

HETEROARYL COMPOUNDS AS MULTI-TARGET PROTEIN KINASE INHIBITORS**Declaration of Priority**

The present disclosure claims priority to Chinese patent application NO. 2024107886661, filed Jun. 18, 2024, the entire contents of which are incorporated by reference herein in its entirety.

5 The present disclosure claims priority to Chinese patent application NO. 2024107883201, filed Jun. 18, 2024, the entire contents of which are incorporated by reference herein in its entirety.

The present disclosure claims priority to Chinese patent application NO. 2023118584567, filed Dec. 30, 2023, the entire contents of which are incorporated by reference herein in its entirety.

Technical Field

10 The present disclosure relates to a compound having kinase inhibitory activity, and to its application in the field of medicine. More specifically, the present invention provides heteroaryl compounds having protein tyrosine kinase activity.

Background

Clinical and preclinical evidence demonstrates that TAMs, as key regulatory immune cells, can promote tumor development. Macrophages primarily exist in two polarized states. Alternatively activated M2 subtype TAMs promote tumor progression by secreting anti-inflammatory cytokines (e.g., interleukin (IL)-10, transforming growth factor- β), whereas activated M1 subtype TAMs enhance immune-mediated tumor killing by producing pro-inflammatory cytokines. To overcome the immunosuppressive and tumor-promoting functions of TAMs, current therapeutic strategies focus on the depletion of TAMs in the tumor microenvironment and the reprogramming of TAMs to promote anti-tumor functions (shifting M2 polarization to M1). The CSF-1R kinase is a product encoded by the proto-oncogene *c-fms* and belongs to the class III receptor tyrosine kinase family, which also includes FMS-like tyrosine kinase 3, stem cell factor receptor, FDGFR, and PDGFR. CSF-1R binds to its ligands, CSF-1 and IL-34, to activate CSF-1R, thereby playing a crucial role in the proliferation, differentiation, and growth of mononuclear phagocytes. In the tumor microenvironment, a large number of macrophages (TAMs) are present, expressing the CSF-1R on their cell surface. When CSF-1 binds to this receptor, macrophages are converted to a pro-tumor state, driving immune suppression and promoting tumor cell growth. Furthermore, high expression of CSF-1R on tumor cells is associated with lower survival rates in certain cancer patients, indicating tumor dependency, making it a potential therapeutic target. By targeting CSF-1R, the development of CSF-1R/CSF-1 inhibitors can effectively reduce the number of TAMs in tumor tissues, promote the generation of anti-tumor macrophages, and help relieve immune suppression. Additionally, it facilitates the infiltration of various immune cells, including T cells and lymphocytes, into the tumor tissue.

30 Cancer cell growth and metastasis depend on the formation of neovascularization. Vascular endothelial growth factor (VEGF) is the most potent pro-angiogenic factor because solid tumors depend on angiogenesis to provide oxygen and nutrients to aid in their growth and, in turn, as a pathway for invasion and metastasis. In addition, the VEGFa-VEGFR2 signaling pathway plays an important role in the tumor microenvironment and significantly promotes the proliferation and infiltration of Treg (regulatory T cells) in tumor tissues in animal models. Inhibition of the VEGFa-VEGFR2 signaling pathway can inhibit tumor growth by regulating Tregs, MDSCs, and M2 macrophages. Inhibition of VEGFR2 significantly reduced Treg levels in tumor tissues, further helping to deregulate immunosuppression.

PDGFR is a transmembrane glycoprotein with tyrosine kinase activity, primarily expressed on mesenchymal-derived cells such as fibroblasts, pericytes, vascular smooth muscle cells, and stromal stem/progenitor cells. PDGFR consists of α and β subunits. Typically, PDGFR α and PDGFR β exist as monomers in an autoinhibited state. Upon binding with platelet-derived growth factor (PDGF), PDGFR monomers dimerize, forming isomers PDGFR- $\alpha\alpha$, PDGFR- $\alpha\beta$, and PDGFR- $\beta\beta$, which mediate a series of downstream signaling responses. The PDGF/PDGFR primarily promotes angiogenesis and vascular maturation, playing a role in growth and development, and is also closely related to the occurrence and progression of various diseases. Due to the characteristics of tumor microvasculature, such as rapid but

immature growth, irregularity, and high permeability, the transport and distribution of chemotherapeutic drugs and oxygen to tumor tissues are hindered, making it easy for tumor cells to metastasize and invade other areas through the leaky vessels. The abnormal vascular system creates a malignant tumor microenvironment characterized by hypoxia, low pH, and elevated interstitial fluid pressure, which interferes with the function of immune cells within the tumor and reduces the efficacy of radiation therapy and chemotherapy. Therefore, the focus of current anti-angiogenic therapy has shifted from simply destroying blood vessels to "normalizing" tumor microvasculature, in order to increase oxygen supply and alter the direction of drug delivery. The root cause of abnormal vascular growth in tumor tissues lies in the disruption of various growth factors within the microenvironment. The PDGF/PDGFR pathway, as a key factor in regulating vascular growth and recruiting pericytes to promote vascular maturation, plays an indispensable role in this process.

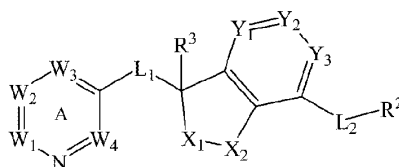
Discoidin domain receptor 1 (DDR1) is a novel receptor tyrosine kinase (RTK) that, upon activation, regulates matrix metalloproteinase (MMP), epithelial mesenchymal transition (EMT), and plays an important role in tumor cell migration. Some studies have shown that inhibition of DDR1 expression can induce autophagy and improve the sensitivity of tumor cells to radiation therapy and chemotherapy.

As is well known, multi-target drugs have obvious advantages over combination drugs and multi-component drugs: due to single component, they are better than combination drugs and multi-component drugs in drug metabolism; they overcome the adverse reactions caused by interactions between components; they are convenient to administer, and there is no problem of dosage or ratio in combination drugs; they have predictable pharmacodynamics (PD) and pharmacokinetic (PK) properties; under the same premise of efficacy, synergistic effects can reduce the dosage of drug administration, thus improving the highly selective single-target drugs.) and pharmacokinetic (PK) properties; under the premise of the same therapeutic effect, due to synergistic effect can make the drug dose lower, thus improving the adverse effects of highly selective single-target drugs; slow down the occurrence of drug resistance.

Summary of the Invention

The purpose of the present invention is to provide a compound with tyrosine kinase inhibitory activity, which can achieve better tumor suppression effect and reduce the occurrence of drug resistance through multi-target synergistic action.

The present disclosure provides a compound having the structure of formula (I) or a pharmaceutically acceptable salt, stereoisomers, isotopic isomers thereof,



Formula (I)

wherein, X_1 represents O, S, NR^a , $(CR^{L^1}R^{L^1})_m$, $C(O)$;

wherein, X_2 represents O, S, NR^a , $(CR^{T^1}R^{T^1})_n$, $C(O)$;

wherein, W_1 independently represents CR^{W1} or N;

wherein, W_2 independently represents CR^{W2} or N;

wherein, W_3 independently represents CR^{W3} or N;

wherein, W_4 independently represents CR^{W4} or N;

wherein, Y_1 independently represents CR^{Y1} or N;

wherein, Y_2 independently represents CR^{Y2} or N;

wherein, Y_3 independently represents CR^{Y3} or N;

wherein, each R^{W1} , R^{W2} , R^{W3} , R^{W4} , R^{Y1} , R^{Y2} , R^{Y3} independently represents hydrogen, deuterium, C_1 - C_6 alkyl, deuterated C_1 - C_6 alkyl, halogen, nitro, $-OR^a$, $-SR^a$, $-P(O)R^aR^b$, $-CN$, $-S(O)_2R^a$, $-S(O)R^a$, $-SF_5$, $-NR^aR^b$, $-CR^aR^bNR^aR^b$, $-NR^aCOR^b$, $-CONR^aR^b$, C_1 - C_6 haloalkyl, C_1 - C_6 haloalkoxy, C_1 - C_6 haloalkylthio, hydroxy (C_1 - C_6 alkyl); or each R^{W1} , R^{W2} , R^{W3} , R^{W4} , R^{Y1} , R^{Y2} , R^{Y3} independently represents C_3 - C_{10} cycloalkyl, C_6 - C_{10} cycloalkenyl, 4-10 membered heterocycloalkyl, 6-10 membered heterocycloalkenyl, C_6 - C_{10} aryl, 5-10 membered heteroaryl, which are substituted by 0-4 substituents selected from deuterium, halogen, C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, C_3 - C_6 cycloalkyl, C_3 - C_6 heterocycloalkyl, $-OR^a$,

oxo, hydroxy (C₁-C₆ alkyl), NR^aR^b, -CR^aR^bNR^aR^b, -CN, C₁-C₆ haloalkyl, C₁-C₆ haloalkoxy, -SO₃R^a, -SR^a, -SF₃, -C(O)R^a, -C(O)OR^a, -OC(O)R^a, -OC(O)NR^aR^b, -NR^aCOR^b and -CONR^aR^b;

or W₁ and W₂ together with the atom which they are attached to form a 5-6 membered saturated or unsaturated ring fused to ring A, and the said ring may optionally contain 0, 1, 2 or 3 heteroatoms selected from O, N, and S;

wherein, L₁ represents absent, -(CR^aR^b)₀-, -CR^aR^bO-, -OCR^aR^b-, -O-, -S-, -S(O)₂-, -C(O)-, -NR^a-, -S(O)₂NR^a-, -OC(O)-, -C(O)O-, -NR^aS(O)₂-, -CR^aR^bNR^a-, or -NR^aCR^aR^b-;

wherein, L₂ represents -C(O)NR^a- or -NR^aC(O)-;

wherein, R² represents a 5-10 membered heteroaryl, which is substituted by 0-4 substituents selected from deuterium, halogen, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₆ cycloalkyl, -OR^a, oxo, hydroxy (C₁-C₆ alkyl), -NR^aR^b, -CR^aR^bNR^aR^b, -CN, C₁-C₆ haloalkyl, C₁-C₆ haloalkoxy, -SO₃R^a, -SR^a, -S(O)₂R^a, -S(O)R^a, -SF₃, -C(O)R^a, -C(O)OR^a, -OC(O)R^a, -OC(O)NR^aR^b, -NR^aCOR^b and -CONR^aR^b;

wherein, R³ represents hydrogen, halogen, C₁-C₆ haloalkyl, C₁-C₆ alkyl, or hydroxy;

or R³ and W₃ together with the atom which they are attached to form a 5-7 membered saturated or unsaturated ring fused to ring A, and the said ring may optionally contain 0, 1 or 2 heteroatoms selected from O, N, and S; and further, the

said ring may optionally be substituted by 0, 1 or 2 substituents selected from deuterium, halogen, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₆ cycloalkyl, -OR^a, oxo, hydroxy (C₁-C₆ alkyl), NR^aR^b, -CN, C₁-C₆ haloalkyl, C₁-C₆ haloalkoxy, -SO₃R^a, -SR^a, -SF₃, -C(O)R^a, -C(O)OR^a, -OC(O)R^a, -OC(O)NR^aR^b, -NR^aCOR^b and -CONR^aR^b;

wherein, each R^a and R^b independently represents hydrogen, deuterium, halogen, C₁-C₆ alkyl, C₁-C₆ haloalkyl, hydroxy (C₁-C₆ alkyl), C₃-C₁₀ cycloalkyl, C₆-C₁₀ aryl, 5-10 membered heteroaryl; or R^a and R^b together with the carbon atom which they are attached to form a 3-6 membered ring, and the said ring may optionally contain 0, 1 or 2 heteroatoms selected from O, N, and S; and further, the said ring may optionally be substituted by halogen, hydroxy and C₁-C₆ alkyl;

wherein, each R^L and R^{L'} independently represents hydrogen, deuterium, halogen, C₁-C₆ alkyl, C₁-C₆ haloalkyl, hydroxy (C₁-C₆ alkyl), C₃-C₁₀ cycloalkyl; or R^L and R^{L'} together with the carbon atom which they are attached to form a 3-6 membered ring, and the said ring may optionally contain 0, 1 or 2 heteroatoms selected from O, N, and S; and further, the said ring may optionally be substituted by halogen, hydroxy and C₁-C₆ alkyl;

wherein, each R^T and R^{T'} independently represents hydrogen, deuterium, halogen, C₁-C₆ alkyl, C₁-C₆ haloalkyl, hydroxy (C₁-C₆ alkyl), C₃-C₁₀ cycloalkyl; or R^T and R^{T'} together with the carbon atom which they are attached to form a 3-6 membered ring, and the said ring may optionally contain 0, 1 or 2 heteroatoms selected from O, N, and S; and further, the said ring may optionally be substituted by halogen, hydroxy and C₁-C₆ alkyl;

wherein, o, m, n represents the integer of 1, 2 or 3.

In some embodiments of the present disclosure, X₁ represents O, S, NR^a, (CR^LR^{L'})_m, C(O);

wherein, X₂ represents O, S, NR^a, (CR^TR^{T'})_n, C(O);

wherein, W₁ independently represents CR^{W1} or N;

wherein, W₂ independently represents CR^{W2} or N;

wherein, W₃ independently represents CR^{W3} or N;

wherein, W₄ independently represents CR^{W4} or N;

wherein, Y₁ independently represents CR^{Y1} or N;

wherein, Y₂ independently represents CR^{Y2} or N;

wherein, Y₃ independently represents CR^{Y3} or N;

wherein, each R^{W1}, R^{W2}, R^{W3}, R^{W4}, R^{Y1}, R^{Y2}, R^{Y3} independently represents hydrogen, deuterium, C₁-C₆ alkyl, deuterated C₁-C₆ alkyl, halogen, nitro, -OR^a, -SR^a, -P(O)R^aR^b, -CN, -S(O)₂R^a, -S(O)R^a, -SF₃, -NR^aR^b, -CR^aR^bNR^aR^b, -NR^aCOR^b, -CONR^aR^b, C₁-C₆ haloalkyl, C₁-C₆ haloalkoxy, C₁-C₆ haloalkylthio, hydroxy (C₁-C₆ alkyl); or each R^{W1}, R^{W2}, R^{W3}, R^{W4}, R^{Y1}, R^{Y2}, R^{Y3} independently represents C₃-C₁₀ cycloalkyl, C₆-C₁₀ cycloalkenyl, 4-10 membered heterocycloalkyl, 6-10 membered heterocycloalkenyl, C₆-C₁₀ aryl, 5-10 membered heteroaryl, which are substituted by 0-4 substituents selected from deuterium, halogen, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₆ cycloalkyl, C₃-C₆ heterocycloalkyl, -OR^a, oxo, hydroxy (C₁-C₆ alkyl), NR^aR^b, -CN, C₁-C₆ haloalkyl, C₁-C₆ haloalkoxy, -SO₃R^a, -SR^a, -SF₃, -C(O)R^a, -C(O)OR^a, -OC(O)R^a, -OC(O)NR^aR^b, -NR^aCOR^b and -CONR^aR^b;

or W₁ and W₂ together with the atom which they are attached to form a 5-6 membered saturated or unsaturated ring fused to ring A, and the said ring may optionally contain 0, 1, 2 or 3 heteroatoms selected from O, N, and S;

wherein, L₁ represents absent, -(CR^aR^b)₀-, -CR^aR^bO-, -OCR^aR^b-, -O-, -S-, -S(O)₂-, -C(O)-, -NR^a-, -S(O)₂NR^a-, -OC(O)-, -C(O)O-, -NR^aS(O)₂-, -CR^aR^bNR^a-, or -NR^aCR^aR^b-;

wherein, L₂ represents -C(O)NR^a- or -NR^aC(O)-;

wherein, R² represents a 5-10 membered heteroaryl, which is substituted by 0-4 substituents selected from deuterium, halogen, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₆ cycloalkyl, -OR^a, oxo, hydroxy (C₁-C₆ alkyl), -NR^aR^b, -CR^aR^bNR^aR^b, -CN, C₁-C₆ haloalkyl, C₁-C₆ haloalkoxy, -SO₃R^a, -SR^a, -S(O)₂R^a, -S(O)R^a, -SF₃, -C(O)R^a, -C(O)OR^a, -OC(O)R^a, -OC(O)NR^aR^b, -NR^aCOR^b and -CONR^aR^b;

wherein, R³ represents hydrogen, halogen, C₁-C₆ haloalkyl, C₁-C₆ alkyl, or hydroxy;

or R³ and W₃ together with the atom which they are attached to form a 5-7 membered saturated or unsaturated ring fused to ring A, and the said ring may optionally contain 0, 1 or 2 heteroatoms selected from O, N, and S; and further, the

said ring may optionally be substituted by 0, 1 or 2 substituents selected from deuterium, halogen, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₆ cycloalkyl, -OR^a, oxo, hydroxy (C₁-C₆ alkyl), NR^aR^b, -CN, C₁-C₆ haloalkyl, C₁-C₆ haloalkoxy, -SO₃R^a, -SR^a, -S(O)₂R^a, -S(O)R^a, -SF₃, -C(O)R^a, -C(O)OR^a, -OC(O)R^a, -OC(O)NR^aR^b, -NR^aCOR^b and -CONR^aR^b;

wherein, each R^a and R^b independently represents hydrogen, deuterium, halogen, C₁-C₆ alkyl, C₁-C₆ haloalkyl, hydroxy

(C₁-C₆ alkyl), C₃-C₁₀ cycloalkyl, C₆-C₁₀ aryl, 5-10 membered heteroaryl; or R^a and R^b together with the carbon atom which they are attached to form a 3-6 membered ring, and the said ring may optionally contain 0, 1 or 2 heteroatoms selected from O, N, and S; and further, the said ring may optionally be substituted by halogen, hydroxy and C₁-C₆ alkyl;

5 wherein, each R^L and R^{L'} independently represents hydrogen, deuterium, halogen, C₁-C₆ alkyl, C₁-C₆ haloalkyl, hydroxy (C₁-C₆ alkyl), C₃-C₁₀ cycloalkyl; or R^L and R^{L'} together with the carbon atom which they are attached to form a 3-6 membered ring, and the said ring may optionally contain 0, 1 or 2 heteroatoms selected from O, N, and S; and further, the said ring may optionally be substituted by halogen, hydroxy and C₁-C₆ alkyl;

10 wherein, each R^T and R^{T'} independently represents hydrogen, deuterium, halogen, C₁-C₆ alkyl, C₁-C₆ haloalkyl, hydroxy (C₁-C₆ alkyl), C₃-C₁₀ cycloalkyl; or R^T and R^{T'} together with the carbon atom which they are attached to form a 3-6 membered ring, and the said ring may optionally contain 0, 1 or 2 heteroatoms selected from O, N, and S; and further, the said ring may optionally be substituted by halogen, hydroxy and C₁-C₆ alkyl;

wherein, o, m, n represents the integer of 1, 2 or 3.

In some embodiments of the present disclosure, wherein W₁ represents CH, CCH₃, CF, CCF₃, CCHF₂, CCF₂H, C(OCH₃), CNH₂, CNHCH₃, CN(CH₃)₂, CCH₂NHCH₃, CCH₂N(CH₃)₂, C(CN) or N.

15 In some embodiments of the present disclosure, wherein W₃ represents CH, CCH₃, CF, CCF₃, CCHF₂, CCH₂F, C(OCH₃), CNH₂, CNHCH₃, C(CN) or N.

In some embodiments of the present disclosure, wherein W₄ represents CH, CCH₃, CF, CCF₃, CCHF₂, CCH₂F, C(OCH₃), CNH₂, CNHCH₃, C(CN) or N.

20 In some embodiments of the present disclosure, wherein Y₁ represents CH, CCH₃, CF, CCl, CCF₃, CCHF₂, CCH₂F, C(OCH₃), C(CN) or N.

In some embodiments of the present disclosure, wherein Y₂ represents CH, CCH₃, CF, CCl, CCF₃, CCHF₂, CCH₂F, C(OCH₃), C(CN) or N.

In some embodiments of the present disclosure, wherein Y₃ represents CH, CCH₃, CF, CCl, CCF₃, CCHF₂, CCH₂F, C(OCH₃), C(CN) or N.

25 In some embodiments of the present disclosure, wherein X₁ represents -CH₂-, -CF₂-, -CHF-, -O-, -S-, -CHOH-, -CH₂CH₂- or -C(CH₃)₂.

In some embodiments of the present disclosure, wherein X₂ represents -CH₂-, -CF₂-, -CHF-, -O-, -S-, -CHOH-, -CH₂CH₂- or -C(CH₃)₂.

In some embodiments of the present disclosure, wherein L₁ represents -CH₂-, -CHF-, -CF₂-, -O-, -NH- or -NCH₃-.

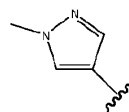
30 In some embodiments of the present disclosure, wherein R^{W2} represents C₁-C₆ alkyl, halogen, -OH, O(C₁-C₆ alkyl); or R^{W2} represents C₃-C₁₀ cycloalkyl, C₆-C₁₀ cycloalkenyl, 4-10 membered heterocycloalkyl, 6-10 membered heterocycloalkenyl, C₆-C₁₀ aryl, 5-10 membered heteroaryl, which are substituted by 0-4 substituents selected from deuterium, halogen, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₆ cycloalkyl, C₃-C₆ heterocycloalkyl, -OR^a, oxo, hydroxy (C₁-C₆ alkyl), NR^aR^b, -CR^aR^bNR^aR^b, -CN, C₁-C₆ haloalkyl, C₁-C₆ haloalkoxy, -SO₃R^a, -SR^a, -SF₅, -C(O)R^a, -C(O)OR^a, -OC(O)R^a, -OC(O)NR^aR^b, -NR^aCOR^b and -CONR^aR^b.

40 In some embodiments of the present disclosure, wherein R^{W2} represents C₃-C₁₀ cycloalkyl, C₆-C₁₀ cycloalkenyl, 4-10 membered heterocycloalkyl, 6-10 membered heterocycloalkenyl, C₆-C₁₀ aryl, 5-10 membered heteroaryl, which are substituted by 0-4 substituents selected from deuterium, halogen, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₆ cycloalkyl, C₃-C₆ heterocycloalkyl, -OR^a, oxo, hydroxy (C₁-C₆ alkyl), -CN, C₁-C₆ haloalkyl, C₁-C₆ haloalkoxy, -SO₃R^a, -SR^a, -SF₅, -C(O)R^a, -C(O)OR^a, -OC(O)R^a, -OC(O)NR^aR^b, -NR^aCOR^b and -CONR^aR^b.

In some embodiments of the present disclosure, wherein R^{W2} represents C₃-C₁₀ cycloalkyl, C₆-C₁₀ cycloalkenyl, 4-10 membered heterocycloalkyl, 6-10 membered heterocycloalkenyl, C₆-C₁₀ aryl, 5-10 membered heteroaryl, which are substituted by 0-4 substituents selected from deuterium, halogen, C₁-C₆ alkyl, -OR^a, hydroxy (C₁-C₆ alkyl), -CN and C₁-C₆ haloalkyl.

45 In some embodiments of the present disclosure, wherein R^{W2} represents 5-10 membered heteroaryl, which is substituted by 0-4 substituents selected from deuterium, halogen, C₁-C₆ alkyl, -OR^a, hydroxy (C₁-C₆ alkyl), -CN and C₁-C₆ haloalkyl.

50 In some embodiments of the present disclosure, wherein R^{W2} represents pyrazolyl, triazolyl, oxazolyl, isoxazolyl, thiazolyl, imidazolyl, which are substituted by 0-4 substituents selected from deuterium, halogen, C₁-C₆ alkyl, -OR^a, hydroxy (C₁-C₆ alkyl), -CN and C₁-C₆ haloalkyl.



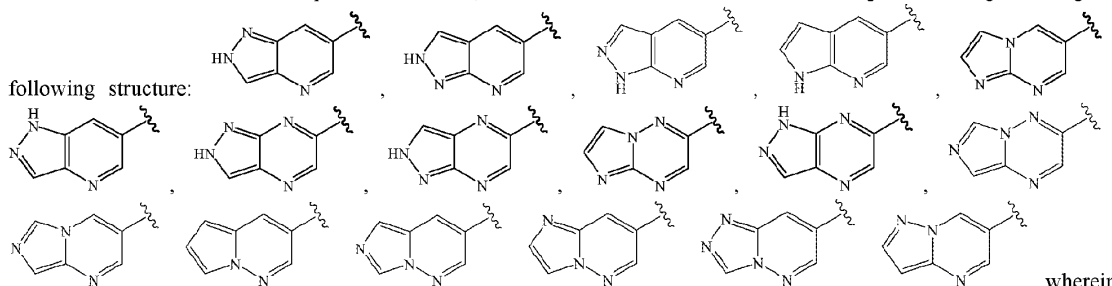
In some embodiments of the present disclosure, wherein R^{W2} represents

In some embodiments of the present disclosure, wherein R^2 represents 5-10 membered heteroaryl, which is substituted by 0-4 substituents selected from deuterium, halogen, C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, C_3 - C_6 cycloalkyl, $-OR^a$, oxo, hydroxy (C_1 - C_6 alkyl), $-NR^aR^b$, $-CR^aR^bNR^aR^b$, $-CN$, C_1 - C_6 haloalkyl, C_1 - C_6 haloalkoxy, $-SO_3R^a$, $-SR^a$, $-SF_5$, $-C(O)R^a$, $-C(O)OR^a$, $-OC(O)R^a$, $-OC(O)NR^aR^b$, $-NR^aCOR^b$ and $-CONR^aR^b$.

