 - 5.10 (m, 1H), 2.86 (d, J = 7.2 Hz, 2H), 2.29 (m, 1H), 1.50 - 1.40 (m, 10H), 0.98 (d, J = 6.7 Hz, 6H).	466	10, 1

59		¹ H NMR (400 MHz, CD ₃ OD): δ 9.34 (s, 1H), 8.47-8.34 (m, 2H), 8.02 (s, 1H), 7.61-7.53 (m, 2H), 7.41 - 7.35 (m, 2H), 5.12 - 5.00 (m, 1H), 4.65 - 4.48 (m, 1H), 1.74 - 1.64 (m, 3H), 1.55 - 1.45 (m, 9H), 1.44 - 1.41 (m, 2H), 0.76 - 0.59 (m, 1H), 0.56-0.44 (m, 1H), 0.41-0.30 (m, 2H).	484	10, 39
60		¹ H NMR (400 MHz, CD ₃ OD): δ 9.35 (s, 1H), 8.59-8.46 (m, 1H), 8.41 (s, 1H), 8.06-7.95 (m, 1H), 7.59 - 7.50 (m, 2H), 7.42 - 7.32 (m, 2H), 6.45-6.28 (m, 1H), 5.24-5.17 (m, 2H), 5.15-5.09 (m, 2H), 5.08 - 4.99 (m, 1H), 1.49 - 1.44 (m, 8H), 1.43-1.41 (m, 2H).	472	10, 40
61		¹ H NMR (400 MHz, CD ₃ OD): δ 9.32 (s, 1H), 8.43 (s, 1H), 8.35 (s, 1H), 8.00 (s, 1H), 7.63-7.47 (m, 2H), 7.39-7.24 (m, 2H), 5.17-5.01 (m, 1H), 4.51- 4.36 (m, 2H), 1.63-1.35 (m, 11H), 0.57-0.41 (m, 4H).	470	10, 41

62		¹ H NMR (400 MHz, CD ₃ OD): δ 9.32 (s, 1H), 8.42 (s, 1H), 8.33 (s, 1H), 8.01 (s, 1H), 7.63-7.51 (m, 2H), 7.46-7.28 (m, 2H), 5.15-4.99 (m, 1H), 4.67 - 4.53 (m, 2H), 3.04-2.85 (m, 1H), 2.09-1.80 (m, 7H), 1.52-1.40 (m, 9H).	484	10, 42
63		¹ H NMR (400 MHz, CD ₃ OD): δ 9.48 (s, 1H), 8.64 (s, 1H), 8.62-8.57 (m, 1H), 8.54 (s, 0.36H), 8.41 (s, 1H), 8.39-8.33 (m, 1H), 8.12-8.03 (m, 1H), 7.98 (s, 1H), 7.58-7.49 (m, 2H), 7.47 - 7.40 (m, 1H), 7.38 - 7.30 (m, 2H), 5.10 - 4.99 (m, 1H), 1.47-1.45 (m, 6H), 1.43-1.38 (m, 2H), 1.30-1.25 (m, 2H).	493	10, 43
64		¹ H NMR (400 MHz, CD ₃ OD) δ 9.35 (s, 1H), 8.41 (s, 1H), 8.37 (s, 1H), 8.05 (s, 1H), 7.58 (d, J = 8.1 Hz, 2H), 7.38 (d, J = 8.2 Hz, 2H), 4.47 (d, J = 7.1 Hz, 2H), 3.88 (d, J = 7.1 Hz, 2H), 1.46 - 1.39 (m, 4H), 1.34 - 1.22 (m, 2H), 0.61 - 0.57 (m, 2H), 0.56 - 0.47 (m, 4H), 0.45 - 0.42 (m, 2H).	482	41, 48

Compound 23

***N*-(1-(3-fluoro-4-(1-methyl-6-oxo-1,6-dihydropyrimidin-5-yl)phenyl)cyclopropyl)-1-isopropyl-1*H*-pyrazolo[3,4-*d*]pyrimidine-6-carboxamide**

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(A) *N*-(1-(4-bromo-3-fluorophenyl)cyclopropyl)-1-isopropyl-1*H*-pyrazolo[3,4-*d*]pyrimidine-6-carboxamide

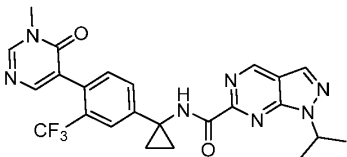
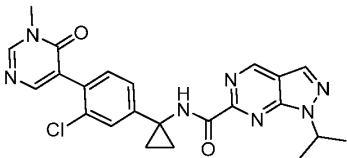
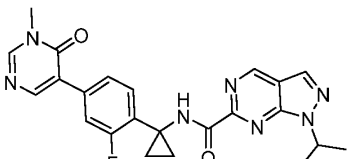
The mixture of 1-(4-bromo-3-fluorophenyl)cyclopropan-1-amine (100 mg, 0.43 mmol), 1-isopropyl-1*H*-pyrazolo[3,4-*d*]pyrimidine-6-carboxylic acid (90 mg, 0.43 mmol),
 10 HATU (196 mg, 0.52 mmol), and TEA (130 mg, 0.52 mmol) in DCM (10 mL) was stirred at room temperature under nitrogen atmosphere for 2 hours. The solvent was removed. The residue was purified by flash column chromatography (eluting with gradient MeOH/H₂O (+0.1% HCOOH) = 10% - 80%) to obtain 100 mg of the product as white solid. MS (*m/z*) = 419 [*M*+*H*]⁺.

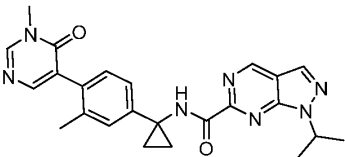
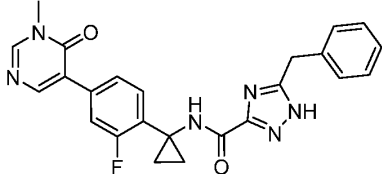
(B) *N*-(1-(3-fluoro-4-(1-methyl-6-oxo-1,6-dihydropyrimidin-5-yl)phenyl)cyclopropyl)-1-isopropyl-1*H*-pyrazolo[3,4-*d*]pyrimidine-6-carboxamide

The mixture of *N*-(1-(4-bromo-3-fluorophenyl)cyclopropyl)-1-isopropyl-1*H*-pyrazolo[3,4-*d*]pyrimidine-6-carboxamide (100 mg, 0.24 mmol), (1-methyl-6-oxo-1,6-dihydropyrimidin-5-yl)boronic acid (38 mg, 0.24 mmol), K₂CO₃ (100 mg, 0.72 mmol),
 20 and Pd(dppf)Cl₂ (12 mg, 0.02 mmol) in 10 mL of dioxane/H₂O (3 : 1) was stirred at 120°C under nitrogen atmosphere for 5 hours. The solvent was removed, and the residue was purified by flash column chromatography (eluting with gradient MeOH/H₂O (+0.1% HCOOH) = 10% - 80%) to give the crude product. The crude product was purified by Pre-TLC (DCM/MeOH = 15/1) to give 50 mg of the product as white solid. MS (*m/z*) =
 25 448 [*M*+*H*]⁺.

¹H NMR (400 MHz, DMSO) δ 9.76 (s, 1H), 9.43 (d, *J* = 1.8 Hz, 1H), 8.48 (d, *J* = 5.4 Hz, 2H), 7.97 (s, 1H), 7.36 (t, *J* = 7.9 Hz, 1H), 7.12 - 7.08 (m, 2H), 5.35 - 5.24 (m, 1H), 3.45 (s, 3H), 1.51 (d, *J* = 6.7 Hz, 6H), 1.40 - 1.34 (m, 4H).

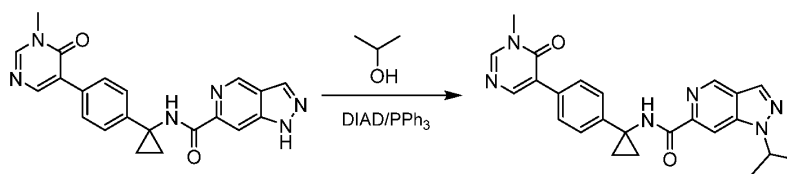
The following compounds were prepared according to the procedure of Compound
 30 23 using the corresponding intermediates and reagents under appropriate conditions that will be recognized by one skilled in the art.

Compound	Structure	¹ H-NMR	MS	Intermediates used
24		¹ H NMR (400 MHz, DMSO) δ 9.84 (s, 1H), 9.42 (s, 1H), 8.49 (d, J = 10.3 Hz, 2H), 7.80 (s, 1H), 7.68 (s, 1H), 7.56 (d, J = 8.1 Hz, 1H), 7.30 (d, J = 8.1 Hz, 1H), 5.38 - 5.20 (m, 1H), 3.44 (s, 3H), 1.51 (d, J = 6.7 Hz, 6H), 1.42 - 1.38 (m, 4H).	498	6
25		¹ H NMR (400 MHz, DMSO) δ 9.77 (s, 1H), 9.42 (s, 1H), 8.49 (d, J = 12.0 Hz, 2H), 7.89 (s, 1H), 7.39 (d, J = 1.2 Hz, 1H), 7.30 - 7.21 (m, 2H), 5.34 - 5.23 (m, 1H), 3.45 (s, 3H), 1.51 (d, J = 6.7 Hz, 6H), 1.40 - 1.33 (m, 4H).	464	6, 26
26		¹ H NMR (400 MHz, DMSO) δ 9.49 (s, 1H), 9.38 (s, 1H), 8.46 (d, J = 11.9 Hz, 2H), 8.18 (s, 1H), 7.67 - 7.60 (m, 1H), 7.55 - 7.45 (m, 2H), 5.29 - 5.20 (m, 1H), 3.46 (s, 3H), 1.49 (d, J = 6.7 Hz, 6H), 1.32 - 1.27 (m, 4H).	448	6, 28

27		¹ H NMR (400 MHz, DMSO) δ 9.66 (s, 1H), 9.42 (s, 1H), 8.52 - 8.45 (m, 2H), 7.81 (s, 1H), 7.14 - 7.10 (m, 2H), 7.07 - 7.00 (m, 1H), 5.34 - 5.25 (m, 1H), 3.45 (s, 3H), 2.09 (s, 3H), 1.51 (d, J = 6.7 Hz, 6H), 1.34 - 1.27 (m, 4H).	444	6
48		¹ H NMR (400 MHz, CDCl ₃) δ 8.06 (s, 1H), 7.95 (s, 1H), 7.74 - 7.63 (m, 3H), 7.56 - 7.47 (m, 3H), 5.46 (d, J = 5.9 Hz, 1H), 5.43 - 5.37 (m, 1H), 5.36 (s, 2H), 1.38 (d, J = 6.8 Hz, 3H).	445	6, 28

Compound 28

1-isopropyl-N-(1-(4-(1-methyl-6-oxo-1,6-dihydropyrimidin-5-yl)phenyl)cyclopropyl)-1H-pyrazolo[4,3-c]pyridine-6-carboxamide



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To a solution of *N*-(1-(4-(1-methyl-6-oxo-1,6-dihydropyrimidin-5-yl)phenyl)cyclopropyl)-1*H*-pyrazolo[4,3-*c*]pyridine-6-carboxamide (this compound was prepared according to the procedure of Compound 1 using 5-bromo-3-methylpyrimidin-4(3*H*)-one, tert-butyl (1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)cyclopropyl)carbamate and 1*H*-pyrazolo[4,3-*c*]pyridine-6-carboxylic acid as the raw materials) (60.0 mg, 0.16 mmol) and isopropanol (18.6 mg, 0.31 mmol) in a mixed solvent of DCM (4 mL) and THF (4 mL) was added DIAD (62.6 mg, 0.31 mmol)

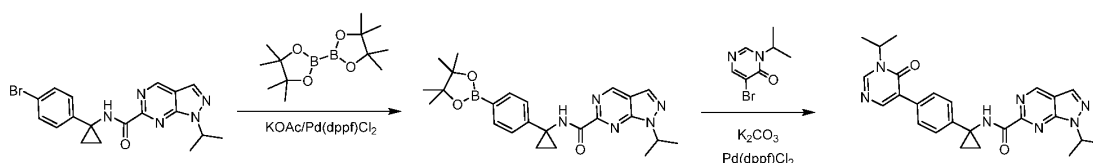
10

and PPh₃ (81.2 mg, 0.31 mmol). The reaction mixture was reacted at room temperature overnight. The mixture was concentrated under reduced pressure, and the residue was purified by flash column chromatography (eluting with gradient MeOH/H₂O = 10% - 100%) to give 35 mg of the title product. MS (m/z) = 429 [M+H]⁺.

¹H NMR (400 MHz, DMSO) δ 9.51 (s, 1H), 9.19 - 9.09 (m, 1H), 8.43 (s, 1H), 8.41 (s, 1H), 8.31 (s, 1H), 8.07 (s, 1H), 7.57 (d, *J* = 8.3 Hz, 2H), 7.24 (d, *J* = 8.3 Hz, 2H), 5.35 - 4.97 (m, 1H), 3.45 (s, 3H), 1.48 (d, *J* = 6.6 Hz, 6H), 1.41 - 1.26 (m, 4H).

Compound 29

1-isopropyl-*N*-(1-(4-(1-isopropyl-6-oxo-1,6-dihydropyrimidin-5-yl)phenyl)cyclopropyl)-1*H*-pyrazolo[3,4-*d*]pyrimidine-6-carboxamide



(A) 1-isopropyl-*N*-(1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)cyclopropyl)-1*H*-pyrazolo[3,4-*d*]pyrimidine-6-carboxamide

The mixture of *N*-(1-(4-bromophenyl)cyclopropyl)-1-isopropyl-1*H*-pyrazolo[3,4-*d*]pyrimidine-6-carboxamide (this compound was prepared according to the procedure of Compound 23(A) using 1-(4-bromophenyl)cyclopropan-1-amine and 1-isopropyl-1*H*-pyrazolo[3,4-*d*]pyrimidine-6-carboxylic acid as the raw materials) (1 g, 2.5 mmol), Bis(pinacolato)diboron (952 mg, 3.75 mmol), KOAc (735 mg, 7.5 mmol), and Pd(dppf)Cl₂ (92 mg, 0.13 mmol) in dioxane (30 mL) was stirred at 120°C under nitrogen atmosphere for 5 hours. The solvent was removed. The residue was purified by flash column chromatography (eluting with gradient MeOH/H₂O (+0.1% HCOOH) = 10% - 80%) to give 800 mg of the product as yellow solid. MS (m/z) = 448 [M+H]⁺.

(B) 1-isopropyl-*N*-(1-(4-(1-isopropyl-6-oxo-1,6-dihydropyrimidin-5-

yl)phenyl)cyclopropyl)-1*H*-pyrazolo[3,4-*d*]pyrimidine-6-carboxamide

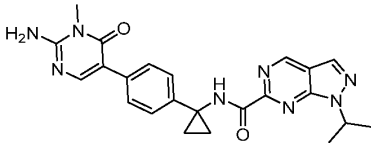
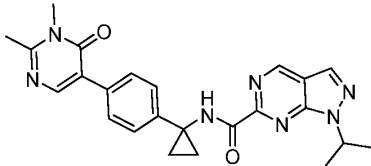
To a solution of 1-isopropyl-*N*-(1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)cyclopropyl)-1*H*-pyrazolo[3,4-*d*]pyrimidine-6-carboxamide (120 mg, 0.27 mmol) and 5-bromo-3-isopropylpyrimidin-4(3*H*)-one (59 mg, 0.27 mmol) in a mixed solvent of dioxane (10 mL) and water (2 mL) was added Pd(dppf)Cl₂ (20 mg, 0.027 mmol) and potassium carbonate (112 mg, 0.81 mmol) under nitrogen atmosphere. The

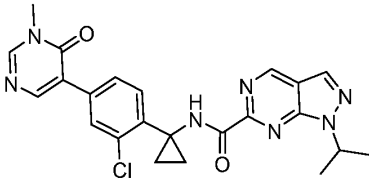
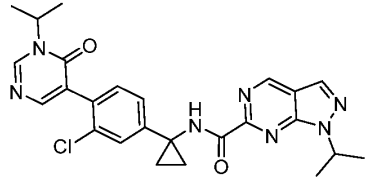
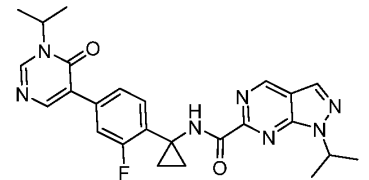
reaction mixture was heated to reflux and reacted for 2 hours, and then cooled to room temperature. The mixture was concentrated under reduced pressure, and the residue was purified by flash column chromatography (eluting with MeOH/H₂O(+0.5%HCOOH) = 60% : 40%) to give 23 mg of the product as pale yellow solid. MS (m/z) = 458.2 [M+H]⁺.

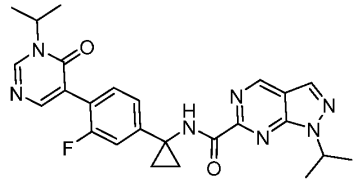
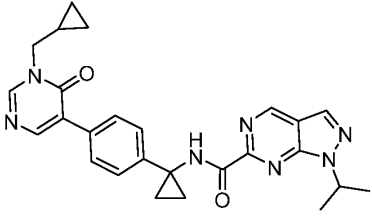
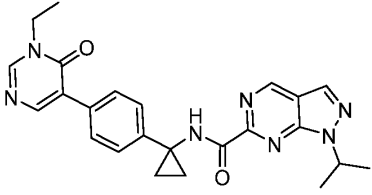
¹H NMR (400 MHz, DMSO) δ 9.72 (s, 1H), 9.43 (s, 1H), 8.53 (s, 1H), 8.48 (s, 1H), 8.07 (s, 1H), 7.58 (d, J = 8.3 Hz, 2H), 7.27 (d, J = 8.3 Hz, 2H), 5.38 - 5.26 (m, 1H), 5.03 - 4.90 (m, 1H), 1.51 (d, J = 6.7 Hz, 6H), 1.39 (d, J = 6.9 Hz, 6H), 1.34 (d, J = 8.4 Hz, 4H).

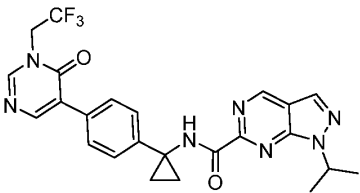
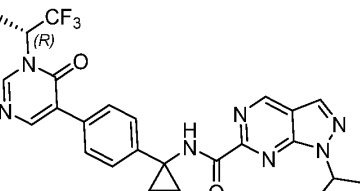
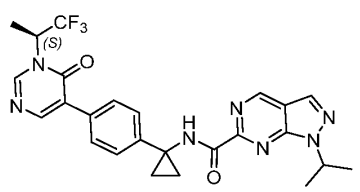
The following compounds were prepared according to the procedure of Compound 29 using the corresponding intermediates and reagents under appropriate conditions that

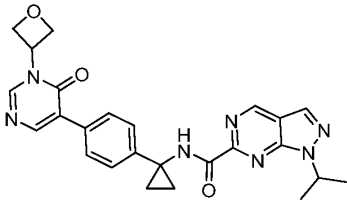
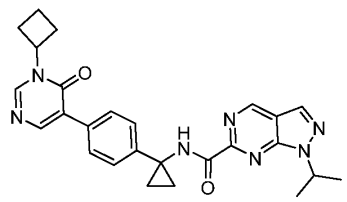
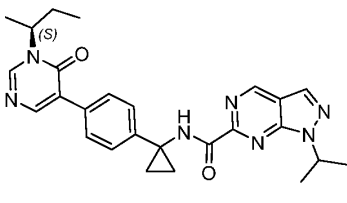
will be recognized by one skilled in the art.

