Abstract: Disclosed are compounds of Formula (I), methods of using the compounds as immunomodulators, and pharmaceutical compositions comprising such compounds. The compounds are useful in treating, preventing or ameliorating diseases or disorders such as cancer or infections.
BICYCLIC HETEROAROMATIC COMPOUNDS AS IMMUNOMODULATORS

FIELD OF THE INVENTION

The present application is concerned with pharmaceutically active compounds. The disclosure provides compounds as well as their compositions and methods of use. The compounds modulate PD-1/PD-L1 protein/protein interaction and are useful in the treatment of various diseases including infectious diseases and cancer.

BACKGROUND OF THE INVENTION

The immune system plays an important role in controlling and eradicating diseases such as cancer. However, cancer cells often develop strategies to evade or to suppress the immune system in order to favor their growth. One such mechanism is altering the expression of co-stimulatory and co-inhibitory molecules expressed on immune cells (Postow et al, J. Clinical Oncology 2015, 1-9). Blocking the signaling of an inhibitory immune checkpoint, such as PD-1, has proven to be a promising and effective treatment modality.

Programmed cell death-1 (PD-1), also known as CD279, is a cell surface receptor expressed on activated T cells, natural killer T cells, B cells, and macrophages (Greenwald et al, Annu. Rev. Immunol 2005, 23:515-548; Okazaki and Honjo, Trends Immunol 2006, (4): 195-201). It functions as an intrinsic negative feedback system to prevent the activation of T-cells, which in turn reduces autoimmunity and promotes self-tolerance. In addition, PD-1 is also known to play a critical role in the suppression of antigen-specific T cell response in diseases like cancer and viral infection (Sharpe et al, Nat Immunol 2007 8, 239-245; Postow et al, J. Clinical Oncol 2015, 1-9).

The structure of PD-1 consists of an extracellular immunoglobulin variable-like domain followed by a transmembrane region and an intracellular domain (Parry et al, Mol Cell Biol 2005, 9543-9553). The intracellular domain contains two phosphorylation sites located in an immunoreceptor tyrosine-based inhibitory motif and an immunoreceptor tyrosine-based switch motif, which suggests that PD-1 negatively regulates T cell receptor-mediated signals. PD-1 has two ligands, PD-L1 and PD-L2 (Parry et al, Mol Cell Biol 2005, 9543-9553; Latchman et al, Nat Immunol 2001, 2, 261-268), and they differ in their expression patterns. PD-L1 protein is upregulated on macrophages and dendritic cells in response to lipopolysaccharide and GM-CSF treatment, and on T cells and B cells upon T cell receptor and B cell receptor signaling. PD-L1 is also highly expressed on almost all

Activation of the PD-1 signaling axis also attenuates PKC-θ activation loop phosphorylation, which is necessary for the activation of NF-κB and API pathways, and for cytokine production such as IL-2, IFN-γ and TNF (Sharpe et al, Nat Immunol 2007, 8, 239-245; Carter et al, Eur J Immunol 2002, 32(3):634-43; Freeman et al, J Exp Med 2000, 192(7): 1027-34).

Several lines of evidence from preclinical animal studies indicate that PD-1 and its ligands negatively regulate immune responses. PD-1-deficient mice have been shown to develop lupus-like glomerulonephritis and dilated cardiomyopathy (Nishimura et al, Immunity 1999, 11:141-151; Nishimura et al, Science 2001, 291:319-322). Using an LCMV model of chronic infection, it has been shown that PD-L1/PD-L1 interaction inhibits activation, expansion and acquisition of effector functions of virus-specific CD8 T cells (Barber et al, Nature 2006, 439, 682-7). Together, these data support the development of a therapeutic approach to block the PD-1-mediated inhibitory signaling cascade in order to augment or "rescue" T cell response. Accordingly, there is a need for new compounds that block PD-L1/PD-L1 protein/protein interaction.

**SUMMARY**

The present disclosure provides, inter alia, a compound of Formula (I):

![Chemical Structure](image)
or a pharmaceutically acceptable salt or a stereoisomer thereof, wherein constituent variables are defined herein.

The present disclosure further provides a pharmaceutical composition comprising a compound disclosed herein, or a pharmaceutically acceptable salt or a stereoisomer thereof, and one or more pharmaceutically acceptable excipient or carrier.

The present disclosure further provides methods of inhibiting PD-1/PD-L1 interaction, said method comprising administering to a patient a compound disclosed herein, or a pharmaceutically acceptable salt or a stereoisomer thereof.

The present disclosure further provides methods of treating a disease or disorder associated with inhibition of PD-1/PD-L1 interaction, said method comprising administering to a patient in need thereof a therapeutically effective amount of a compound of disclosed herein, or a pharmaceutically acceptable salt or a stereoisomer thereof.

The present disclosure further provides methods of enhancing, stimulating and/or increasing the immune response in a patient, said method comprising administering to the patient in need thereof a therapeutically effective amount of a compound disclosed herein, or a pharmaceutically acceptable salt or a stereoisomer thereof.