In some embodiments of the present disclosure, wherein R^2 represents 5-10 membered heteroaryl, which is substituted by 0-4 substituents selected from deuterium, halogen, C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, C_3 - C_6 cycloalkyl, $-OR^a$, oxo, hydroxy (C_1 - C_6 alkyl), $-NR^aR^b$, $-CR^aR^bNR^aR^b$, $-CN$, C_1 - C_6 haloalkyl, C_1 - C_6 haloalkoxy, or $-C(O)R^a$.

In some embodiments of the present disclosure, wherein W_1 and W_2 combine to form a ring fused to ring A having the

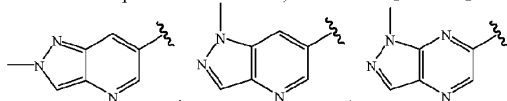
following structure:



the said ring may optionally be substituted by 0, 1 or 2 substituents selected from deuterium, halogen, C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, C_3 - C_6 cycloalkyl, $-OR^a$, oxo, hydroxy (C_1 - C_6 alkyl), NR^aR^b , $-CR^aR^bNR^aR^b$, $-CN$, C_1 - C_6 haloalkyl, C_1 - C_6 haloalkoxy, $-SO_3R^a$, $-SR^a$, $-SF_5$, $-C(O)R^a$, $-C(O)OR^a$, $-OC(O)R^a$, $-OC(O)NR^aR^b$, $-NR^aCOR^b$ and $-CONR^aR^b$; and wherein the wavy line indicates the point of attachment with L_1 .

In some embodiments of the present disclosure, wherein W_1 and W_2 combine to form a ring fused to ring A having the

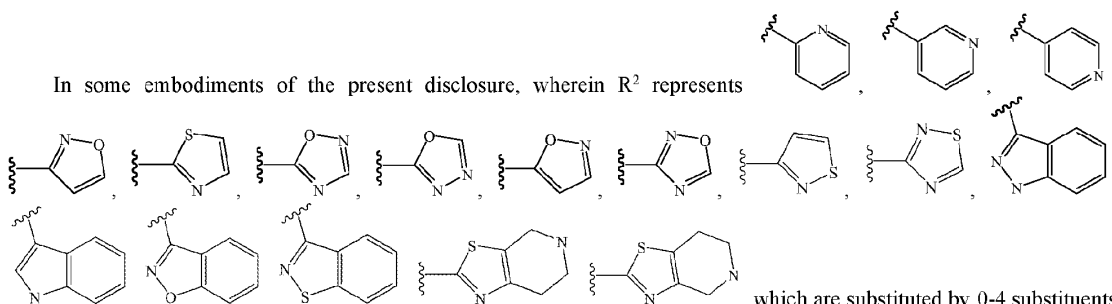
following structure:



, wherein the wavy line indicates the point of attachment with L_1 .

In some embodiments of the present disclosure, wherein R^2 represents pyridinyl, indazolyl, indolyl, thiazolyl, isothiazolyl, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, pyridazinyl, piperazinyl, pyrazinyl, benzothienyl, 1,2-benzisoxazolyl, benzo[d]isothiazolyl, which are substituted by 0-4 substituents selected from deuterium, halogen, C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, C_3 - C_6 cycloalkyl, $-OR^a$, oxo, hydroxy (C_1 - C_6 alkyl), $-NR^aR^b$, $-CR^aR^bNR^aR^b$, $-CN$, C_1 - C_6 haloalkyl, and C_1 - C_6 alkoxy.

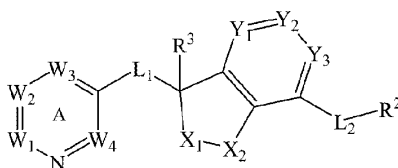
In some embodiments of the present disclosure, wherein R^2 represents



which are substituted by 0-4 substituents selected from deuterium, halogen, C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, C_3 - C_6 cycloalkyl, $-OR^a$, oxo, hydroxy (C_1 - C_6 alkyl), $-NR^aR^b$, $-CR^aR^bNR^aR^b$, $-CN$, C_1 - C_6 haloalkyl, and C_1 - C_6 alkoxy.

In some embodiments of the present disclosure, wherein R^3 represents hydrogen or CH_3 .

The present disclosure provides a compound having the structure of formula (I) or a pharmaceutically acceptable salt, stereoisomers, isotopic isomers thereof,



Formula (I)

Wherein, X_1 represents O, S, NR^a , $(CR^L R^L)_m$, $C(O)$;

Wherein, X_2 represents O, S, NR^a , $(CR^T R^T)_n$, $C(O)$;

wherein, W_1 independently represents CR^{W1} or N;

wherein, W_2 independently represents CR^{W2} ;

wherein, W_3 independently represents CR^{W3} or N;

wherein, W_4 independently represents CR^{W4} or N;

wherein, Y_1 independently represents CR^{Y1} or N;

wherein, Y_2 independently represents CR^{Y2} or N;

wherein, Y_3 independently represents CR^{Y3} or N;

wherein, each R^{W1} , R^{W2} , R^{W3} , R^{W4} , R^{Y1} , R^{Y2} , R^{Y3} independently represents hydrogen, deuterium, C_1 - C_6 alkyl, deuterated C_1 - C_6 alkyl, halogen, nitro, $-OR^a$, $-SR^a$, $-P(O)R^aR^b$, $-CN$, $-S(O)_2R^a$, $-S(O)R^a$, $-SF_5$, $-NR^aR^b$, $-CR^aR^bNR^aR^b$, $-NR^aCOR^b$, $-CONR^aR^b$, C_1 - C_6 haloalkyl, C_1 - C_6 haloalkoxy, C_1 - C_6 haloalkylthio, hydroxy (C_1 - C_6 alkyl); or each R^{W1} , R^{W2} , R^{W3} , R^{W4} , R^{Y1} , R^{Y2} , R^{Y3} independently represents C_3 - C_{10} cycloalkyl, C_6 - C_{10} cycloalkenyl, 4-10 membered heterocycloalkyl, 6-10 membered heterocycloalkenyl, C_6 - C_{10} aryl, 5-10 membered heteroaryl, which are substituted by 0-4 substituents selected from deuterium, halogen, C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, C_3 - C_6 cycloalkyl, C_3 - C_6 heterocycloalkyl, $-OR^a$, oxo, hydroxy (C_1 - C_6 alkyl), NR^aR^b , $-CN$, C_1 - C_6 haloalkyl, C_1 - C_6 haloalkoxy, $-SO_3R^a$, $-SR^a$, $-SF_5$, $-C(O)R^a$, $-C(O)OR^a$, $-OC(O)R^a$, $-OC(O)NR^aR^b$, $-NR^aCOR^b$ and $-CONR^aR^b$;

or W_1 and W_2 together with the atom which they are attached to form a 5-6 membered saturated or unsaturated ring fused to ring A, and the said ring may optionally contain 0, 1, 2 or 3 heteroatoms selected from O, N, and S;

wherein, L_1 represents absent, $-(CR^aR^b)_o$, $-CR^aR^bO$, $-OCR^aR^b$, $-O$, $-S$, $-S(O)_2$, $-C(O)$, $-NR^a$, $-S(O)_2NR^a$, $-OC(O)$, $-C(O)O$, $-NR^aS(O)_2$, $-CR^aR^bNR^a$, or $-NR^aCR^aR^b$;

wherein, L_2 represents $-C(O)NR^a$ or $-NR^aC(O)$;

wherein, R^2 represents 5-10 membered heteroaryl, which is substituted by 0-4 substituents selected from deuterium, halogen, C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, C_3 - C_6 cycloalkyl, $-OR^a$, oxo, hydroxy (C_1 - C_6 alkyl), $-NR^aR^b$, $-CR^aR^bNR^aR^b$, $-CN$, C_1 - C_6 haloalkyl, C_1 - C_6 haloalkoxy, $-SO_3R^a$, $-SR^a$, $-S(O)_2R^a$, $-S(O)R^a$, $-SF_5$, $-C(O)R^a$, $-C(O)OR^a$, $-OC(O)R^a$, $-OC(O)NR^aR^b$, $-NR^aCOR^b$ and $-CONR^aR^b$;

wherein, R^3 represents hydrogen, halogen, C_1 - C_6 haloalkyl, C_1 - C_6 alkyl, or hydroxy;

or R^3 and W_3 together with the atom which they are attached to form a 5-7 membered saturated or unsaturated ring fused to ring A, and the said ring may optionally contain 0, 1 or 2 heteroatoms selected from O, N, and S; and further, the said ring may optionally be substituted by 0, 1 or 2 substituents selected from deuterium, halogen, C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, C_3 - C_6 cycloalkyl, $-OR^a$, oxo, hydroxy (C_1 - C_6 alkyl), NR^aR^b , $-CN$, C_1 - C_6 haloalkyl, C_1 - C_6 haloalkoxy, $-SO_3R^a$, $-SR^a$, $-SF_5$, $-C(O)R^a$, $-C(O)OR^a$, $-OC(O)R^a$, $-OC(O)NR^aR^b$, $-NR^aCOR^b$ and $-CONR^aR^b$;

wherein, each R^a and R^b independently represents hydrogen, deuterium, halogen, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, hydroxy (C_1 - C_6 alkyl), C_3 - C_{10} cycloalkyl, C_6 - C_{10} aryl, 5-10 membered heteroaryl; or R^a and R^b together with the carbon atom which they are attached to form a 3-6 membered ring, and the said ring may optionally contain 0, 1 or 2 heteroatoms selected from O, N, and S; and further, the said ring may optionally be substituted by halogen, hydroxy and C_1 - C_6 alkyl;

wherein, each R^L and R^L independently represents hydrogen, deuterium, halogen, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, hydroxy (C_1 - C_6 alkyl), C_3 - C_{10} cycloalkyl; or R^L and R^L together with the carbon atom which they are attached to form a 3-6 membered ring, and the said ring may optionally contain 0, 1 or 2 heteroatoms selected from O, N, and S; and further, the said ring may optionally be substituted by halogen, hydroxy and C_1 - C_6 alkyl;

wherein, each R^T and R^T independently represents hydrogen, deuterium, halogen, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, hydroxy (C_1 - C_6 alkyl), C_3 - C_{10} cycloalkyl; or R^T and R^T together with the carbon atom which they are attached to form a 3-6 membered ring, and the said ring may optionally contain 0, 1 or 2 heteroatoms selected from O, N, and S; and further, the said ring may optionally be substituted by halogen, hydroxy and C_1 - C_6 alkyl;

wherein, o, m, n represents 1, 2 or 3.

In some embodiments of the present disclosure, wherein W_1 represents CH, CCH_3 , CF, CCF_3 , $CCHF_2$, CCF_2H , $C(OCH_3)$, CNH_2 , $CNHCH_3$, $CN(CH_3)_2$, CCH_2NHCH_3 , $CCH_2N(CH_3)_2$, $C(CN)$ or N.

In some embodiments of the present disclosure, wherein W_3 represents CH, CCH_3 , CF, CCF_3 , $CCHF_2$, CCH_2F , $C(OCH_3)$, CNH_2 , $CNHCH_3$, $C(CN)$ or N.

In some embodiments of the present disclosure, wherein W_4 represents CH, CCH_3 , CF, CCF_3 , $CCHF_2$, CCH_2F , $C(OCH_3)$, CNH_2 , $CNHCH_3$, $C(CN)$ or N.

In some embodiments of the present disclosure, wherein Y_1 represents CH, CCH₃, CF, CCl, CCF₃, CCHF₂, CCH₂F, C(OCH₃), C(CN) or N.

In some embodiments of the present disclosure, wherein Y_2 represents CH, CCH₃, CF, CCl, CCF₃, CCHF₂, CCH₂F, C(OCH₃), C(CN) or N.

5 In some embodiments of the present disclosure, wherein Y_3 represents CH, CCH₃, CF, CCl, CCF₃, CCHF₂, CCH₂F, C(OCH₃), C(CN) or N.

In some embodiments of the present disclosure, wherein X_1 represents -CH₂-, -CF₂-, -CHF-, -O-, -S-, -CHOH-, -CH₂CH₂- or -C(CH₃)₂.

10 In some embodiments of the present disclosure, wherein X_2 represents -CH₂-, -CF₂-, -CHF-, -O-, -S-, -CHOH-, -CH₂CH₂- or -C(CH₃)₂.

In some embodiments of the present disclosure, wherein L_1 represents -CH₂-, -CHF-, -CF₂-, -O-, -NH- or -NCH₃-.

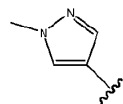
In some embodiments of the present disclosure, wherein R^{W2} represents C₁-C₆ alkyl, halogen, -OH, O(C₁-C₆ alkyl); or R^{W2} represents C₃-C₁₀ cycloalkyl, C₆-C₁₀ cycloalkenyl, 4-10 membered heterocycloalkyl, 6-10 membered heterocycloalkenyl, C₆-C₁₀ aryl, 5-10 membered heteroaryl, which are substituted by 0-4 substituents selected from deuterium, halogen, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₆ cycloalkyl, C₃-C₆ heterocycloalkyl, -OR^a, oxo, hydroxy (C₁-C₆ alkyl), NR^aR^b, -CR^aR^bNR^aR^b, -CN, C₁-C₆ haloalkyl, C₁-C₆ haloalkoxy, -SO₃R^a, -SR^a, -SF₅, -C(O)R^a, -C(O)OR^a, -OC(O)R^a, -OC(O)NR^aR^b, -NR^aCOR^b and -CONR^aR^b.

20 In some embodiments of the present disclosure, wherein R^{W2} represents C₃-C₁₀ cycloalkyl, C₆-C₁₀ cycloalkenyl, 4-10 membered heterocycloalkyl, 6-10 membered heterocycloalkenyl, C₆-C₁₀ aryl, 5-10 membered heteroaryl, which are substituted by 0-4 substituents selected from deuterium, halogen, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₆ cycloalkyl, C₃-C₆ heterocycloalkyl, -OR^a, oxo, hydroxy (C₁-C₆ alkyl), -CN, C₁-C₆ haloalkyl, C₁-C₆ haloalkoxy, -SO₃R^a, -SR^a, -SF₅, -C(O)R^a, -C(O)OR^a, -OC(O)R^a, -OC(O)NR^aR^b, -NR^aCOR^b and -CONR^aR^b.

25 In some embodiments of the present disclosure, wherein R^{W2} represents C₃-C₁₀ cycloalkyl, C₆-C₁₀ cycloalkenyl, 4-10 membered heterocycloalkyl, 6-10 membered heterocycloalkenyl, C₆-C₁₀ aryl, 5-10 membered heteroaryl, which are substituted by 0-4 substituents selected from deuterium, halogen, C₁-C₆ alkyl, -OR^a, hydroxy (C₁-C₆ alkyl), -CN and C₁-C₆ haloalkyl.

In some embodiments of the present disclosure, wherein R^{W2} represents 5-10 membered heteroaryl, which is substituted by 0-4 substituents selected from deuterium, halogen, C₁-C₆ alkyl, -OR^a, hydroxy (C₁-C₆ alkyl), -CN and C₁-C₆ haloalkyl.

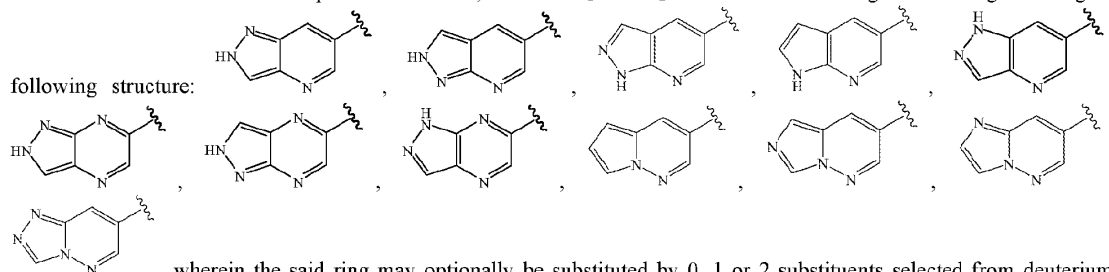
30 In some embodiments of the present disclosure, wherein R^{W2} represents pyrazolyl, triazolyl, oxazolyl, isoxazolyl, thiazolyl, imidazolyl, which are substituted by 0-4 substituents selected from deuterium, halogen, C₁-C₆ alkyl, -OR^a, hydroxy (C₁-C₆ alkyl), -CN and C₁-C₆ haloalkyl.



In some embodiments of the present disclosure, wherein R^{W2} represents

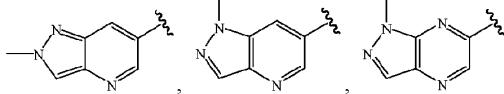
35 In some embodiments of the present disclosure, wherein R^2 represents 5-10 membered heteroaryl, which is substituted by 0-4 substituents selected from deuterium, halogen, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₆ cycloalkyl, -OR^a, oxo, hydroxy (C₁-C₆ alkyl), -NR^aR^b, -CR^aR^bNR^aR^b, -CN, C₁-C₆ haloalkyl, C₁-C₆ haloalkoxy, -SO₃R^a, -SR^a, -SF₅, -C(O)R^a, -C(O)OR^a, -OC(O)R^a, -OC(O)NR^aR^b, -NR^aCOR^b and -CONR^aR^b.

In some embodiments of the present disclosure, wherein W_1 and W_2 combine to form a ring fused to ring A having the



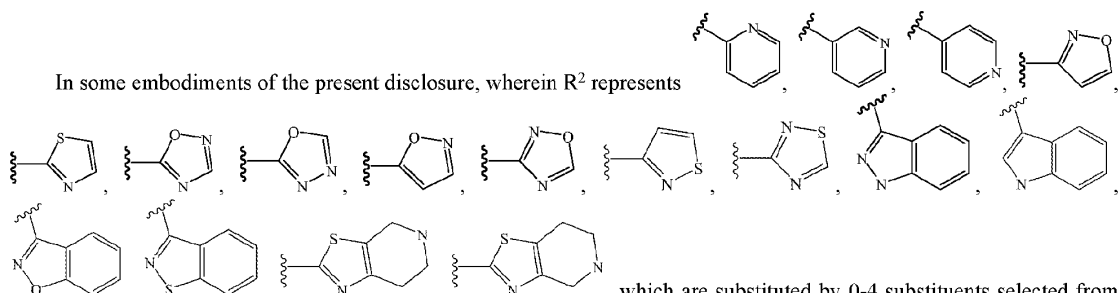
-NR^aCOR^b and -CONR^aR^b; and wherein the wavy line indicates the point of attachment with L₁.

In some embodiments of the present disclosure, wherein W₁ and W₂ combine to form a ring fused to ring A having the

following structure: , wherein the wavy line indicates the point of attachment with L₁.

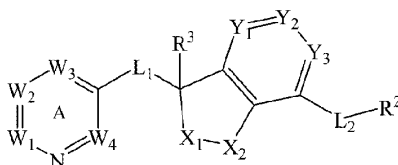
- 5 In some embodiments of the present disclosure, wherein R² represents pyridinyl, indazolyl, indolyl, thiazolyl, isothiazolyl, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, pyridazinyl, piperazinyl, pyrazinyl, benzothienyl, 1,2-benzisoxazolyl, benzo[d]isothiazolyl, which are substituted by 0-4 substituents selected from deuterium, halogen, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₆ cycloalkyl, -OR^a, oxo, hydroxy (C₁-C₆ alkyl), -NR^aR^b, -CR^aR^bNR^aR^b, -CN, C₁-C₆ haloalkyl, and C₁-C₆ alkoxy.

- 10 In some embodiments of the present disclosure, wherein R² represents

, which are substituted by 0-4 substituents selected from deuterium, halogen, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₆ cycloalkyl, -OR^a, oxo, hydroxy (C₁-C₆ alkyl), -NR^aR^b, -CR^aR^bNR^aR^b, -CN, C₁-C₆ haloalkyl, and C₁-C₆ alkoxy.

- 15 In some embodiments of the present disclosure, wherein R³ represents hydrogen or CH₃.

The present disclosure provides a compound having the structure of formula (I) or a pharmaceutically acceptable salt, stereoisomers, isotopic isomers thereof,



Formula (I)

- Wherein, X₁ represents O, S, NR^a, (CR^LR^L)_m, C(O);
 20 Wherein, X₂ represents O, S, NR^a, (CR^TR^T)_n, C(O);
 wherein, W₁ independently represents CR^{W1} or N;
 wherein, W₂ independently represents N;
 wherein, W₃ independently represents CR^{W3} or N;
 wherein, W₄ independently represents CR^{W4} or N;
 25 wherein, Y₁ independently represents CR^{Y1} or N;
 wherein, Y₂ independently represents CR^{Y2} or N;
 wherein, Y₃ independently represents CR^{Y3} or N;
 wherein, each R^{W1}, R^{W3}, R^{W4}, R^{Y1}, R^{Y2}, R^{Y3} independently represents hydrogen, deuterium, C₁-C₆ alkyl, deuterated
 C₁-C₆ alkyl, halogen, nitro, -OR^a, -SR^a, -P(O)R^aR^b, -CN, -S(O)₂R^a, -S(O)R^a, -SF₅, -NR^aR^b, -CR^aR^bNR^aR^b, -NR^aCOR^b,
 30 -CONR^aR^b, C₁-C₆ haloalkyl, C₁-C₆ haloalkoxy, C₁-C₆ haloalkylthio, hydroxy (C₁-C₆ alkyl); or each R^{W1}, R^{W2}, R^{W3}, R^{W4}, R^{Y1},
 R^{Y2}, R^{Y3} independently represents C₃-C₁₀ cycloalkyl, C₆-C₁₀ cycloalkenyl, 4-10 membered heterocycloalkyl, 6-10
 membered heterocycloalkenyl, C₆-C₁₀ aryl, 5-10 membered heteroaryl, which are substituted by 0-4 substituents selected
 from deuterium, halogen, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₆ cycloalkyl, C₃-C₆ heterocycloalkyl, -OR^a, oxo,
 hydroxy (C₁-C₆ alkyl), NR^aR^b, -CN, C₁-C₆ haloalkyl, C₁-C₆ haloalkoxy, -SO₃R^a, -SR^a, -SF₅, -C(O)R^a, -C(O)OR^a, -OC(O)R^a,
 35 -OC(O)NR^aR^b, -NR^aCOR^b and -CONR^aR^b;
 or W₁ and W₂ together with the atom which they are attached to form a 5-6 membered saturated or unsaturated ring
 fused to ring A, and the said ring may optionally contain 0, 1, 2 or 3 heteroatoms selected from O, N, and S;
 wherein, L₁ represents absent, -(CR^aR^b)₀-, -CR^aR^bO-, -OCR^aR^b-, -O-, -S-, -S(O)₂-, -C(O)-, -NR^a-, -S(O)₂NR^a-, -OC(O)-,
 -C(O)O-, -NR^aS(O)₂-, -CR^aR^bNR^a-, or -NR^aCR^aR^b-;

wherein, L_2 represents $-C(O)NR^a-$ or $-NR^aC(O)-$;

wherein, R^2 represents 5-10 membered heteroaryl, which are substituted by 0-4 substituents selected from deuterium, halogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, $-OR^a$, oxo, hydroxy (C_1-C_6 alkyl), $-NR^aR^b$, $-CR^aR^bNR^aR^b$, $-CN$, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, $-SO_3R^a$, $-SR^a$, $-S(O)_2R^a$, $-S(O)R^a$, $-SF_5$, $-C(O)R^a$, $-C(O)OR^a$, $-OC(O)R^a$, $-OC(O)NR^aR^b$, $-NR^aCOR^b$ and $-CONR^aR^b$;

wherein, R^3 represents hydrogen, halogen, C_1-C_6 haloalkyl, C_1-C_6 alkyl, or hydroxy;

or R^3 and W_3 together with the atom which they are attached to form a 5-7 membered saturated or unsaturated ring fused to ring A, and the said ring may optionally contain 0, 1 or 2 heteroatoms selected from O, N, and S; and further, the said ring may optionally be substituted by 0, 1 or 2 substituents selected from deuterium, halogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, $-OR^a$, oxo, hydroxy (C_1-C_6 alkyl), NR^aR^b , $-CN$, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, $-SO_3R^a$, $-SR^a$, $-SF_5$, $-C(O)R^a$, $-C(O)OR^a$, $-OC(O)R^a$, $-OC(O)NR^aR^b$, $-NR^aCOR^b$ and $-CONR^aR^b$;

wherein, each R^a and R^b independently represents hydrogen, deuterium, halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, hydroxy (C_1-C_6 alkyl), C_3-C_{10} cycloalkyl, C_6-C_{10} aryl, 5-10 membered heteroaryl; or R^a and R^b together with the carbon atom which they are attached to form a 3-6 membered ring, and the said ring may optionally contain 0, 1 or 2 heteroatoms selected from O, N, and S; and further, the said ring may optionally be substituted by halogen, hydroxy and C_1-C_6 alkyl;

wherein, each R^L and $R^{L'}$ independently represents hydrogen, deuterium, halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, hydroxy (C_1-C_6 alkyl), C_3-C_{10} cycloalkyl; or R^L and $R^{L'}$ together with the carbon atom which they are attached to form a 3-6 membered ring, and the said ring may optionally contain 0, 1 or 2 heteroatoms selected from O, N, and S; and further, the said ring may optionally be substituted by halogen, hydroxy and C_1-C_6 alkyl;

wherein, each R^T and $R^{T'}$ independently represents hydrogen, deuterium, halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, hydroxy (C_1-C_6 alkyl), C_3-C_{10} cycloalkyl; or R^T and $R^{T'}$ together with the carbon atom which they are attached to form a 3-6 membered ring, and the said ring may optionally contain 0, 1 or 2 heteroatoms selected from O, N, and S; and further, the said ring may optionally be substituted by halogen, hydroxy and C_1-C_6 alkyl;

wherein, o, m, n represents 1, 2 or 3.