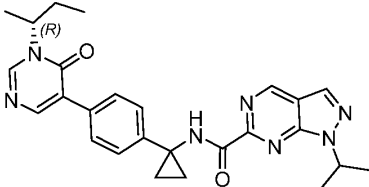
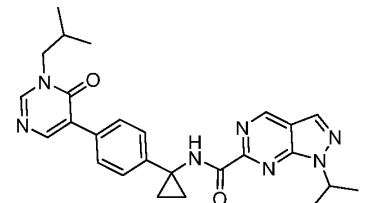
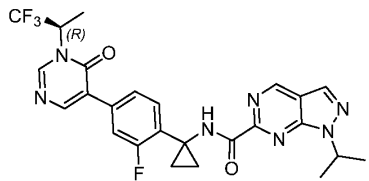
Compound	Structure	¹ H-NMR	MS	Intermediates used
30		¹ H NMR (400 MHz, DMSO) δ 9.68 (s, 1H), 9.44 (s, 1H), 8.49 (s, 1H), 7.79 (s, 1H), 7.52 (d, J = 8.4 Hz, 2H), 7.22 (d, J = 8.6 Hz, 4H), 5.37 - 5.26 (m, 1H), 3.32 (s, 3H), 1.53 (d, J = 6.7 Hz, 6H), 1.31 (d, J = 12.5 Hz, 4H).	445	5
31		¹ H NMR (400 MHz, DMSO) δ 9.72 (s, 1H), 9.44 (s, 1H), 8.50 (s, 1H), 8.00 (s, 1H), 7.59 (d, J = 8.4 Hz, 2H), 7.29 (d, J = 8.4 Hz, 2H), 5.41 - 5.23 (m, 1H), 3.50 (s, 3H), 2.52 (s, 3H), 1.53 (d, J = 6.7 Hz, 6H), 1.41 - 1.29 (m, 4H).	444	2

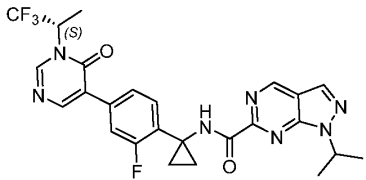
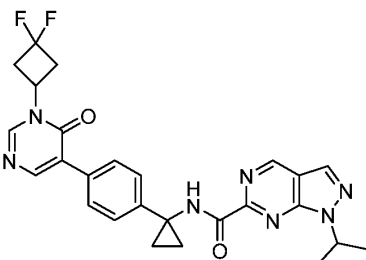
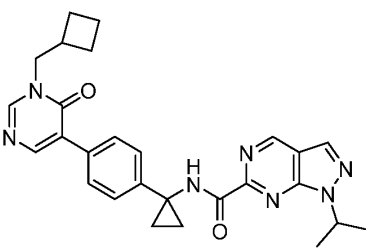
32		¹ H NMR (400 MHz, CD ₃ OD) δ 9.25 (s, 1H), 8.36 (s, 1H), 8.30 (s, 1H), 8.06 (s, 1H), 7.84 (d, J = 8.0 Hz, 1H), 7.72 (d, J = 1.4 Hz, 1H), 7.58 - 7.47 (m, 1H), 5.40 - 5.27 (m, 1H), 3.53 (s, 3H), 1.53 (d, J = 6.7 Hz, 6H), 1.44 - 1.29 (m, 4H).	464	27
33		¹ H NMR (400 MHz, CD ₃ OD) δ 9.34 (s, 1H), 8.50 (s, 1H), 8.37 (s, 1H), 7.89 (s, 1H), 7.50 (s, 1H), 7.35 - 7.25 (m, 2H), 5.52 - 5.39 (m, 1H), 5.08 - 4.99 (m, 1H), 1.58 (d, J = 6.4 Hz, 6H), 1.49 (d, 6H), 1.47 - 1.43 (m, 4H).	492	10, 26
34		¹ H NMR (400 MHz, CD ₃ OD) δ 9.28 (s, 1H), 8.44 (s, 1H), 8.33 (s, 1H), 8.07 (s, 1H), 7.78 - 7.69 (m, 1H), 7.45 (d, J = 11.9 Hz, 1H), 7.38 (d, J = 7.5 Hz, 1H), 5.47 - 5.33 (m, 1H), 5.13 - 5.02 (m, 1H), 1.54 (d, J = 5.7 Hz, 6H), 1.47 (d, J = 6.1 Hz, 6H), 1.41 - 1.36 (m, 4H).	476	10, 28

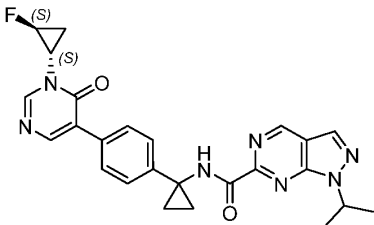
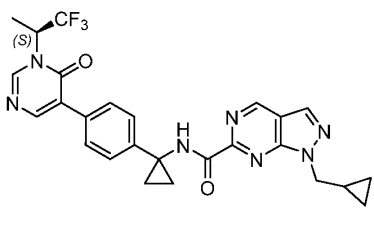
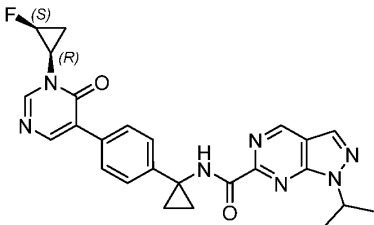
35		¹ H NMR (400 MHz, CD ₃ OD) δ 9.34 (s, 1H), 8.48 (s, 1H), 8.37 (s, 1H), 7.97 (s, 1H), 7.46 - 7.34 (m, J = 7.5 Hz, 1H), 7.21 - 7.13 (m, J = 8.5 Hz, 2H), 5.53 - 5.39 (m, 1H), 5.08 - 4.99 (m, 1H), 1.57 (d, J = 6.3 Hz, 6H), 1.49 (d, 6H), 1.47 - 1.40 (m, 4H).	476	10, 29
36		¹ H NMR (400 MHz, CD ₃ OD) δ 9.33 (s, 1H), 8.39 (s, 1H), 8.36 (s, 1H), 8.04 (s, 1H), 7.58 (d, J = 7.8 Hz, 2H), 7.38 (d, J = 7.8 Hz, 2H), 5.51 - 5.33 (m, 1H), 3.87 (d, J = 7.1 Hz, 2H), 1.56 (d, J = 6.5 Hz, 6H), 1.49 - 1.40 (m, 4H), 1.36 - 1.27 (m, 1H), 0.63 - 0.52 (m, 2H), 0.47 - 0.35 (m, 2H).	470	4
37		¹ H NMR (400 MHz, CDCl ₃) δ 9.19 (s, 1H), 8.83 (s, 1H), 8.22 (s, 1H), 8.08 (s, 1H), 7.99 (s, 1H), 7.59 (d, J = 7.7 Hz, 2H), 7.44 (d, J = 7.6 Hz, 2H), 5.52 - 5.41 (m, 1H), 4.03 (q, J = 7.1 Hz, 2H), 1.58 (d, J = 6.5 Hz, 6H), 1.49 - 1.40 (m, 7H).	444	11

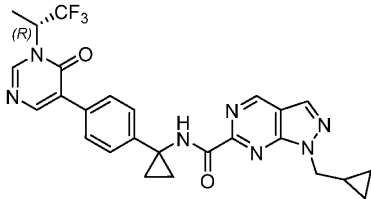
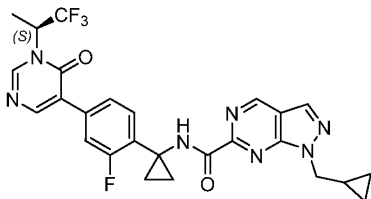
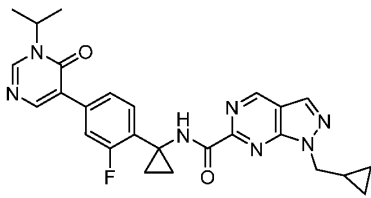
38		¹ H NMR (400 MHz, CDCl ₃) δ 9.19 (s, 1H), 8.83 (s, 1H), 8.23 (s, 1H), 8.08 (s, 1H), 8.00 (s, 1H), 7.58 (d, J = 7.5 Hz, 2H), 7.44 (d, J = 7.8 Hz, 2H), 5.52 - 5.39 (m, 1H), 4.66 (q, J = 8.5 Hz, 2H), 1.59 (d, J = 6.6 Hz, 6H), 1.52 - 1.43 (m, 4H).	498	12
39		¹ H NMR (400 MHz, CDCl ₃) δ 9.19 (s, 1H), 8.84 (s, 1H), 8.23 (s, 1H), 8.17 (s, 1H), 7.99 (s, 1H), 7.57 (d, J = 7.5 Hz, 2H), 7.45 (d, J = 7.5 Hz, 2H), 5.96 - 5.85 (m, 1H), 5.52 - 5.39 (m, 1H), 1.69 (d, J = 7.4 Hz, 3H), 1.59 (d, J = 6.6 Hz, 6H), 1.51 - 1.42 (m, 4H).	512	14
40		¹ H NMR (400 MHz, CDCl ₃) δ 9.19 (s, 1H), 8.84 (s, 1H), 8.23 (s, 1H), 8.17 (s, 1H), 7.99 (s, 1H), 7.57 (d, J = 8.0 Hz, 2H), 7.45 (d, J = 8.1 Hz, 2H), 5.97 - 5.84 (m, 1H), 5.53 - 5.40 (m, 1H), 1.69 (d, J = 7.3 Hz, 3H), 1.59 (d, J = 6.7 Hz, 6H), 1.52 - 1.43 (m, 4H).	512	13

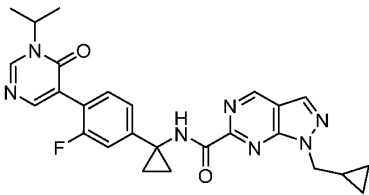
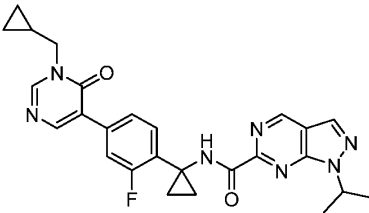
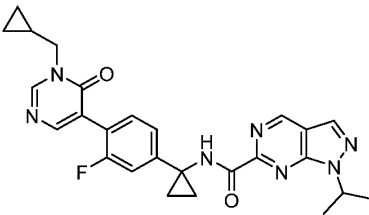
41		¹ H NMR (400 MHz, DMSO) δ 9.72 (s, 1H), 9.42 (s, 1H), 8.47 (s, 1H), 8.46 (s, 1H), 8.13 (s, 1H), 7.58 (d, J = 8.3 Hz, 2H), 7.27 (d, J = 8.4 Hz, 2H), 5.44 (p, J = 7.4 Hz, 1H), 5.35 - 5.24 (m, 1H), 4.86 (dt, J = 18.7, 7.2 Hz, 4H), 1.51 (d, J = 6.7 Hz, 6H), 1.37 - 1.29 (m, 4H).	472	16
42		¹ H NMR (400 MHz, DMSO) δ 9.73 (s, 1H), 9.42 (s, 1H), 8.50 (s, 1H), 8.47 (s, 1H), 8.08 (s, 1H), 7.57 (d, J = 8.4 Hz, 2H), 7.26 (d, J = 8.4 Hz, 2H), 5.30 (dt, J = 13.3, 6.6 Hz, 1H), 4.98 - 4.80 (m, 1H), 2.41 - 2.32 (m, 4H), 1.83 - 1.73 (m, 2H), 1.50 (d, J = 6.7 Hz, 6H), 1.37 - 1.29 (m, 4H).	470	15
43		¹ H NMR (400 MHz, DMSO) δ 9.73 (s, 1H), 9.42 (s, 1H), 8.48 (d, J = 1.4 Hz, 2H), 8.07 (s, 1H), 7.58 (d, J = 8.4 Hz, 2H), 7.27 (d, J = 8.4 Hz, 2H), 5.38 - 5.19 (m, 1H), 4.79 - 4.72 (m, 1H), 1.84 - 1.71 (m, 2H), 1.50 (d, J = 6.7 Hz, 6H), 1.37 (d, J = 6.9 Hz, 3H), 1.33 (d, J = 9.4 Hz, 4H), 0.78 (t, J = 7.4 Hz, 3H).	472	17

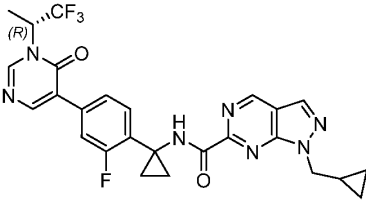
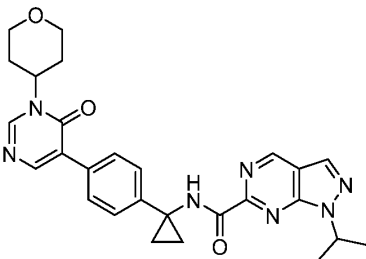
44		¹ H NMR (400 MHz, DMSO) δ 9.73 (s, 1H), 9.42 (s, 1H), 8.48 (d, J = 1.1 Hz, 2H), 8.07 (s, 1H), 7.58 (d, J = 8.4 Hz, 2H), 7.27 (d, J = 8.4 Hz, 2H), 5.38 - 5.21 (m, 1H), 4.87 - 4.69 (m, 1H), 1.85 - 1.70 (m, 2H), 1.50 (d, J = 6.7 Hz, 6H), 1.37 (d, J = 6.9 Hz, 3H), 1.33 (d, J = 9.4 Hz, 4H), 0.78 (t, J = 7.4 Hz, 3H).	472	18
45		¹ H NMR (400 MHz, DMSO) δ 9.73 (s, 1H), 9.42 (s, 1H), 8.47 (s, 1H), 8.42 (s, 1H), 8.08 (s, 1H), 7.58 (d, J = 8.3 Hz, 2H), 7.27 (d, J = 8.3 Hz, 2H), 5.42 - 5.17 (m, 1H), 3.76 (d, J = 7.3 Hz, 2H), 2.06 (dt, J = 13.7, 6.7 Hz, 1H), 1.50 (d, J = 6.6 Hz, 6H), 1.33 (d, J = 9.3 Hz, 4H), 0.85 (d, J = 6.7 Hz, 6H).	472	19
46		¹ H NMR (400 MHz, CDCl ₃) δ 9.15 (s, 1H), 8.87 (s, 1H), 8.23 - 8.14 (m, 2H), 8.01 (s, 1H), 7.89 - 7.79 (m, 1H), 7.41 (d, J = 11.8 Hz, 1H), 7.31 (d, J = 8.0 Hz, 1H), 5.98 - 5.78 (m, 1H), 5.53 - 5.32 (m, 1H), 1.71 - 1.67 (d, J = 7.3 Hz, 3H), 1.56 (d, J = 5.4 Hz, 6H), 1.41 - 1.33 (m, 4H).	530	14, 28

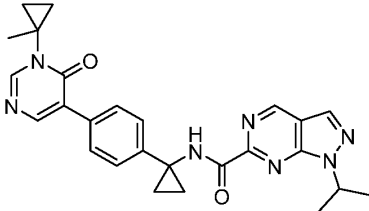
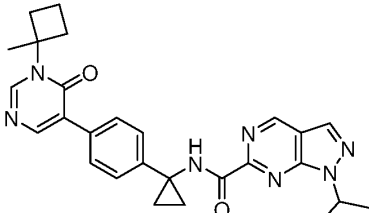
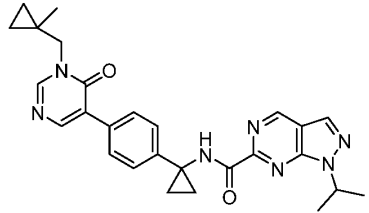
47		¹ H NMR (400 MHz, CDCl ₃) δ 9.20 (s, 1H), 8.89 (s, 1H), 8.26 - 8.19 (m, 2H), 8.02 (s, 1H), 7.86 - 7.72 (m, 1H), 7.39 (d, J = 11.0 Hz, 1H), 7.29 (d, J = 7.6 Hz, 1H), 5.95 - 5.82 (m, 1H), 5.48 - 5.35 (m, 1H), 1.70 (d, J = 7.3 Hz, 3H), 1.56 (d, J = 6.6 Hz, 6H), 1.40 - 1.32 (m, 4H).	530	13, 28
65		¹ H NMR (400 MHz, CD ₃ OD) δ 9.34 (s, 1H), 8.36 (d, J = 4.9 Hz, 2H), 8.06 (s, 1H), 7.58 (d, J = 8.1 Hz, 2H), 7.38 (d, J = 8.1 Hz, 2H), 5.57 - 5.39 (m, 1H), 4.74 - 4.69 (m, 1H), 3.27 - 3.17 (m, 2H), 3.16 - 3.08 (m, 2H), 1.58 (d, J = 6.6 Hz, 6H), 1.46 - 1.44 (m, 4H).	506	44
66		¹ H NMR (400 MHz, CDCl ₃) δ 9.17 (s, 1H), 8.83 (s, 1H), 8.20 (s, 1H), 7.99 (d, J = 26.6 Hz, 2H), 7.56 (d, J = 8.0 Hz, 2H), 7.41 (d, J = 8.1 Hz, 2H), 5.46 - 5.40 (m, 1H), 3.96 (d, J = 7.2 Hz, 2H), 2.82 - 2.75 (m, 1H), 2.12 - 1.99 (m, 2H), 1.89 - 1.85 (m, 2H), 1.80 - 1.73 (m, 2H), 1.55 (d, J = 6.6 Hz, 6H), 1.48 - 1.36 (m, 4H).	484	46

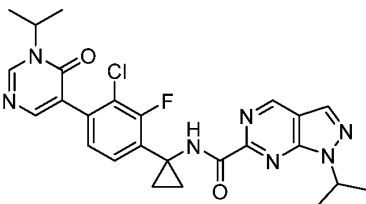
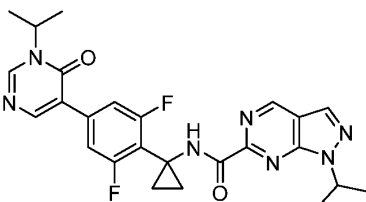
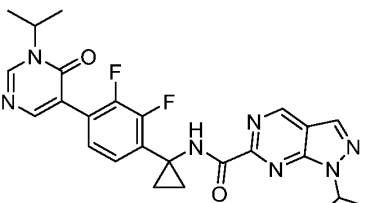
67		¹ H NMR (400 MHz, CD ₃ OD) δ 9.34 (s, 1H), 8.54 (s, 1H), 8.37 (s, 1H), 8.24 (s, 1H), 8.02 (s, 1H), 7.59 (d, J = 8.5 Hz, 2H), 7.39 (d, J = 8.6 Hz, 2H), 5.51 - 5.40 (m, 1H), 4.99 - 4.89 (m, 1H), 4.85 - 4.78 (m, 1H), 3.70 - 3.60 (m, 1H), 1.81 - 1.70 (m, 1H), 1.58 (d, J = 6.7 Hz, 6H), 1.49 - 1.41 (m, 4H).	474	47
68		¹ H NMR (400 MHz, CDCl ₃) δ 9.22 (s, 1H), 8.82 (s, 1H), 8.23 (s, 1H), 8.16 (s, 1H), 7.99 (s, 1H), 7.57 (d, J = 8.2 Hz, 2H), 7.44 (d, J = 8.3 Hz, 2H), 5.93-5.88 (m, 1H), 4.45 (d, J = 7.3 Hz, 2H), 1.68 (d, J = 7.4 Hz, 3H), 1.54-1.41 (m, 4H), 0.88-0.85 (m, 1H), 0.61 - 0.56 (m, 2H), 0.53-0.49 (m, 2H).	524	13, 41
69		¹ H NMR (400 MHz, CD ₃ OD) δ 9.33 (s, 1H), 8.37 (s, 1H), 8.36 (s, 1H), 8.05 (s, 1H), 7.58 (d, J = 8.3 Hz, 2H), 7.37 (d, J = 8.3 Hz, 2H), 5.48 - 5.41 (m, 1H), 5.05 - 5.02 (m, 1H), 4.92 - 4.87 (m, 1H), 1.64 - 1.59 (m, 1H), 1.57 (d, J = 6.6 Hz, 6H), 1.54 - 1.48 (m, 1H), 1.48 - 1.40 (m, 4H).	474	49