**DETAILED DESCRIPTION**

1. **Compounds**

   This disclosure provides, *inter alia*, a compound of Formula (I):

   ![Chemical Structure](image)

   (I)

   or a pharmaceutically acceptable salt or a stereoisomer thereof, wherein:

   - ring A is 5- to 14-membered heteroaryl, 4- to 14-membered heterocycloalkyl, C₆₋₁₀ aryl or C₃₋₁₄ cycloalkyl, wherein the 5- to 14-membered heteroaryl and 4- to 14-membered heterocycloalkyl each has 1-4 heteroatoms as ring members selected from B, P, N, O and S,

   - wherein the P, N or S atom as ring members is optionally oxidized and one or more carbon atoms as ring members are each optionally replaced by a carbonyl group; and wherein ring A is optionally substituted with 1, 2, 3, 4 or 5 R⁶ substituents;

   - L is a bond, -C(0)NR¹³⁻, -NR¹³C(0)⁻, -C(=S)NR¹³⁻, -NR¹³C(=S)⁻, -C(=NR¹³)NR¹³⁻, -NR¹³C(=NR¹³)⁻, -C(=NOR¹³)⁻, -NR¹³C(=NOR¹³)⁻, -C(=NCN)NR¹³⁻, -NR¹³C(=NCN)⁻, O⁻,
(CR
14R
)q,-(CR
14R
)q-0-, -0 (CR
14R
)q-, -NR
13-, -(CR
14R
)q-NR
13-, -NR
13-(CR
14R
)q-, -CH=CH-, —C= C-, -SO2NR
13-, -N R
15S0
2-, -NR
15S0
2NR
13-, -N R
15C(0)0-, -OC (0 )NR
13 or-
NR
15C(0 )NR
13-; 
X is N or CR
17; 
R
3 is methyl, halo, CN or C1-4 haloalkyl; 
R
4 is C1-4 alkyl, C1-4 alkoxy, C1-4 haloalkyl, C1-4 haloalkoxy, C3-6 cycloalkyl, phenyl, 5-6 membered heteroaryl and 4-
2-10 selected membered C
COOH, substituent substituents; carbon alkyl-
NHR
heteroaryl, heterocycloalkyl, 1-4 alkynyl, C1-4 halo, C1-4 alkoxy, C1-4 alkynyl, C1-6 haloalkyl, C1-6 haloalkoxy, C1-6 cycloalkyl, 5-14 membered heteroaryl, 4-10 membered heterocycloalkyl, C6-10 aryl-C1-4 alkyl-, C3-10 cycloalkyl-C1-4 alkyl-, (5-14 membered heteroaryl)-C1-4 alkyl-, (4-10 membered heterocycloalkyl)-C1-4 alkyl-, CN, N0-2, OR
20, SR
20, NHOR
20, C(0 )R
20, C(0 )NR
20-R
20, C(0 )OR
20, C(0 )NR
20-S(0 )2R
20, OC(0 )R
20, OC(0 )NR
20-R
20, NHR
20, NR
20-R
20, NR
20-C(0 )R
20, NR
20-C(=NR
20)R
20, NR
20-C(0 )OR
20, NR
20-C(0 )NR
20-R
20, C(=NR
20)R
20, C(=NR
20)NR
20-R
20, NR
20-C(=NR
20)NR
20-R
20, NR
20-S(0 )2R
20, NR
20-S(0 )2R
20, NR
20-NR
20-R
20, wherein the C1-6 alkyl, C1-4 alkenyl, C1-4 alkynyl, C6-10 aryl, C3-10 cycloalkyl, 5-14 membered heteroaryl, 4-10 membered heterocycloalkyl, C6-10 aryl-C4 alkyl-, C3-10 cycloalkyl-
C1-4 alkyl-, (5-14 membered heteroaryl)-C4 alkyl- and (4-10 membered heterocycloalkyl)-C4 alkyl- of R6, R7, R17 and R18 are each optionally substituted with 1, 2, 3, 4 or 5 independently selected R8 substituents; 
or two R8 substituents attached to the same ring carbon atom taken together with the ring carbon atom to which they are attached form spiro C3-6 cycloalkyl or spiro 4- to 7-membered heterocycloalkyl, each of which is optionally substituted with 1, 2, or 3 independently selected R9 substituents; 
each R13 is independently H, C1-6 haloalkyl or C1-6 alkyl optionally substituted with a substituent selected from C1-4 alkyl, C1-4 alkoxy, CI-4 haloalkoxy, CN, halo, OH, -COOH, NH2, -NHCl -alkyl and -N(C1-4 alkyl)2; 
R14 and R15 are each independently selected from H, halo, CN, OH, -COOH, C1-4 alkyl, C1-4 alkoxy, -NHCl -alkyl, -N(C1-4 alkyl)2, C1-4 haloalkyl, C1-4 haloalkoxy, C1-4 cycloalkyl, phenyl, 5-6 membered heteroaryl and 4-6 membered heterocycloalkyl, wherein the C1-4 alkyl, C1-4 alkoxy, C1-4 haloalkoxy, C1-4 cycloalkyl, phenyl, 5-6 membered heteroaryl and 4-
6 membered heterocycloalkyl of R₁⁴ or R₁⁵ are each optionally substituted with 1, 2, or 3 independently selected R⁸ substituents;