In some embodiments of the present disclosure, wherein W_1 represents CH, CCH_3 , CF, CCF_3 , $CCHF_2$, CCF_2H , $C(OCH_3)$, CNH_2 , $CNHCH_3$, $CN(CH_3)_2$, CCH_2NHCH_3 , $CCH_2N(CH_3)_2$, $C(CN)$ or N.

In some embodiments of the present disclosure, wherein W_3 represents CH, CCH_3 , CF, CCF_3 , $CCHF_2$, CCH_2F , $C(OCH_3)$, CNH_2 , $CNHCH_3$, $C(CN)$ or N.

In some embodiments of the present disclosure, wherein W_4 represents CH, CCH_3 , CF, CCF_3 , $CCHF_2$, CCH_2F , $C(OCH_3)$, CNH_2 , $CNHCH_3$, $C(CN)$ or N.

In some embodiments of the present disclosure, wherein Y_1 represents CH, CCH_3 , CF, CCl, CCF_3 , $CCHF_2$, CCH_2F , $C(OCH_3)$, $C(CN)$ or N.

In some embodiments of the present disclosure, wherein Y_2 represents CH, CCH_3 , CF, CCl, CCF_3 , $CCHF_2$, CCH_2F , $C(OCH_3)$, $C(CN)$ or N.

In some embodiments of the present disclosure, wherein Y_3 represents CH, CCH_3 , CF, CCl, CCF_3 , $CCHF_2$, CCH_2F , $C(OCH_3)$, $C(CN)$ or N.

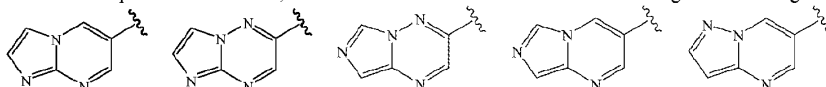
In some embodiments of the present disclosure, wherein X_1 represents $-CH_2-$, $-CF_2-$, $-CHF-$, $-O-$, $-S-$, $-CHOH-$, $-CH_2CH_2-$ or $-C(CH_3)_2$.

In some embodiments of the present disclosure, wherein X_2 represents $-CH_2-$, $-CF_2-$, $-CHF-$, $-O-$, $-S-$, $-CHOH-$, $-CH_2CH_2-$ or $-C(CH_3)_2$.

In some embodiments of the present disclosure, wherein L_1 represents $-CH_2-$, $-CHF-$, $-CF_2-$, $-O-$, $-NH-$ or $-NCH_3-$.

In some embodiments of the present disclosure, wherein R^2 represents 5-10 membered heteroaryl, which is substituted by 0-4 substituents selected from deuterium, halogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, $-OR^a$, oxo, hydroxy (C_1-C_6 alkyl), $-NR^aR^b$, $-CR^aR^bNR^aR^b$, $-CN$, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, $-SO_3R^a$, $-SR^a$, $-SF_5$, $-C(O)R^a$, $-C(O)OR^a$, $-OC(O)R^a$, $-OC(O)NR^aR^b$, $-NR^aCOR^b$ and $-CONR^aR^b$.

In some embodiments of the present disclosure, wherein W_1 and W_2 combine to form a ring fused to ring A having the



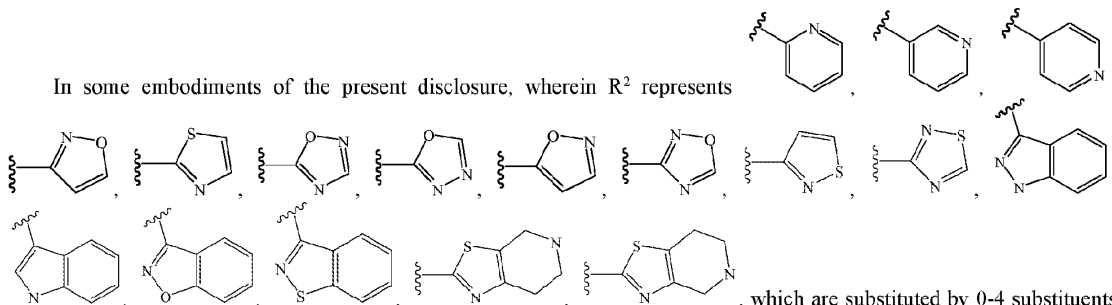
following structure:

the said ring may optionally be substituted by 0, 1 or 2 substituents selected from deuterium, halogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, $-OR^a$, oxo, hydroxy (C_1-C_6 alkyl), NR^aR^b , $-CR^aR^bNR^aR^b$, $-CN$, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, $-SO_3R^a$, $-SR^a$, $-SF_5$, $-C(O)R^a$, $-C(O)OR^a$, $-OC(O)R^a$, $-OC(O)NR^aR^b$, $-NR^aCOR^b$ and $-CONR^aR^b$; and wherein the wavy line indicates the point of attachment with L_1 .

In some embodiments of the present disclosure, wherein R^2 represents pyridinyl, indazolyl, indolyl, thiazolyl,

isothiazolyl, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, pyridazinyl, piperazinyl, pyrazinyl, benzothieryl, 1,2-benzisoxazolyl, benzod[isothiazolyl, which are substituted by 0-4 substituents selected from deuterium, halogen, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₆ cycloalkyl, -OR^a, oxo, hydroxy (C₁-C₆ alkyl), -NR^aR^b, -CR^aR^bNR^aR^b, -CN, C₁-C₆ haloalkyl, and C₁-C₆ alkoxy.

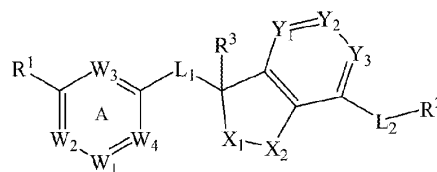
5 In some embodiments of the present disclosure, wherein R^2 represents



selected from deuterium, halogen, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₆ cycloalkyl, -OR^a, oxo, hydroxy (C₁-C₆ alkyl), -NR^aR^b, -CR^aR^bNR^aR^b, -CN, C₁-C₆ haloalkyl, and C₁-C₆ alkoxy.

10 In some embodiments of the present disclosure, wherein R³ represents hydrogen or CH₃.

The present disclosure provides a compound having the structure of formula (II) or a pharmaceutically acceptable salt, stereoisomers, isotopic isomers thereof.



Formula (II)

Wherein, X₁ represents O, S, NR^a, (CR^aR^L)_m, C(O);
Wherein, X₂ represents O, S, NR^a, (CR^aR^T)_n, C(O);
wherein, W₁ independently represents CR^{W1} or N;
wherein, W₂ independently represents CR^{W2} or N;
wherein, W₃ independently represents CR^{W3} or N;
wherein, W₄ independently represents CR^{W4} or N;
wherein, Y₁ independently represents CR^{Y1} or N;
wherein, Y₂ independently represents CR^{Y2} or N;
wherein, Y₃ independently represents CR^{Y3} or N;
wherein, each R^{W1}, R^{W2}, R^{W3}, R^{W4}, R^{Y1}, R^{Y2}, R^{Y3} independently represents hydrogen, deuterium, C₁-C₆ alkyl, deuterated C₁-C₆ alkyl, halogen, nitro, -OR^a, -SR^a, -P(O)R^aR^b, -CN, -S(O)₂R^a, -S(O)R^a, -SF₅, -NR^aR^b, -CR^aR^bNR^aR^b, -NR^aCOR^b, -CONR^aR^b, C₁-C₆ haloalkyl, C₁-C₆ haloalkoxy, C₁-C₆ haloalkylthio, hydroxy (C₁-C₆ alkyl); or each R^{W1}, R^{W2}, R^{W3}, R^{W4}, R^{Y1}, R^{Y2}, R^{Y3} independently represents C₃-C₁₀ cycloalkyl, C₆-C₁₀ cycloalkenyl, 4-10 membered heterocycloalkyl, 6-10 membered heterocycloalkenyl, C₆-C₁₀ aryl, 5-10 membered heteroaryl, which are substituted by 0-4 substituents selected from deuterium, halogen, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₆ cycloalkyl, -OR^a, oxo, hydroxy (C₁-C₆ alkyl), NR^aR^b, -CN, C₁-C₆ haloalkyl, C₁-C₆ haloalkoxy, -SO₃R^a, -SR^a, -SF₅, -C(O)R^a, -C(O)OR^a, -OC(O)R^a, -OC(O)NR^aR^b, -NR^aCOR^b and -CONR^aR^b;
or W₁ and W₂ together with the atom which they are attached to form a 5-6 membered saturated or unsaturated ring fused to ring A, and the said ring may optionally contain 0, 1, 2 or 3 heteroatoms selected from O, N, and S;
or W₁ and W₄ together with the atom which they are attached to form a 5-6 membered saturated or unsaturated ring fused to ring A, and the said ring may optionally contain 0, 1, 2 or 3 heteroatoms selected from O, N, and S;
wherein, L₁ represents absent, -(CR^aR^b)_o-, -CR^aR^bO-, -OCR^aR^b-, -O-, -S-, -S(O)₂-, -C(O)-, -NR^a-, -S(O)₂NR^a-, -OC(O)-, -C(O)O-, -NR^aS(O)₂-, -CR^aR^bNR^a-, or -NR^aCR^aR^b-,
wherein, L₂ represents absent, -(CR^aR^b)_o-, -CR^aR^bO-, -OCR^aR^b-, -O-, -C(O)-, -NR^a-, -S(O)₂NR^a-, -OC(O)-, -C(O)O-, -NR^aS(O)₂-, -CR^aR^bNR^a-, -NR^aCR^aR^b-, -NR^aC(O)NR^bCR^aR^b-, -NR^aC(O)O-, -NR^aC(O)-, or -C(O)NR^a-.
Wherein, R¹ represents hydrogen, deuterium, C₁-C₆ alkyl, deuterated C₁-C₆ alkyl, halogen, -OR^a, -SR^a, -P(O)R^aR^b, -CN, -S(O)₂R^a, -S(O)R^a, -SF₅, -NR^aR^b, C₁-C₆ haloalkyl, C₁-C₆ haloalkoxy, C₁-C₆ haloalkylthio, hydroxy (C₁-C₆ alkyl); or R¹ represents C₃-C₁₀ cycloalkyl, C₆-C₁₀ cycloalkenyl, 4-10 membered heterocycloalkyl, 6-10 membered heterocycloalkenyl, C₆-C₁₀ aryl, and 5-10 membered heteroaryl, which are substituted by 0-4 substituents that selected from deuterium, halogen, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₆ cycloalkyl, -OR^a, oxo, hydroxy (C₁-C₆ alkyl), NR^aR^b, -CN, C₁-C₆ haloalkyl,

C₁-C₆ haloalkoxy, -SO₃R^a, -SR^a, -SF₅, -C(O)R^a, -C(O)OR^a, -OC(O)R^a, -OC(O)NR^aR^b, -NR^aCOR^b and -CONR^aR^b;

or R¹ and W₂ together with the atom which they are attached to form a 5-6 membered saturated or unsaturated ring fused to ring A, and the said ring may optionally contain 0, 1 or 2 heteroatoms selected from O, N, and S; and further, the said ring may optionally substituted by 0, 1 or 2 substituents selected from deuterium, halogen, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₆ cycloalkyl, -OR^a, oxo, hydroxy (C₁-C₆ alkyl), NR^aR^b, -CN, C₁-C₆ haloalkyl, C₁-C₆ haloalkoxy, -SO₃R^a, -SR^a, -SF₅, -C(O)R^a, -C(O)OR^a, -OC(O)R^a, -OC(O)NR^aR^b, -NR^aCOR^b and -CONR^aR^b;

wherein, R² represents C₁-C₆ alkyl, C₃-C₁₀ cycloalkyl, C₆-C₁₀ cycloalkenyl, 4-10 membered heterocycloalkyl, 6-10 membered heterocycloalkenyl, C₆-C₁₀ aryl, and 5-10 membered heteroaryl; which are substituted by 0-4 substituents selected from deuterium, halogen, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₆ cycloalkyl, -OR^a, oxo, hydroxy (C₁-C₆ alkyl), -NR^aR^b, -CR^aR^bNR^aR^b, -CN, C₁-C₆ haloalkyl, C₁-C₆ haloalkoxy, -SO₃R^a, -SR^a, -S(O)₂R^a, -S(O)R^a, -SF₅, -C(O)R^a, -C(O)OR^a, -OC(O)R^a, -OC(O)NR^aR^b, -NR^aCOR^b and -CONR^aR^b;

wherein, R³ represents hydrogen, halogen, C₁-C₆ haloalkyl, C₁-C₆ alkyl, or hydroxy;

or R³ and W₃ together with the atom which they are attached to form a 5-7 membered saturated or unsaturated ring fused to ring A, and the said ring may optionally contain 0, 1 or 2 heteroatoms selected from O, N, and S; and further, the said ring may optionally be substituted by 0, 1 or 2 substituents selected from deuterium, halogen, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₆ cycloalkyl, -OR^a, oxo, hydroxy (C₁-C₆ alkyl), NR^aR^b, -CN, C₁-C₆ haloalkyl, C₁-C₆ haloalkoxy, -SO₃R^a, -SR^a, -SF₅, -C(O)R^a, -C(O)OR^a, -OC(O)R^a, -OC(O)NR^aR^b, -NR^aCOR^b and -CONR^aR^b;

wherein, each R^a and R^b independently represents hydrogen, C₁-C₆ alkyl, C₁-C₆ haloalkyl, hydroxy (C₁-C₆ alkyl), C₃-C₁₀ cycloalkyl; or R^a and R^b together with the carbon atom which they are attached to form a 3-6 membered ring, and the said ring may optionally contain 0, 1 or 2 heteroatoms selected from O, N, and S; and further, the said ring may optionally be substituted by halogen, hydroxy and C₁-C₆ alkyl;

wherein, each R^L and R^{L'} independently represents hydrogen, C₁-C₆ alkyl, C₁-C₆ haloalkyl, hydroxy (C₁-C₆ alkyl), C₃-C₁₀ cycloalkyl; or R^L and R^{L'} together with the carbon atom which they are attached to form a 3-6 membered ring, and the said ring may optionally contain 0, 1 or 2 heteroatoms selected from O, N, and S; and further, the said ring may be optionally substituted by halogen, hydroxy and C₁-C₆ alkyl;

wherein, each R^T and R^{T'} independently represents hydrogen, C₁-C₆ alkyl, C₁-C₆ haloalkyl, hydroxy (C₁-C₆ alkyl), C₃-C₁₀ cycloalkyl; or R^T and R^{T'} together with the carbon atom which they are attached to form a 3-6 membered ring, and the said ring may optionally contain 0, 1 or 2 heteroatoms selected from O, N, and S; and further, the said ring may optionally be substituted by halogen, hydroxy and C₁-C₆ alkyl;

wherein, o, m, n represents 1, 2 or 3.

In some embodiments of the present disclosure, wherein W₁ represents CH, CCH₃, CF, CCF₃, CCHF₂, CHF₂, COCH₃, C(CN) or N.

In some embodiments of the present disclosure, wherein W₁ represents N.

In some embodiments of the present disclosure, wherein W₂ represents CH, CCH₃, CF, CCF₃, CCHF₂, CHF₂, COCH₃, CNH₂, CNHCH₃, CN(CH₃)₂, CH₂NCH₃, CH₂N(CH₃)₂, C(CN) or N.

In some embodiments of the present disclosure, wherein W₃ represents CH, CCH₃, CF, CCF₃, CCHF₂, CHF₂, COCH₃, C(CN) or N.

In some embodiments of the present disclosure, wherein W₄ represents CH, CCH₃, CF, CCF₃, CCHF₂, CHF₂, COCH₃, CNH₂, CNHCH₃, C(CN) or N.

In some embodiments of the present disclosure, wherein Y₁ represents CH, CCH₃, CF, CCl, CCF₃, CCHF₂, CHF₂, COCH₃, C(CN) or N.

In some embodiments of the present disclosure, wherein Y₂ represents CH, CCH₃, CF, CCl, CCF₃, CCHF₂, CHF₂, COCH₃, C(CN) or N.

In some embodiments of the present disclosure, wherein Y₃ represents CH, CCH₃, CF, CCl, CCF₃, CCHF₂, CHF₂, COCH₃, C(CN) or N.

In some embodiments of the present disclosure, wherein X₁ represents CH₂, CF₂, CHF, O, S, CHOH, CH₂CH₂ or C(CH₃)₂.

In some embodiments of the present disclosure, wherein X₂ represents CH₂, CF₂, CHF, O, S, CHOH, CH₂CH₂ or C(CH₃)₂.

In some embodiments of the present disclosure, wherein L₁ represents CH₂, CF₂, O, NH or NCH₃.

In some embodiments of the present disclosure, wherein L₂ represents -NHC(O)-, -C(O)NH-, -NHC(O)NH-, -NHC(O)O-, -CH₂NH-, -NHCH₂-, -CH₂O-, -OCH₂-, -NH-.

In some embodiments of the present disclosure, wherein R¹ represents C₁-C₆ alkyl, halogen, -OH, O(C₁-C₆ alkyl); or R¹ represents C₃-C₁₀ cycloalkyl, C₆-C₁₀ cycloalkenyl, 4-10 membered heterocycloalkyl, 6-10 membered heterocycloalkenyl,

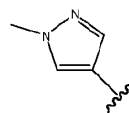
C₆-C₁₀ aryl, 5-10 membered heteroaryl, which are substituted by 0-4 substituents selected from deuterium, halogen, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₆ cycloalkyl, -OR^a, oxo, hydroxy (C₁-C₆ alkyl), NR^aR^b, -CR^aR^bNR^aR^b, -CN, C₁-C₆ haloalkyl, C₁-C₆ haloalkoxy, -SO₃R^a, -SR^a, -SF₅, -C(O)R^a, -C(O)OR^a, -OC(O)R^a, -OC(O)NR^aR^b, -NR^aCOR^b and -CONR^aR^b.

5 In some embodiments of the present disclosure, wherein R¹ represents C₃-C₁₀ cycloalkyl, C₆-C₁₀ cycloalkenyl, 4-10 membered heterocycloalkyl, 6-10 membered heterocycloalkenyl, C₆-C₁₀ aryl, 5-10 membered heteroaryl, which are substituted by 0-4 substituents selected from deuterium, halogen, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₆ cycloalkyl, -OR^a, oxo, hydroxy (C₁-C₆ alkyl), NR^aR^b, -CR^aR^bNR^aR^b, -CN, C₁-C₆ haloalkyl, C₁-C₆ haloalkoxy, -SO₃R^a, -SR^a, -SF₅, -C(O)R^a, -C(O)OR^a, -OC(O)R^a, -OC(O)NR^aR^b, -NR^aCOR^b and -CONR^aR^b.

10 In some embodiments of the present disclosure, wherein R¹ represents C₃-C₁₀ cycloalkyl, C₆-C₁₀ cycloalkenyl, 4-10 membered heterocycloalkyl, 6-10 membered heterocycloalkenyl, C₆-C₁₀ aryl, 5-10 membered heteroaryl, which are substituted by 0-4 substituents selected from deuterium, halogen, C₁-C₆ alkyl, -OR^a, hydroxy (C₁-C₆ alkyl), -CN and C₁-C₆ haloalkyl.

15 In some embodiments of the present disclosure, wherein R¹ represents 5-10 membered heteroaryl, which is substituted by 0-4 substituents selected from deuterium, halogen, C₁-C₆ alkyl, -OR^a, hydroxy (C₁-C₆ alkyl), -CN and C₁-C₆ haloalkyl.

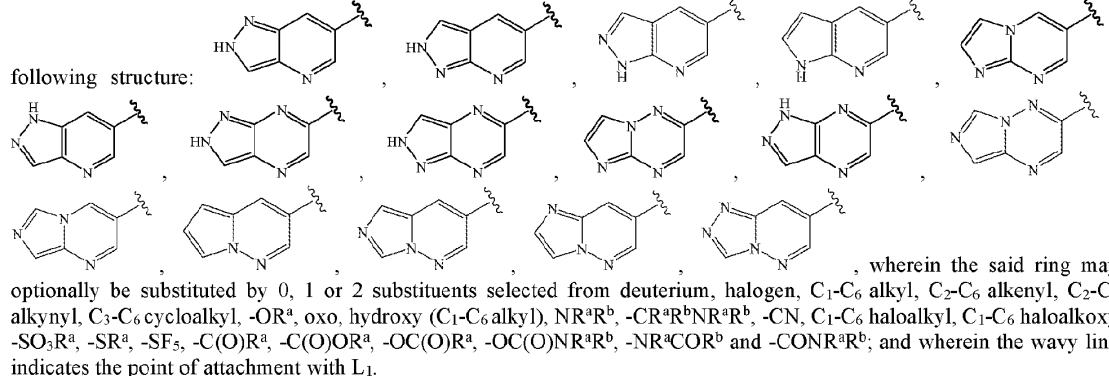
In some embodiments of the present disclosure, wherein R¹ represents pyrazolyl, triazolyl, oxazolyl, isoxazolyl, thiazolyl, imidazolyl, which are substituted by 0-4 substituents selected from deuterium, halogen, C₁-C₆ alkyl, -OR^a, hydroxy (C₁-C₆ alkyl), -CN and C₁-C₆ haloalkyl.



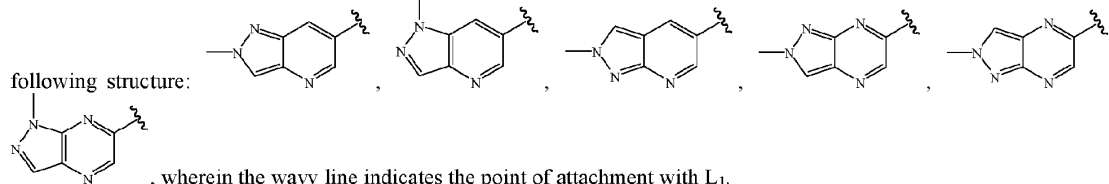
In some embodiments of the present disclosure, wherein R¹ represents

20 In some embodiments of the present disclosure, wherein R² represents C₃-C₁₀ cycloalkyl, C₆-C₁₀ cycloalkenyl, 4-10 membered heterocycloalkyl, 6-10 membered heterocycloalkenyl, C₆-C₁₀ aryl, 5-10 membered heteroaryl, which are substituted by 0-4 substituents selected from deuterium, halogen, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₆ cycloalkyl, -OR^a, oxo, hydroxy (C₁-C₆ alkyl), -NR^aR^b, -CR^aR^bNR^aR^b, -CN, C₁-C₆ haloalkyl, C₁-C₆ haloalkoxy, -SO₃R^a, -SR^a, -SF₅, -C(O)R^a, -C(O)OR^a, -OC(O)R^a, -OC(O)NR^aR^b, -NR^aCOR^b and -CONR^aR^b.

25 In some embodiments of the present disclosure, wherein R¹ and W₂ combine to form a ring fused to ring A having the

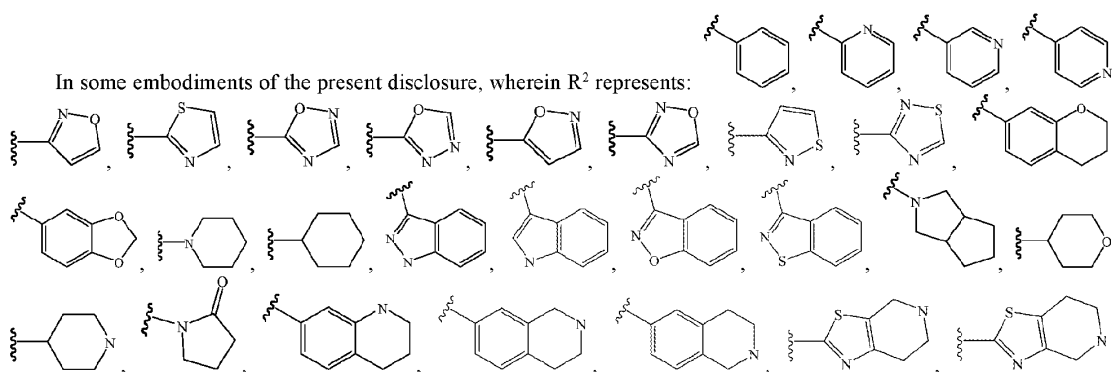


In some embodiments of the present disclosure, wherein R¹ and W₂ combine to form a ring fused to ring A having the

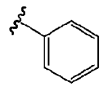


40 In some embodiments of the present disclosure, wherein R² represents phenyl, pyridinyl, indazolyl, indolyl, thiazolyl, isothiazolyl, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, pyridazinyl, piperazinyl, pyrazinyl, cyclohexyl, benzothienyl, 1,2-benzisoxazolyl, benzo[d] isothiazolyl, which are substituted by 0-4 substituents selected from deuterium, halogen, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₆ cycloalkyl, -OR^a, oxo, hydroxy (C₁-C₆ alkyl), -NR^aR^b, -CR^aR^bNR^aR^b, -CN, C₁-C₆ haloalkyl, and C₁-C₆ alkoxy.