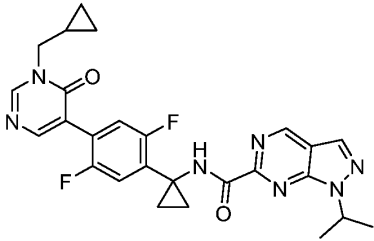
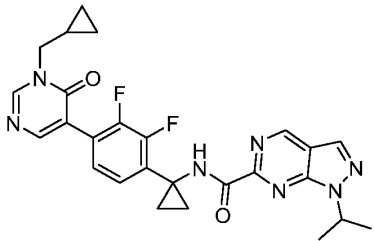
70		¹ H NMR (400 MHz, CDCl ₃) δ 9.21 (s, 1H), 8.82 (s, 1H), 8.23 (s, 1H), 8.16 (s, 1H), 7.99 (s, 1H), 7.57 (d, J = 8.0 Hz, 2H), 7.44 (d, J = 8.2 Hz, 2H), 5.92-5.88 (m, 1H), 4.45 (d, J = 7.6 Hz, 2H), 1.68 (d, J = 7.3 Hz, 3H), 1.47-1.44 (m, 4H), 0.89-0.85 (m, 1H), 0.61-0.57 (m, 2H), 0.52-0.48 (m, 2H).	524	14, 41
71		¹ H NMR (400 MHz, CDCl ₃) δ 9.17 (s, 1H), 8.87 (s, 1H), 8.19 (s, 2H), 8.01 (s, 1H), 7.82 (s, 1H), 7.41 (d, J = 11.8 Hz, 1H), 7.31 (d, J = 7.5 Hz, 1H), 5.90-5.86 (m, 1H), 4.43 (d, J = 6.8 Hz, 2H), 1.69 (d, J = 7.1 Hz, 3H), 1.40-1.35 (m, 4H), 0.88-0.84 (m, 1H), 0.59-0.55 (m, 2H), 0.50-0.46 (m, 2H).	542	13, 28, 41
72		¹ H NMR (400 MHz, CDCl ₃): δ 9.18 (s, 1H), 8.86 (s, 1H), 8.20 (s, 1H), 8.15 (s, 1H), 7.99 (s, 1H), 7.84-7.74 (m, 1H), 7.48-7.40 (m, 1H), 7.34-7.29 (m, 1H), 5.20-5.05 (m, 1H), 4.51-4.35 (m, 2H), 1.48-1.46 (m, 6H), 1.41-1.34 (m, 5H), 0.61-0.45 (m, 4H).	488	10, 28, 41

73		¹ H NMR (400 MHz, CD ₃ OD): δ 9.36 (s, 1H), 8.48 (s, 1H), 8.37 (s, 1H), 8.00-7.95 (m, 1H), 7.44-7.37 (m, 1H), 7.22-7.11 (m, 2H), 5.11-4.96 (m, 1H), 5.12-4.96 (m, 2H), 1.50-1.45 (m, 11H), 0.56-0.50 (m, 4H).	488	10, 29, 41
74		¹ H NMR (400 MHz, CDCl ₃) δ 9.15 (s, 1H), 8.87 (s, 1H), 8.19 (s, 1H), 8.16 (s, 1H), 8.02 (s, 1H), 7.82 (t, J = 8.0 Hz, 1H), 7.48 - 7.41 (m, 1H), 7.36 - 7.30 (m, 1H), 5.48 - 5.35 (m, 1H), 3.83 (d, J = 7.2 Hz, 2H), 1.56 (d, J = 6.7 Hz, 6H), 1.41 - 1.33 (m, 4H), 1.30 - 1.24 (m, 1H), 0.69 - 0.63 (m, 2H), 0.43 - 0.38 (m, 2H).	488	28, 48
75		¹ H NMR (400 MHz, CDCl ₃) δ 9.19 (s, 1H), 8.82 (s, 1H), 8.23 (s, 1H), 8.18 (s, 1H), 8.01 - 7.95 (m, 1H), 7.44 (t, J = 7.8 Hz, 1H), 7.20 - 7.15 (m, 2H), 5.52 - 5.40 (m, 1H), 3.83 (d, J = 7.2 Hz, 2H), 1.58 (d, J = 6.7 Hz, 6H), 1.51 - 1.42 (m, 4H), 1.32 - 1.25 (m, 1H), 0.68 - 0.63 (m, 2H), 0.43 - 0.39 (m, 2H).	488	29, 48

76		¹ H NMR (400 MHz, CDCl ₃) δ 9.17 (s, 1H), 8.87 (s, 1H), 8.20 - 8.19 (m, 1H), 8.18 (s, 1H), 8.01 (s, 1H), 7.82 (t, J = 8.0 Hz, 1H), 7.41 (dd, J = 11.7, 1.6 Hz, 1H), 7.31 (dd, J = 8.0, 1.7 Hz, 1H), 5.97 - 5.79 (m, 1H), 4.42 (d, J = 7.2 Hz, 2H), 1.69 (d, J = 7.4 Hz, 3H), 1.40-1.36 (m, 5H), 0.60 - 0.53 (m, 2H), 0.51 - 0.45 (m, 2H).	542	14, 28, 41
77		¹ H NMR (400 MHz, CD ₃ OD) δ 9.34 (s, 1H), 8.43 (s, 1H), 8.37 (s, 1H), 8.03 (s, 1H), 7.58 (d, J = 8.4 Hz, 2H), 7.39 (d, J = 8.4 Hz, 2H), 5.51 - 5.40 (m, 1H), 4.98 - 4.92 (m, 1H), 4.10 - 4.04 (m, 2H), 3.60 - 3.53 (m, 2H), 2.14 - 2.06 (m, 2H), 1.92 - 1.87 (m, 2H), 1.57 (d, J = 6.7 Hz, 6H), 1.48 - 1.42 (m, 4H).	500	51

78		¹ H NMR (400 MHz, CD ₃ OD) δ 9.34 (s, 1H), 8.45 (s, 1H), 8.37 (s, 1H), 8.01 (s, 1H), 7.58 (d, J = 8.0 Hz, 2H), 7.39 (d, J = 8.1 Hz, 2H), 5.54 - 5.38 (m, 1H), 1.58 (d, J = 6.6 Hz, 6H), 1.53 (s, 3H), 1.48 - 1.45 (m, 2H), 1.44 - 1.40 (m, 2H), 1.15 - 1.10 (m, 2H), 1.06 - 1.03 (m, 2H).	470	52
79		¹ H NMR (400 MHz, CD ₃ OD) δ 9.33 (s, 1H), 8.36 (s, 1H), 8.17 (s, 1H), 8.01 (s, 1H), 7.59 - 7.51 (m, 2H), 7.41 - 7.33 (m, 2H), 5.48 - 5.39 (m, 1H), 2.65 - 2.50 (m, 2H), 2.45 - 2.35 (m, 2H), 2.06 - 1.95 (m, 1H), 1.90 - 1.81 (m, 1H), 1.68 (s, 3H), 1.56 (d, J = 4.6 Hz, 6H), 1.49 - 1.40 (m, 4H).	484	53
86		¹ H NMR (400 MHz, CD ₃ OD) δ 9.33 (s, 1H), 8.37 (s, 1H), 8.35 (s, 1H), 8.02 (s, 1H), 7.57 (d, J = 8.4 Hz, 2H), 7.38 (d, J = 8.5 Hz, 2H), 5.51 - 5.37 (m, 1H), 3.97 (s, 2H), 1.56 (d, J = 6.7 Hz, 6H), 1.47 - 1.40 (m, 4H), 1.04 (s, 3H), 0.72 - 0.69 (m, 2H), 0.42 - 0.36 (m, 2H).	484	54

91		¹H NMR (400 MHz, CD₃OD): δ 9.29 (s, 1H), 8.53 (s, 1H), 8.34 (s, 1H), 7.90 (s, 1H), 7.76-7.58 (m, 1H), 7.22-7.00 (m, 1H), 5.50-5.32 (m, 1H), 5.11-4.95 (m, 1H), 1.60-1.52 (m, 6H), 1.51-1.45 (m, 6H), 1.43-1.32 (m, 4H).	510	10, 58
92		¹H NMR (400 MHz, CDCl₃): δ 9.19 (s, 1H), 8.79 (s, 1H), 8.23 (s, 1H), 8.12 (s, 1H), 7.97 (s, 1H), 7.60-7.54 (m, 2H), 7.48-7.40 (m, 2H), 5.20-5.08 (m, 1H), 4.58-4.41 (m, 1H), 1.67-1.62 (m, 3H), 1.49-1.39 (m, 12H), 0.74-0.63 (m, 1H), 0.48-0.30 (m, 3H).	494	10, 59
93		¹H NMR (400 MHz, CDCl₃): δ 9.15 (s, 1H), 8.86 (s, 1H), 8.19 (s, 1H), 8.18 (s, 1H), 7.93 (s, 1H), 7.58 (t, J = 7.4 Hz, 1H), 7.15 (t, J = 7.2 Hz, 1H), 5.50 - 5.36 (m, 1H), 5.19 - 5.03 (m, 1H), 1.56 (d, J = 6.9 Hz, 6H), 1.47 (d, J = 6.9 Hz, 6H), 1.41-1.34 (m, 4H).	494	10, 56

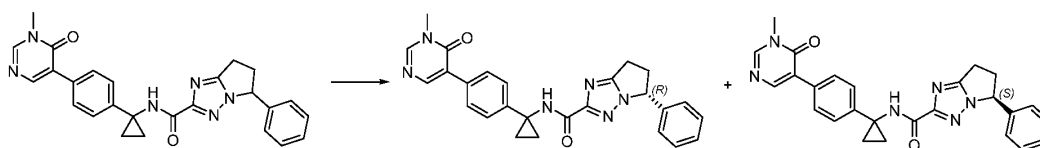
94		¹H NMR (400 MHz, CDCl₃) δ 9.15 (s, 1H), 8.85 (s, 1H), 8.19 (s, 2H), 8.02 (d, J = 1.8 Hz, 1H), 7.59-7.53 (m, 1H), 7.33 - 7.25 (m, 1H), 5.49 - 5.36 (m, 1H), 3.82 (d, J = 7.2 Hz, 2H), 1.56 (d, J = 6.7 Hz, 6H), 1.41 - 1.31 (m, 4H), 1.30 - 1.22 (m, 1H), 0.65 (q, J = 5.5 Hz, 2H), 0.40 (q, J = 5.2 Hz, 2H).	506	48, 57
95		¹H NMR (400 MHz, CDCl₃) δ 9.15 (d, J = 0.6 Hz, 1H), 8.87 (s, 1H), 8.21 (s, 1H), 8.20 (s, 1H), 7.96 (s, 1H), 7.56-7.57 (m, 1H), 7.23 - 7.10 (m, 1H), 5.49 - 5.35 (m, 1H), 3.83 (d, J = 7.2 Hz, 2H), 1.56 (d, J = 6.5 Hz, 6H), 1.46 - 1.33 (m, 4H), 1.33 - 1.20 (m, 1H), 0.70 - 0.60 (m, 2H), 0.45-0.37 (m, 2H).	506	48, 56

Compound 53 and Compound 54

(S)-N-(1-(4-(1-methyl-6-oxo-1,6-dihydropyrimidin-5-yl)phenyl)cyclopropyl)-5-phenyl-6,7-dihydro-5H-pyrrolo[1,2-b][1,2,4]triazole-2-carboxamide

and

(R)-N-(1-(4-(1-methyl-6-oxo-1,6-dihydropyrimidin-5-yl)phenyl)cyclopropyl)-5-phenyl-6,7-dihydro-5H-pyrrolo[1,2-b][1,2,4]triazole-2-carboxamide



The racemic compound *N*-(1-(4-(1-methyl-6-oxo-1,6-dihydropyrimidin-5-yl)phenyl)cyclopropyl)-5-phenyl-6,7-dihydro-5H-pyrrolo[1,2-b][1,2,4]triazole-2-carboxamide (this compound was prepared according to the procedure of Compound 1 using 5-bromo-3-methylpyrimidin-4(3*H*)-one, tert-butyl (1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)cyclopropyl)carbamate and Intermediate 20 as the raw materials) was resolved by chiral HPLC to provide the optically pure enantiomers

Compound 53 and Compound 54 (HPLC conditions: column: OJ-H 4.6 x 150 mm; mobile phase: n-hexane/EtOH = 60/40; flow rate = 0.5 mL/min; detector: UV 254 nm). The first eluent (Compound 53, *R_f* = 3.028 min) was 100% ee, MS (*m/z*): 453 [*M*+*H*]⁺. The second eluent (Compound 54, *R_f* = 4.915 min) was 99.78% ee, MS (*m/z*): 453 [*M*+*H*]⁺.

Compound 53: ¹H NMR (400 MHz, CDCl₃) δ: 8.09 (s, 1H), 8.00 (s, 1H), 7.71 (s, 1H), 7.61 - 7.54 (m, 2H), 7.39 - 7.32 (m, 5H), 7.16 - 7.08 (m, 2H), 5.48 - 5.40 (m, 1H), 3.57 (s, 3H), 3.29 - 2.95 (m, 3H), 2.76 - 2.59 (m, 1H), 1.45 - 1.34 (m, 4H).

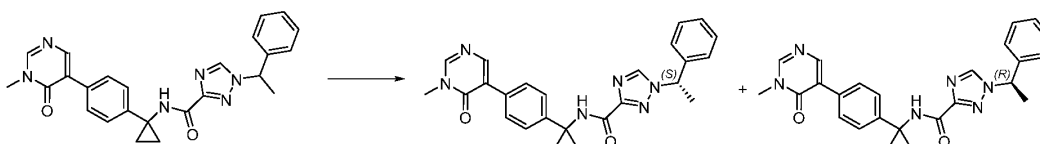
Compound 54: ¹H NMR (400 MHz, CDCl₃) δ: 8.09 (s, 1H), 8.00 (s, 1H), 7.71 (s, 1H), 7.61 - 7.55 (m, 2H), 7.39 - 7.31 (m, 5H), 7.18 - 7.06 (m, 2H), 5.51 - 5.39 (m, 1H), 3.56 (s, 3H), 3.28 - 2.97 (m, 3H), 2.74 - 2.60 (m, 1H), 1.44 - 1.34 (m, 4H).

Compound 55 and Compound 56

(R)-N-(1-(4-(1-methyl-6-oxo-1,6-dihydropyrimidin-5-yl)phenyl)cyclopropyl)-1-(1-phenyl ethyl)-1*H*-1,2,4-triazole-3-carboxamide

and

(S)-N-(1-(4-(1-methyl-6-oxo-1,6-dihydropyrimidin-5-yl)phenyl)cyclopropyl)-1-(1-phenylethyl)-1*H*-1,2,4-triazole-3-carboxamide



The racemic compound *N*-(1-(4-(1-methyl-6-oxo-1,6-dihydropyrimidin-5-yl)phenyl)cyclopropyl)-1-(1-phenylethyl)-1*H*-1,2,4-triazole-3-carboxamide (this compound was prepared according to the procedure of Compound 1 using 5-bromo-3-methylpyrimidin-4(3*H*)-one, tert-butyl (1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)cyclopropyl)carbamate and Intermediate 34 as the raw materials) was resolved by chiral HPLC to provide the optically pure enantiomers Compound 55 and Compound 56 (HPLC conditions: column: Daicel OJ 4.6 x 150 mm; mobile phase: n-hexaneisopropanol (0.1% diethylamine) = 60/40; flow rate = 0.5 mL/min; detector: UV 254 nm). The first eluent (Compound 55, *R_f* = 4.676 min) was 99.85% ee, MS (*m/z*): 441 [M+H]⁺. The second eluent (Compound 56, *R_f* = 5.955 min) was 99.89% ee, MS (*m/z*): 441 [M+H]⁺.

Compound 55: ¹H NMR (400 MHz, CD₃OD) δ 8.54 (s, 1H), 8.36 (s, 1H), 8.04 (s, 1H), 7.59 - 7.53 (m, 2H), 7.35 (d, *J* = 4.4 Hz, 4H), 7.33 - 7.27 (m, 3H), 5.83 - 5.68 (m, *J* = 7.1 Hz, 1H), 3.55 (s, 3H), 1.93 (d, *J* = 7.1 Hz, 3H), 1.39 - 1.33 (m, 4H).

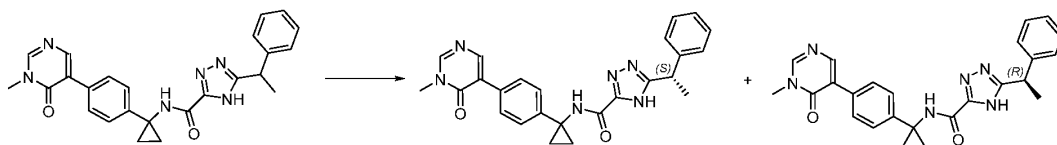
Compound 56: ¹H NMR (400 MHz, CD₃OD) δ 8.55 (s, 1H), 8.36 (s, 1H), 8.04 (s, 1H), 7.59 - 7.54 (m, 2H), 7.35 (d, *J* = 3.7 Hz, 4H), 7.33 - 7.29 (m, 3H), 5.82 - 5.66 (m, 1H), 3.55 (s, 3H), 1.93 (d, *J* = 7.1 Hz, 3H), 1.39 - 1.34 (m, 4H).

Compound 57 and Compound 58

(*R*)-*N*-(1-(4-(1-methyl-6-oxo-1,6-dihydropyrimidin-5-yl)phenyl)cyclopropyl)-5-(1-phenylethyl)-4*H*-1,2,4-triazole-3-carboxamide

and

(*S*)-*N*-(1-(4-(1-methyl-6-oxo-1,6-dihydropyrimidin-5-yl)phenyl)cyclopropyl)-5-(1-phenylethyl)-4*H*-1,2,4-triazole-3-carboxamide



The racemic compound *N*-(1-(4-(1-methyl-6-oxo-1,6-dihydropyrimidin-5-yl)phenyl)cyclopropyl)-5-(1-phenylethyl)-4*H*-1,2,4-triazole-3-carboxamide (this compound was prepared according to the procedure of Compound 1 using 5-bromo-3-methylpyrimidine-4(3*H*)-one, tert-butyl (1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)cyclopropyl)carbamate and Intermediate 35 as the raw materials) was resolved by chiral HPLC to provide the optically pure enantiomers Compound 57 and Compound

58 (HPLC conditions: column: Daicel OJ 4.6 x 150 mm; mobile phase: n-hexane/ethanol (0.1% diethylamine) = 60:40; flow rate: 0.5 mL/ minute; detector: UV 254 nm). The first eluent (Compound 57, R_f = 6.485 min) was 100% ee, MS (m/z): 441 [M+H]⁺. The second eluent (Compound 58, R_f = 6.979 min) was 99.90% ee, MS (m/z): 441 [M+H]⁺.

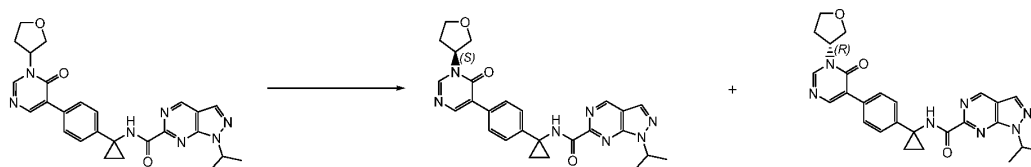
5 Compound 57: ¹H NMR (400 MHz, DMSO) δ 9.26 (s, 1H), 8.44 (s, 1H), 8.06 (s, 1H), 7.58 - 7.54 (m, 2H), 7.35 - 7.26 (m, 4H), 7.26 - 7.14 (m, 3H), 4.38 - 4.21 (m, 1H), 3.45 (s, 3H), 1.61 (d, *J* = 7.2 Hz, 3H), 1.28 - 1.22 (m, 4H)

Compound 58: ¹H NMR (400 MHz, DMSO) δ 9.24 (s, 1H), 8.44 (s, 1H), 8.06 (s, 1H), 7.62 - 7.53 (m, 2H), 7.35 - 7.26 (m, 4H), 7.26 - 7.13 (m, 3H), 4.36 - 4.25 (m, 1H),
10 3.45 (s, 3H), 1.61 (d, *J* = 7.2 Hz, 3H), 1.28 - 1.22 (m, 4H).

Compound 80 and Compound 81

(R)-1-i-propyl-N-(1-(4-(6-oxo-1-(tetrahydrofuran-3-yl)-1,6-dihydropyrimidin-5-yl)phenyl)cyclopropyl)-1*H*-pyrazolo[3,4-*d*]pyrimidine-6-carboxamide
and

15 **(S)-1-i-propyl-N-(1-(4-(6-oxo-1-(tetrahydrofuran-3-yl)-1,6-dihydropyrimidin-5-yl)phenyl)cyclopropyl)-1*H*-pyrazolo[3,4-*d*]pyrimidine-6-carboxamide**



The racemic compound 1-i-propyl -*N*-(1-(4-(6-oxo-1-(tetrahydrofuran-3-yl)-1,6-dihydropyrimidin-5-yl)phenyl)cyclopropyl)-1*H*-pyrazolo[3,4-*d*]pyrimidine-6-carboxamide (this compound was prepared according to the procedure of Compound 29 using 1-(4-bromophenyl)cyclopropan-1-amine, 1-i-propyl-1*H*-pyrazolo[3,4-*d*]pyrimidine-6-carboxylic acid and Intermediate 45 as the raw materials) was resolved by chiral HPLC to provide the optically pure enantiomers Compound 80 and Compound 81 (HPLC conditions: column: AD-H 4.6 x 50 mm; mobile phase: CO₂ : IPA (0.1% DEA) = 60 : 40; flow rate: 4 mL/minute; detector: UV 254 nm). The first eluent (Compound 80, R_f = 2.933 min) was 100% ee, MS (m/z): 486.2 [M+H]⁺. The second eluent (Compound 81, R_f = 3.691 min) was 99.17% ee, MS (m/z): 486.2 [M+H]⁺.

Compound 80: ¹H NMR (400 MHz, CDCl₃) δ 9.19 (s, 1H), 8.83 (s, 1H), 8.25 (s, 1H), 8.23 - 8.20 (m, 1H), 7.98 (s, 1H), 7.59 - 7.54 (m, 2H), 7.47 - 7.41 (m, 2H), 5.59 - 5.50 (m, 1H), 5.51 - 5.41 (m, 1H), 4.18 (td, *J* = 8.6, 6.1 Hz, 1H), 4.13 - 4.06 (m, 1H),
30 5.50 (m, 1H), 5.51 - 5.41 (m, 1H), 4.18 (td, *J* = 8.6, 6.1 Hz, 1H), 4.13 - 4.06 (m, 1H),

3.98 - 3.84 (m, 2H), 2.61 (dtd, $J = 14.5, 8.7, 6.0$ Hz, 1H), 2.14 - 2.04 (m, 1H), 1.57 (s, 6H), 1.49 (dd, $J = 7.1, 5.5$ Hz, 2H), 1.45 - 1.41 (m, 2H).

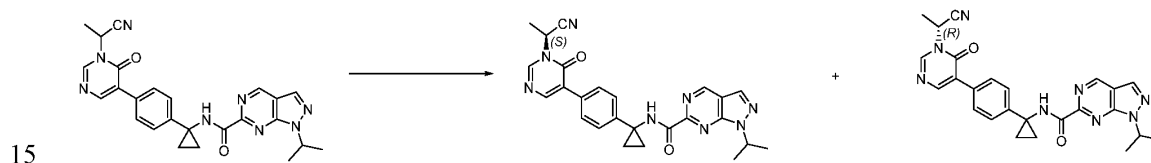
Compound 81: ^1H NMR (400 MHz, CDCl_3) δ 9.19 (s, 1H), 8.83 (s, 1H), 8.25 (s, 1H), 8.22 (d, $J = 0.4$ Hz, 1H), 8.00 - 7.96 (m, 1H), 7.58 - 7.55 (m, 2H), 7.46 - 7.43 (m, 2H), 5.58 - 5.51 (m, 1H), 5.52 - 5.41 (m, 1H), 4.18 (td, $J = 8.6, 6.0$ Hz, 1H), 4.09 (d, $J = 11.3$ Hz, 1H), 3.98 - 3.86 (m, 2H), 2.61 (dtd, $J = 14.5, 8.7, 6.1$ Hz, 1H), 2.08 (ddd, $J = 16.5, 11.1, 5.0$ Hz, 1H), 1.59 (s, 6H), 1.49 (dd, $J = 7.2, 5.5$ Hz, 2H), 1.44 (d, $J = 4.5$ Hz, 2H).

Compound 82 and Compound 83

10 **(R)-N-(1-(4-(1-(1-cyanoethyl)-6-oxo-1,6-dihydropyrimidin-5-yl)phenyl)cyclopropyl)-1-i-propyl-1H-pyrazolo[3,4-d]pyrimidine-6-carboxamide**

and

(S)-N-(1-(4-(1-(1-cyanoethyl)-6-oxo-1,6-dihydropyrimidin-5-yl)phenyl)cyclopropyl)-1-i-propyl-1H-pyrazolo[3,4-d]pyrimidine-6-carboxamide



The racemic compound *N*-(1-(4-(1-(1-cyanoethyl)-6-oxo-1,6-dihydropyrimidin-5-yl)phenyl)cyclopropyl)-1-*i*-propyl-1H-pyrazolo[3,4-d]pyrimidine-6-carboxamide (this compound was prepared according to the procedure of Compound 29 using 1-(4-bromophenyl)cyclopropan-1-amine, 1-*i*-propyl-1H-pyrazolo[3,4-d]pyrimidine-6-carboxylic acid and Intermediate 36 as the raw materials) was resolved by chiral HPLC to provide the optically pure enantiomers Compound 82 and Compound 83 (HPLC conditions: column: AD-H 4.6 x 50 mm; mobile phase: CO_2 : IPA (0.1% DEA) = 60/40; flow rate: 4 mL/minute; detector: UV 254 nm). The first eluent (Compound 82, $R_f = 1.554$ min) was 100% ee, MS (m/z): 469.2 $[\text{M}+\text{H}]^+$. The second eluent (Compound 83, $R_f = 2.063$ min) was 99.88% ee, MS (m/z): 469.2 $[\text{M}+\text{H}]^+$.

Compound 82: ^1H NMR (400 MHz, CDCl_3) δ 9.21 (s, 1H), 8.85 (s, 1H), 8.36 (s, 1H), 8.23 (s, 1H), 8.03 (s, 1H), 7.55 (d, $J = 8.2$ Hz, 2H), 7.43 (d, $J = 8.1$ Hz, 2H), 5.98 - 5.84 (m, 1H), 5.55 - 5.40 (m, 1H), 1.81 (d, $J = 7.1$ Hz, 3H), 1.58 (d, $J = 6.6$ Hz, 6H), 1.51 - 1.43 (m, 4H).

Compound 83: ^1H NMR (400 MHz, CDCl_3) δ 9.19 (s, 1H), 8.84 (s, 1H), 8.34 (s, 1H), 8.23 (s, 1H), 8.02 (s, 1H), 7.55 (d, $J = 8.3$ Hz, 2H), 7.44 (d, $J = 8.3$ Hz, 2H), 5.90 (q, $J = 7.0$ Hz, 1H), 5.45 (dt, $J = 13.1, 6.6$ Hz, 1H), 1.81 (d, $J = 7.1$ Hz, 3H), 1.58 (d, $J = 6.7$ Hz, 6H), 1.52 - 1.42 (m, 4H).

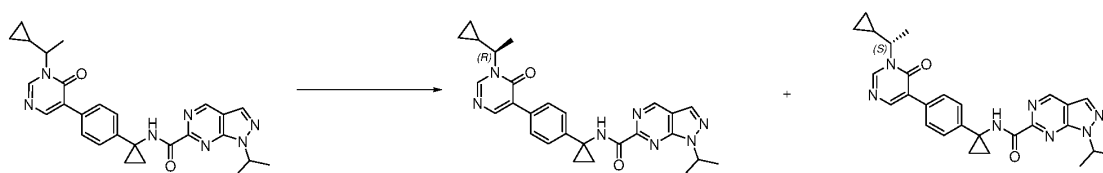
5

Compound 84 and Compound 85

(R)-N-(1-(4-(1-(1-cyclopropylethyl)-6-oxo-1,6-dihydropyrimidin-5-yl)phenyl)cyclopropyl)-1-i-propyl-1H-pyrazolo[3,4-d]pyrimidine-6-carboxamide
and

(S)-N-(1-(4-(1-(1-cyclopropylethyl)-6-oxo-1,6-dihydropyrimidin-5-yl)phenyl)cyclopropyl)-1-i-propyl-1H-pyrazolo[3,4-d]pyrimidine-6-carboxamide

10



The racemic compound *N*-(1-(4-(1-(1-cyclopropylethyl)-6-oxo-1,6-dihydropyrimidin-5-yl)phenyl)cyclopropyl)-1-i-propyl-1*H*-pyrazolo[3,4-d]pyrimidine-6-carboxamide (this compound was prepared according to the procedure of Compound 29 using 1-(4-bromophenyl)cyclopropan-1-amine, 1-i-propyl-1*H*-pyrazolo[3,4-d]pyrimidine-6-carboxylic acid and Intermediate 50 as the raw materials) was resolved by chiral HPLC to provide the optically pure enantiomers Compound 84 and Compound 85 (HPLC conditions: column: IG-H 4.6 x 150 mm; mobile phase: ethanol : acetonitrile = 90/10; flow rate: 0.5 mL/ minute; detector: UV 254 nm). The first eluent (Compound 84, $R_f = 21.601$ min) was 100% ee, MS (m/z): 484.2 $[\text{M}+\text{H}]^+$. The second eluent (Compound 85, $R_f = 27.267$ min) was 100% ee, MS (m/z): 484.2 $[\text{M}+\text{H}]^+$.

Compound 84: ^1H NMR (400 MHz, CD_3OD) δ 9.33 (s, 1H), 8.57 (s, 1H), 8.36 (s, 1H), 8.03 (s, 1H), 7.57 (d, $J = 8.4$ Hz, 2H), 7.38 (d, $J = 8.4$ Hz, 2H), 5.47 - 5.40 (, 1H), 4.16 - 4.08 (m, 1H), 1.56 (d, $J = 6.7$ Hz, 6H), 1.52 (d, $J = 6.8$ Hz, 3H), 1.46 - 1.40 (m, 4H), 0.91 - 0.72 (m, 2H), 0.60 - 0.42 (m, 2H), 0.31 - 0.25 (m, 1H).

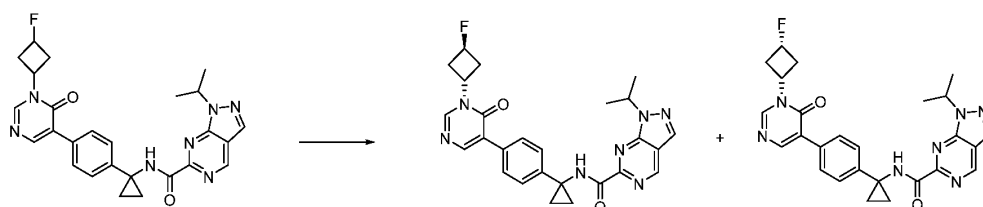
Compound 85: ^1H NMR (400 MHz, CD_3OD) δ 9.34 (s, 1H), 8.57 (s, 1H), 8.36 (s, 1H), 8.04 (s, 1H), 7.57 (d, $J = 8.4$ Hz, 2H), 7.39 (d, $J = 8.4$ Hz, 2H), 5.48 - 5.41 (m, 1H), 4.16 - 4.09 (m, 1H), 1.57 (d, $J = 6.7$ Hz, 6H), 1.53 (d, $J = 6.8$ Hz, 3H), 1.45 (d, $J = 11.8$ Hz, 4H), 0.98 - 0.73 (m, 2H), 0.60 - 0.44 (m, 2H), 0.32 - 0.26 (td, $J = 9.7, 5.1$ Hz, 1H).

30

Compound 87 and Compound 88

***N*-(1-(4-(1-(*trans*-3-fluorocyclobutyl)-6-oxo-1,6-dihydropyrimidin-5-yl)phenyl)cyclopropyl)-1-*i*-propyl-1*H*-pyrazolo[3,4-*d*]pyrimidine-6-carboxamide**
and

5 ***N*-(1-(4-(1-(*cis*-3-fluorocyclobutyl)-6-oxo-1,6-dihydropyrimidin-5-yl)phenyl)cyclopropyl)-1-*i*-propyl-1*H*-pyrazolo[3,4-*d*]pyrimidine-6-carboxamide**



The compound *N*-(1-(4-(1-(3-fluorocyclobutyl)-6-oxo-1,6-dihydropyrimidin-5-yl)phenyl)cyclopropyl)-1-*i*-propyl-1*H*-pyrazolo[3,4-*d*]pyrimidine-6-carboxamide (this
10 compound was prepared according to the procedure of Compound 29 using 1-(4-bromophenyl)cyclopropan-1-amine, 1-*i*-propyl-1*H*-pyrazolo[3,4-*d*]pyrimidine-6-carboxylic acid and Intermediate 55 as the raw materials) was resolved by chiral HPLC to provide Compound 87 and Compound 88 (HPLC conditions: column: OD-H 4.6 x 50 mm; Mobile phase: CO₂ : IPA (0.1% DEA) = 60 : 40; flow rate: 4 mL/minute; detector:
15 UV 254 nm). The first eluent (Compound 87, *R_f* = 14.930 min) was 100% ee, MS (*m/z*): 488.2 [*M*+*H*]⁺. The second eluent (Compound 88, *R_f* = 21.254 min) was 100% ee, MS (*m/z*): 488.2 [*M*+*H*]⁺.

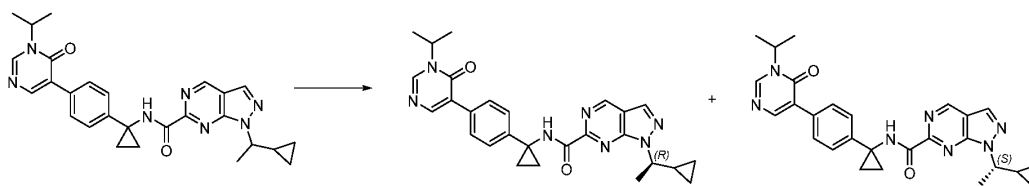
Compound 87: ¹H NMR (400 MHz, CD₃OD) δ 9.32 (s, 1H), 8.35 (s, 1H), 8.32 (s, 1H), 8.02 (s, 1H), 7.55 (d, *J* = 8.4 Hz, 2H), 7.36 (d, *J* = 8.4 Hz, 2H), 5.51 - 5.39 (m, 1H),
20 5.37 - 5.20 (m, 1H), 5.19 - 5.12 (m, 1H), 2.92 - 2.73 (m, 4H), 1.56 (d, *J* = 6.7 Hz, 6H), 1.47 - 1.40 (m, 4H).

Compound 88: ¹H NMR (400 MHz, CD₃OD) δ 9.33 (s, 1H), 8.38 (s, 1H), 8.36 (s, 1H), 8.05 (s, 1H), 7.57 (d, *J* = 8.5 Hz, 2H), 7.37 (d, *J* = 8.6 Hz, 2H), 5.48 - 5.39 (m, 1H),
25 5.07 - 4.90 (m, 1H), 4.45 - 4.34 (m, 1H), 3.08 - 2.98 (m, 2H), 2.67 - 2.52 (m, 2H), 1.57 (d, *J* = 6.7 Hz, 6H), 1.47 - 1.41 (m, 4H).

Compound 89 and Compound 90

(*R*)-1-(1-cyclopropylethyl)-*N*-(1-(4-(1-*i*-propyl-6-oxo-1,6-dihydropyrimidin-5-yl)phenyl)cyclopropyl)-1*H*-pyrazolo[3,4-*d*]pyrimidine-6-carboxamide
and

(S)-1-(1-cyclopropylethyl)-N-(1-(4-(1-i-propyl-6-oxo-1,6-dihydropyrimidin-5-yl)phenyl)cyclopropyl)-1*H*-pyrazolo[3,4-*d*]pyrimidine-6-carboxamide



The racemic compound 1-(1-cyclopropylethyl)-*N*-(1-(4-(1-i-propyl-6-oxo-1,6-dihydropyrimidin-5-yl)phenyl)cyclopropyl)-1*H*-pyrazolo[3,4-*d*]pyrimidine-6-carboxamide (namely, Compound 59) was resolved by chiral HPLC to provide the optically pure enantiomers Compound 89 and Compound 90 (HPLC conditions: column: AS-H 4.6 x 15 mm; Mobile phase: CO₂ : ETOH (0.1% DEA) = 70 : 30; flow rate: 2.5 mL/ minute; detector: UV 254 nm). The first eluent (Compound 89, *R_f* = 3.919 minute min) was 100% ee, MS (*m/z*): 484.2 [M+H]⁺. The second eluent (Compound 90, *R_f* = 4.260 min) was 100% ee, MS (*m/z*): 484.2 [M+H]⁺.

Compound 89: ¹H NMR (400 MHz, CDCl₃) δ 9.19 (s, 1H), 8.79 (s, 1H), 8.23 (s, 1H), 8.12 (s, 1H), 7.97 (s, 1H), 7.60-7.54 (m, 2H), 7.48-7.40 (m, 2H), 5.20-5.08 (m, 1H), 4.58-4.41 (m, 1H), 1.67-1.62 (m, 3H), 1.49- 1.39 (m, 11H), 0.74-0.63 (m, 1H), 0.48-0.30 (m, 3H).

Compound 90: ¹H NMR (400 MHz, CDCl₃) δ 9.19 (s, 1H), 8.80 (s, 1H), 8.23 (s, 1H), 8.13 (s, 1H), 7.97 (s, 1H), 7.61-7.53 (m, 2H), 7.49-7.37 (m, 2H), 5.26-5.03 (m, 1H), 4.69-4.36 (m, 1H), 1.69-1.65 (m, 3H), 1.50-1.44 (m, 9H), 1.43-1.39 (m, 2H), 0.73-0.69 (m, 1H), 0.46-0.31 (m, 3H).