In some embodiments of the present disclosure, wherein R² represents:

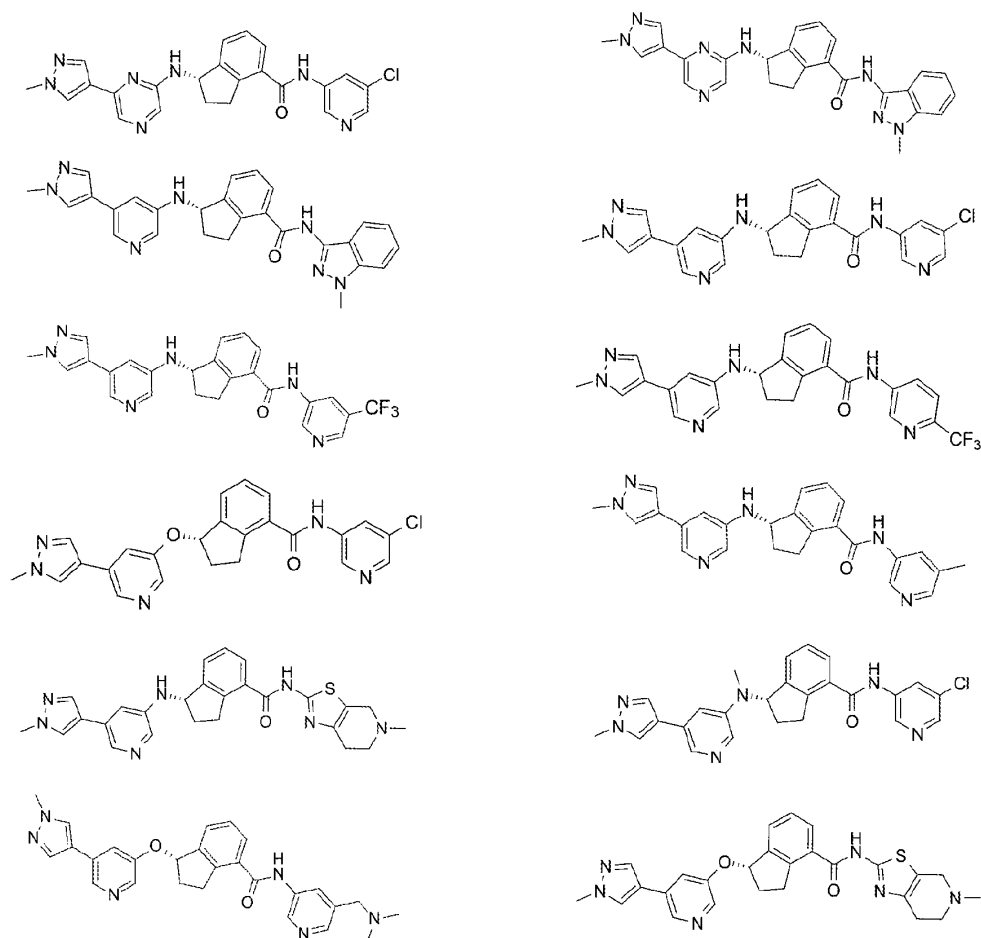


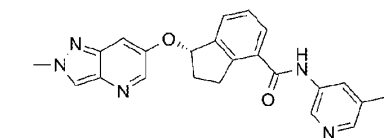
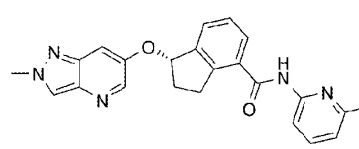
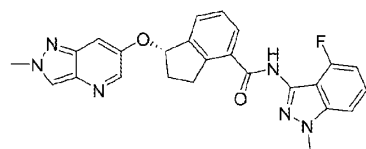
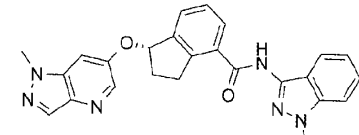
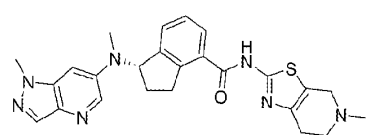
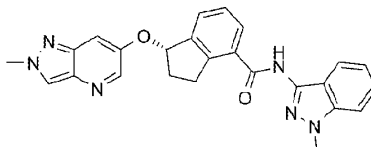
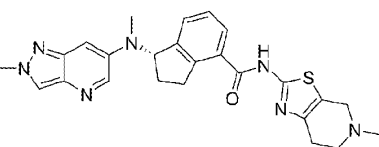
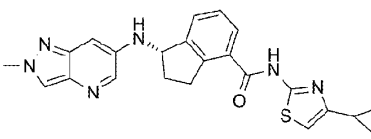
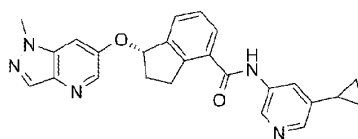
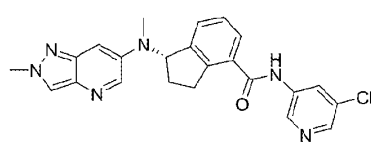
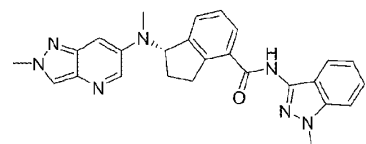
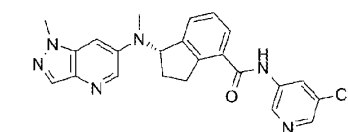
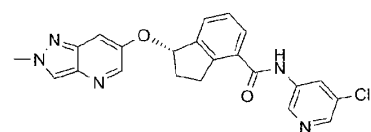
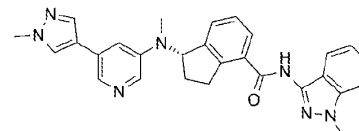
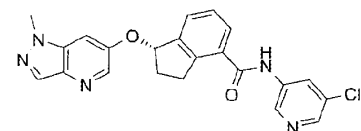
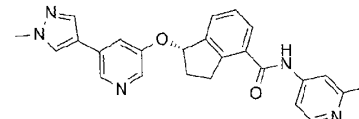
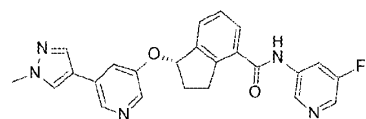
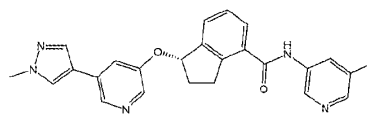
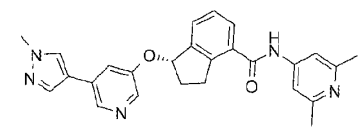
5 which are substituted by 0-4 substituents selected from deuterium, halogen, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₆ cycloalkyl, -OR^a, oxo, hydroxy (C₁-C₆ alkyl), -NR^aR^b, -CR^aR^bNR^aR^b, -CN, C₁-C₆ haloalkyl, and C₁-C₆ alkoxy.

In some embodiments of the present disclosure, wherein R² represents: , which is substituted by 0-4 substituents selected from deuterium, halogen, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₆ cycloalkyl, -OR^a, oxo, hydroxy (C₁-C₆ alkyl), -NR^aR^b, -CR^aR^bNR^aR^b, -CN, C₁-C₆ haloalkyl, and C₁-C₆ alkoxy.

10 In some embodiments of the present disclosure, wherein R³ represents hydrogen or CH₃.

Specifically, the present disclosure provides compounds having the following structures:





In addition, the present disclosure further provides a pharmaceutical composition, wherein, said pharmaceutical composition comprises the aforementioned compound, its tautomer, stereoisomer, hydrate, solvate, pharmaceutically acceptable salt or prodrug thereof, and a pharmaceutically acceptable excipients.

- 5 It should be understood that within the scope of the present invention, the above technical features of the present invention and the technical features specifically described in the following (e.g., embodiments) can be combined with each other, thereby forming a new or preferred technical solution. Due to space limitations, it will not be repeated herein.

DETAILED DESCRIPTION OF THE INVENTION

Definitions

- 10 Unless otherwise stated, the definitions of groups and terms specified in the specification and claims of the present application, including definitions of examples, exemplary definitions, preferred definitions, definitions recorded in the table, definitions of specific compounds in the embodiments, and the like, can be arbitrarily combined and combined with each other. Such a combination and a combined group definition and compound structure should fall within the scope of the description of the present application.

- 15 Unless otherwise defined, the technical terms used herein have the same meaning as commonly understood by a person skilled in the art to which the subject matter belongs. Unless otherwise stated, all patents, patent applications, and publications cited herein are incorporated herein by reference in their entirety. If there are a plurality of definitions to the terms herein, the definition of the present chapter is defined.

- 20 It is to be understood that both the foregoing general description and the following detailed description are exemplary and are for explanation only and are not intended to limit the subject matter of the present invention. In the present application, unless otherwise specifically stated, the singular also includes the plural. It must be noted that the singular forms used in this specification and the claims include the plural forms of the recited thing, unless expressly stated otherwise herein. It should also be noted that, unless otherwise stated, "or", "and/or". In addition, the terms "comprising" and other forms, such as "comprising", "containing", and "including" are not intended to be limiting.

- 25 Unless otherwise specified, conventional methods within the art, such as mass spectrometry, NMR, IR and UV/VIS spectroscopy, and pharmacological methods, are employed. Unless specifically defined, the terms used herein to analyze chemical, organic synthetic chemistry, and related descriptions of drugs and pharmaceutical chemistry are known in the art. Standard techniques may be used in chemical synthesis, chemical analysis, drug preparation, formulation and delivery, and in the treatment of patients. For example, the reaction and purification may be carried out using a manufacturer's description of the kit, or in a manner well known in the art or a description of the invention. The techniques and methods described above may generally be implemented in accordance with conventional methods well known in the art, in accordance with a number of summaries cited and discussed in this specification and in more specific documents. In the present specification, groups and substituents thereof may be selected by those skilled in the art to provide stable structural moieties and compounds.

- 35 Unless otherwise indicated, in addition to the specific structure of the compound, the compound of the present disclosure may also be extended and interpreted to further include a pharmaceutically acceptable salt, a stereoisomer, an isotopic isomer (for example, a deuterated compound), a solvate, a hydrate, a prodrug, and a metabolite of the compound, that is, a pharmaceutically acceptable salt, a stereoisomer, an isotopic isomer, a solvate, a hydrate, a prodrug, and a metabolite of the compound also fall within the scope of protection of the compound.

- 40 Preferably, the above pharmaceutical composition of the present disclosure may further comprise a second active substance, the second active substance is an anti-tumor drug, and the anti-tumor drug comprises one or more of a chemotherapeutic drug, a targeted tumor therapeutic drug, or a tumor therapeutic antibody drug.

In addition, the present disclosure also provides a compound of the present disclosure, a pharmaceutically acceptable salt, an ester, a prodrug, a stereoisomer or an isotope derivative thereof, a method for treating a disease by inhibiting CSF1R, VEGFR, PDGFR or DDR1, or combination thereof, and a preferred disease being a tumor.

- 45 Unless otherwise stated, the term "alkyl" itself or as part of another substituent refers to a straight-chain (ie, unbranched) or branched, or cyclic hydrocarbon group, or a combination thereof, which may be saturated, mono- or polyunsaturated, may include a divalent or polyvalent group having a specified number of carbon atoms (ie, C₁-C₁₀ refers to 1 to 10 carbon atoms). Examples of saturated hydrocarbyl groups include, but are not limited to, groups such as methyl, ethyl, n-propyl, isopropyl, n-butyl, t-butyl, isobutyl, sec-butyl, cyclohexyl, cyclohexylmethyl, cyclopropylmethyl and the like, such as n-pentyl, n-hexyl, n-heptyl, n-octyl and other homologues and isomers. An unsaturated alkyl group is an alkyl group having one or more double bonds or triple bonds. Examples of unsaturated alkyl groups include, but are not limited to, vinyl, 2-propenyl, crotyl, 2-isopentenyl, 2-(Butadienyl), 2,4-pentadiene, 3-(1,4-pentadiene), ethynyl, 1-propynyl, 3-propynyl,

3-butynyl, and higher homologues and isomers. An alkyl group defined as a hydrocarbyl group is referred to as "homoalkyl". The alkyl is optionally substituted with one or more halogen atoms.

The term "haloalkyl" or "halogenated alkyl" refers to an alkyl group as defined above, wherein one or more hydrogen atoms are replaced by halogen atoms.

5 The term "alkylene" itself or as part of another substituent refers to a divalent group derived from an alkyl group, such as, but not limited to, $-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2-$, $-\text{CH}_2\text{CH}=\text{CHCH}_2-$, $-\text{CH}_2\text{C}\equiv\text{CCH}_2-$, $-\text{CH}_2\text{CH}_2\text{CH}(\text{CH}_2\text{CH}_2\text{CH}_3)\text{CH}_2-$. Alkyl (or alkylene) typically has from 1 to 24 carbon atoms and the present disclosure preferably has a group having 10 or less carbon atoms. "Lower alkyl" or "lower alkylene" refers to a shorter alkyl or alkylene group, typically having 8 or fewer carbon atoms. The alkylene is optionally substituted with one or more halogen atoms.

10 The term "alkenyl" refers to an unsaturated branched or straight chain hydrocarbon group having at least one carbon-carbon double bond derived from the removal of a hydrogen atom from a single carbon atom of an olefin molecule. The group may be in the Z-form or E-form (cis or trans) surrounding one or more double bonds. Typical alkenyl groups include, but are not limited to, vinyl groups; propenyl (eg, prop-1-en-1-yl, prop-1-en-2-yl, prop-2-en-1-yl (allyl) and prop-2-en-2-yl); butenyl (eg, butyl-1-en-1-yl, butan-1-en-2-yl, 2-methyl-prop-1-en-1-yl, butan-2-en-1-yl, butan-2-en-1-yl, butan-2-en-2-yl, butyl-1,3-diene-1-yl and butyl-1,3-diene-2-yl); and the like. In some embodiments, the alkenyl group has 15 from 2 to 20 carbon atoms, and in other embodiments, from 2 to 6 carbon atoms. Alkenyl groups having 2 to 6 carbon atoms may be referred to as (C_2 - C_6) alkenyl groups.

20 The term "alkynyl" refers to a carbon chain containing at least one carbon-carbon triple bond, which may be linear or branched, or a combination thereof. Examples of alkynyl groups include ethynyl, propargyl, 3-methyl-1-pentynyl, 2-heptynyl, and the like. The alkynyl group is optionally substituted with one or more halogen atoms.

The term "cycloalkyl" refers to a monocyclic or bicyclic saturated carbocyclic ring, each having 3 to 10 carbon atoms. "Condensed analogs" of cycloalkyl means that the monocyclic ring is fused to an aryl or heteroaryl group, wherein the attachment site is in the non-aromatic moiety. Examples of cycloalkyl and their Condensed analogs include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, tetrahydronaphthyl, decahydronaphthyl, dihydroindenyl, and the like. The cycloalkyl is 25 optionally substituted with one or more halogen atoms. Further, the term "cycloalkyl" in the present disclosure includes a bridge ring system and a spiro ring system.

The term "cycloalkenyl" refers to a cyclic hydrocarbon group having a carbon-carbon double bond in a ring, the number of carbon-carbon double bonds is not limited on the basis of a valence bond principle, for example, 1, 2, or 3, and the definition of the cycloalkenyl group also includes a fused cycloalkenyl group formed by fused with a cycloalkyl group or other cycloalkenyl groups. Examples of cycloalkenyl groups include, but are not limited to, cyclopropene, cyclobutene, 30 cyclopentene and cyclohexene, cyclobutadiene, cyclopentadiene, 1,3,5 - cycloheptatriene, 1,3,5,7 - cyclooctadiene, and the like.

35 The term "heterocyclic alkenyl" refers to a heterocyclic hydrocarbon group having a carbon-carbon double bond in the ring, wherein the atoms comprising the ring include, in addition to carbon atoms, at least one heteroatom selected from nitrogen, oxygen or sulfur. The heterocyclic alkenyl group may be non-aromatic.

The term "oxo" refers to the group formed by the substitution of two hydrogens on a carbon atom with the same oxygen, also known as carbonyl ($=\text{O}$). The N-oxide of an aromatic heterocycle may also be represented as an oxo-aromatic heterocycle, such as a pyridine N-oxide.

40 The term "alkylthio" refers to $-\text{SR}$, where R represents any straight or branched alkyl group. Examples of alkylthio include, but are not limited to $-\text{SCH}_3$, $-\text{SCH}_2\text{CH}_3$, and the like.

The term "hydroxy (C_1 - C_6 alkyl)" or "hydroxy C_1 - C_6 alkyl" refers to a group obtained by the substitution of hydrogen atoms of any of the C_1 - C_6 alkyl groups with hydroxyl groups. The term "halo (C_1 - C_6 alkyl)" refers to a group obtained by substitution of any hydrogen atom of C_1 - C_6 alkyl with halo. The term " $(\text{CH}_3)_2\text{N}$ -(C_1 - C_6 alkyl)" means that any hydrogen atom of a C_1 - C_6 alkyl group is replaced with a dimethylamino group.

45 The term "alkoxy" refers to a straight-chain or branched alkoxy group having a number of carbon atoms shown. C_1 - C_6 alkoxy, for example, including methoxy, ethoxy, propoxy, isopropoxy, etc.

Unless otherwise stated, the term "heteroalkyl" or in combination with another term refers to a stable straight-chain or branched, or cyclic hydrocarbyl group consisting of at least one carbon atom and at least one heteroatom selected from O, N, P, Si, S, or a cyclic hydrocarbon group, or a combination thereof, wherein the nitrogen atom, the phosphorus atom, or the sulfur atom may optionally be oxidized and the nitrogen atom may optionally be quaternized. Heteroatoms O, N, P, S, and Si may be placed anywhere within the heteroalkyl group or at a location where the alkyl group is connected to the rest of the molecule. For example, but not limited to, $-\text{CH}_2\text{CH}_2\text{OCH}_3$, $-\text{CH}_2\text{CH}_2\text{NHCH}_3$, $-\text{CH}_2\text{CH}_2\text{N}(\text{CH}_3)\text{CH}_3$, $-\text{CH}_2\text{SCH}_2\text{CH}_3$, $-\text{CH}_2\text{CH}_2\text{S}(\text{O})\text{CH}_3$, $-\text{CH}_2\text{CH}_2\text{S}(\text{O})_2\text{CH}_3$, $-\text{CH}=\text{CHOCH}_3$, $-\text{Si}(\text{CH}_3)_3$, $-\text{CH}_2\text{CH}=\text{NOCH}_3$, $-\text{CH}=\text{CHN}(\text{CH}_3)\text{CH}_3$, $-\text{OCH}_3$, $-\text{OCH}_2\text{CH}_3$ and $-\text{CN}$. Up to two or three heteroatoms may be continuous. For example, 55 $-\text{CH}_2\text{NHCH}_3$ and $-\text{CH}_2\text{OSi}(\text{CH}_3)_3$. Similarly, the term "heteroalkylene" alone or in combination with other terms means

a divalent group derived from a heteroalkyl, such as, but not limited to, $-\text{CH}_2-\text{CH}_2-\text{S}-\text{CH}_2-\text{CH}_2-$ and $-\text{CH}_2-\text{S}-\text{CH}_2-\text{CH}_2-\text{NH}-\text{CH}_2-$. For heteroalkylene, heteroatoms may be at either end or both ends of the chain (eg. alkyleneoxy, alkylene dioxy, alkylamine, alkylene diamino, etc.). Furthermore, for alkylene and heteroalkylene linking groups, the writing direction of molecular formula of the linking group does not represent the orientation of the linking group. For example, the formula $-\text{C}(\text{O})\text{OR}'-$ represents $-\text{C}(\text{O})\text{OR}'-$ and $-\text{R}'\text{OC}(\text{O})-$. As noted above, heteroalkyl as used herein includes those groups attached to the rest of the molecule through heteroatoms, such as $-\text{C}(\text{O})\text{R}'$, $-\text{C}(\text{O})\text{NR}'$, $-\text{NR}'\text{R}''$, $-\text{OR}'$, $-\text{SR}'$ and/or $-\text{SO}_2\text{R}'$. In referring to "heteroalkyl" and then to specific heteroalkyl groups such as $-\text{NR}'\text{R}''$, it should be understood that the terms heteroalkyl and $-\text{NR}'\text{R}''$ are not repetitive and mutually exclusive. Rather, these specific heteroalkyl groups are cited for clarity. Thus, the term "heteroalkyl" should not be construed as excluding specific heteroalkyl groups such as $-\text{NR}'\text{R}''$.

The term "heteroatom" refers to an atom other than carbon or hydrogen. Heteroatoms are typically independently selected from oxygen, sulfur, nitrogen, silicon and phosphorus, but are not limited to these atoms. In embodiments in which two or more heteroatoms are present, the two or more heteroatoms can all be the same as one another, or some or all of the two or more heteroatoms can each be different from the others.

The term "cycloalkoxy" refers to a cycloalkyl group as defined above, such as cyclopropoxy, bonded to an oxygen atom.

The term "haloalkoxy" or "halogenated alkoxy" refers to an alkoxy group as defined above in which one or more hydrogen atoms are replaced by halo atoms.

The term "aryl" refers to a monocyclic or bicyclic aryl group containing only carbon atoms. The "Condensed analogs" of the aryl group refers to the fusing of an aryl group to a monocyclic cycloalkyl group or a monocyclic heterocyclic group, where the attachment point is located in the aryl moiety. Examples of aryl and fused ring analogs thereof include phenyl, naphthyl, indanyl, indenyl, tetrahydronaphthyl, 2,3-dihydrobenzofuran, dihydrobenzopyran, 1,4-benzodioxane, and the like.

The term "heteroaryl" refers to a monocyclic or bicyclic aryl group containing at least one heteroatom selected from N, O and S. The "Condensed analogs" of heteroaryl refers to the fusing of a heteroaryl group to a monocyclic cycloalkyl group or a monocyclic heterocyclic group, where the attachment point is located in the aryl moiety. Examples of heteroaryl groups include pyrrolyl, isoxazolyl, isothiazolyl, pyrazolyl, pyridyl, oxazolyl, oxadiazolyl, thiadiazolyl, thiazolyl, imidazolyl, triazolyl, tetrazolyl, furyl, triazinyl, thienyl, pyrimidinyl, pyridazinyl, pyrazinyl, benzoxazolyl, benzothiazolyl, benzimidazolyl, benzofuranyl, benzothieryl, furo(2,3-b)pyridyl, quinolinyl, indolyl, isoquinolinyl, and the like.

"Substituted or unsubstituted": the defined alkyl, aryl, and heteroaryl are unsubstituted or substituted with at least one substituent selected from the group consisting of substituents. The substituents are selected from the following group: halogen atom, alkyl group having 1 to 6 carbon atoms, alkoxy group having 1 to 6 carbon atoms, haloalkyl group having 1 to 6 carbon atoms, haloalkoxy group having 1 to 6 carbon atoms, $-\text{CN}$, alkynyl group having 2 to 6 carbon atoms, alkanoyl group having 1 to 6 carbon atoms, cycloalkyl group having 3 to 7 ring atoms, heteroaryl group, aryl group, aryloxy group having 7 to 10 carbon atoms, arylcarbonyl group, aminocarbonyl group, alkenyl groups having 2 to 5 carbon atoms, alkylthio groups having 1 to 6 carbon atoms, aminosulfinyl groups, aminosulfonyl groups, hydroxyl groups, $-\text{SF}_5$, hydroxyalkyl groups having 1 to 4 carbon atoms, nitro groups, amino groups, carboxyl groups, alkoxycarbonyl groups having 2 to 5 carbon atoms, alkoxyalkyl groups having 1 to 4 carbon atoms, alkylsulfonyl groups having 1 to 4 carbon atoms, alkanoylamino groups having 1 to 4 carbon atoms, alkanoyl (alkyl) amino groups having 1 to 6 carbon atoms, alkanoylamino alkyl groups having 1 to 6 carbon atoms in the alkanoyl and alkyl moieties, alkylsulfonylamino alkyl groups having 1 to 6 carbon atoms in the alkanoyl group and each alkyl moiety, alkylsulfonamido groups having from 1 to 4 carbon atoms, monoalkylaminocarbonyl or dialkylaminocarbonyl groups having from 1 to 6 carbon atoms, monoalkylaminosulfinyl or dialkylamino sulfinyl groups having from 1 to 6 carbon atoms, monoalkylaminosulfonyl groups having from 1 to 6 carbon atoms, or dialkylaminosulfonyl groups, an aminoalkyl group having 1 to 4 carbon atoms, a monoalkylamine group having 1 to 6 carbon atoms, or a dialkylamine group, an aralkyl group having from 1 to 6 carbon atoms in each alkyl moiety, a heteroaralkyl group having from 1 to 4 carbon atoms in the alkyl moiety, a heteroarylalkoxy group having from 1 to 4 carbon atoms in the alkoxy moiety, and an alkylsulfonamido group having from 1 to 4 carbon atoms.