Example 2. RIPK1 kinase activity assay

1. Reagents and materials

RIPK1 recombination protein: synthesized by Shanghai Medicilon Inc. under the commission by Hutchison MediPharma Limited (50 g of cell pellet was resuspended in 250 mL of lysis buffer (50 mM Tris, pH 7.5, 250 mM NaCl, 1 mM DTT, protease inhibitor 1 : 50), the cells were ultrasonically lysed using a sonicator (the power set to 4) on ice for 3 × 30 minutes; then centrifugation was carried out at 4°C, at 15,000 g for 30 minutes to clarify the suspension, the soluble pellet was resuspended into 10 mL of glutathione agarose, and incubated at 4°C for 2 hours; then the beads were loaded into the column and washed with lysis buffer (no protease inhibitors) to baseline, and eluted with 20 mM of reduced glutathione (50 mM Tris, pH 8). The fractions identified by SDS-

PAGE as containing the protein of interest were collected (10 mL of total volume), concentrated to about 5 mL and loaded into 300 mL superdex75 column (GE Healthcare) equilibrated with buffer (50 mM Tris, pH 7.5, 150 mM NaCl, 1 mM DTT, 10% glycerol, pH 7.5). RIP1 protein was eluted as a dimer from the superdex75 column. The protein concentration was determined by the Bradford assay using BSA as the standard. The yield was 12.5 mg at 0.63 mg/mL. The protein was aliquoted and frozen at -80°C for later use.

The sequence of the RIPK1 recombinant protein was:

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1  MHHHHHHHHH HSPILGYWKI KGLVQPTRLL LEYLEEKYEE HLYERDEGDK
10  51  WRNKKFELGL EFPNLPYYID GDVKLTQSMA IIRYIADKHN MLGGCPKERA
    101  EISMLEGAVL DIRYGVSRIA YSKDFETLKV DFLSKLPEML KMFEDRLCHK
    151  TYLNGDHVTH PDFMLYDALD VVLYMDPMCL DAFPKLVCFK KRIEAIPQID
    201  KYLKSSKYIA WPLQGWQATF GGGDHPPKSD LVPRGSENLY FQGMQPDMSL
    251  NVIKMKSSDF LESAELDSSG FGKVS LCFHR TQGLMIMKT VYKGPNCIEHN
15  301  EALLEEAKMM NRLRHSRVVK LLGVIIIEEGK YSLVMEYMEK GNLMHVLKAE
    351  MSTPLSVKGR IILEIIEGMC YLHGKGVVHK DLKPENILVD NDFHIKIADL
    401  GLASF KMWSK LNNEEHNELR EVDGTAKKNG GTLYYMAPEH LNDVNAKPTE
    451  KSDVYSFAVV LWAI FANKEP YENAICEQQL IMCIKSGNRP DVDDITEYCP
    501  REIISLMKLC WEANPEARPT FPGIEEKFRP FYLSQLEESV EEDVKSLKKE
20  551  YSNENAVVKR MQSLQLDCVA VPSSRSNSAT EQPGSLHSSQ GLGMGPVEES
    601  WFAPSLEHPQ EENEPSLQ

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ADP-Glo Kinase Kit: Promega, Cat# V9102;

384-well microplate (White, Flat bottom, Polystyrene): Corning, Cat# 3574;

96-well microplate (V-bottom, Polystyrene): Thermo Scientific Nunc, Cat# 277143;

Envision multi-mode plate reader: PerkinElmer;

Mixmate Shaker: Eppendorf;

TS-2102 shaking incubator: TENSUC.

2. Methods

(1) Principle:

ADP-Glo Kinase kit can be used to measure ADP level in kinase activity assay so as to distinguish the inhibitory effects of different compounds on RIPK1 kinase activity. The ADP-Glo assay was usually divided into three steps. Firstly, the kinase converted ATP to ADP and phosphorylated the substrate at the same time; secondly, ATP digestion reagent was added to degrade all ATP in the reaction system; finally, a detection reagent

was added to reduce ADP to ATP, and energy from ATP was transferred to fluorescein which thus emitting a chemical luminescence that can be detected. Assay procedure can refer to manufacture's technical manual.

(2) Reagent preparation:

5 1.33× kinase buffer: 5× kinase buffer stock (250 mM of NaCl, 150 mM of MgCl₂, 2.5 mg/ml BSA (bovine serum albumin), 0.1% CHAPS (3-[(3-cholamidopropyl)-dimethyl-ammonio]-1-propane sulfonate), and 5 mM of dithiothreitol) was diluted with water to 1.33× kinase buffer;

10 RIPK1 enzyme solution: the kinase was dissolved in 1.33× kinase buffer to make 40 nM as the final working concentration;

ATP solution: 10 mM ATP stock solution in water was dissolved in 1.33× kinase buffer to make 10 μM as the final working concentration;

15 4× compound preparation: the compound was diluted in a 3-fold gradient, and finally 4% DMSO aqueous solution containing different concentrations of the compound was obtained. The final concentrations of the test compound were 10, 3.33, 1.11, 0.37, 0.12, 0.04, 0.014, and 0.005 μM.

(3) Specific steps of the experiment:

The assay set up two control groups, one was 100% inhibition group (no enzyme treatment), another was 0% inhibition group (no inhibitor treatment), each control group
20 contained 8 replicate wells. 2.5 μl of serially diluted compound was added to each well of a 384-well plate, with double replicate wells, and 4% DMSO solution was added to control wells. Then 5 μl of RIPK1 enzyme solution was added to each well except 100% inhibition control, 5 ul of buffer was added to 100% inhibition control, after that, 2.5 μl of ATP solution was added to all wells, the plate was vibrated at 1000 rpm for 30 seconds
25 to perform transient centrifuge; finally the 384-well assay plate was put in the shaking incubator, and incubated at room temperature for 3 hours. After the enzymatic reaction was completed, 5 μl of ATP depletion reagent was added to each well, the mixture was centrifuged transiently, then the 384-well assay plate was put in the shaking incubator, and incubated at room temperature for 1 hour. 5 μl of ADP detection reagent was added
30 to each well, and the mixture was centrifuged transiently, and incubated at room temperature for 0.5 hour.

3. Detecting

The 384-well plate was taken out and the signal value of each well was determined using the Envision multi-mode plate reader.

4. Calculating

The mean of the signal values of the 100% inhibition group and the 0% inhibition group was used as the reference value, the inhibition rate of each concentration of every compound was calculated according to the signal value of each well, and the IC₅₀ value was processed by model 205 in XL-Fit 5.3 software (ID Business Solutions Limited).

The inhibition rate was calculated following the formula as below:

Inhibition rate (%) = 100% × (mean signal value of 0% inhibition group - signal value of testing well)/(mean signal value of 0% inhibition group - mean signal value of 100% inhibition group)

5. Test results

Compound No.	IC ₅₀ (μM)	Compound No.	IC ₅₀ (μM)	Compound No.	IC ₅₀ (μM)	Compound No.	IC ₅₀ (μM)
1	0.028	23	0.049	43	0.032	67	0.049
2	0.063	24	0.089	44	0.037	68	0.043
3	0.035	25	0.053	45	0.040	69	0.021
4	0.026	26	0.022	46	0.035	70	0.051
5	0.057	27	0.046	47	0.029	71	0.110
6	0.056	28	0.095	48	0.053	72	0.065
7	0.039	29	0.019	53	0.121	73	0.052
8	0.022	30	0.035	54	0.027	74	0.062
9	0.037	31	0.432	55	0.023	75	0.051
10	0.026	32	82.5@3 μM*	56	0.189	76	0.051
11	0.038	33	0.059	57	0.531	77	0.042
12	0.009	34	0.065	58	0.139	78	0.033
13	0.022	35	0.047	59	0.026	80	0.042
14	0.018	36	0.042	60	0.059	81	0.039
15	0.030	37	0.041	61	0.014	82	0.051
16	0.025	38	0.048	62	0.021	83	0.047

17	0.015	39	0.059	63	0.037	84	0.045
18	0.038	40	0.052	64	0.017	85	0.030
19	0.071	41	0.061	65	0.036	79	0.021
22	0.055	42	0.056	66	0.048	86	0.014
87	0.041	90	0.054	93	0.035		
88	0.041	91	0.072	94	0.027		
89	0.048	92	0.104	95	0.028		

*: Inhibition rate at the compound concentration of 3 μ M

Example 3. U937 Cell Viability Assay

1. Reagents and materials

U937 cell line (human histiocytic lymphoma cell line): purchased from ATCC

- 5 (American Type Culture Collection) Cell Bank, cultured in a 5% CO₂, 37°C incubator, and RPMI 1640 medium which contains L-glutamine, 1.5 g/L sodium bicarbonate, 2.383 g/L HEPES solution, 0.11 g/L sodium pyruvate and 4.5 g/L glucose, plus 10% fetal bovine serum (FBS) was used.

RPMI 1640 medium: GIBCO, Cat# A10491-01;

- 10 Fetal bovine serum (FBS): GIBCO, Cat# 10099-141C;

Dimethyl sulfoxide (DMSO): Sigma, Cat# D2650;

Recombinant Human TNF- α Protein (hTNF- α): R&D system, Cat# 210-TA-100;

Pan-Caspase inhibitor (Z-VAD-FMK): Selleckchem, Cat# S7023;

CellTiter-Glo 2.0 Cell Viability Assay kit: Promega, Cat# G9242;

- 15 Microwell plate reader: Envision, Perkin Elmer;

96-well plate: Corning, Cat# 3917.

2. Methods

The U937 cells at the logarithmic phase were taken out, centrifuged to remove the medium, washed with RPMI 1640 medium containing 1% FBS, and diluted with 1%

- 20 FBS-containing RPMI 1640 medium to 2.5×10^5 cells/ml, inoculated at 70 μ L/well into a 96-well plate, i.e., 1.75×10^4 cells/well. The plate was cultured in a 5% CO₂, 37°C cell incubator. After incubating for 1 hour, the test compound was diluted to the corresponding concentrations using DMSO with 3-fold serial dilution, then the corresponding concentration of DMSO diluted solution was diluted into 1% FBS-
- 25 containing RPMI 1640 medium, and 10 μ L/well of the diluted test compound with

different concentrations (final concentration of test compound was 1.0, 0.333, 0.111, 0.037, 0.012, 0.004, 0.0014 and 0.0005 μM , while final concentration of DMSO was 0.3%) or 10 μL /well control solution (3% DMSO) were added to the cell culture system respectively, with the total volume being 80 μL /well; Then 10 μL of Z-VAD-FMK
5 solution diluted with 1% FBS-containing RPMI 1640 medium (final concentration of 50 μM) or 10 μL of control solution (2.5% DMSO) was added to each well, with the total volume being 90 μL /well. The plate was incubated in a 5% CO_2 , 37°C cell culture incubator for 1 hour.

After being cultured for 1 hour, 10 μL of human recombinant TNF- α protein diluted
10 with 1% FBS-containing RPMI 1640 medium (final concentration of 0.1 $\mu\text{g}/\text{mL}$) or 10 μL /well control solution (1% FBS-containing RPMI 1640 medium) was added to each well. The plate was incubated in a 5% CO_2 , 37°C cell culture incubator for 20 hours.

The cell culture plate was taken out from the incubator, and left to stand at room temperature for 30 minutes. Meanwhile, CellTiter-Glo viability assay kit was put from
15 freezer to room temperature, and 50 μL of CellTiter-Glo reagent was added to all wells, the plate was shaken for 1 minutes, protected from light at room temperature for 10 minutes then read the plate on Envision to get the luminescence signal.

3. Detecting

The 96-well plate in the dark was taken out, and the chemiluminescence was
20 determined using the Envision microwell plate reader as the signal value of each well.

The mean signal value of the wells of the mixed solution of recombinant human TNF-alpha protein (final concentration of 0.1 $\mu\text{g}/\text{mL}$) and Pan-Caspase inhibitor (final concentration of 50 μM) was used as the lower value, and the mean signal value of the wells without stimulation was used as the upper value. According to the signal value of
25 each well, the inhibition rate of each concentration of every compound was calculated, and the IC_{50} value of compound was obtained by Model 205 in XL-Fit 5.3 software (ID Business Solutions Limited).

The inhibition rate was calculated following the formula as below:

Inhibition rate % = $[(\text{Luminescence readout of treated compound} - \text{Luminescence readout of positive control}) / (\text{Luminescence readout of negative control} - \text{Luminescence readout of positive control})] \times 100\%$, wherein
30

Luminescence readout of treated compound: referred to the signal value of U937 cells treated with recombinant human TNF-alpha protein, Pan-Caspase inhibitor and test compound.

Luminescence readout of positive control: referred to the signal value of U937 cells
5 treated with recombinant human TNF-alpha protein, Pan-Caspase inhibitor and no compound.

Luminescence readout of negative control: referred to the signal value of U937 cells without any special treatment.

4. Test results

Compound No.	IC ₅₀ (μM)	Compound No.	IC ₅₀ (μM)	Compound No.	IC ₅₀ (μM)	Compound No.	IC ₅₀ (μM)
1	0.021	23	0.057	45	0.002	72	0.002
2	0.170	24	0.161	46	0.002	73	0.002
3	0.021	25	0.032	47	0.002	74	0.001
4	0.017	26	0.012	48	0.039	75	0.002
5	0.024	27	0.102	53	0.554	76	0.003
6	0.021	28	0.135	54	0.012	77	0.010
7	0.068	29	0.003	55	0.007	78	0.008
8	0.014	30	0.008	59	0.003	80	0.009
9	0.052	33	0.010	60	0.066	81	0.008
10	0.008	34	0.007	61	0.003	82	0.018
11	0.139	35	0.011	62	0.002	83	0.017
12	0.018	36	0.003	63	0.051	84	0.001
13	0.004	37	0.014	64	0.002	85	0.002
14	0.003	38	0.013	65	0.007	79	0.002
15	0.020	39	0.006	66	0.003	86	0.001
16	0.002	40	0.012	67	0.091	87	0.011
17	0.001	41	0.064	68	0.006	88	0.011
18	0.082	42	0.007	69	0.009	89	0.005
19	0.003	43	0.002	70	0.002	90	0.004
22	0.003	44	0.002	71	0.003	91	0.011
92	0.100	93	0.006	94	0.003	95	0.003

10 According to the assay described above, the compounds of the present invention showed good potency in inhibiting the U937 cell line necroptosis.

Example 4. L929 Cell Viability Assay

1. Reagents and materials

L929 cell line (mouse fibroblastoma cell line): purchased from ATCC (American Type Culture Collection) Cell Bank, cultured in 5% CO₂, 37°C incubator, and MEM
5 medium which contains L-Glutamine, with 10% FBS was used.

MEM medium: GIBCO, Cat# 11095080;

Fetal bovine serum (FBS): GIBCO, Cat# 10099-141C;

Dimethyl sulfoxide (DMSO): Sigma, Cat# D2650;

0.25% Trypsin-EDTA: GIBCO, Cat# 25200072;

10 Recombinant Mouse TNF-alpha Protein (mTNF-α): R&D system, Cat# 410-MT-050;

Pan-Caspase inhibitor (Z-VAD-FMK): Selleckchem, Cat# S7023;

CellTiter-Glo 2.0 Cell Viability Assay kit: Promega, Cat# G9242;

Microwell plate reader: Envision, Perkin Elmer;

15 96-well plate: Corning, Cat# 3917.

2. Methods

The L929 cells at the logarithmic phase were taken out, and the supernatant was discarded. After trypsinization and cell shedding, 10% FBS-containing medium was added for neutralization, and the supernatant was discarded after centrifugation. The cells
20 were re-suspended using 10% FBS-containing medium, adjusted to 7×10^4 cells/ml, added to 96-well microplate at 70 μL/well, i.e., 4.9×10^3 cells/well. Then the plate was incubated in a 5% CO₂, 37°C cell incubator overnight.

After incubating overnight, the 96-well plate was taken out, the medium was discarded, and the plate was washed with 1% FBS-containing MEM medium. Then 1%
25 FBS-containing MEM medium was added at 70 μL/well, and the plate was cultured in a 5% CO₂, 37°C cell incubator. After incubating for 1 hour, the test compound was diluted to the corresponding concentrations using DMSO with 3-fold serial dilution, then the corresponding concentration of DMSO diluted solution was diluted into 1% FBS-containing MEM medium, and 10 μL/well of the diluted test compound with different
30 concentrations (final concentrations of test compound were 10, 3.33, 1.11, 0.37, 0.12, 0.04, 0.014 and 0.005 μM, while final concentration of DMSO was 0.3%) or 10 μL/well control solution (3% DMSO) were added to the cell culture system respectively, with the

total volume being 80 μL /well. Then 10 μL of Z-VAD-FMK solution diluted with 1% FBS-containing MEM medium (final concentration of 5 μM) or 10 μL of control solution (2.5% DMSO) was added to each well, with the total volume being 90 μL /well. The plate was incubated in a 5% CO_2 , 37°C cell culture incubator for 1 hour.

- 5 After incubating for 1 hour, 10 μL of recombinant mouse TNF- α protein solution diluted with 1% FBS-containing MEM medium (final concentration of 0.1 $\mu\text{g/mL}$) or 10 μL control solution (1% FBS-containing MEM medium) was added to each well. The plate was incubated in a 5% CO_2 , 37°C cell culture incubator for 20 hours.

- 10 The cell culture plate was taken out from the incubator, and left to stand at room temperature for 30 minutes. Meanwhile, CellTiter-Glo viability assay kit was put from freezer to room temperature, and 50 μL of CellTiter-Glo reagent was added to all wells, the plate was shaken for 1 minutes, protected from light at room temperature for 10 minutes then read the plate on Envision to get the luminescence signal.

3. Detecting

- 15 The 96-well plate in the dark was taken out, and the chemiluminescence was determined using the Envision microwell plate reader as the signal value of each well.

- 20 The mean signal value of the wells of the mixed solution of recombinant mouse TNF- α protein (final concentration of 0.1 $\mu\text{g/mL}$) and Pan-Caspase inhibitor (final concentration of 5 μM) was used as the lower value, and the mean signal value of the wells without stimulation was used as the upper value. According to the signal value of each well, the inhibition rate of each concentration of every compound was calculated, and the IC_{50} value of compound was obtained by Model 205 in XL-Fit 5.3 software (ID Business Solutions Limited).

The inhibition rate was calculated following the formula as below:

- 25 Inhibition rate % = $\frac{[\text{Luminescence readout of treated compound} - \text{Luminescence readout of positive control}]}{[\text{Luminescence readout of negative control} - \text{Luminescence readout of positive control}]} \times 100\%$, wherein

- 30 Luminescence readout of treated compound: referred to the signal value of L929 cells treated with recombinant mouse TNF- α protein, Pan-Caspase inhibitor and test compound.

Luminescence readout of positive control: referred to the signal value of L929 cells treated with recombinant mouse TNF- α protein, Pan-Caspase inhibitor and no compound.

- Luminescence readout of negative control: referred to the signal value of L929 cells
5 without any special treatment.

4. Test results

Compound No.	IC ₅₀ (μ M)	Compound No.	IC ₅₀ (μ M)	Compound No.	IC ₅₀ (μ M)	Compound No.	IC ₅₀ (μ M)
1	1.252	25	7.603	54	0.578	77	0.151
2	7.453	26	0.846	55	0.259	78	0.044
3	4.275	28	5.699	59	0.017	80	0.297
4	0.721	29	0.034	60	9.077	81	0.258
5	2.503	30	2.586	61	0.048	82	0.359
6	0.299	33	0.665	62	0.027	83	0.199
8	1.762	34	0.078	63	9.424	84	0.007
9	2.814	35	0.154	64	0.079	85	0.013
10	0.676	36	0.084	65	0.861	79	0.010
11	9.124	37	0.186	66	0.053	86	0.019
12	1.018	38	0.152	67	5.650	87	0.393
13	0.195	39	0.059	68	0.032	88	0.335
14	0.181	40	0.109	69	0.098	89	0.038
15	2.365	41	1.97	70	0.012	90	0.012
16	0.007	42	0.119	71	0.020	91	0.786
17	0.025	43	0.016	72	0.016	92	3.131
18	1.719	44	0.028	73	0.041	93	0.148
19	0.061	45	0.058	74	0.030	94	0.050
22	0.028	46	0.019	75	0.041	95	0.145
23	2.705	47	0.024	76	0.032		

According to the assay described above, the compounds of the present invention showed good efficacy in inhibiting the L929 cell necroptosis.

Example 5. Effect of the compound of the present invention on

10

TNF- α induced IL-1 β in human whole blood

1. Reagents and Materials

Human blood samples were collected by venipuncture from healthy volunteers, with signed consent from each volunteer before blood collection;

RPMI 1640 medium: L-Glutamine, 1.5 g/L NaHCO₃, 2.383 g/L HEPES solution, 0.11 g/L sodium pyruvate and 4.5 g/L Glucose; Gibco, catalog: A10491-01;

5 Dimethyl sulfoxide (DMSO): Sigma, catalog: D2650;

Recombinant Human TNF- α Protein (hTNF- α): R&D system, catalog: 210-TA-100;

Pan-Caspase inhibitor (Z-VAD-FMK): Selleckchem, catalog: S7023;

Smac Mimetic-164 (SM-164): APEXBIO, catalog: A8815;

10 Human IL-1 beta/IL-1F2 Quantikine ELISA Kit: R&D systems, catalog: SLB50;

Envision Multimode Microplate Reader: PerkinElmer;

96-well clear flat bottom TC-treated culture microplate: Falcon, catalog: 353072;

96-well Microplate (U bottom): Corning, catalog: 3799.

2. Assay Protocol

15 Human whole blood was anti-coagulated with heparin and used in human whole blood assay immediately. Fresh heparinized human whole blood was diluted with an equal volume of RPMI 1640 medium, aliquoted the diluted blood into 96-well plate, 90 μ L each well.

Compound preparation: dilute the compound stock using DMSO and perform 3-
20 fold serial dilution to 8-points. Then transfer the diluted compounds to RPMI 1640 medium and mix.

Compound treatment and stimulation: transfer 5 μ L of the diluted compound to appropriate wells of the plate. The final concentration of the compound was 1.0, 0.333, 0.111, 0.037, 0.012, 0.004, 0.0014 and 0.0005 μ M, and each well contained 0.3%DMSO.
25 For positive and negative control wells, add 5 μ L of RPMI 1640 medium with 3%DMSO. And incubate the plate at 5% CO₂, 37°C for 1 hour.

Then 5 μ L of the mixture of stimuli (TNF- α , Z-VAD-FMK and SM-164) was added with the final concentration of 20 μ M, 1 μ M and 0.01 μ g/mL except negative control wells. The negative control wells were added same volume of RPMI 1640 medium.

30 After incubation 6 hours in a 37°C/5% CO₂ incubator, each well was added with 100 μ L of PBS, and centrifuged at 4000rpm for 10 minutes. The 110 μ L of supernatant per well was collected, and stored at -80°C for ELISA.

3. Detection

Prepared 100 μL of IL-1 β standards (in duplicate) in designated wells. ELISA was operated according to manufacturer's instruction. In the end, measured the ELISA plate absorbance at 450 nm/570 nm using Envision.

5 4. Data Calculation

Inhibition rates of compounds on TNF- α , Z-VAD-FMK and SM-164 induced IL-1 β Production in human whole blood were calculated as follows:

IL-1 β level was calculated with IL-1 β standard curve (standard curve fitting equation is four parameters logistic model)

10

$$\text{Inhibition rate \%} = \frac{\text{IL-1}\beta \text{ level}_{\text{stimulated}} - \text{IL-1}\beta \text{ level}_{\text{compound}}}{\text{IL-1}\beta \text{ level}_{\text{stimulated}} - \text{IL-1}\beta \text{ level}_{\text{non-stimulated}}} \times 100$$

IL-1 β level_{stimulated}: the concentration of IL-1 β in the positive control wells which added

15 TNF- α , Z-VAD-FMK, SM-164 and no compound;

IL-1 β level_{non-stimulated}: the concentration of IL-1 β in the negative control wells without the treatment of TNF- α , Z-VAD-FMK, SM-164 and compound;

IL-1 β level_{compound}: the concentration of IL-1 β in the wells with the treatment of TNF- α , Z-VAD-FMK, SM-164 and compound.

20 The IC₅₀ value of compound is determined with XLFit 5 software (ID Business Solutions Limited).

5. Results

Compound	IC ₅₀ (μM)	Compound	IC ₅₀ (μM)	Compound	IC ₅₀ (μM)	Compound	IC ₅₀ (μM)
29	0.004	60	0.010	72	0.039	85	0.005
36	0.004	61	0.011	73	0.021	86	0.013
41	0.018	64	0.012	74	0.013	89	0.018
46	0.006	68	0.043	75	0.011	90	0.007
47	0.009	70	0.008	76	0.009		
59	0.004	71	0.038	84	0.005		

According to the assay described above, the test compounds showed good potency in inhibiting TNF- α , Z-VAD-FMK and SM-164 induced IL-1 β Production in human whole blood.

Example 6. *In vivo* target inhibition of RIPK1 of the compound of the present invention in mouse SIRS model

Objective: To evaluate the *in vivo* efficacy of the compound of the present invention on TNF- α + zVAD-FMK induced hypothermia in the mice Systemic Inflammatory Response Syndrome (SIRS) model.

Methods: Before the model induction, C57BL/6 mice (male, 6-8 weeks, purchased from Shanghai Lingchang Biotechnology) were grouped randomly by body weight. Each group was orally administered with vehicle, positive compound 1mg/kg (GSK-547) and different doses of the compound of the present invention (the test compound), respectively, according to the grouping table (Table1).

Table 1 Grouping information for the IVTI study

Group	Dose (mg/kg)	Number of animals in each group	Vehicle	Model induction	Read outs
Control	-	6	0.5%CMC, pH2.1	zVAD-FMK(16.7mg/kg)	• Temperature measured 3h post model induction • Serum cytokine/chemokine tested 3h post model induction • Survival observation
Vehicle	-	6		TNF- α (0.325 mg/kg)+zVAD-FMK(16.7mg/kg) with i.v. injection, 0.5 h post compound dosing	
GSK-547-1	1	6			
Test Compound-0.01	0.01	6			
Test Compound-0.03	0.03	6			
Test Compound-0.1	0.1	6			
Test Compound-0.3	0.3	6			
Test Compound-1	1	6			

After 30 minutes of oral dosing, mice were injected intravenously with zVAD-FMK (eybridge, Lot#S02910-074-01) (16.7mg/kg) or TNF- α (Novoprotein Scientific, Cat# CF09) + zVAD-FMK (0.325 mg/kg+16.7mg/kg) in phosphate-buffered saline (PBS) pH 7.2 and contained 2.5% DMSO. Body temperature was measured 3 hours post the model induction by rectal probe. And the cytokine and chemokine levels in the plasma were detected 3 hours post the model induction by ELISA. All the animals were monitored the survival status until 72 hours after the model induction.

Result:

To investigate the *in vivo* efficacy of the compound of the present invention in TNF-induced SIRS, mice were pretreated with the compound of the present invention. The test compound could protect mice from hypothermia induced by TNF- α in a dose-dependent manner. Mortality and systemic inflammation could be decreased by the test compound pretreatment.

Example 7. *In vivo* efficacy of the compound of the present invention on the model of bovine type II collagen induced arthritis in DBA1 mice

Objective:

To investigate *in vivo* efficacy of the compound of the present invention on the model of bovine type II collagen induced arthritis in DBA1 mice

Animals:

DBA1 mice, male, 7-9 weeks old, 18-20g, provided by Vital River Laboratory Animal Technology Co., Ltd. (Peking, P.R.China).

Methods:

Bovine type II collagen (CII, Chondrex. Cat: 20021) were dissolved in 100mM HOAc (SPGC Sinopharm Chemical Reagent Co., Ltd (Shanghai, P.R.China), Cat: 10000218.) at 8 mg/ml and stored by stirring in 4°C over night. 8 mg/ml Type II collagen was mixed with equal volume of CFA (Sigma, Cat#: F5881) and made an emulsion on ice using a high-speed homogenizer (FLUKO Equipment Shanghai Co., Ltd.).

Before immunization, five mice were randomly grouped as normal (naive) group. The other mice were anaesthetized with intraperitoneal injection of isoflurane, and injected subcutaneously at the base of the tail with 0.05 ml of the emulsion (4 mg/ml CII/CFA), about 1.5-2 cm from the body on day 0 and day 21.

After the symptoms of arthritis showed in mouse model at Day 24 post the first immunization, mice challenged with CII/CFA were randomly grouped and administrated as the Table 2. The YiSaiPu (Sunshine Guojian Pharmaceutical (Shanghai) Co, Ltd)-treated group was intraperitoneally injected every other day (qod), while the control group and the compound of the present invention (the test compound)-treated group was orally administrated daily.

Table 2 Grouping and dosing regimen

Group	Dose (mg/kg)	Number of animals in each group	Model induction	Vehicle	Route	Dose	Dose volumes
Vehicle	-	10	200 µg CII+25µg CFA/mouse emulsion on day0 and 21	0.5%CMC, pH=2.1	p.o., bid	after arthritis onset day24-44	10mL/kg BW
Test compound	15	10		Saline	i.p., qod		
YiSaiPu	25	10					
Naive	-	5	-	-	-	-	-

The severity of arthritic symptoms of four paws in arthritis mice was scored every other day after arthritis onset, as following criteria:

- 5 0, No evidence of erythema and swelling;
- 1, Erythema and mild swelling confined to hemed-foot (tarsals) or ankle joint;
- 2, Erythema and mild swelling extending from the ankle to the mid-foot;
- 3, Erythema and moderate swelling extending from the ankle to the metatarsal joints;
- 4, Erythema and severe swelling encompass the ankle, foot, and digits.
- 10 The severity of arthritis was determined by the sum of the scores from four paws.

Score =sum of separate score of four paws.

Repeated One-Way ANOVA followed by Dunnett's test was used to calculate the differences between vehicle and compound treated groups by JMP.

- 15 The arthritic score of each animal prior to dosing was considered as the baseline (or 100% of achievable inhibition of inflammation). Arthritic score change (SC) in each mouse was calculated according to the equation, wherein ScoreD24 was the score at the starting day to dose and ScoreDt is the score at dosing day Dt:

$$SCDt = \text{ScoreDt} - \text{ScoreD24}.$$

- Area under the curve (AUC) of score was calculated from score change in each mouse based on Trapezoidal rule:

$$AUC_{\text{score}} = 1/2 \times (SCDt + SCD(t-2)) \times (Dt - D(t-2)) + 1/2 \times (SCD(t-2) + SCD(t-4)) \times (D(t-2) - D(t-4)) + \dots + 1/2 \times (SCD26 + SCD24) \times (D26 - D24)$$

The effects of treatment on arthritic score change were calculated based on AUC values.

Percent inhibition of AUC was calculated using the following formula:

Inhibition Rate (%) = $(AUC_{\text{vehicle}} - AUC_{\text{treatment}}) / (AUC_{\text{vehicle}}) \times 100\%$.

Result:

Immunization of the mice challenged with bovine Collagen II developed severe inflammation and edema in the paws. The arthritic score was measured by visual scoring
5 to evaluate the *in vivo* efficacy of the test compound on this model.

Vehicle treatment in this study resulted in a progressive increase in arthritis score. The treatment was initiated from day 24 post immunization. Treatment of YiSaiPu, a positive control, at 25 mg/kg QOD from day 24 to the end, significantly blocked arthritis compared with vehicle control. And the test compound at 15 mg/kg could ameliorate the
10 paw swelling as well.

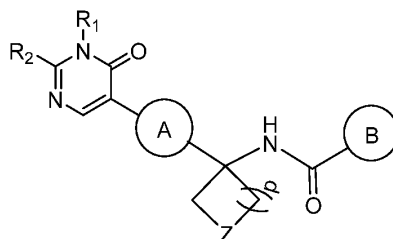
The entire content of all patents and non-patent documents listed herein are incorporated into herein by reference, as if their respective content are listed one by one.

Although specific embodiments and examples are provided herein to illustrate the
15 present invention, same are not intended to limit the scope of the present invention. Based on the present disclosure, a person skilled in the art would have been able to arrive, in an obvious way, at other modifications or equivalent solutions without departing from the spirit of the present invention, and these modifications and equivalent solutions are all within the scope of the present invention.

20

CLAIMS

1. A compound of formula (I):



(I)

or a pharmaceutically acceptable salt thereof, or a solvate, a racemic mixture, an enantiomer, a diastereomer or a tautomer thereof, wherein

R₁ is hydrogen, C₁₋₆ alkyl, C₁₋₆ haloalkyl, cyano-substituted C₁₋₆ alkyl, -(C₁₋₆ alkylene)_n-C₃₋₆ cycloalkyl, -(C₁₋₆ alkylene)_n-phenyl, -(C₁₋₆ alkylene)_n-4-6 membered heterocyclyl or -(C₁₋₆ alkylene)_n-5-6 membered heteroaryl; wherein the C₃₋₆ cycloalkyl, phenyl, 4-6 membered heterocyclyl and 5-6 membered heteroaryl are each optionally substituted with one or more groups independently chosen from: halogen, -CN, -OH, -NH₂, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, -O(C₁₋₆ alkyl), -O(C₁₋₆ haloalkyl), -NH(C₁₋₆ alkyl) and -N(C₁₋₆ alkyl)₂;

R₂ is hydrogen, halogen, -CN, -NH₂, C₁₋₆ alkyl, C₁₋₆ haloalkyl, -O(C₁₋₆ alkyl), -O(C₁₋₆ haloalkyl), -NH(C₁₋₆ alkyl) or -N(C₁₋₆ alkyl)₂;

Z is O, NR₃ or CR₄R₅;

R₃ is hydrogen or C₁₋₆ alkyl;

R₄ and R₅ are each independently chosen from: hydrogen, halogen, -CN, -OH, C₁₋₆ alkyl, C₁₋₆ haloalkyl, -O(C₁₋₆ alkyl), -O(C₁₋₆ haloalkyl) and C₃₋₆ cycloalkyl;

Ⓐ is phenyl or 5-6 membered heteroaryl, each of which is optionally substituted with one or more groups independently chosen from: halogen, -CN, -OH, -NH₂, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, -O(C₁₋₆ alkyl), -O(C₁₋₆ haloalkyl), -NH(C₁₋₆ alkyl) and -N(C₁₋₆ alkyl)₂;

Ⓑ is 5-12 membered heteroaryl, which is optionally substituted with one or more groups independently chosen from: halogen, -CN, -OH, oxo, -NH₂, C₁₋₆ alkyl, C₁₋₆

haloalkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, -O(C₁₋₆ alkyl), -O(C₁₋₆ haloalkyl), -NH(C₁₋₆ alkyl), -N(C₁₋₆ alkyl)₂, -(C₁₋₆ alkylene)_n-C₃₋₆ cycloalkyl, -(C₁₋₆ alkylene)_n-phenyl, -(C₁₋₆ alkylene)_n-4-6 membered heterocyclyl and -(C₁₋₆ alkylene)_n-5-6 membered heteroaryl; wherein the phenyl, C₃₋₆ cycloalkyl, 4-6 membered heterocyclyl and 5-6 membered

5 heteroaryl are each optionally substituted with one or more groups independently chosen from: halogen, -CN, -OH, -NH₂, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, -O(C₁₋₆ alkyl), -O(C₁₋₆ haloalkyl), -NH(C₁₋₆ alkyl), -N(C₁₋₆ alkyl)₂ and C₃₋₆ cycloalkyl;

n is 0 or 1;

and p is 0 or 1.

10

2. The compound of formula (I), or a pharmaceutically acceptable salt thereof, or a solvate, a racemic mixture, an enantiomer, a diastereomer or a tautomer thereof according to claim 1, wherein R₁ is C₁₋₆ alkyl, C₁₋₆ haloalkyl, cyano-substituted C₁₋₆ alkyl, -(C₁₋₆ alkylene)_n-C₃₋₆ cycloalkyl or -(C₁₋₆ alkylene)_n-4-6 membered heterocyclyl; wherein
15 the C₃₋₆ cycloalkyl and 4-6 membered heterocyclyl are each optionally substituted with one or more groups independently chosen from: halogen, -CN, -OH, -NH₂, C₁₋₆ alkyl, C₁₋₆ haloalkyl, -O(C₁₋₆ alkyl), -O(C₁₋₆ haloalkyl), -NH(C₁₋₆ alkyl) and -N(C₁₋₆ alkyl)₂.

3. The compound of formula (I), or a pharmaceutically acceptable salt thereof, or
20 a solvate, a racemic mixture, an enantiomer, a diastereomer or a tautomer thereof according to claim 2, wherein R₁ is C₁₋₆ alkyl, C₁₋₆ haloalkyl, cyano-substituted C₁₋₆ alkyl, -(C₁₋₆ alkylene)_n-C₃₋₆ cycloalkyl or -(C₁₋₆ alkylene)_n-4-6 membered heterocyclyl; wherein the C₃₋₆ cycloalkyl and 4-6 membered heterocyclyl are each optionally substituted with one or more groups independently chosen from: halogen and C₁₋₆ alkyl.

25

4. The compound of formula (I), or a pharmaceutically acceptable salt thereof, or a solvate, a racemic mixture, an enantiomer, a diastereomer or a tautomer thereof according to claim 3, wherein R₁ is C₁₋₆ alkyl, and preferably, R₁ is methyl or i-propyl.

30 5. The compound of formula (I), or a pharmaceutically acceptable salt thereof, or a solvate, a racemic mixture, an enantiomer, a diastereomer or a tautomer thereof according to claim 3, wherein R₁ is C₁₋₆ haloalkyl, -(C₁₋₆ alkylene)_n-C₃₋₆ cycloalkyl or -

(C₁₋₆ alkylene)_n-4-6 membered heterocyclyl; wherein the C₃₋₆ cycloalkyl is optionally substituted with one or more groups independently chosen from: halogen and C₁₋₆ alkyl; preferably, R₁ is -(C₁₋₆ alkylene)_n-C₃₋₆ cycloalkyl, wherein the C₃₋₆ cycloalkyl is optionally substituted with one or more halogen, and n is 0 or 1; or R₁ is 4-6 membered heterocyclyl, wherein the 4-6 membered heterocyclyl is oxetanyl, tetrahydrofuranyl or tetrahydropyranyl.

6. The compound of formula (I), or a pharmaceutically acceptable salt thereof, or a solvate, a racemic mixture, an enantiomer, a diastereomer or a tautomer thereof according to any one of claims 1-5, wherein R₂ is hydrogen, -NH₂, C₁₋₆ alkyl, -NH(C₁₋₆ alkyl) or -N(C₁₋₆ alkyl)₂; preferably, R₂ is hydrogen, -NH₂ or C₁₋₆ alkyl; and more preferably, R₂ is hydrogen.