As used herein, the term "heterocycle" or "heterocyclic" or "heterocycloalkyl" or "heterocyclyl" refers to a saturated, partially saturated or unsaturated group (but not aromatic) having a monocyclic or fused ring (including a bridged ring system and a spiro ring system, with 1 to 10 carbon atoms in the ring and 1 to 4 heteroatoms selected from nitrogen, sulfur or oxygen, in a fused ring system, one or more rings may be cycloalkyl, aryl, or heteroaryl as long as the connection point is in the non-aromatic moiety. In one embodiment, the nitrogen atoms and/or sulfur atoms of the heterocyclic group are optionally oxidized to provide N-oxide, sulfinyl, and sulfonyl moieties. Examples of "heterocyclyl" and their Condensed analogs include pyrrolidinyl, piperidinyl, piperazinyl, imidazolidinyl, 2,3-dihydrofuran(2,3-b)pyridyl, benzoxazinyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, indolyl, and the like. The term also includes non-aromatic partially unsaturated monocyclic rings, such as 2- or 4- pyridone or N-substituted-(1H,3H)-pyrimidine-2,4-dione (N-substituted uracil) linked by nitrogen atoms.

As used herein, the term "substituted heterocyclic" or "substituted heterocycloalkyl" or "substituted heterocyclyl" refers to a heterocyclic group substituted with 1 to 5 (eg, 1 to 3) substituents that are identical to the substituents defined by the substituted cycloalkyl.

5 Unless otherwise stated, the term "halosubstituted" or "halogen" itself or as part of another substituent refers to fluorine, chlorine, bromine, or iodine atoms. In addition, the term "haloalkyl" refers to a monohaloalkyl group and a polyhaloalkyl group. For example, the term "(C₁-C₆)haloalkyl" refers to, but is not limited to, trifluoromethyl, 2,2,2-trifluoroethyl, pentafluoroethyl, 4-chlorobutyl, 3-bromopropyl, and the like.

10 "Prodrug" refers to a substance that is converted into a parent drug substance in vivo. In some cases, prodrugs are often used due to the easier administration of the prodrug than the parent drug. For example, prodrugs can be orally bioavailable and parent drugs cannot. In the pharmaceutical composition, the prodrug may also have a higher solubility than the parent drug. Examples of prodrugs are, but are not limited to, any of the compounds of formula (I) may be administered in the form of an ester (prodrug) to promote transport across cell membranes. Water solubility in cell membranes is detrimental to migration, and once in water-soluble beneficial cells, the ester is subsequently metabolized and hydrolyzed into an active material carboxylic acid. Another example of a prodrug may be a short peptide (polyamino acid) bonded to an acid group, 15 wherein the peptide is metabolized to release the active portion.

The term "comprising" or "comprise" is meant to be open ended, i.e., all-encompassing and non-limiting. It may be used herein synonymously with "having" or "including". Comprising is intended to include each and every indicated or recited component or element(s) while not excluding any other components or elements.

"Pharmaceutically acceptable" refers to generally recognized for use in animals, and more particularly in humans.

20 "Pharmaceutically acceptable salt" refers to a salt of a compound that is pharmaceutically acceptable and that possesses the desired pharmacological activity of the parent compound.

Optical Isomer-Diastereomer-Geometric Isomer-Tautomer:

25 The compound of formula (I) contains one or more asymmetric centers, and thus can be used as racemates and racemic mixtures, single enantiomer, diastereomeric mixtures, and single diastereomer. The present disclosure should comprise all of these isomeric forms of the compound of formula (I).

Some of the compounds described herein contain olefinic double bonds, unless stated otherwise, refer to two geometric isomers, including E and Z.

Some compounds of the present disclosure may contain one or more ring systems, so cis- and trans-isomers may be present. The present disclosure is intended to encompass all such cis- and trans-isomers.

30 Some of the compounds described herein may have different sites connected to hydrogen atoms, referred to as tautomers. Such an example may be a ketone and its enol form known as a ketone-enol tautomer. Single tautomer and mixtures thereof are included in the compounds of the present disclosure.

35 The compounds of the present invention can be separated into diastereoisomeric pairs of enantiomers, such as by fractional crystallization from a suitable solvent, such as methanol or ethyl acetate, or mixtures thereof. A pair of such enantiomers can be separated into individual stereoisomers by conventional methods, such as using optically active amines or acids as resolution reagents or in chiral HPLC columns.

Alternatively, any enantiomers of the compounds of the present invention can be obtained by stereotactic synthesis using optically pure feedstocks or reagents of known configurations.

40 A stable isotope-labeled analog: one or more protons in the compound of the present disclosure may be replaced with deuterium atoms, thereby providing a deuterated analog with improved pharmacological activity.

Salts and Dosage Forms

It should be understood that the compounds of the present invention, as used herein, also include pharmaceutically acceptable salts.

Examples

45 The information provided by the present disclosure is only intended to assist the reader in understanding. Neither the information provided nor the cited references is an admission to the prior art of the present invention. Each reference cited is incorporated herein in its entirety and for any purpose.

All documents mentioned in the present disclosure are incorporated herein by reference as if each document is individually incorporated by reference. In addition, it should be understood that after reading the above teaching content

of the present disclosure, those skilled in the art may make various changes or modifications to this application, and these equivalent forms also fall within the scope defined by the appended claims of the present disclosure.

The present invention is further described below with reference to specific embodiments. It should be understood that the following description is only the most preferred embodiments of the present invention, and should not be considered as a limitation on the protection scope of the present invention. On the basis of fully understanding the present disclosure, the experimental methods without specific conditions in the following embodiments are usually made according to conventional conditions or according to conditions suggested by manufacturers, and those skilled in the art can make non-essential changes to the technical solutions of the present disclosure, and such modifications should be regarded as included in the protection scope of the present disclosure.

Unless otherwise specified, the raw materials and reagents used in the following embodiments are all commercially available commodities, or may be prepared by a known method.

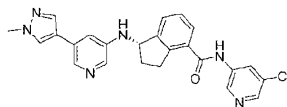
The present application has the following definitions:

Symbol or Unit:

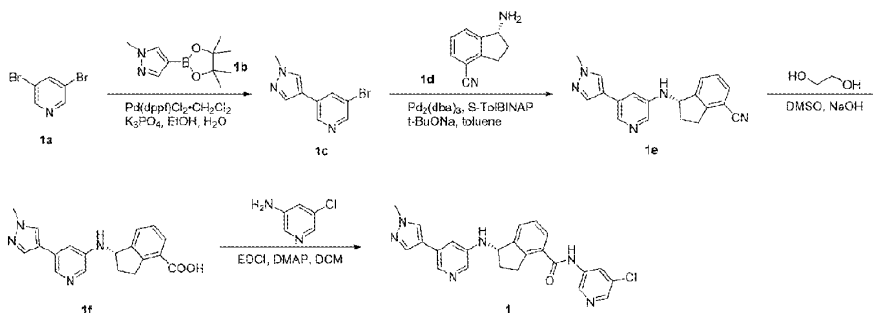
IC₅₀: half inhibitory concentration refers to the concentration at half the maximum inhibitory effect is reached.

Example 1

(S)-N-(5-chloropyridin-3-yl)-1-((5-(1-methyl-1H-pyrazol-4-yl)pyridin-3-yl)amino)-2,3-dihydro-1H-indene-4-carboxamide



Compound **1** was prepared by the following steps:



Step 1: To a solution of 3,5-dibromopyridine **1a** (2370 mg, 10 mmol) in ethanol (12 mL) was added Pd(dppf)Cl₂·CH₂Cl₂ (82 mg, 0.1 mmol), compound **1b** (2195 mg, 10.5 mmol), water (2.5 mL) and K₃PO₄ (6360 mg, 30 mmol). The resulting mixture was degassed with N₂ for three times, then heated to reflux and stirred for 2 h. TLC showed the reaction was complete. After natural cooling to room temperature, the separated organic layer was concentrated in vacuum and purified by column chromatography to give the desired product **1c** (1888 mg, yield: 80.0%). ESI-MS(M/S): 238.1 [M+H]⁺.

Step 2: To a solution of **1c** (947.2 mg, 4.1 mmol) in toluene (4 mL) was added (S)-1-amino-2,3-dihydro-1H-indene-4-carbonitrile **1d** (530 mg, 3.4 mmol), Pd₂(dba)₃ (153.6 mg, 0.05 mmol), S-Tol-BINAP (456 mg, 0.2 mmol) and sodium tert-butoxide (646.4 mg, 2.0 mmol). The resulting mixture was degassed with N₂ for three times, then heated to 80 °C and stirred for 6 h. TLC showed the reaction was complete. The mixture was concentrated in vacuum and purified by column chromatography to give the desired product **1e** (711 mg, yield: 55.0%). ESI-MS(M/S): 316.3 [M+H]⁺.

Step 3: To a solution of **1e** (158 mg, 0.5 mmol) in DMSO (1.8 mL) was added 50% aqueous NaOH (0.9 mL) and glycol (0.9 mL). The reaction mixture was refluxed overnight. TLC showed the reaction was complete. The reaction mixture was diluted with water, and then adjusted to pH = 4 with concentrated hydrochloric acid. The large amount of

solid precipitated was collected by filtration to give the desired product **1f** (105 mg, yield: 63%). ESI-MS(M/S): 335.3 [M+H]⁺.

Step 4: To a solution of **1f** (100 mg, 0.3 mmol) in CH₂Cl₂ (0.5 mL) was added 3-amino-5-chloropyridine (77.1 mg, 0.6 mmol), DMAP (7.3 mg, 0.06 mmol), triethylamine (40.4 mg, 0.4 mmol) and EDCI (115.2 mg, 0.6 mmol). The reaction mixture was stirred at room temperature for 8 h. TLC showed the reaction was complete. The mixture was washed with water twice. The separated organic layer was dried, concentrated and purified by column chromatography to give the desired product **1** (91 mg, yield: 68%). ESI-MS(M/S): 445.2 [M+H]⁺. ¹H NMR (62 MHz, acetone-*d*₆) δ 10.63 (s, 1H), 8.84 (d, *J* = 1.6 Hz, 1H), 8.37 (s, 2H), 8.16 – 7.76 (m, 4H), 7.44 (t, *J* = 11.2 Hz, 4H), 6.24 (d, *J* = 8.4 Hz, 1H), 5.32 – 4.95 (m, 1H), 3.86 (s, 3H), 3.21 – 2.56 (m, 3H), 2.00 – 1.64 (m, 1H).

Example 2

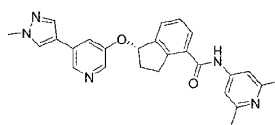
The preparation of compounds **2a-2e** refers to the synthesis of compound **1** in example 1.

Table 1

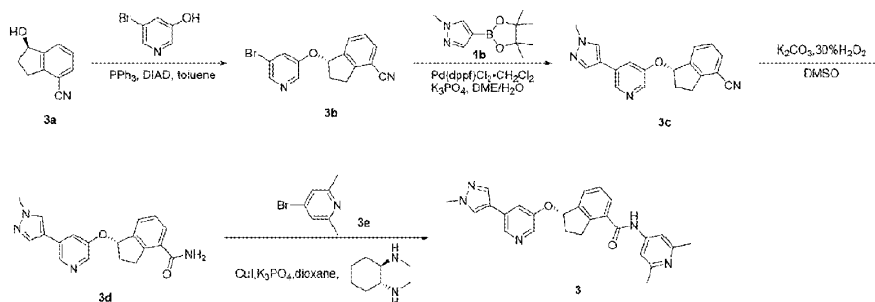
Cpds	Structure	MS [M+1] ⁺	¹ H NMR
2a		464.2	¹ H NMR (62 MHz, acetone- <i>d</i> ₆) δ 9.90 (s, 1H), 8.44 – 6.73 (m, 12H), 5.54 – 4.83 (m, 1H), 3.93 (d, <i>J</i> = 5.1 Hz, 6H), 3.36 (dt, <i>J</i> = 10.2, 6.9 Hz, 2H), 2.90 – 2.17 (m, 2H), 1.74 (t, <i>J</i> = 8.3 Hz, 1H).
2b		479.2	¹ H NMR (62 MHz, acetone- <i>d</i> ₆) δ 10.81 (s, 1H), 9.06 (s, 1H), 8.76 – 6.82 (m, 10H), 6.25 (d, <i>J</i> = 8.3 Hz, 1H), 5.10 (dq, <i>J</i> = 10.8, 6.2, 5.2 Hz, 1H), 3.87 (s, 3H), 3.19 – 2.64 (m, 2H), 2.45 – 1.49 (m, 2H).
2c		479.2	¹ H NMR (62 MHz, acetone- <i>d</i> ₆) δ 9.94 (s, 1H), 9.17 (d, 1H), 8.85 – 8.57 (m, 2H), 8.19 – 8.08 (m, 1H), 8.07 – 7.90 (m, 2H), 7.89 – 7.57 (m, 2H), 7.56 – 7.18 (m, 3H), 5.64 – 4.94 (m, 2H), 3.92 (s, 3H), 3.53 – 2.97 (m, 2H), 2.72 – 2.21 (m, 1H), 1.84 – 1.10 (m, 1H).
2d		425.2	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.38 (s, 1H), 8.70 (d, <i>J</i> = 2.3Hz, 1H), 8.17 (s, 2H), 8.10-8.03 (m, 2H), 7.94 (d, <i>J</i> = 2.6Hz, 1H), 7.87 (s, 1H), 7.66 (d, <i>J</i> = 7.5Hz, 1H), 7.48 (d, <i>J</i> = 7.4Hz, 1H), 7.38 (t, <i>J</i> = 7.6Hz, 1H), 7.27 (t, <i>J</i> = 2.2Hz, 1H), 6.26 (d, <i>J</i> = 8.4Hz, 1H), 5.15 (d, <i>J</i> = 7.8Hz, 1H), 3.87 (s, 3H), 3.32-3.02 (m, 2H), 2.74-2.53 (m, 2H), 1.83 (s, 3H).
2e		486.2	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 12.40 (s, 1H), 8.17 (s, 1H), 8.05 (s, 1H), 7.93 (s, 1H), 7.87 (s, 1H), 7.76 (d, <i>J</i> = 7.6 Hz, 1H), 7.49 (d, <i>J</i> = 7.5 Hz, 1H), 7.35 (t, <i>J</i> = 7.6 Hz, 1H), 7.27-7.25 (m, 1H), 6.26 (d, <i>J</i> = 8.5 Hz, 1H), 5.17-5.11 (m, 1H), 3.87 (s, 3H), 3.54 (s, 2H), 3.30-3.23 (m, 1H), 3.13-3.05 (m, 1H), 2.75-2.68 (m, 4H), 2.61-2.53 (m, 1H), 2.40 (s, 3H), 1.87-1.80 (m, 1H).

Example 3

(S)-N-(2,6-dimethylpyridin-4-yl)-1-((5-(1-methyl-1H-pyrazol-4-yl)pyridin-3-yl)oxy)-2,3-dihydro-1H-indene-4-carboxamide



Compound **3** was prepared by the following steps:



Step 1: To a solution of **3a** (1.9 g, 11.9 mmol), 5-bromo-3-hydroxypyridine (3.1 g, 17.9 mmol) and PPh₃ (5.0 g, 17.9 mmol) in toluene (19 mL) was added dropwise DIAD (3.6 g, 17.9 mmol) while keeping the inner temperature below -10 °C under N₂. The resulting mixture was stirred at -10 °C for another 1 h. TLC showed the reaction was complete. Then water (1 mL) was added to the reaction mixture, and the resulting mixture was allowed to warm to room temperature and stirred for 0.5 h. The solid precipitated was filtered and washed with toluene. The combined filtrates were concentrated to dryness in vacuum, and purified by column chromatography to give the desired product **3b** (1.9 g, yield: 43.6%). ESI-MS(*m/z*): 315.1 [M+H]⁺.

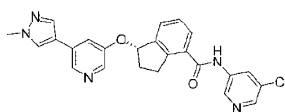
Step 2: To a mixture of **3b** (1.9 g, 6.0 mmol), **1b** (1.9 g, 9.0 mmol), K₃PO₄ (3.8 g, 18.0 mmol) and Pd(dppf)Cl₂·CH₂Cl₂ (245 mg, 0.3 mmol) was added DME (8.4 mL) and water (3.2 mL). The resulting mixture was refluxed under N₂ for 1 h. TLC showed the reaction was complete. The reaction mixture was diluted with CH₂Cl₂ (200 mL), washed with water (50 mL*2), and dried over Na₂SO₄. After concentration, the mixture was purified by column chromatography to give product **3c** (1.7 g, yield: 89.6%). ESI-MS(*m/z*): 317.1 [M+H]⁺.

Step 3: To a suspension of **3c** (1235 mg, 3.9 mmol) and K₂CO₃ (1619 mg, 11.7 mmol) in DMSO (14.4 mL) was added dropwise 30% H₂O₂ (7.2 mL) slowly. The reaction mixture was stirred at room temperature for 1 h. After the reaction was complete, the reaction mixture was diluted with water (50 mL), and extracted with ethyl acetate (150 mL*4). The combined organic layers were washed with water (30 mL*2), dried over Na₂SO₄ and concentrated. The residue was purified by silica gel chromatography to give product **3d** (412 mg, yield: 31.6%). ESI-MS(*m/z*): 335.1 [M+H]⁺.

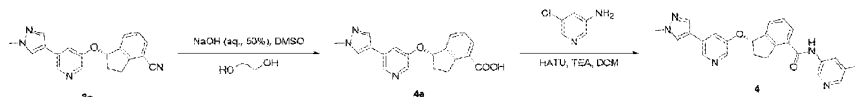
Step 4: A mixture of **3d** (50 mg, 0.12 mmol), compound **3e** (49 mg, 0.18 mmol), K₃PO₄ (64 mg, 0.3 mmol), CuI (4 mg, 0.02 mmol) and (1*R*,2*R*)-(-)-N,N'-dimethyl-1, 2-cyclohexanediamine (5.3 mg, 0.04 mmol) in 1,4-dioxane (0.5 mL) was degassed with N₂ for three times, then reacted at 80 °C until TLC showed the reaction was complete. After cooling down, the reaction mixture was diluted with ethyl acetate (20 mL), washed with ammonium hydroxide (20 mL*2) and water (20 mL). The organic layer was dried over Na₂SO₄, concentrated to dryness in vacuum and purified by column chromatography to give product **3** (42 mg, yield: 58.1%). ESI-MS(*m/z*): 440.2 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.48 (s, 1H), 8.48 (s, 1H), 8.31 (s, 1H), 8.19 (d, *J* = 2.6 Hz, 1H), 8.03 (s, 1H), 7.72 (d, *J* = 7.8 Hz, 2H), 7.65 (d, *J* = 7.5 Hz, 1H), 7.44 (d, *J* = 2.6 Hz, 3H), 6.08 (dd, *J* = 6.6, 3.7 Hz, 1H), 3.89 (s, 3H), 3.28 (t, *J* = 7.4 Hz, 1H), 3.18 – 3.07 (m, 1H), 2.70 – 2.56 (m, 2H), 2.40 (s, 6H), 2.17 – 2.05 (m, 1H).

Example 4

(*S*)-N-(5-chloropyridin-3-yl)-1-((5-(1-methyl-1H-pyrazol-4-yl)pyridin-3-yl)oxy)-2,3-dihydro-1H-indene-4-carboxamide



Compound **4** was prepared by the following steps:



Step 1: To a stirred solution of **3c** (948 mg, 3.0 mmol) in DMSO (5.0 mL) was added 50% aqueous NaOH (5.0 mL) and glycol (5.0 mL). The reaction mixture was heated to 110 °C and stirred until TLC showed the reaction was complete. After natural cooling to below 30 °C, the mixture was adjusted to pH = 6-7 with 1N hydrochloric acid. The large amount of solid precipitated was filtered and the filter cake was washed with water (5.0 mL) and dried in vacuum at 50 °C to give product **4a** as a light brown solid (665 mg, yield: 66.5%).

Step 2: To a solution of **4a** (34 mg, 0.1 mmol) and 3-amino-5-chloropyridine (33 mg, 0.2 mmol) in CH₂Cl₂ (0.5 mL) was added triethylamine (20 mg, 0.2 mmol) and HATU (76 mg, 0.2 mmol). The reaction mixture was stirred at 25 °C until TLC showed the reaction was complete, then concentrated to dryness in vacuum and purified by column chromatography to give product **4** (18 mg, yield: 38.0%). ESI-MS(*m/z*): 446.1[M+H]⁺. ¹H NMR (62 MHz, acetone-*d*₆) δ 9.87 (s, 1H), 8.87-8.84(d, 1H), 8.48-7.28 (m, 10H), 6.14-5.97 (t, 1H), 3.94 (s, 3H), 3.44-3.24(m, 2H), 2.78-2.22(m, 2H).

Example 5

The preparation of compounds **5a-5c** refers to the synthesis of compound **3** in example 3 or compound **4** in example 4.

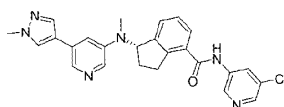
Table 2

Cpds	Structure	MS [M+1] ⁺	¹ H NMR
5a		487.2	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 12.42 (s, 1H), 8.47 (d, <i>J</i> = 1.6 Hz, 1H), 8.31 (s, 1H), 8.19 (d, <i>J</i> = 2.7 Hz, 1H), 8.02 (s, 1H), 7.86 (d, <i>J</i> = 7.6 Hz, 1H), 7.71 (d, <i>J</i> = 2.3 Hz, 1H), 7.64 (d, <i>J</i> = 7.5 Hz, 1H), 7.41 (t, <i>J</i> = 7.6 Hz, 1H), 6.07 (dd, <i>J</i> = 6.7, 3.8 Hz, 1H), 3.89 (s, 3H), 3.52 (s, 2H), 3.25 – 3.14 (m, 2H), 2.71 (d, <i>J</i> = 5.7 Hz, 4H), 2.66 – 2.58 (m, 1H), 2.39 (s, 3H), 2.13 – 2.07 (m, 1H).
5b		469.2	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.49 (s, 1H), 8.80 (s, 1H), 8.48 (s, 1H), 8.31 (s, 1H), 8.21 (s, 3H), 8.03 (s, 1H), 7.80 – 7.63 (m, 3H), 7.44 (t, <i>J</i> = 7.6 Hz, 1H), 6.08 (s, 1H), 3.89 (s, 3H), 3.42 (s, 2H), 3.32 (d, <i>J</i> = 8.6 Hz, 1H), 3.17 (d, <i>J</i> = 8.1 Hz, 1H), 2.65 (dd, <i>J</i> = 14.0, 6.9 Hz, 1H), 2.17 (s, 6H).
5c		426.2	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.43 (s, 1H), 8.70 (d, <i>J</i> = 2.3 Hz, 1H), 8.47 (d, <i>J</i> = 1.6 Hz, 1H), 8.31 (s, 1H), 8.23 – 8.14 (m, 2H), 8.04 (d, <i>J</i> = 13.5 Hz, 2H), 7.78 – 7.69 (m, 2H), 7.64 (d, <i>J</i> = 7.5 Hz, 1H), 7.44 (t, <i>J</i> = 7.6 Hz, 1H), 6.08 (dd, <i>J</i> = 6.7, 3.7 Hz, 1H), 3.89 (s, 3H), 3.36 – 3.28 (m, 1H), 3.18 – 3.10 (m, 1H), 2.68 – 2.59 (m, 1H), 2.32 (s, 3H), 2.15 – 2.07 (m, 1H).

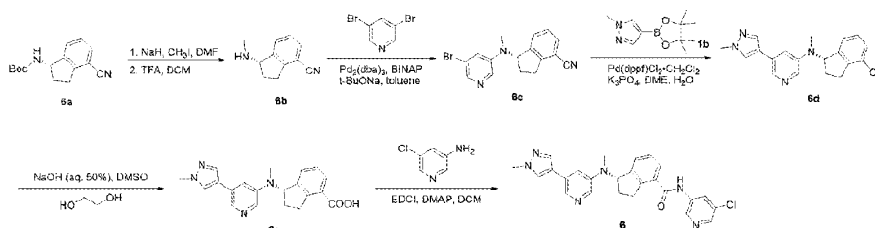
5d		426.2	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.56 (s, 1H), 8.48 (d, <i>J</i> = 1.6 Hz, 1H), 8.34 (d, <i>J</i> = 5.6 Hz, 1H), 8.31 (s, 1H), 8.19 (d, <i>J</i> = 2.8 Hz, 1H), 8.03 (s, 1H), 7.75 – 7.70 (m, 2H), 7.67 – 7.63 (m, 2H), 7.54 (dd, <i>J</i> = 5.7, 1.9 Hz, 1H), 7.45 (t, <i>J</i> = 7.6 Hz, 1H), 6.08 (dd, <i>J</i> = 6.6, 3.7 Hz, 1H), 3.89 (s, 3H), 3.33 – 3.26 (m, 1H), 3.19 – 3.06 (m, 1H), 2.69 – 2.59 (m, 1H), 2.45 (s, 3H), 2.17 – 2.04 (m, 2H).
5e		430.2	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.75 (s, 1H), 8.76 (d, <i>J</i> = 1.8 Hz, 1H), 8.48 (d, <i>J</i> = 1.6 Hz, 1H), 8.34 (d, <i>J</i> = 2.6 Hz, 1H), 8.31 (s, 1H), 8.21 (dd, <i>J</i> = 10.5, 2.5 Hz, 2H), 8.03 (s, 1H), 7.78 (d, <i>J</i> = 7.6 Hz, 1H), 7.71 (t, <i>J</i> = 2.3 Hz, 1H), 7.67 (d, <i>J</i> = 7.5 Hz, 1H), 7.46 (t, <i>J</i> = 7.6 Hz, 1H), 6.08 (dd, <i>J</i> = 6.7, 3.7 Hz, 1H), 3.89 (s, 3H), 3.33 – 3.29 (m, 1H), 3.19 – 3.11 (m, 1H), 2.68 – 2.60 (m, 1H), 2.15 – 2.07 (m, 1H).