7. The compound of formula (I), or a pharmaceutically acceptable salt thereof, or a solvate, a racemic mixture, an enantiomer, a diastereomer or a tautomer thereof according to any one of claims 1-6, wherein p is 0, and Z is CR₄R₅; more preferably, p is 0, and Z is CH₂.

8. The compound of formula (I), or a pharmaceutically acceptable salt thereof, or a solvate, a racemic mixture, an enantiomer, a diastereomer or a tautomer thereof

according to any one of claims 1-7, wherein  is phenyl or 5-6 membered heteroaryl, each of which is optionally substituted with one or more groups independently chosen from: halogen, C₁₋₆ alkyl and C₁₋₆ haloalkyl;

preferably,  is phenyl or pyridyl, each of which is optionally substituted with one or more groups independently chosen from: halogen, C₁₋₆ alkyl and C₁₋₆ haloalkyl;

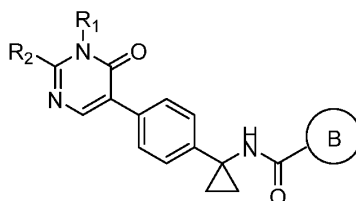
more preferably,  is phenyl, which is optionally substituted with one or more

groups independently chosen from: halogen, C₁₋₆ alkyl or C₁₋₆ haloalkyl; or  is pyridyl.

9. The compound of formula (I), or a pharmaceutically acceptable salt thereof, or a solvate, a racemic mixture, an enantiomer, a diastereomer or a tautomer thereof

according to any one of claims 1-8, wherein  is 5-12 membered heteroaryl, preferably 5-10 membered heteroaryl, more preferably 5-9 membered heteroaryl, which is optionally substituted with one or more groups independently chosen from: halogen, C₁₋₆ alkyl, -(C₁₋₆ alkylene)_n-C₃₋₆ cycloalkyl, -(C₁₋₆ alkylene)_n-phenyl, -(C₁₋₆ alkylene)_n-4-6 membered heterocyclyl and -(C₁₋₆ alkylene)_n-5-6 membered heteroaryl; and wherein the phenyl, C₃₋₆ cycloalkyl, 4-6 membered heterocyclyl and 5-6 membered heteroaryl are each optionally substituted with one or more halogen.

10. The compound of formula (I), or a pharmaceutically acceptable salt thereof, or a solvate, a racemic mixture, an enantiomer, a diastereomer or a tautomer thereof according to claim 1, wherein the compound of formula (I) is the compound of formula (I-1):



(I-1)

wherein

R₁ is C₁₋₆ alkyl, C₁₋₆ haloalkyl, cyano-substituted C₁₋₆ alkyl, -(C₁₋₆ alkylene)_n-C₃₋₆ cycloalkyl or -(C₁₋₆ alkylene)_n-4-6 membered heterocyclyl; wherein the C₃₋₆ cycloalkyl and 4-6 membered heterocyclyl are each optionally substituted with one or more groups independently chosen from: halogen and C₁₋₆ alkyl; preferably, R₁ is C₁₋₆ alkyl, C₁₋₆ haloalkyl, -(C₁₋₆ alkylene)_n-C₃₋₆ cycloalkyl or -(C₁₋₆ alkylene)_n-4-6 membered heterocyclyl; wherein the C₃₋₆ cycloalkyl is optionally substituted with one or more groups independently chosen from: halogen and C₁₋₆ alkyl;

R₂ is hydrogen, -NH₂, C₁₋₆ alkyl, -NH(C₁₋₆ alkyl) or -N(C₁₋₆ alkyl)₂; preferably, R₂ is hydrogen, -NH₂ or C₁₋₆ alkyl; and more preferably, R₂ is hydrogen;



- is 5-12 membered heteroaryl, preferably 5-10 membered heteroaryl, more preferably 5-9 membered heteroaryl, which is optionally substituted with one or more groups independently chosen from: halogen, C_{1-6} alkyl, $-(C_{1-6} \text{ alkylene})_n-C_{3-6}$ cycloalkyl, $-(C_{1-6} \text{ alkylene})_n$ -phenyl, $-(C_{1-6} \text{ alkylene})_n$ -4-6 membered heterocyclyl and $-(C_{1-6} \text{ alkylene})_n$ -5-6 membered heteroaryl; wherein the phenyl, C_{3-6} cycloalkyl, 4-6 membered heterocyclyl and 5-6 membered heteroaryl are each optionally substituted with one or more halogen;
- and n is 0 or 1.

11. The compound of formula (I), or a pharmaceutically acceptable salt thereof, or a solvate, a racemic mixture, an enantiomer, a diastereomer or a tautomer thereof

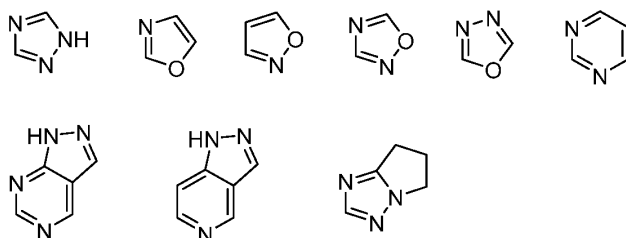


- according to any one of claims 1-10, wherein is triazolyl, oxazolyl, isoxazolyl, oxadiazolyl, pyrimidyl, pyrazolopyrimidyl, pyrazolopyridyl or dihydropyrrolotriazolyl, each of which is optionally substituted with one or more groups independently chosen from: halogen, C_{1-6} alkyl, $-(C_{1-6} \text{ alkylene})_n-C_{3-6}$ cycloalkyl, $-(C_{1-6} \text{ alkylene})_n$ -phenyl, $-(C_{1-6} \text{ alkylene})_n$ -4-6 membered heterocyclyl and $-(C_{1-6} \text{ alkylene})_n$ -5-6 membered heteroaryl; wherein the phenyl, C_{3-6} cycloalkyl, 4-6 membered heterocyclyl and 5-6 membered heteroaryl are each optionally substituted with one or more halogen.

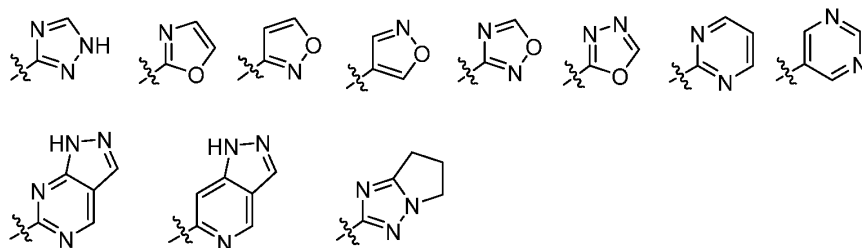
12. The compound of formula (I), or a pharmaceutically acceptable salt thereof, or a solvate, a racemic mixture, an enantiomer, a diastereomer or a tautomer thereof according to claim 11, wherein



is chosen from



5 membered heteroaryl are each optionally substituted with one or more halogen;

preferably, 

10 phenyl, $-(C_{1-6} \text{ alkylene})_n$ -4-6 membered heterocyclyl and $-(C_{1-6} \text{ alkylene})_n$ -5-6 membered

15 a solvate, a racemic mixture, an enantiomer, a diastereomer or a tautomer thereof

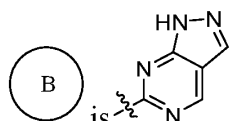
according to claim 12, wherein  is , which is optionally substituted with

cycloalkyl, $-(C_{1-6} \text{ alkylene})_n$ -phenyl, $-(C_{1-6} \text{ alkylene})_n$ -4-6 membered heterocyclyl and $-(C_{1-6} \text{ alkylene})_n$ -5-6 membered heteroaryl; and wherein the C_{3-6} cycloalkyl, 4-6

20 membered heterocyclyl and 5-6 membered heteroaryl are each optionally substituted with

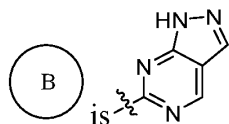
a solvate, a racemic mixture, an enantiomer, a diastereomer or a tautomer thereof

25 according to claim 13, wherein



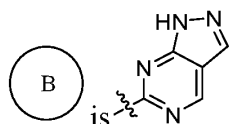
is B , which is optionally substituted with one or more groups independently chosen from: C_{1-6} alkyl;

or



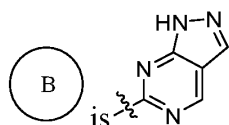
- 5 independently chosen from: $-(\text{C}_{1-6} \text{ alkylene})_n\text{-C}_{3-6} \text{ cycloalkyl}$, wherein n is 0 or 1; wherein the C_{3-6} cycloalkyl is optionally substituted with one or more halogen;

or



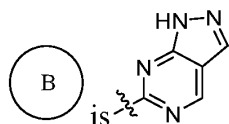
is B , which is optionally substituted with one or more groups independently chosen from: $-(\text{C}_{1-6} \text{ alkylene})_n\text{-phenyl}$, wherein n is 0 or 1;

- 10 or



is B , which is optionally substituted with one or more groups independently chosen from: 4-6 membered heterocyclyl; wherein the 4-6 membered heterocyclyl is oxetanyl;

or



- 15 independently chosen from: 5-6 membered heteroaryl; wherein the 5-6 membered heteroaryl is pyridyl.

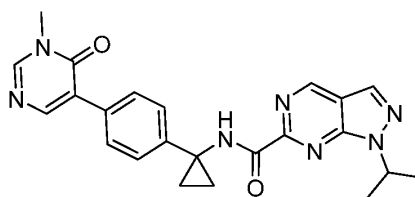
15. The compound of formula (I), or a pharmaceutically acceptable salt thereof
20 according to claim 1, wherein the compound of formula (I) is chosen from Compounds 1-19, 22-48 and 53-95:

Compound

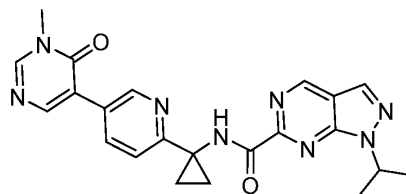
Structure

No.

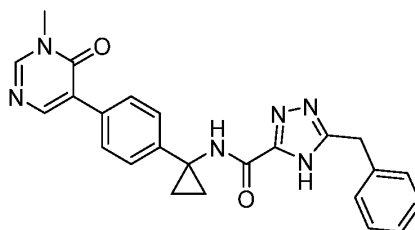
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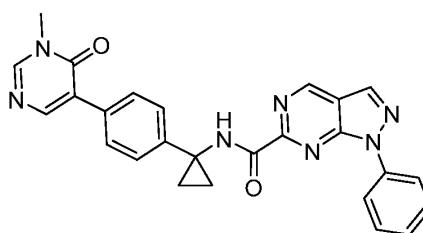
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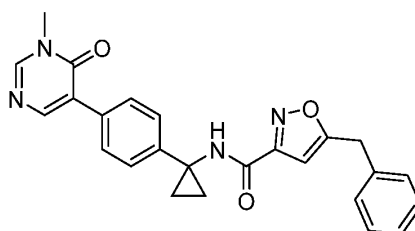
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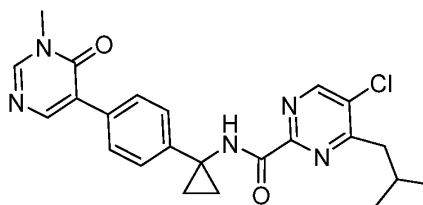
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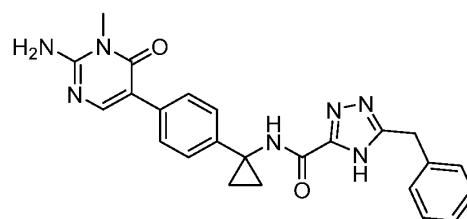
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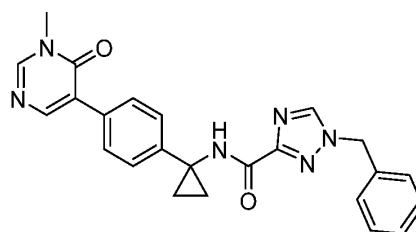
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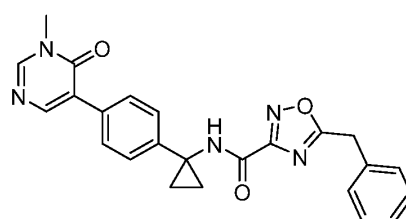
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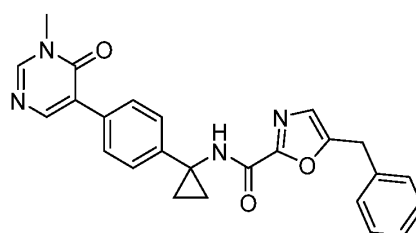
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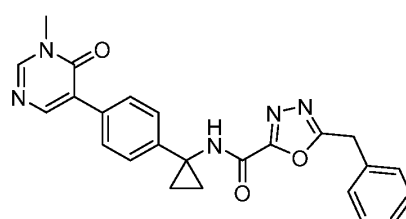
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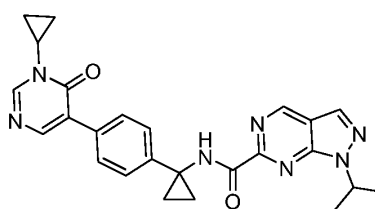
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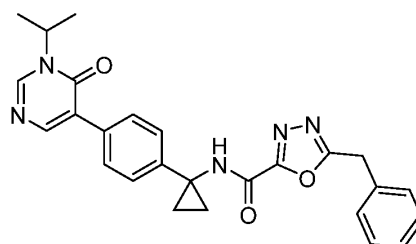
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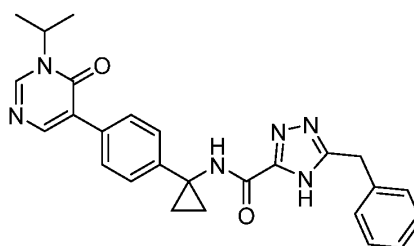
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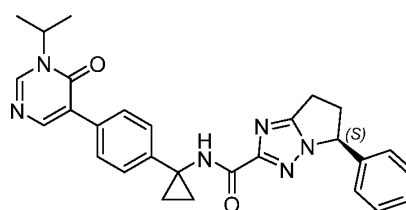
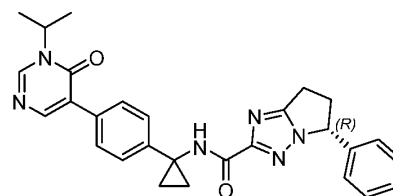


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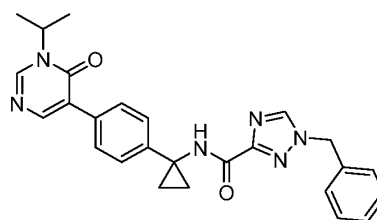