Example 6

(S)-N-(5-chloropyridin-3-yl)-1-(methyl(5-(1-methyl-1H-pyrazol-4-yl)pyridin-3-yl)amino)-2,3-dihydro-1H-indene-4-carboxamide



5 Compound 6 was prepared by the following steps:



Step 1: To a stirred solution of **6a** (5.16 g, 20.0 mmol) in DMF (25 mL) was added 60% NaH (880 mg, 22.0 mmol) at 0 °C in portions, followed by addition of MeI (3.55 g, 25.0 mmol) after being stirred for 15 min. The resulting mixture was stirred at 25 °C until TLC analysis showed the reaction was complete. The reaction mixture was quenched by the addition of water (100 mL) with stirring, then extracted with EtOAc (100 mL*2). The combined organic layers were washed with brine (100 mL *2), dried over Na₂SO₄, and concentrated to dryness under reduced pressure. A solution of the light yellow solid (4.5 g, 16.7 mmol) obtained above and CF₃COOH (10 mL) in CH₂Cl₂ (30 mL) was stirred at 25 °C until TLC analysis showed the reaction was complete, then diluted with CH₂Cl₂ (30 mL), and adjusted to pH > 13 with 10% aqueous NaOH. The resulting mixture was stirred for a moment, then the aqueous layer was discarded, and the organic layer was washed with brine (50 mL), dried over Na₂SO₄, and concentrated to dryness under reduced pressure to give compound **6b** as brown solid (2.6g, yield: 91%).

Step 2: To a solution of **6b** (2.6 g, 15.1 mmol), 3,5-dibromopyridine (5.4 g, 22.1 mmol) in toluene (25 mL) was added Pd₂(dba)₃ (274 mg, 0.3 mmol), BINAP (934 mg, 1.5 mmol) and *t*-BuONa (4.3 g, 45.3 mmol). The resulting mixture was degassed with N₂ for three times, then heated at 90 °C until TLC analysis showed the reaction was complete. After the mixture was cooled to 30 °C, the mixture was diluted with EtOAc (75 mL), washed with water (100 mL), dried over Na₂SO₄, and concentrated to dryness under reduced pressure. The residue was purified on an ISCO chromatography to

give compound **6c** as brown thick liquid (2.7 g, yield: 55%).

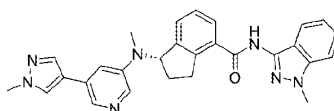
Step 3: To a solution of **6c** (2.7 g, 8.2 mmol) and **1b** (2.6g, 12.3 mmol) in a mixture of solvent DME (12 mL) and water (6 mL) was added K_3PO_4 (3.0 g, 24.6 mmol) and $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (335 mg, 0.41 mmol). The resulting mixture was degassed with N_2 for three times, then stirred at 90 °C until TLC analysis showed the reaction was complete. After natural cooling to 30 °C, the reaction mixture was allowed to stand and the aqueous phase was removed. The collected organic layer was concentrated to dryness under reduced pressure. The thick liquid was redissolved in CH_2Cl_2 (30 mL), washed with water (30 mL), dried over Na_2SO_4 , and concentrated to dryness under reduced pressure. The residue was purified on an ISCO chromatography to give compound **6d** as yellow thick liquid (1.8 g, yield: 67%).

Step 4: To a stirred solution of **6d** (1.8 g, 5.5 mmol) in DMSO (9.0 mL) was added 50% aqueous NaOH (9.0 mL) and glycol (9.0 mL). The resulting mixture was heated to 110 °C and stirred until TLC analysis showed the reaction was complete. After natural cooling to 30 °C, the reaction mixture was adjusted to pH = 6-7 with 1N HCl. The resulting precipitate was collected by filtration, washed with water (9.0 mL), and dried under vacuum at 50 °C to give compound **6e** as light brown solid (1.6 g, yield: 88%).

Step 5: To a solution of **6e** (57.7 mg, 0.17 mmol), 3-amino-5-chloropyridine (32.0 mg, 0.25 mmol) and DMAP (4 mg, 0.03 mmol) in CH_2Cl_2 (0.5 mL) was added EDCI (48 mg, 0.25 mmol). The resulting mixture was stirred at room temperature until TLC analysis showed the reaction was complete. The mixture was concentrated to dryness under reduced pressure and the residue was purified by chromatography to give compound **6** (54 mg, yield: 71%). ESI-MS (m/z): 459.2 $[M+H]^+$. 1H NMR (62 MHz, acetone- d_6) δ 9.88 (s, 1H), 8.85 (d, $J = 2.5$, 1H), 8.50 (t, $J = 2.5$, 1H), 8.33 (d, $J = 2.5$, 1H), 8.21 (s, 1H), 8.18 (s, 1H), 8.05 (s, 1H), 7.86-7.34 (m, 5H), 5.75 (t, $J = 8.0$, 1H), 3.92 (s, 3H), 3.46-3.25 (m, 2H), 2.73 (s, 3H), 2.68-2.21 (m, 2H).

Example 7

(S)-1-(methyl(5-(1-methyl-1H-pyrazol-4-yl)pyridin-3-yl)amino)-N-(1-methyl-1H-indazol-3-yl)-2,3-dihydro-1H-indene-4-carboxamide

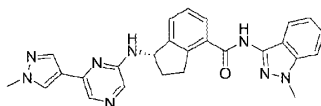


The preparation of compound **7** refers to the synthesis of compound **6** in example 6.

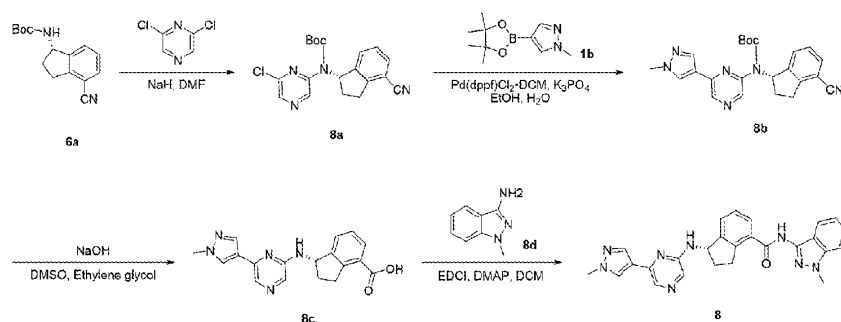
ESI-MS (m/z): 478.3 $[M+H]^+$. 1H NMR (62 MHz, acetone- d_6) δ 9.95 (s, 1H), 8.28-8.11 (m, 2H), 8.10-8.00 (m, 1H), 7.99-7.76 (m, 3H), 7.76-7.52 (m, 1H), 7.51-7.28 (m, 4H), 7.27-6.84 (m, 1H), 5.75 (t, 1H), 3.95 (d, $J = 5.1$ Hz, 6H), 3.66-3.15 (m, 2H), 2.73 (s, 3H), 2.65-2.14 (m, 1H), 1.93-1.68 (m, 1H).

Example 8

(S)-N-(1-methyl-1H-indazol-3-yl)-1-((6-(1-methyl-1H-pyrazol-4-yl)pyrazin-2-yl)amino)-2,3-dihydro-1H-indene-4-carboxamide



Compound **8** was prepared by the following steps:



Step 1: To a stirred solution of **6a** (5683 mg, 22.0 mmol) in DMF (15 mL) was added NaH (60%, 960 mg, 24.0 mmol) in portions at 0 °C. The mixture was stirred for 30 min at 0 °C, followed by addition of a solution of 2,6-dichloropyrazine (2979 mg, 20.0 mmol) in DMF (5 mL). After 1 h, TLC analysis showed the reaction was complete. The reaction mixture was quenched by addition of saturated aqueous NH₄Cl (10 mL), and extracted with EtOAc (20 mL*3). The combined organic phases were concentrated to dryness, and the residue was purified by chromatography to give compound **8a** as a white solid (5340 mg, yield: 72%). ESI-MS (m/z): 371.1 [M+H]⁺.

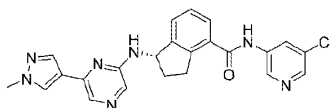
Step 2: The solution of **8a** (5340 mg, 14.4 mmol), **1b** (4494 mg, 21.6 mmol), Pd(dppf)Cl₂·CH₂Cl₂ (1167 mg, 1.44 mmol) and K₃PO₄ (9170 mg, 43.2 mmol) in mixed solvent of EtOH (30 mL) and water (15 mL) was heated to 80 °C and reacted for 3h under N₂ atmosphere. TLC analysis showed the reaction was complete. The separated organic phase was purified by chromatography to give compound **8b** as a red brown solid (5098 mg, yield: 85%). ESI-MS (m/z): 417.2 [M+H]⁺.

Step 3: To a solution of **8b** (2082 mg, 5.0 mmol) in a mixed solvent of DMSO (8.0 mL) and glycol (2 mL) was added 50% aqueous NaOH (2 mL). The resulting mixture was heated to 100 °C and stirred for 12 h. TLC analysis showed the reaction was complete. After cooling to room temperature, conc. HCl (3 mL) was added. The resulting precipitate was collected by filtration, and dried to give compound **8c** as light green solid (1459 mg, yield: 87%). ESI-MS (m/z): 336.1 [M+H]⁺.

Step 4: To a solution of **8c** (34 mg, 0.10 mmol) and compound **8d** (16 mg, 0.12 mmol) in CH₂Cl₂ (0.5 mL) was added EDCI (29 mg, 0.12 mmol) and DMAP (3 mg, 0.02 mmol) in turn. The resulting mixture was stirred at room temperature for 5 h. TLC analysis showed the reaction was complete. The mixture was wash with 5% aqueous NaHCO₃, the separated organic phase was purified by silica gel chromatography to give compound **8** as a white solid (30 mg, yield: 72%). ESI-MS (m/z): 465.2 [M+H]⁺. ¹H NMR (62 MHz, acetone-*d*₆) δ 9.76 (s, 1H), 8.15 (s, 1H), 8.09 (s, 1H), 8.05-7.87 (m, 2H), 7.84 (s, 1H), 7.78 (d, *J*=1.6Hz, 1H), 7.73-7.49 (m, 2H), 7.48-7.36 (m, 2H), 7.35-6.95 (m, 2H), 6.60 (d, *J*=7.9Hz, 1H), 5.74 (t, *J*=7.6Hz, 1H), 3.96 (d, *J*=4.9Hz, 6H), 3.66-3.05 (m, 2H), 2.85-2.23 (m, 1H), 1.93-1.00 (m, 1H).

Example 9

(S)-N-(5-chloropyridin-3-yl)-1-((6-(1-methyl-1H-pyrazol-4-yl)pyrazin-2-yl)amino)-2,3-dihydro-1H-indene-4-carboxamide

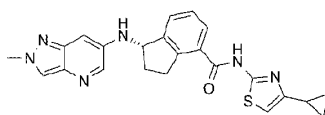


The preparation of compound **9** refers to the synthesis of compound **8** in example 8.

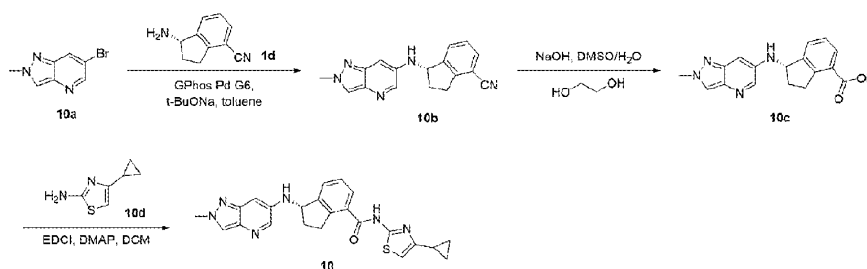
ESI-MS (m/z): 446.1 [M+H]⁺. ¹H NMR (62 MHz, acetone-*d*₆) δ 9.78 (s, 1H), 8.85 (d, *J*=2.2Hz, 2H), 8.53 (t, *J*=2.2Hz, 1H), 8.33 (d, *J*=2.2Hz, 1H), 8.14 (s, 1H), 8.08 (s, 1H), 7.96 (s, 1H), 7.83 (s, 1H), 7.79-7.57 (m, 2H), 7.56-7.07 (m, 2H), 7.45-7.11 (m, 1H), 6.57 (d, *J*=7.8Hz, 1H), 5.71 (t, *J*=11.0Hz, 1H), 3.93 (s, 3H), 3.57-3.00 (m, 2H), 2.75-2.22 (m, 1H), 1.88-0.72 (m, 1H).

Example 10

(S)-N-(4-cyclopropylthiazol-2-yl)-1-((2-methyl-2H-pyrazolo[4,3-b]pyridin-6-yl)amino)-2,3-dihydro-1H-indene-4-carboxamide



5 Compound **10** was prepared by the following steps:



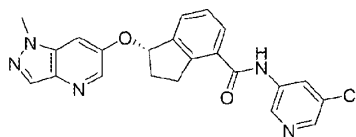
Step 1: To a 100 mL two-necked round bottom flask was added compound **10a** (2000 mg, 9.43 mmol), compound **1d** (1788 mg, 11.30 mmol), toluene (19 mL), sodium *t*-butoxide (1267 mg, 13.22 mmol) and GPhos Pd G6 (888 mg, 0.94 mmol) in turn. The resulting mixture was stirred well and degassed with N₂ for three times, then heated to 90°C and stirred for 3 h. The reaction was complete detected by TLC. After natural cooling to 30°C, the reaction mixture was partitioned between EtOAc (100 mL) and H₂O (100 mL). The aqueous layer was discarded and the separated organic layer was dried over anhydrous sodium sulfate, and concentrated to dryness under reduced pressure. The residue was purified on an ISCO chromatography to afford compound **10b** (2.5 g, yield: 92%). ESI-MS(M/S): 290.1 [M+H]⁺.

Step 2: To a 100 mL flask was added compound **10b** (2.5 g, 8.65 mmol), DMSO (12 mL), ethylene glycol (12 mL), H₂O (12 mL) and NaOH (6.0 g, 150.00 mmol) sequentially. The resulting mixture was heated to 110 °C and stirred for 3 h. The reaction was complete detected by TLC. After natural cooling to about 30°C, the pH was adjusted to 6-7 with aqueous HCl (3 M). A large amount of solid was precipitated, and the suspension was stirred for a while, then filtered under reduced pressure. The filter cake was washed with H₂O (6 mL × 2) and dried in vacuo at about 50°C to give compound **10c** (2.4 g, yield: 89.9%). ESI-MS(M/S): 307.1 [M-H]⁻.

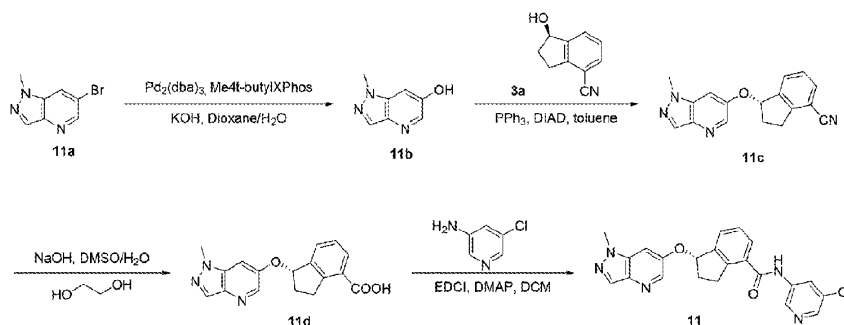
Step 3: To a 4 mL vial was added compound **10c** (61 mg, 0.2 mmol), compound **10d** (56 mg, 0.4 mmol), DMAP (3 mg, 0.02 mmol), CH₂Cl₂ (0.5 mL) and EDCI (77 mg, 0.4 mmol) sequentially. The resulting mixture was stirred at 25°C for 3 h. The reaction was complete detected by TLC. The reaction mixture was concentrated to dryness under reduced pressure and the residue was purified on an ISCO chromatography to afford compound **10** (57.7 mg, yield: 67.0%). ESI-MS(M/S): 431.2 [M+H]⁺. ¹H NMR (62 MHz, acetone-*d*₆) δ 12.42 (s, 1H), 8.31 (s, 1H), 8.16 (d, *J* = 2.4 Hz, 1H), 7.82 – 7.70 (m, 1H), 7.67 – 7.13 (m, 2H), 6.89 – 6.83 (m, 2H), 6.40 (d, *J* = 8.2 Hz, 1H), 5.11 – 4.99 (m, 1H), 4.05 (s, 3H), 3.25 – 3.05 (m, 2H), 2.12 – 1.91 (m, 2H), 0.92 – 0.78 (m, 4H).

Example 11

(S)-N-(5-chloropyridin-3-yl)-1-((1-methyl-1H-pyrazolo[4,3-b]pyridin-6-yl)oxy)-2,3-dihydro-1H-indene-4-carboxamide



Compound **11** was prepared by the following steps:



Step 1: To a 250 mL three-necked flask was added compound **11a** (2360 mg, 10.0 mmol), 1,4-dioxane (27 mL), H₂O (9 mL), KOH (1680 mg, 30.0 mmol), Me₄t-butylXPhos (674 mg, 1.4 mmol), and Pd₂(dba)₃ (229 mg, 0.25 mmol) sequentially. The mixture was stirred well and degassed with N₂ for three times, then heated to 90 °C and stirred for 3 h. The reaction was complete detected by TLC. After natural cooling to about 30 °C, the separated upper organic phase was discarded, and the aqueous phase was diluted with water (9 mL) and washed with CH₂Cl₂ (20 mL), then adjusted to pH = 8-9 with concentrated HCl, further adjusted to 6-7 with 3 N aqueous HCl. A large amount of solid was precipitated and the suspension was stirred for a while, then filtered under reduced pressure. The filter cake was washed with water (9 mL) and dried in vacuo at about 50 °C to give compound **11b** (1495 mg, yield: 99.5%). ESI-MS(M/S): 150.1 [M+H]⁺.

Step 2: To a 100 mL two-necked flask was added compound **11b** (1490 mg, 10.0 mmol), compound **3a** (1749 mg, 11.0 mmol), PPh₃ (3935 mg, 15.0 mmol), and toluene (20 mL) sequentially. The mixture was stirred well and degassed with N₂ for three times, then cooled to -15--20 °C. DIAD (3034 mg, 15.0 mmol) was then added dropwise to the above mixture and the reaction temperature was kept below -10 °C during the dropwise addition. The resulting mixture was stirred at -15--10 °C for 3 h. The reaction was complete detected by TLC. The reaction mixture was concentrated to dryness to obtain thick liquid which was redissolved in EtOH (6 mL). After being stirred for a moment, a large amount of solid was precipitated. The resulting suspension was continued to stir at 25 °C for 2 h, then filtered. The filter cake was washed with EtOH (3 mL) and dried in vacuo at about 50 °C to give compound **11c** (1970 mg, yield: 67.9%). ESI-MS(M/S): 291.1 [M+H]⁺.

Step 3: To a 100 mL flask was sequentially added compound **11c** (1.67 g, 5.7 mmol), DMSO (8.5 mL), ethylene glycol (8.5 mL), H₂O (8.5 mL), and NaOH (4.0 g, 100.0 mmol) in turn. The resulting mixture was heated to 110 °C and stirred for about 3 h. The reaction was complete detected by TLC. After natural cooling to 30 °C, the pH was adjusted to 6-7 with 3 N aqueous HCl. A large amount of solid was precipitated. The suspension was stirred for a moment, then filtered under reduced pressure. The filter cake was washed with H₂O (4.5 mL x2) and dried in vacuo at about 50 °C to give compound **11d** (1.67 g, yield: 95.1%). ESI-MS(M/S): 308.1 [M-H]⁻.

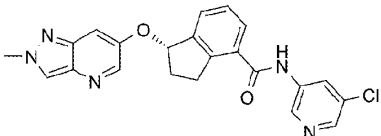
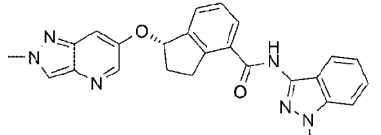
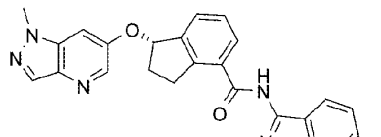
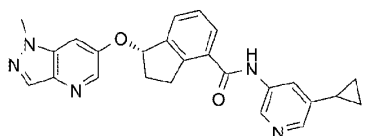
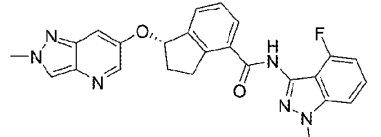
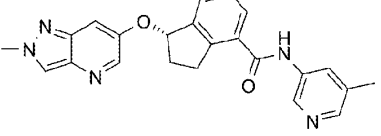
Step 4: To a 4 mL vial was added compound **11d** (31 mg, 0.1 mmol), 3-amino-5-chloropyridine (25 mg, 0.2 mmol), DMAP (3 mg, 0.02 mmol), CH₂Cl₂ (0.5 mL) and EDCI (38 mg, 0.2 mmol) sequentially. The resulting mixture was stirred at 25 °C for 3 h. The reaction was complete detected by TLC. The reaction mixture was concentrated to dryness under reduced pressure and the residue was purified on an ISCO chromatography to afford compound **11** (26 mg, yield: 61.0%). ESI-MS(M/S): 420.1 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.71 (s, 1H), 8.85 (s, 1H), 8.44–8.37 (m, 2H), 8.24 (s, 1H), 8.16 (s, 1H), 7.90 (s, 1H), 7.79 (d, *J* = 7.7 Hz, 1H), 7.71 (d, *J* = 7.5 Hz, 1H), 7.47 (t, *J* = 7.6 Hz, 1H), 6.11–6.05 (m,

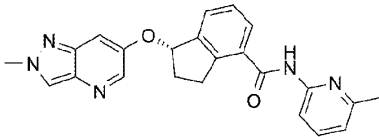
1H), 4.07 (s, 3H), 3.41–3.35 (m, 1H), 3.25–3.12 (m, 1H), 2.76–2.64 (m, 1H), 2.24–2.10 (m, 1H).

Example 12

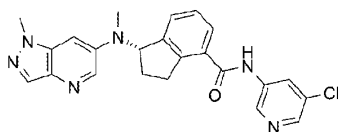
The preparation of compounds **12a–12g** refers to the synthesis of compound **11** in example 11.

Table 3

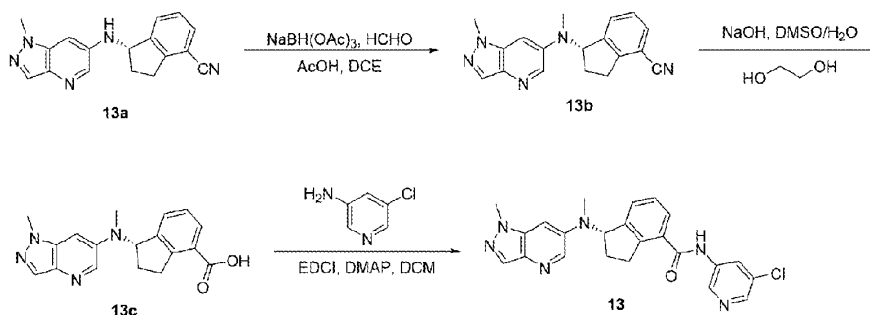
Cpds	Structure	MS [M+1] ⁺	¹ H NMR
12a		420.1	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.71 (s, 1H), 8.85 (s, 1H), 8.55 (s, 1H), 8.40 (s, 1H), 8.38 (s, 1H), 8.21 (s, 1H), 7.78 (d, <i>J</i> = 7.6 Hz, 1H), 7.72–7.62 (m, 2H), 7.46 (t, <i>J</i> = 7.6 Hz, 1H), 6.04–6.01 (m, 1H), 4.16 (s, 3H), 3.34–3.27 (m, 1H), 3.20–3.13 (m, 1H), 2.69–2.60 (m, 1H), 2.17–2.10 (m, 1H).
12b		439.2	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.72 (s, 1H), 8.55 (s, 1H), 8.22 (s, 1H), 7.84 (d, <i>J</i> = 7.6 Hz, 1H), 7.78 (d, <i>J</i> = 8.2 Hz, 1H), 7.70–7.60 (m, 3H), 7.47–7.37 (m, 2H), 7.13 (t, <i>J</i> = 7.5 Hz, 1H), 6.11–5.98 (m, 1H), 4.16 (s, 3H), 4.01 (s, 3H), 3.33–3.27 (m, 1H), 3.27–3.17 (m, 1H), 2.73–2.61 (m, 1H), 2.20–2.08 (m, 1H).
12c		439.2	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.74 (s, 1H), 8.25 (s, 1H), 8.16 (s, 1H), 7.91 (s, 1H), 7.86 (d, <i>J</i> = 7.6 Hz, 1H), 7.79 (d, <i>J</i> = 8.2 Hz, 1H), 7.68 (d, <i>J</i> = 7.5 Hz, 1H), 7.62 (d, <i>J</i> = 8.5 Hz, 1H), 7.49–7.38 (m, 2H), 7.13 (t, <i>J</i> = 7.5 Hz, 1H), 6.13–6.04 (m, 1H), 4.08 (s, 3H), 4.02 (s, 3H), 3.45–3.34 (m, 1H), 3.30–3.18 (m, 1H), 2.79–2.65 (m, 1H), 2.22–2.10 (m, 1H).
12d		426.2	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.40 (s, 1H), 8.70 (s, 1H), 8.24 (s, 1H), 8.19–8.13 (m, 2H), 7.89 (s, 1H), 7.84 (s, 1H), 7.76 (d, <i>J</i> = 7.6 Hz, 1H), 7.68 (d, <i>J</i> = 7.5 Hz, 1H), 7.45 (t, <i>J</i> = 7.6 Hz, 1H), 6.13–6.03 (m, 1H), 4.07 (s, 3H), 3.34–3.28 (m, 1H), 3.23–3.09 (m, 1H), 2.77–2.63 (m, 1H), 2.21–2.08 (m, 1H), 2.04–1.92 (m, 1H), 1.07–0.97 (m, 2H), 0.79–0.65 (m, 2H).
12e		457.2	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.54 (s, 1H), 8.55 (s, 1H), 8.22 (s, 1H), 7.83–7.78 (m, 1H), 7.68–7.66 (m, 2H), 7.51–7.39 (m, 3H), 6.92–6.84 (m, 1H), 6.05–6.02 (m, 1H), 4.16 (s, 3H), 4.04 (s, 3H), 3.35–3.30 (m, 1H), 3.24–3.17 (m, 1H), 2.71–2.51 (m, 1H), 2.17–2.09 (m, 1H).
12f		400.2	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.45 (s, 1H), 8.70 (s, 1H), 8.55 (s, 1H), 8.21 (s, 1H), 8.17 (s, 1H), 8.07 (s, 1H), 7.75 (d, <i>J</i> = 7.6 Hz, 1H), 7.67–7.65 (m, 2H), 7.44 (t, <i>J</i> = 7.6 Hz, 1H), 6.04–6.01 (m, 1H), 4.16 (s, 3H), 3.33–3.28 (m, 1H), 3.21–3.08 (m, 1H), 2.69–2.60 (m, 1H), 2.32 (s, 3H), 2.15–2.11 (m, 1H).