15 and 16

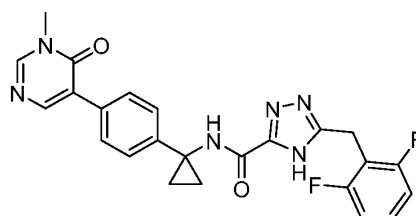
and



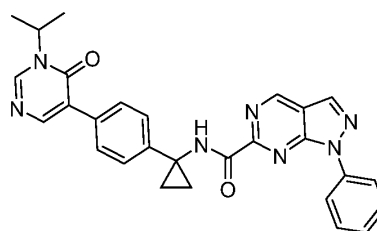
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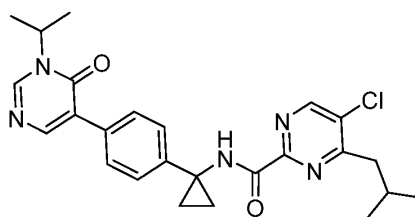
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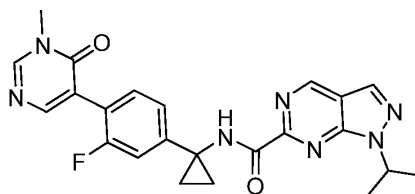
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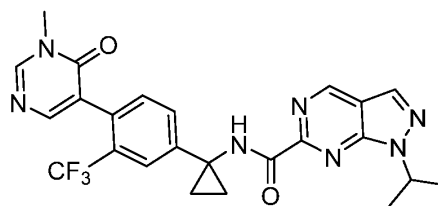
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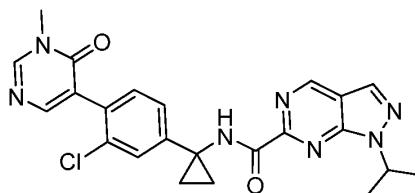
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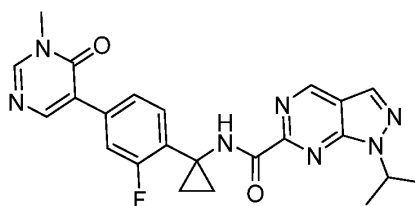
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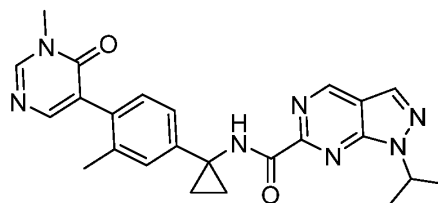
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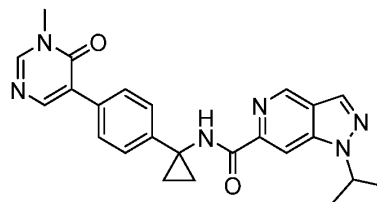
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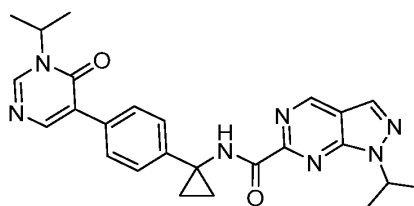
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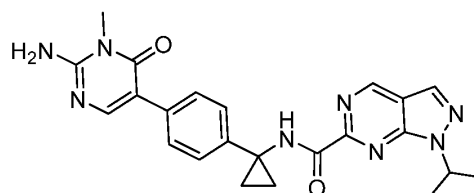
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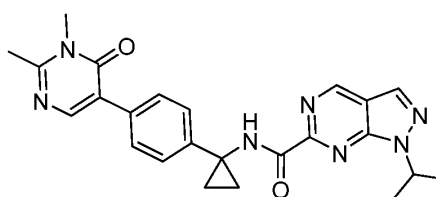
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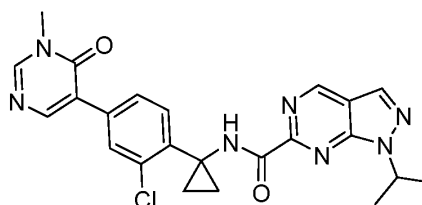
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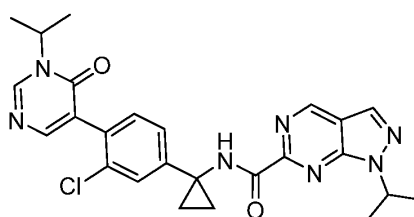
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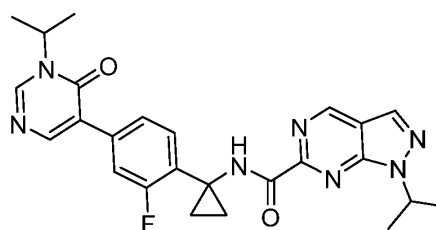
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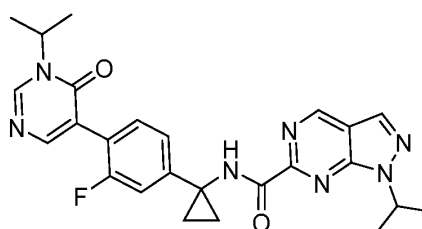
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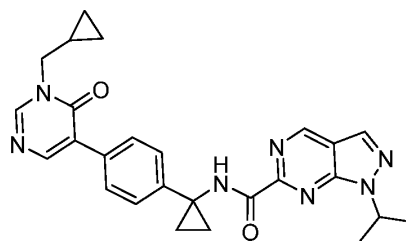
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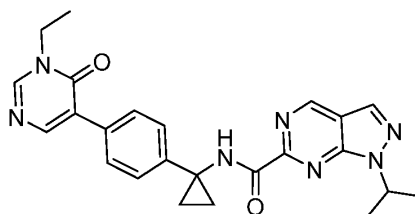
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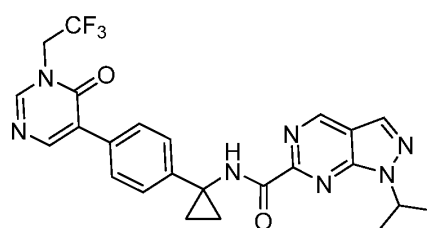
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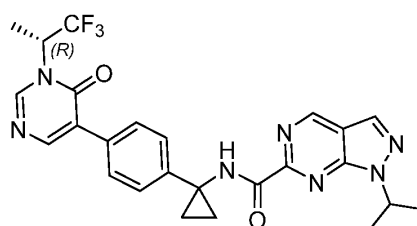
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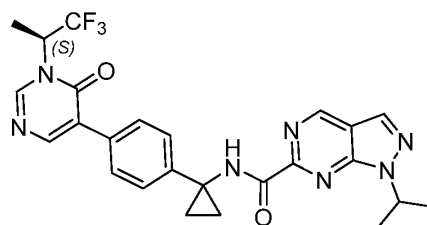
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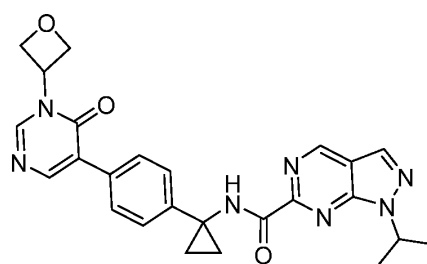
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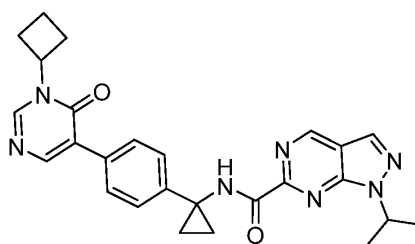
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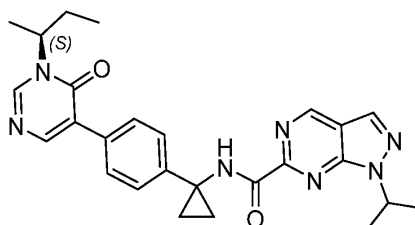
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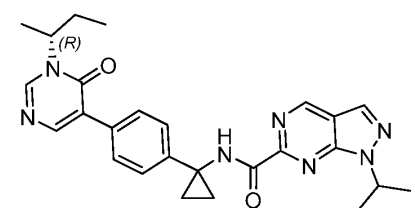
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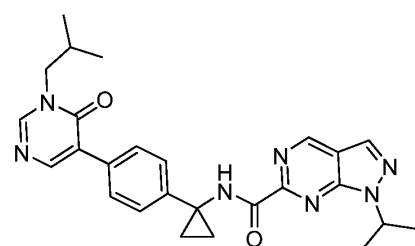
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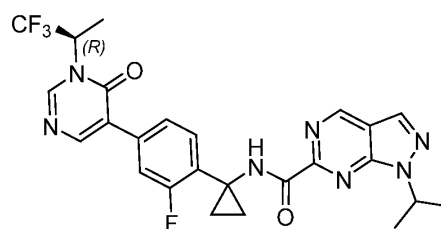
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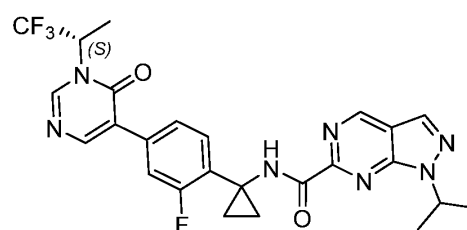
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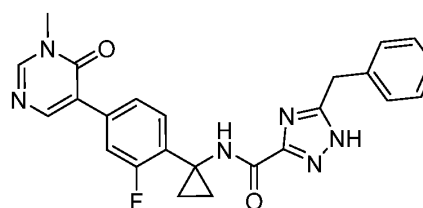
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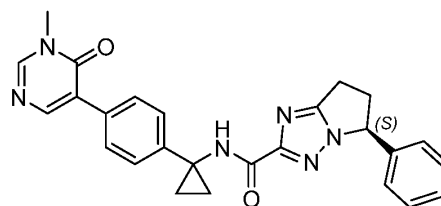


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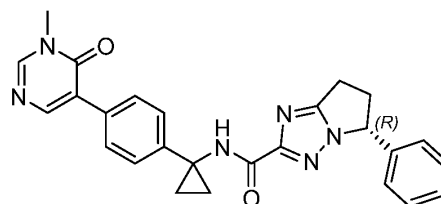
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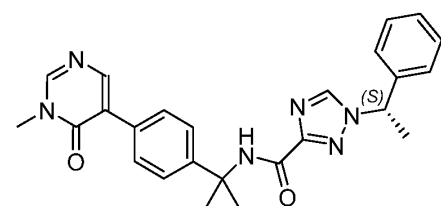
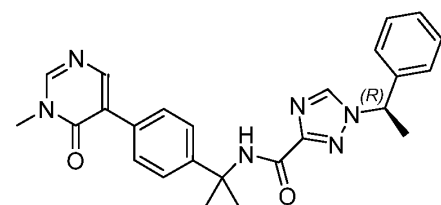
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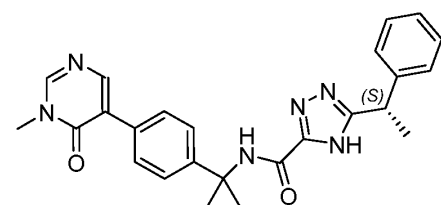
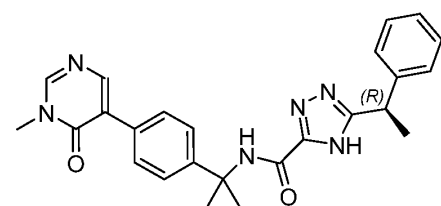
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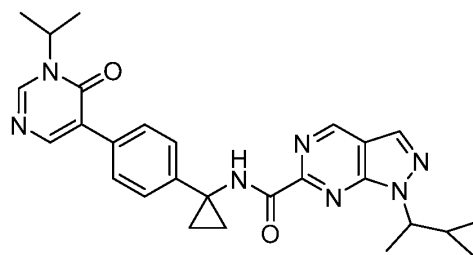


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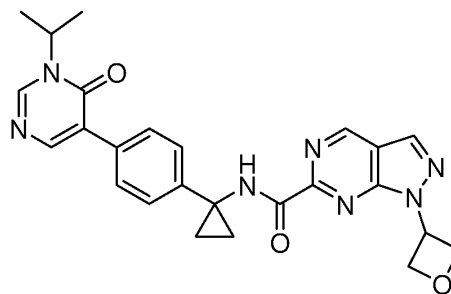
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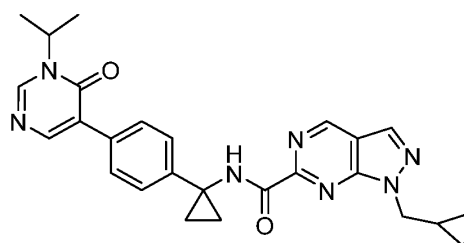
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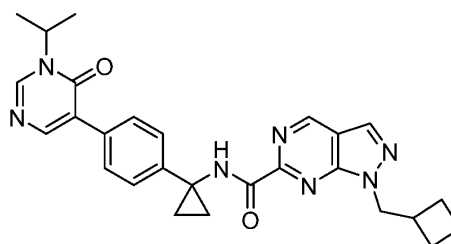
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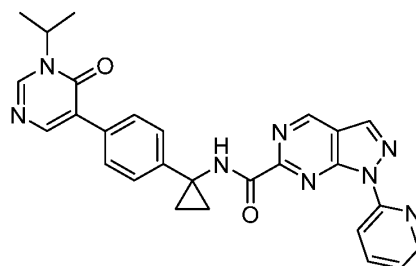
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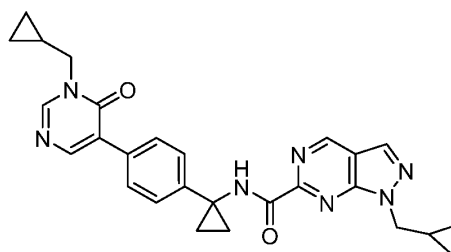
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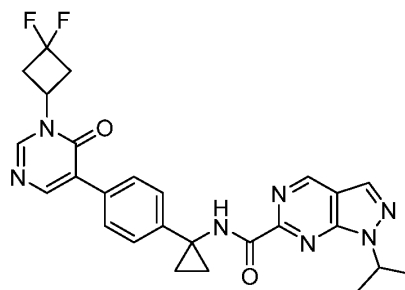
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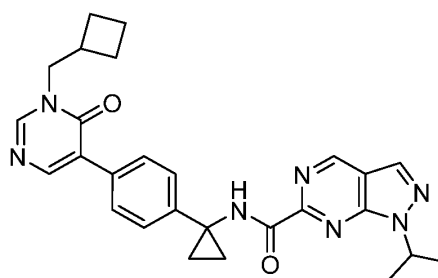
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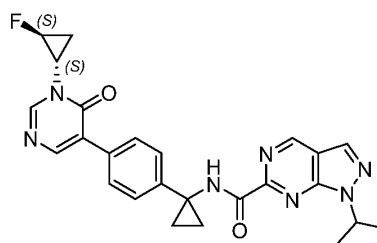
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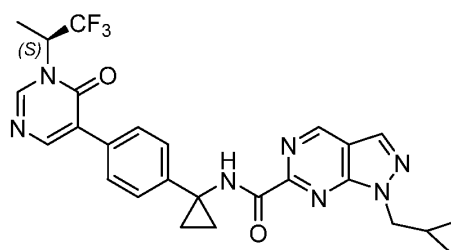
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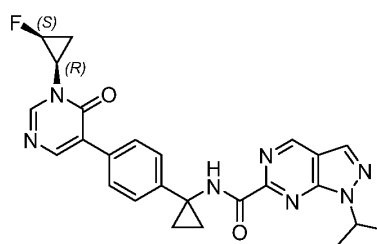
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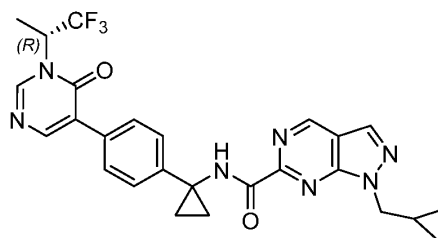
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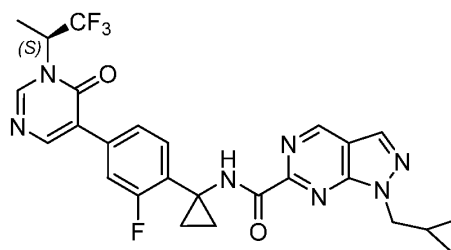
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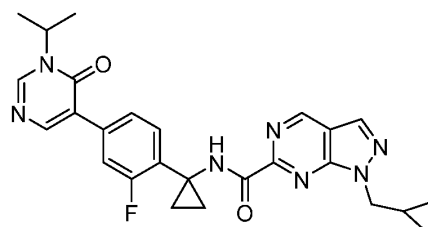
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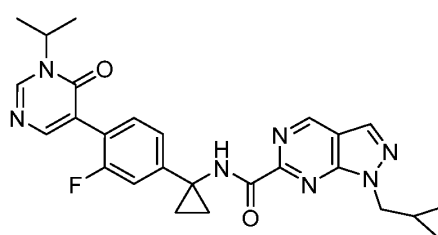
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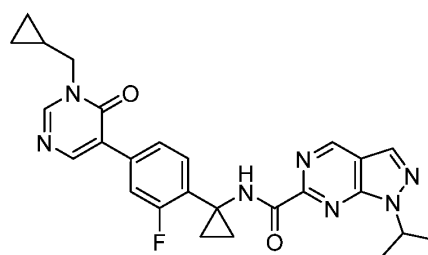
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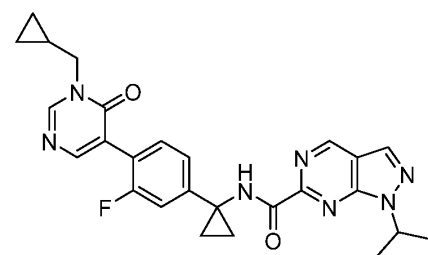
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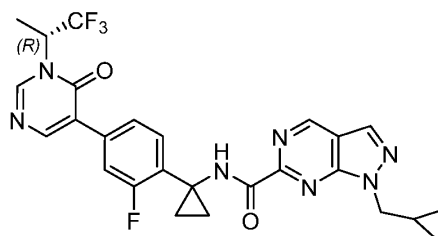
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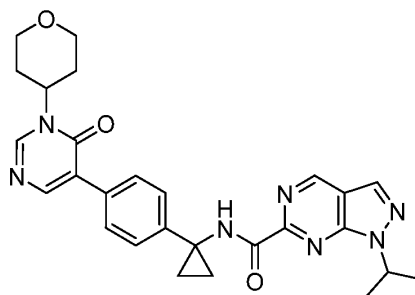
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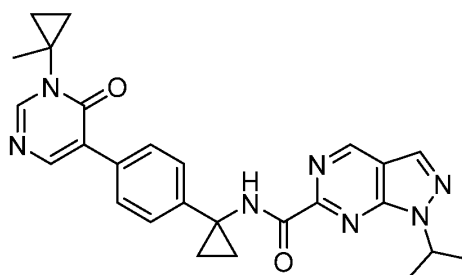
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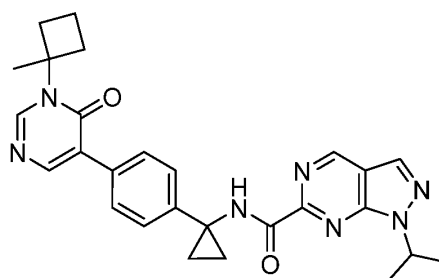
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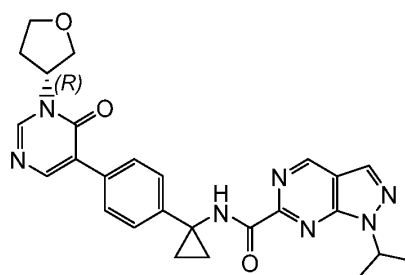


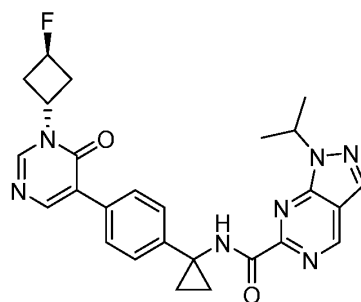
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80 and 81

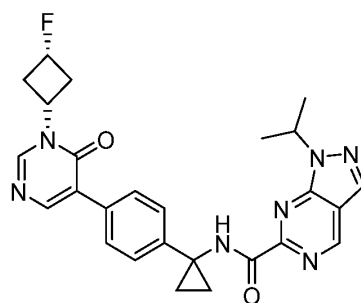
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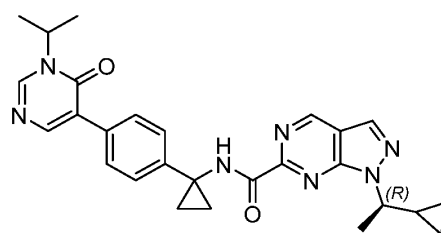
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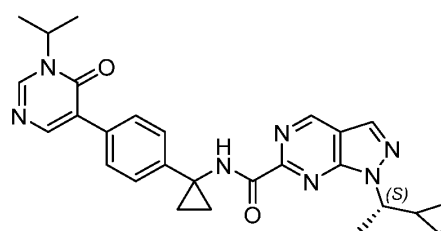


89 and 90

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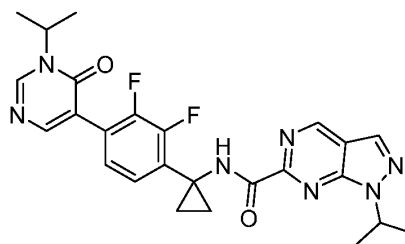


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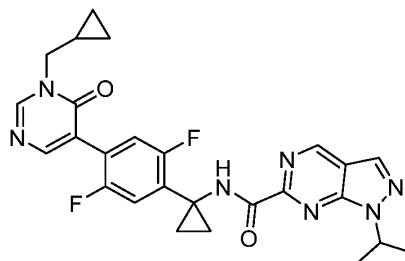


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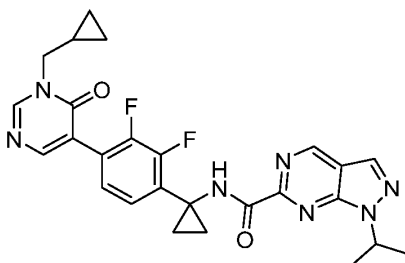
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16. A pharmaceutical composition, comprising the compound or a pharmaceutically acceptable salt thereof according to any one of claims 1-15, and optionally comprising a pharmaceutically acceptable carrier.

5

17. A method of *in vivo* or *in vitro* inhibiting the activity of RIPK1, comprising contacting RIPK1 with an effective amount of the compound or a pharmaceutically acceptable salt thereof according to any one of claims 1-15.

10 18. A method of treating a disease partially or completely mediated by RIPK1 in a subject, comprising administering to the subject an effective amount of the compound or a pharmaceutically acceptable salt thereof according to any one of claims 1-15.

15 19. The method according to claim 18, wherein the disease is chosen from an autoimmune disease, an inflammatory disease, a neurodegenerative disease and cancer.

20. The compound or a pharmaceutically acceptable salt thereof according to any one of claims 1-15, for use as a medicament.

21. The compound or a pharmaceutically acceptable salt thereof according to any one of claims 1-15, for use in the treatment of a disease partially or completely mediated by RIPK1 in a subject.

22. The compound or a pharmaceutically acceptable salt thereof according to claim 21, wherein the disease is chosen from an autoimmune disease, an inflammatory disease, a neurodegenerative disease and cancer.

23. Use of the compound or a pharmaceutically acceptable salt thereof according to any one of claims 1-15 in the manufacture of a medicament for treating a disease partially or completely mediated by RIPK1 in a subject.

24. The use according to claim 23, wherein the disease is chosen from an autoimmune disease, an inflammatory disease, a neurodegenerative disease and cancer.

25. A pharmaceutical combination, comprising the compound or a pharmaceutically acceptable salt thereof according to any one of claims 1-15, and at least one additional therapeutic agent.

26. The pharmaceutical combination according to claim 25, wherein the therapeutic agent is an anti-inflammatory agent or an anti-neoplastic agent; preferably, the anti-neoplastic agent is chosen from a radiotherapeutic agent, a chemotherapeutic agent, an immunotherapeutic agent and a targeted therapeutic agent.