12g		400.2 ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.68 (s, 1H), 8.55 (s, 1H), 8.21 (s, 1H), 8.05 – 7.99 (m, 1H), 7.78 – 7.69 (m, 2H), 7.68 – 7.60 (m, 2H), 7.37 (t, <i>J</i> = 7.5 Hz, 1H), 7.03 (d, <i>J</i> = 7.4 Hz, 1H), 6.04 – 6.00 (m, 1H), 4.16 (s, 3H), 3.32 – 3.24 (m, 1H), 3.22 – 3.14 (m, 1H), 2.68 – 2.60 (m, 1H), 2.44 (s, 3H), 2.15 – 2.08 (m, 1H).
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Example 13

(S)-N-(5-chloropyridin-3-yl)-1-(methyl(1-methyl-1H-pyrazolo[4,3-b]pyridin-6-yl)amino)-2,3-dihydro-1H-inden-5-4-carboxamide

5 Compound 13 was prepared by the following steps:



Step 1: To a 250 mL flask was sequentially added compound **13a** (The preparation refers to the synthesis of compound **10c** in example 10.) (2.3 g, 7.96 mmol), 40% formalin (720 mg, 24.0 mmol), 1,2-dichloroethane (80 mL), and AcOH (8 mL), followed by addition of sodium triacetoxyborohydride (5.1 g, 24.0 mmol) in portions with stirring at 25°C. The resulting mixture was stirred at 25°C for 1 h. TLC showed the starting material was not consumed. 40% formalin (72 mg, 2.4 mmol) and sodium triacetoxyborohydride (510 mg, 2.4 mmol) were added sequentially and the mixture was continued to stir at 25°C for 1 h. TLC showed the starting material remained unconsumed. 40% formalin (360 mg, 12.0 mmol), sodium triacetoxyborohydride (2.5 g, 12.0 mmol) and 1,2-dichloroethane (20 mL) was added again and the mixture was stirred at 25°C for another 1 h. The reaction was complete detected by TLC. The reaction mixture was diluted with CH₂Cl₂ (100 mL), sequentially washed with 5% aq. NaOH (100 mL x3) and water (100 mL) and dried over anhydrous Na₂SO₄. After concentration to dryness under reduced pressure, the residue was purified on an ISCO chromatography to afford compound **13b** (1.7 g, yield: 70.4%). ESI-MS(M/S): 304.2 [M+H]⁺.

Step 2: To a 100 mL flask was sequentially added compound **13b** (1.3 g, 4.3 mmol), DMSO (8 mL), ethylene glycol (4 mL), H₂O (4 mL) and NaOH (2.0 g, 50.0 mmol). The resulting mixture was heated to 110 °C and stirred for about 3 h. The reaction was complete detected by TLC. After natural cooling to 30°C, the pH was adjusted to 6-7 with 3 M aqueous HCl. A large amount of solid was precipitated and the suspension was stirred for a moment, then filtered. The filter cake was washed with H₂O (4 mL x 2) and dried in vacuo at about 50 °C to give compound **13c** (1.1 g, yield: 81.1%). ESI-MS(M/S): 321.1 [M-H]⁻.

Step 3: To a 4 mL vial was sequentially added compound **13c** (64 mg, 0.2 mmol), 3-amino-5-chloropyridine (50 mg, 0.4 mmol), DMAP (3 mg, 0.02 mmol), CH₂Cl₂ (0.5 mL) and EDCI (77 mg, 0.4 mmol). The resulting mixture was stirred

at 25°C for 3 h. The reaction was complete detected by TLC. The mixture was concentrated to dryness under reduced pressure and the residue was purified on an ISCO chromatography to afford compound **13** (53 mg, yield: 62.1%). ESI-MS(M/S): 433.2 [M+H]⁺. ¹H NMR (62 MHz, acetone-*d*₆) δ 9.82 (s, 1H), 8.84 (d, *J* = 2.2 Hz, 1H), 8.55 – 8.48 (m, 2H), 8.33 (d, *J* = 2.3 Hz, 1H), 7.92 (s, 1H), 7.85 – 7.62 (m, 1H), 7.55 – 7.19 (m, 3H), 5.96 – 5.62 (m, 1H), 3.98 (s, 3H), 3.40 – 3.12 (m, 2H), 2.78 (s, 3H), 2.63 – 1.98 (m, 2H).

Example 14

The preparation of compounds **14a-14d** refer to the synthesis of compound **13** in example 13.

Table 4

Cpds	Structure	MS [M+1] ⁺	¹ H NMR
14a		433.2	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.68 (s, 1H), 8.84 (s, 1H), 8.64 (s, 1H), 8.43 (s, 1H), 8.40 – 8.38 (m, 2H), 7.69 (d, <i>J</i> = 7.2 Hz, 1H), 7.43 – 7.36 (m, 2H), 7.14 (s, 1H), 5.75 – 5.71 (m, 1H), 4.11 (s, 3H), 3.30 – 3.19 (m, 1H), 3.13 – 3.05 (m, 1H), 2.63 (s, 3H), 2.47 – 2.34 (m, 1H), 2.05 – 1.99 (m, 1H).
14b		452.2	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.69 (s, 1H), 8.65 (s, 1H), 8.43 (s, 1H), 7.79 – 7.74 (m, 2H), 7.62 (d, <i>J</i> = 8.5 Hz, 1H), 7.46 – 7.29 (m, 3H), 7.19 – 7.07 (m, 2H), 5.77 – 5.51 (m, 1H), 4.11 (s, 3H), 4.01 (s, 3H), 3.33 – 3.27 (m, 1H), 3.14 – 3.08 (m, 1H), 2.64 (s, 3H), 2.44 – 2.37 (m, 1H), 2.08 – 1.99 (m, 1H).
14c		474.2	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 12.39 (s, 1H), 8.63 (s, 1H), 8.43 (s, 1H), 7.82 – 7.70 (m, 1H), 7.41 – 7.29 (m, 2H), 7.14 (s, 1H), 5.77 – 7.72 (m, 1H), 4.11 (s, 3H), 3.53 (s, 2H), 3.31 – 3.25 (m, 1H), 3.15 – 3.04 (m, 1H), 2.74 – 2.68 (m, 4H), 2.61 (s, 3H), 2.39 (s, 3H), 2.39 – 2.31 (m, 1H), 2.07 – 1.97 (m, 1H).
14d		474.2	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 12.42 (s, 1H), 8.54 (s, 1H), 8.03 (s, 1H), 7.81 – 7.77 (m, 1H), 7.38 – 7.33 (m, 3H), 5.84 – 5.80 (m, 1H), 3.98 (s, 3H), 3.55 (s, 2H), 3.31 – 3.28 (m, 1H), 3.15 – 3.07 (m, 1H), 2.74 – 2.71 (m, 4H), 2.69 (s, 3H), 2.49 – 2.43 (m, 1H), 2.40 (s, 3H), 2.05 – 1.98 (m, 1H).

10 In vitro inhibitory activity of kinases

CSF-1R, PDGFR-α, KDR (VEGFR2) and KIT in vitro Kinase Activity Assay:

1. Materials and Instruments

ENVISION (Perkinelmer, 2104)

White 384-well MicroPlate (Cat#264706, Nunc)

15 HTRF kinEASE TK kit main reagents (Cat #62TKOPEC, Cisbio)

TK-biotin substrate

Streptavidin-XL665
 TK Antibody-Cryptate
 5× Enzymatic buffer (5×KB)
 Staphylococcal enterotoxin B (SEB)
 5 HTRF Detection buffer
 CSF-1R (Cat # PV3249, Invitrogen)
 PDGFR- α (Cat # PV3811, Invitrogen)
 KDR (Cat # PV3660, Invitrogen)
 KIT (Cat #08-156, Cerna)
 10 ATP 10 mM (Cat #PV3227, Invitrogen)
 DTT 1 M (Cat #D5545, Sigma)
 MgCl₂ 1 M (Cat #M8266, Sigma)
 MnCl₂ 1 M (Cat #244589, Sigma)

2. Experimental Procedure

2.1 Reagent Preparation

Table 5 Composition and Concentration Table of Each Component in the Kinase Reaction System

	Final Concentration in the Kinase Reaction Step (10 μ L)				Final Concentration in the Total Reaction (20 μ L)	
	Enzyme Concentration	ATP	TK-substrate	Enzyme Reaction Time	Streptavidin-XL665	TK Antibody-Cryptate
CSF-1R	10 ng/well	5 μ M	1 μ M	60 min	125 nM	1:100 dilution
PDGFR- α	0.8 ng/well	5 μ M	1 μ M	40 min	125 nM	1:100 dilution
KDR	0.1 ng/well	0.2 μ M	0.2 μ M	30 min	25 nM	1:100 dilution
KIT	2 ng/well	20 μ M	1 μ M	30 min	125 nM	1:100 dilution

Table 6 Components of 1 mL 1× Kinase Buffer (μ L)

Kinase	5×Enzyme buffer	MgCl ₂	MnCl ₂	DTT	SEB	ddH ₂ O
CSF-1R	200	5	1	1	20	773
PDGFR- α	200	5	1	1	8	785
KDR	200 μ L	5	1	1	10	783
KIT	200 μ L	5	1	0	10	784

5×Substrate-TK and ATP Working Solution

The specific concentrations of Substrate-TK and ATP are shown in Table 5.

Dilute Substrate-TK and ATP to 5× of the reaction concentration using 1× Kinase Buffer.

5× Enzyme Working Solution

The concentrations of the four kinases are shown in Table 5. Prepare the 5× enzyme working solution using 1× Kinase Buffer.

4× Sa-XL665 Working Solution

The concentration of Sa-XL665 in the reaction is shown in Table 5. Prepare the 4× Sa-XL665 working solution using Detection Buffer.

4× TK-Ab-Cryptate Working Solution

Dilute TK-Ab-Cryptate 100 times using Detection Buffer to prepare the working solution.

2.2 Experimental Procedure

After all reagents were prepared according to the methods described above, except for the enzyme, they were equilibrated to room temperature before starting the sample addition.

a) First, 2.5% DMSO solutions were prepared separately using the pre-prepared 1× kinase buffer (DMSO

concentrations that were too high could affect the reaction, so the final concentration of DMSO was controlled at 1%). Then, the corresponding 2.5% DMSO solution for the enzyme was used to dilute the test compounds. Compounds were screened with two concentrations of 100 nM and 10 nM. Except for the control wells, 4 μ L of the diluted test compound solution was added to the reaction wells, and 4 μ L of the pre-prepared 2.5% DMSO solution was added to the control wells.

5 b) 2 μ L of the pre-prepared TK-biotin substrate solution at the corresponding concentration for the kinase was added to all reaction wells.

c) 2 μ L of the pre-prepared enzyme solution at the corresponding concentration was added to all reaction wells except the negative control wells. For the negative control wells, 2 μ L of 1 $\times$ kinase buffer corresponding to the enzyme was added to make up the volume. The plate was sealed with sealing film, mixed gently, and incubated at room temperature for 10 min to allow the compounds to fully interact with the enzyme.

d) 2 μ L of the ATP solution at the corresponding concentration for the enzyme was added to all reaction wells to initiate the kinase reaction. ATP concentrations and reaction times for enzyme screening are shown in Table 5

10 e) Five minutes before the end of the kinase reaction, the detection solution was prepared. The detection buffer from the kit was used to prepare detection solutions for Streptavidin-XL665 and TK antibody europium cryptate (1:100) at the appropriate concentrations for the two enzymes.

f) After the kinase reaction was completed, 5 μ L of the diluted Streptavidin-XL665 solution was added to all reaction wells. After mixing, the diluted TK antibody europium cryptate detection solution was immediately added.

g) The plate was sealed and mixed, incubated at room temperature for 1 hour, and the fluorescence signal was detected using the ENVISION (PerkinElmer) instrument (excitation at 320 nm, emission at 665 nm and 615 nm). The inhibition rate for each well was calculated based on the full-activity control wells and background signal wells, and the average value of the replicates was taken.

Experimental Procedure as follows:

2.3 Data Analysis

Table 7

Kinase Assay		Control	
Enzyme Step (10 μ L)	Sample	Negative	Positive
Compound	4 μ L	4 μ L 2.5% DMSO/kinase buffer	4 μ L 2.5% DMSO/kinase buffer
TK Substrate-biotin	2 μ L	2 μ L	2 μ L
Kinase	2 μ L	2 μ L Kinase buffer	2 μ L
Seal the plate, incubate at room temperature for 10 min			
ATP	2 μ L	2 μ L	2 μ L
Seal the plate, the incubation times of the kinases at room temperature are shown in Table 5			
Detection Step (10 μ L)			
Sa-XL665	5 μ L	5 μ L	5 μ L
TK Ab-Cryptate	5 μ L	5 μ L	5 μ L
Seal the plate, incubate at room temperature for 1 hour			
Excitation at 320 nm, emission at 665 nm and 615 nm			

Emission Ratio (ER)= 665 nm Emission signal/ 615 nm Emission signal

Inhibition rate = (ER_{positive}-ER_{sample})/(ER_{positive}-ER_{negative})*100%

DDR1 in vitro Kinase Activity Assay:

1. Materials and Instruments

ENVISION (PerkinElmer, 2104)

White 384-well MicroPlate(Cat#264706, Nunc)

DDR1 (Cat # PV6047, Invitrogen)

5X Kinase Buffer A (Cat # PV3189, Invitrogen)

Kinase Tracer 178 (Cat # PV5593, Invitrogen)

LanthaScreen® Eu-anti-GST Antibody(Cat # PV5594, Invitrogen)

2. Experimental Procedure

Table 8 Composition and Concentration Table of Each Component in the Kinase Reaction System

	Final Concentration in the Kinase Reaction Step (15 μ L)			
	Enzyme Concentration	LanthaScreen® Eu-anti-GST Antibody	Kinase Tracer 178	Enzyme Reaction Time
DDR1	5nM	2nM	10nM	60min

2.1 Reagent Preparation

The compounds to be tested were tested at two concentrations of 100 nM and 10 nM.

Kinase/Antibody Mixtures Preparation: Dilute Kinase/Antibody Mixtures with 1 $\times$ Kinase Buffer to form 3X working solutions with final concentrations of 5 nM kinase and 2 nM Eu-Anti-GST Antibody, respectively.

5 Kinase Tracer 178 Preparation: Dilute Kinase Tracer 178 with 1 X Kinase Buffer to make a 3 $\times$ working solution with a final concentration of 10nM.

2.2 Experimental Procedure

After all reagents were prepared according to the methods described above, except for the enzyme, they were equilibrated to room temperature before starting the sample addition.

10 a) First, 3% DMSO solutions were prepared separately using the pre-prepared 1 $\times$ kinase buffer (DMSO concentrations that were too high could affect the reaction, so the final concentration of DMSO was controlled at 1%). Then, the corresponding 3% DMSO solution for the enzyme was used to dilute the test compounds. Compounds were screened with two concentrations of 100 nM and 10 nM. Except for the control wells, 5 μ L of the diluted test compound solution was added to the reaction wells, and 5 μ L of the pre-prepared 3% DMSO solution was added to the control wells.

15 b) 5 μ L of the pre-prepared Kinase/Antibody mixtures was added to all reaction wells except the negative control wells. For the negative control wells, 5 μ L of 1 $\times$ kinase buffer corresponding to the enzyme was added to make up the volume.

c) 5 μ L of the pre-prepared Kinase Tracer 178 solution was added to all reaction wells.

20 d) The plate was sealed and mixed, incubated at room temperature for 1 hour, and the fluorescence signal was detected using the ENVISION (PerkinElmer) instrument (excitation at 340 nm, emission at 665 nm and 615 nm). The inhibition rate for each well was calculated based on the full-activity control wells and background signal wells, and the average value of the replicates was taken.

Experimental Procedure as follows:

Table 9

	Kinase Assay	Control	
Enzyme Step (10 μ L)	Sample	Negative	Positive
Compounds	5 μ L	5 μ L 3%DMSO/kinase buffer	5 μ L 3%DMSO/kinase buffer
Kinase/Antibody Mixtures	5 μ L	5 μ L Kinase buffer	5 μ L
Kinase Tracer 178	5 μ L	5 μ L	5 μ L
Seal the plate, incubate at room temperature for 1 h			
Excitation at 340 nm, emission at 665 nm and 615 nm			

2.3 Data Analysis

Emission Ratio (ER)= 665 nm Emission signal/ 615 nm Emission signal

Inhibition rate = (ER_{positive}-ER_{sample})/(ER_{positive}-ER_{negative})*100%

Table 10

Cpds	CSF-1R	KIT	PDGFR α	VEGFR2	DDR1
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	100 nM	10 nM	100 nM	10 nM	100 nM	10 nM	100 nM	10 nM	100 nM	10 nM
1	95.30	74.64	97.31	61.85	98.69	72.66	99.55	83.05	104.48	93.18
2b	100.99	40.99	83.29	11.26	99.42	67.57	58.10	26.79	85.57	37.91
2d	96.99	89.70	94.73	58.71	101.05	90.97	101.68	88.43	103.36	94.66
2e	95.85	42.13	95.04	60.10	100.33	75.48	82.55	29.21	61.41	32.35
3	97.35	57.56	63.71	21.79	74.34	13.85	99.10	52.95	89.85	81.44
4	100.34	79.36	48.61	22.06	86.22	40.45	100.67	92.26	101.49	69.39
5a	95.44	27.53	53.93	12.07	67.19	14.54	88.93	22.65	53.51	23.12
5b	96.55	71.95	4.90	-3.90	68.27	3.75	84.36	24.61	97.10	65.26
5c	100.70	80.06	62.80	14.53	79.71	23.52	101.65	91.65	96.70	86.05
6	100.33	48.61	15.27	2.36	38.74	7.69	62.63	22.35	88.02	29.66
8	95.80	75.22	100.54	89.58	98.93	94.69	100.02	88.87	101.36	92.12
10	96.27	72.55	94.91	35.27	94.78	29.31	94.91	60.25	99.90	57.22
11	97.32	71.87	54.00	12.61	53.13	13.71	98.27	85.38	103.13	72.50
12a	99.08	78.24	79.09	39.60	89.26	37.84	101.56	96.46	99.63	94.20
12b	103.36	104.80	95.85	91.15	97.18	97.55	95.55	99.14	98.46	97.96
12c	99.14	65.13	92.44	55.99	101.90	88.53	101.01	89.91	93.59	63.97
12g	94.12	15.25	31.42	5.64	85.72	31.96	97.01	93.16	69.74	21.15
14a	96.45	73.65	47.80	21.96	51.18	19.01	91.87	42.99	83.91	14.72
14b	98.35	24.27	104.52	69.91	96.92	69.11	100.43	94.98	97.87	75.13

M-NFS-60 cell in vitro assay procedure

1. Experimental Purpose

To determine the inhibitory activity of compounds on M-NFS-60 cells.

2. Materials

- 5
- M-NFS-60 cell line (ATCC, Cat. No.: CRL-1838)
RPMI-1640 medium (Gibco, domestic subpackage, Cat. No.: C11875500BT)
Recombinant Mouse CSF1/M-CSF (Sino Biological Inc., Cat. No.: 51112-MNAH)
PAN/Serum (BioTECH, Cat. No.: P30-2602)
Trypsin/0.05% Trypsin-EDTA (Gibco,Cat. No.: 25300-062)
- 10
- 0.4% Trypan Blue (Sigma,Cat. No.: T8154-20ml)
Penicillin-Streptomycin (Hyclone, Cat. No.: SV30010)
DMSO(Solarbio, Cat. No.: D8371)
PBS (Solarbio, Cat. No.: P1020)
CCK (AbMole BioScience, Cat. No.: M4839-500Tests)

3. Instruments

Table 11

Instruments	Manufacturer
Biological safety cabinet	ThermoFisherScientific
371 direct-heated CO ₂ incubator	ThermoFisherScientific

Electronic digital display constant temperature water bath	Changzhou Guohua Electric Appliance Co., Ltd.
Inverted microscope	OLYMPUS
Hemocytometer	Shanghai Qiujiang Biochemical Reagent and Instrument Co., Ltd.
Shaker	IKA
4°C refrigerator	ThermoFisherScientific
-20°C refrigerator	Haier
L-500 centrifuge	Hunan Xiangyi Centrifuge
-80°C ultra-low temperature refrigerator	ThermoFisherScientific
Liquid nitrogen storage tank	ThermoFisherScientific
Full-wavelength reader/microplate reader	ThermoFisherScientific

4. Experimental Purpose

4.1 Experimental preparation

1) M-CSF factor stock solution: take 10 μ g of powdered m-CSF factor, add 0.4ml of saline, formulate 25 μ g/ml and store at -80°C.

5 2) M-CSF factor (25ng/ml) medium:
1640(Gibco)+10%PAN+100 $\times$ Penicillin-Streptomycin+100 $\times$ M-CSF stock solution

3) Complete medium:
1640(Gibco)+10%PAN+100 $\times$ Penicillin-Streptomycin

10 4)Compound preparation: 2-3 mg of the compound was added to DMSO to formulate a 30 mM stock solution, -80 °C refrigerator storage

4.2 Experimental procedure

1) Cell resuscitation: the frozen cells in the cryovial were thawed rapidly by shaking in a 37°C water bath, then 4 mL of medium was added. After mixing evenly, they were centrifuged at 125 $\times$ g for 5 min, and the supernatant was discarded. The cells were resuspended and transferred to the culture flasks, and were cultured in a 5% CO₂ fully saturated humidity incubator.

2) Cell passaging: M-NFS-60 cells are semi-suspension cells, which were collected directly in a 15 mL centrifuge tube, centrifuged at 125 $\times$ g for 5 min, and the supernatant was discarded. The cells were resuspended and passaged into new culture flasks at a ratio of 1:5 to 1:10.

20 3) After the newly resuscitated cells were passaged 1-2 times for cell stabilization, compound inhibition assays were started when the cells were in the logarithmic growth phase.

(a) Cell collection and counting: the same as the cell passaging step, centrifuge in two tubes, one tube with M-CSF factor medium to resuspend the cells, the other tube with complete medium to resuspend the cells. Take 10 μ L of cell suspension in each tube, and count the cells by Tapan blue staining.

25 (b) Dilute the cell solution according to the concentration of inoculated cells respectively, the concentration of M-NFS-60 cells inoculated with factor was 5.56 $\times$ 10⁴ cells/mL, and the concentration of inoculated without factor was 5 $\times$ 10⁴ cells/mL.

(c) Seed plate: 384 well plate inoculated with M-NFS-60 cells, 36 μ L/well, triplicate wells, the number of inoculated cells was equivalent to 2000 cells/well, set with blank control, factor free negative control, normal control, DMSO control and experimental wells. The cells were placed in a 5% CO₂ fully saturated humidity incubator for 4 h.

30 (d) Sampling compounds: 96 well plates were used for compound preparation. The compound solution prepared in advance was diluted to corresponding gradient concentration with DMSO. An appropriate amount of the diluted solution in the previous step was added to an equal volume of factor containing medium. The 96 well plates were centrifuged at 1000

rpm for 5 min, which played the role of defoaming and spinning down droplets and condensation. Remove the 384 well plate from the incubator, add the diluted compound solution into each well sequentially, 4 μ L/well; DMSO wells and normal wells were added with corresponding factor containing medium, 4 μ L/ well. Then it was put into CO₂ incubator for 48 h.

- 5 (e) After incubation for 48 h, CCK was added to each well, 4 μ L, and the plates were placed in the incubator for another 2 h, and then the OD (optical density) value at 450 nm was measured by microplate reader.

The experimental flow chart is as follows:

Table 12

Groups Step	Blank control	Negative control	Normal and DMSO control	Test
Cell suspension	40 μ L factor containing medium	40 μ L resuspended cell solution containing complete medium	36 μ L resuspended cell solution containing complete medium	36 μ L resuspended cell solution containing complete medium
Compound solution	/	/	4 μ L factor containing medium	4 μ L Compound solution of corresponding concentration
CCK	4 μ L	4 μ L	4 μ L	4 μ L

4.3 Data Analysis

- 10 Inhibition rate % = 1 - (OD value of the test well - OD value of the blank control) / (OD value of the DMSO well - OD value of the blank control) $\times$ 100%.

The IC₅₀ values for each test compound were fitted using professional graphing and analysis software.

Table 13

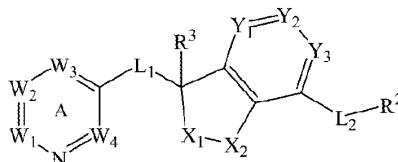
Cpds	M-NFS-60 cell assay IC ₅₀ (nM)	Cpds	M-NFS-60 cell assay IC ₅₀ (nM)
1	****	2a	****
2b	****	2c	****
2d	****	2e	****
3	****	4	****
5a	****	5b	*
5c	****	5d	****
5e	****	6	***
7	****	8	****
9	****	10	****
11	****	12a	****
12b	****	12c	****
12d	****	12e	****
12f	****	12g	****
13	****	14a	****
14b	****	14c	****

14d	***		
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Note: ****: ≤ 50 nM; ***: > 50 nM, < 200 nM; **: ≥ 200 nM, ≤ 500 nM; *: > 500 nM

What is claimed is:

1.A compound having the structure of formula (I) or a pharmaceutically acceptable salt, stereoisomers, isotopic isomers thereof,



Formula (I)

- Wherein, X_1 represents O, S, NR^a , $(CR^L R^L)_m$, $C(O)$;
 Wherein, X_2 represents O, S, NR^a , $(CR^T R^T)_n$, $C(O)$;
 wherein, W_1 independently represents CR^{W1} or N;
 wherein, W_2 independently represents CR^{W2} or N;
 wherein, W_3 independently represents CR^{W3} or N;
 wherein, W_4 independently represents CR^{W4} or N;
 wherein, Y_1 independently represents CR^{Y1} or N;
 wherein, Y_2 independently represents CR^{Y2} or N;
 wherein, Y_3 independently represents CR^{Y3} or N;
 wherein, each R^{W1} , R^{W2} , R^{W3} , R^{W4} , R^{Y1} , R^{Y2} , R^{Y3} independently represents hydrogen, deuterium, C_1 - C_6 alkyl, deuterated C_1 - C_6 alkyl, halogen, nitro, $-OR^a$, $-SR^a$, $-P(O)R^a R^b$, $-CN$, $-S(O)_2 R^a$, $-S(O)R^a$, $-SF_5$, $-NR^a R^b$, $-CR^a R^b NR^a R^b$, $-NR^a COR^b$, $-CONR^a R^b$, C_1 - C_6 haloalkyl, C_1 - C_6 haloalkoxy, C_1 - C_6 haloalkylthio, hydroxy (C_1 - C_6 alkyl); or each R^{W1} , R^{W2} , R^{W3} , R^{W4} , R^{Y1} , R^{Y2} , R^{Y3} independently represents C_3 - C_{10} cycloalkyl, C_6 - C_{10} cycloalkenyl, 4-10 membered heterocycloalkyl, 6-10 membered heterocycloalkenyl, C_6 - C_{10} aryl, 5-10 membered heteroaryl, which are substituted by 0-4 substituents selected from deuterium, halogen, C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, C_3 - C_6 cycloalkyl, C_3 - C_6 heterocycloalkyl, $-OR^a$, oxo, hydroxy (C_1 - C_6 alkyl), $NR^a R^b$, $-CR^a R^b NR^a R^b$, $-CN$, C_1 - C_6 haloalkyl, C_1 - C_6 haloalkoxy, $-SO_3 R^a$, $-SR^a$, $-SF_5$, $-C(O)R^a$, $-C(O)OR^a$, $-OC(O)R^a$, $-OC(O)NR^a R^b$, $-NR^a COR^b$ and $-CONR^a R^b$;
 or W_1 and W_2 together with the atom which they are attached to form a 5-6 membered saturated or unsaturated ring fused to ring A, and the said ring may optionally contain 0, 1, 2 or 3 heteroatoms selected from O, N, and S;
 wherein, L_1 represents absent, $-(CR^a R^b)_o$, $-CR^a R^b O$, $-OCR^a R^b$, $-O$, $-S$, $-S(O)_2$, $-C(O)$, $-NR^a$, $-S(O)_2 NR^a$, $-OC(O)$, $-C(O)O$, $-NR^a S(O)_2$, $-CR^a R^b NR^a$, or $-NR^a CR^a R^b$;
 wherein, L_2 represents $-C(O)NR^a$ or $-NR^a C(O)$;
 wherein, R^2 represents 5-10 membered heteroaryl, which are substituted by 0-4 substituents selected from deuterium, halogen, C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, C_3 - C_6 cycloalkyl, $-OR^a$, oxo, hydroxy (C_1 - C_6 alkyl), $-NR^a R^b$, $-CR^a R^b NR^a R^b$, $-CN$, C_1 - C_6 haloalkyl, C_1 - C_6 haloalkoxy, $-SO_3 R^a$, $-SR^a$, $-S(O)_2 R^a$, $-S(O)R^a$, $-SF_5$, $-C(O)R^a$, $-C(O)OR^a$, $-OC(O)R^a$, $-OC(O)NR^a R^b$, $-NR^a COR^b$ and $-CONR^a R^b$;
 wherein, R^3 represents hydrogen, halogen, C_1 - C_6 haloalkyl, C_1 - C_6 alkyl, or hydroxy;
 or R^3 and W_3 together with the atom which they are attached to form a 5-7 membered saturated or unsaturated ring fused to ring A, and the said ring may optionally contain 0, 1 or 2 heteroatoms selected from O, N, and S; and further, the said ring may optionally be substituted by 0, 1 or 2 substituents selected from deuterium, halogen, C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, C_3 - C_6 cycloalkyl, $-OR^a$, oxo, hydroxy (C_1 - C_6 alkyl), $NR^a R^b$, $-CN$, C_1 - C_6 haloalkyl, C_1 - C_6 haloalkoxy, $-SO_3 R^a$, $-SR^a$, $-SF_5$, $-C(O)R^a$, $-C(O)OR^a$, $-OC(O)R^a$, $-OC(O)NR^a R^b$, $-NR^a COR^b$ and $-CONR^a R^b$;
 wherein, each R^a and R^b independently represents hydrogen, deuterium, halogen, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, hydroxy (C_1 - C_6 alkyl), C_3 - C_{10} cycloalkyl, C_6 - C_{10} aryl, 5-10 membered heteroaryl; or R^a and R^b together with the carbon atom which they are attached to form a 3-6 membered ring, and the said ring may optionally contain 0, 1 or 2 heteroatoms selected from O, N, and S; and further, the said ring may optionally be substituted by halogen, hydroxy and C_1 - C_6 alkyl;
 wherein, each R^L and R^L independently represents hydrogen, deuterium, halogen, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, hydroxy (C_1 - C_6 alkyl), C_3 - C_{10} cycloalkyl; or R^L and R^L together with the carbon atom which they are attached to form a 3-6 membered ring, and the said ring may optionally contain 0, 1 or 2 heteroatoms selected from O, N, and S; and further, the said ring may optionally be substituted by halogen, hydroxy and C_1 - C_6 alkyl;
 wherein, each R^T and R^T independently represents hydrogen, deuterium, halogen, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, hydroxy (C_1 - C_6 alkyl), C_3 - C_{10} cycloalkyl; or R^T and R^T together with the carbon atom which they are attached to form a 3-6 membered ring, and the said ring may optionally contain 0, 1 or 2 heteroatoms selected from O, N, and S; and further, the said ring may optionally be substituted by halogen, hydroxy and C_1 - C_6 alkyl;
 wherein, o, m, n represents the integer of 1, 2 or 3.
- 2.The compound according to claim 1 or a pharmaceutically acceptable salt, stereoisomers, isotopic isomers thereof, wherein W_1 represents CH , CCH_3 , CF , CCF_3 , $CCHF_2$, CCH_2F , $C(OCH_3)$, CNH_2 , $CNHCH_3$, $CN(CH_3)_2$, CCH_2NHCH_3 , $CCH_2N(CH_3)_2$, $C(CN)$ or N.
- 3.The compound according to claim 1 or a pharmaceutically acceptable salt, stereoisomers, isotopic isomers thereof, wherein W_3 represents CH , CCH_3 , CF , CCF_3 , $CCHF_2$, CCH_2F , $C(OCH_3)$, CNH_2 , $CNHCH_3$, $C(CN)$ or N.

4. The compound according to claim 1 or a pharmaceutically acceptable salt, stereoisomers, isotopic isomers thereof, wherein W_4 represents CH, CCH₃, CF, CCF₃, CCHF₂, CCH₂F, C(OCH₃), CNH₂, CNHCH₃, C(CN) or N.

5. The compound according to claim 1 or a pharmaceutically acceptable salt, stereoisomers, isotopic isomers thereof, wherein Y_1 represents CH, CCH₃, CF, CCl, CCF₃, CCHF₂, CCH₂F, C(OCH₃), C(CN) or N.

6. The compound according to claim 1 or a pharmaceutically acceptable salt, stereoisomers, isotopic isomers thereof, wherein Y_2 represents CH, CCH₃, CF, CCl, CCF₃, CCHF₂, CCH₂F, C(OCH₃), C(CN) or N.

7. The compound according to claim 1 or a pharmaceutically acceptable salt, stereoisomers, isotopic isomers thereof, wherein Y_3 represents CH, CCH₃, CF, CCl, CCF₃, CCHF₂, CCH₂F, C(OCH₃), C(CN) or N.

8. The compound according to claim 1 or a pharmaceutically acceptable salt, stereoisomers, isotopic isomers thereof, wherein X_1 represents -CH₂-, -CF₂-, -CHF-, -O-, -S-, -CHOH-, -CH₂CH₂- or -C(CH₃)₂-.

9. The compound according to claim 1 or a pharmaceutically acceptable salt, stereoisomers, isotopic isomers thereof, wherein X_2 represents -CH₂-, -CF₂-, -CHF-, -O-, -S-, -CHOH-, -CH₂CH₂- or -C(CH₃)₂-.

10. The compound according to claim 1 or a pharmaceutically acceptable salt, stereoisomers, isotopic isomers thereof, wherein L_1 represents -CH₂-, -CHF-, -CF₂-, -O-, -NH- or -NCH₃-.

11. The compound according to claim 1 or a pharmaceutically acceptable salt, stereoisomers, isotopic isomers thereof, wherein R^{W2} represents C₁-C₆ alkyl, halogen, -OH, O(C₁-C₆ alkyl); or R^{W2} represents C₃-C₁₀ cycloalkyl, C₆-C₁₀ cycloalkenyl, 4-10 membered heterocycloalkyl, 6-10 membered heterocycloalkenyl, C₆-C₁₀ aryl, 5-10 membered heteroaryl, which are substituted by 0-4 substituents selected from deuterium, halogen, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₆ cycloalkyl, C₃-C₆ heterocycloalkyl, -OR^a, oxo, hydroxy (C₁-C₆ alkyl), NR^aR^b, -CR^aR^bNR^aR^b, -CN, C₁-C₆ haloalkyl, C₁-C₆ haloalkoxy, -SO₃R^a, -SR^a, -SF₅, -C(O)R^a, -C(O)OR^a, -OC(O)R^a, -OC(O)NR^aR^b, -NR^aCOR^b and -CONR^aR^b.

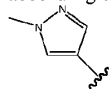
12. The compound according to claim 1 or a pharmaceutically acceptable salt, stereoisomers, isotopic isomers thereof, wherein R^{W2} represents C₃-C₁₀ cycloalkyl, C₆-C₁₀ cycloalkenyl, 4-10 membered heterocycloalkyl, 6-10 membered heterocycloalkenyl, C₆-C₁₀ aryl, 5-10 membered heteroaryl, which are substituted by 0-4 substituents selected from deuterium, halogen, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₆ cycloalkyl, C₃-C₆ heterocycloalkyl, -OR^a, oxo, hydroxy (C₁-C₆ alkyl), -CN, C₁-C₆ haloalkyl, C₁-C₆ haloalkoxy, -SO₃R^a, -SR^a, -SF₅, -C(O)R^a, -C(O)OR^a, -OC(O)R^a, -OC(O)NR^aR^b, -NR^aCOR^b and -CONR^aR^b.

13. The compound according to claim 1 or a pharmaceutically acceptable salt, stereoisomers, isotopic isomers thereof, wherein R^{W2} represents C₃-C₁₀ cycloalkyl, C₆-C₁₀ cycloalkenyl, 4-10 membered heterocycloalkyl, 6-10 membered heterocycloalkenyl, C₆-C₁₀ aryl, 5-10 membered heteroaryl, which are substituted by 0-4 substituents selected from deuterium, halogen, C₁-C₆ alkyl, -OR^a, hydroxy (C₁-C₆ alkyl), -CN and C₁-C₆ haloalkyl.

14. The compound according to claim 1 or a pharmaceutically acceptable salt, stereoisomers, isotopic isomers thereof, wherein R^{W2} represents 5-10 membered heteroaryl, which is substituted by 0-4 substituents selected from deuterium, halogen, C₁-C₆ alkyl, -OR^a, hydroxy (C₁-C₆ alkyl), -CN and C₁-C₆ haloalkyl.

15. The compound according to claim 1 or a pharmaceutically acceptable salt, stereoisomers, isotopic isomers thereof, wherein R^{W2} represents pyrazolyl, triazolyl, oxazolyl, isoxazolyl, thiazolyl, imidazolyl, which are substituted by 0-4 substituents selected from deuterium, halogen, C₁-C₆ alkyl, -OR^a, hydroxy (C₁-C₆ alkyl), -CN and C₁-C₆ haloalkyl.

16. The compound according to claim 1 or a pharmaceutically acceptable salt, stereoisomers, isotopic isomers thereof,

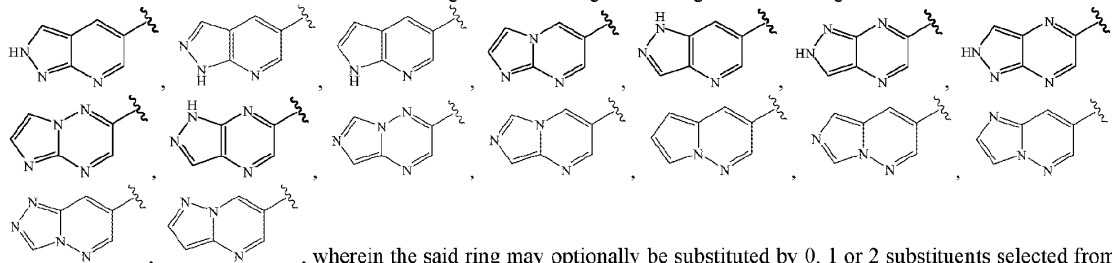


wherein R^{W2} represents

17. The compound according to claim 1 or a pharmaceutically acceptable salt, stereoisomers, isotopic isomers thereof, wherein R^2 represents 5-10 membered heteroaryl, which is substituted by 0-4 substituents selected from deuterium, halogen, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₆ cycloalkyl, -OR^a, oxo, hydroxy (C₁-C₆ alkyl), -NR^aR^b, -CR^aR^bNR^aR^b, -CN, C₁-C₆ haloalkyl, C₁-C₆ haloalkoxy, or -C(O)R^a.

18. The compound according to claim 1 or a pharmaceutically acceptable salt, stereoisomers, isotopic isomers thereof,

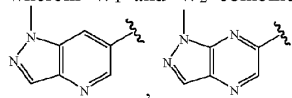
wherein W_1 and W_2 combine to form a ring fused to ring A having the following structure:



wherein the said ring may optionally be substituted by 0, 1 or 2 substituents selected from deuterium, halogen, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₆ cycloalkyl, -OR^a, oxo, hydroxy (C₁-C₆ alkyl), NR^aR^b, -CR^aR^bNR^aR^b, -CN, C₁-C₆ haloalkyl, C₁-C₆ haloalkoxy, -SO₃R^a, -SR^a, -SF₅, -C(O)R^a, -C(O)OR^a, -OC(O)R^a, -OC(O)NR^aR^b, -NR^aCOR^b and -CONR^aR^b; and wherein the wavy line indicates the point of attachment with L_1 .

19. The compound according to claim 1 or a pharmaceutically acceptable salt, stereoisomers, isotopic isomers thereof,

wherein W₁ and W₂ combine to form a ring fused to ring A having the following structure:

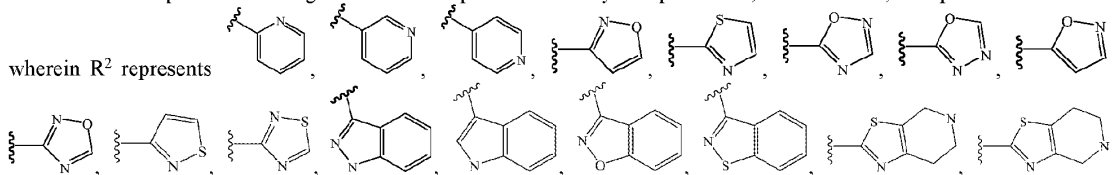


, wherein the wavy line indicates the point of attachment with L₁.

20. The compound according to claim 1 or a pharmaceutically acceptable salt, stereoisomers, isotopic isomers thereof, wherein R² represents pyridinyl, indazolyl, indolyl, thiazolyl, isothiazolyl, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, pyridazinyl, piperazinyl, pyrazinyl, benzothienyl, 1,2-benzisoxazolyl, benzo[d]isothiazolyl, which are substituted by 0-4 substituents selected from deuterium, halogen, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₆ cycloalkyl, -OR^a, oxo, hydroxy (C₁-C₆ alkyl), -NR^aR^b, -CR^aR^bNR^aR^b, -CN, C₁-C₆ haloalkyl, and C₁-C₆ alkoxy.

21. The compound according to claim 1 or a pharmaceutically acceptable salt, stereoisomers, isotopic isomers thereof,

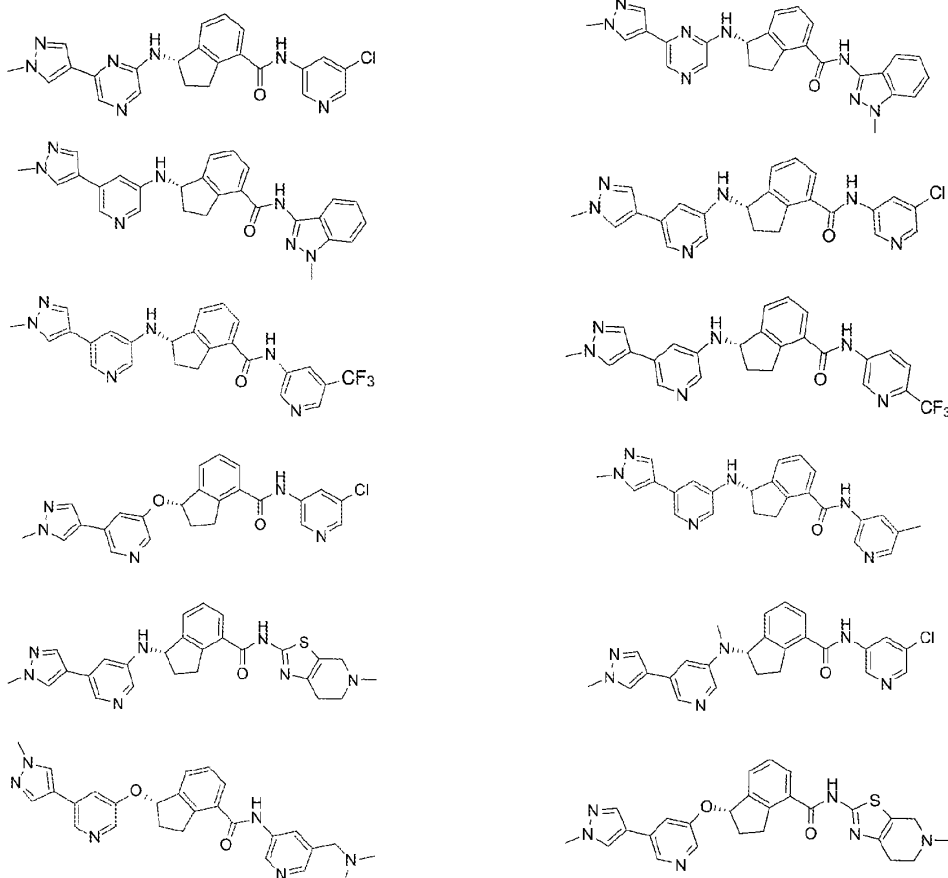
wherein R² represents

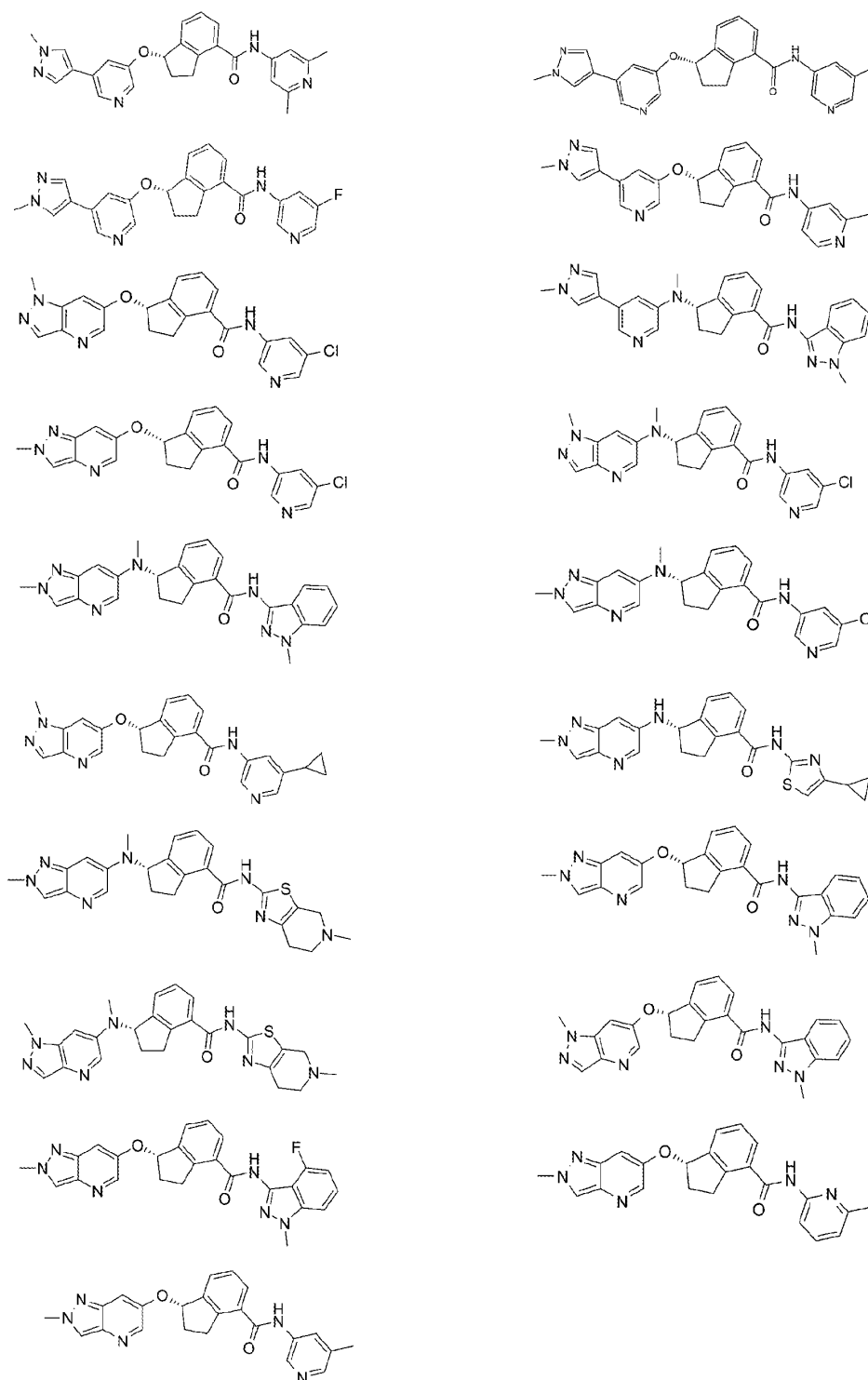


which are substituted by 0-4 substituents selected from deuterium, halogen, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₆ cycloalkyl, -OR^a, oxo, hydroxy (C₁-C₆ alkyl), -NR^aR^b, -CR^aR^bNR^aR^b, -CN, C₁-C₆ haloalkyl, and C₁-C₆ alkoxy.

22. The compound according to claim 1 or a pharmaceutically acceptable salt, stereoisomers, isotopic isomers thereof, wherein R³ represents hydrogen or CH₃.

23. A compounds having the following structures:





24. A pharmaceutical composition, wherein the composition comprises: anyone of the compound as described in claims 1-23, a pharmaceutically acceptable salt, stereoisomers, isotopic isomers thereof; and a pharmaceutically acceptable excipients.