or R₁⁴ and R₁⁵ taken together with the carbon atom to which they are attached form 3-, 4-, 5- or 6-membered cycloalkyl or 3-, 4-, 5- or 6-membered heterocycloalkyl, each of which is optionally substituted with 1 or 2 independently selected R⁸ substituents;

each R⁸ is independently selected from H, CN, Ci-6 alkyl, Ci-4haloalkyl, C₂-6 alkenyl, C₂-6 alkynyl, C₆-₁₀ aryl, C₃-₁₀ cycloalkyl, C₅-₁₄ membered heteroaryl, C₄-₁₄ membered heterocycloalkyl, C₆-₁₀ aryl-Ci-₄ alkyl-, C₃-₁₀ cycloalkyl-Ci-₄ alkyl-, (5-14 membered heteroaryl)-Ci-₄ alkyl-, and (4-₁₄ membered heterocycloalkyl)-Ci-₄ alkyl-, wherein the Ci-₆ alkyl, C₂-₆ alkenyl, C₂-₆ alkynyl, C₆-₁₀ aryl, C₃-₁₀ cycloalkyl, 5-₁₄ membered heteroaryl, 4-₁₄ membered heterocycloalkyl, C₆-₁₀ aryl-Ci-₄ alkyl-, C₃-₁₀ cycloalkyl-Ci-₄ alkyl-, (5-14 membered heteroaryl)-Ci-₄ alkyl- and (4-₁₄ membered heterocycloalkyl)-Ci-₄ alkyl- of R⁸ are each optionally substituted with 1, 2, 3, 4, or 5 independently selected R⁹ substituents;

each R⁹ is independently selected from Ci-6 alkyl, Ci-6haloalkyl, halo, C₆-₁₀ aryl, 5-₁₄ membered heteroaryl, C₃-₁₀ cycloalkyl, 4-₁₄ membered heterocycloalkyl, C₆-₁₀ aryl-Ci-₄ alkyl-, C₃-₁₀ cycloalkyl-Ci-₄ alkyl-, (5-14 membered heteroaryl)-Ci-₄ alkyl-, (4-₁₄ membered heterocycloalkyl)-Ci-₄ alkyl-, CN, NH₂, NHOR ᵇ, OR ᵇ, SR ᵇ, C(0)R ᵇ, C(0)NR ᵇ, C(0)OR ᵇ, C(0)NR ᵇS(0) ᵇ, ᵇ, OC(0)R ᵇ, OC(0)NR ᵇ, NHR ᵇ, N(R)²R ᵇ, N(R)²C(O)R ᵇ, N(R)²C(=NR ᵇ)R ᵇ, N(R)²C(=NC(=S)N)NR ᵇ, N(R)²C(=S)N(R)², S(R)², S(OR)², S(OR)², S(OR)², S(OR)², S(O)²N(R)²C(O)R ᵇ, N(R)²S(0)², N(R)²R ᵇ, -P(0)(OR ᵇ), -B(OH)₂, -B(OR ᵇ)₂ and S(0)²N(R)²R ᵇ, wherein the Ci-₆ alkyl, Ci-6haloalkyl, C₆-₁₀ aryl, 5-₁₄ membered heteroaryl, C₃-₁₀ cycloalkyl, 4-₁₄ membered heterocycloalkyl, C₆-₁₀ aryl-Ci-₄ alkyl-, C₃-₁₀ cycloalkyl-Ci-₄ alkyl-, (5-₁₀ membered heteroaryl)-Ci-₄ alkyl-, and (4-₁₀ membered heterocycloalkyl)-Ci-₄ alkyl-, wherein the Ci-₆ alkyl, Ci-6haloalkyl, C₂-₆ alkenyl, C₂-₆ alkynyl, C₂-₆ aryl, C₆-₁₀ aryl, C₃-₁₀ cycloalkyl, 5-₁₀ membered heteroaryl, 4-₁₀ membered heterocycloalkyl, C₂-₆ aryl-Ci-₄ alkyl-, C₃-₁₀ cycloalkyl-Ci-₄ alkyl-, (5-₁₀ membered heteroaryl)-Ci-₄ alkyl- and (4-₁₀ membered heterocycloalkyl)-Ci-₄ alkyl- of R⁹ are each optionally substituted with 1, 2 or 3 independently selected R¹₀ substituents;
each R substituent is independently selected from halo, C1-6 alkyl, C2-6 alkenyl, C2-6 alkynyl, C6-10 aryl, C3-10 cycloalkyl, 5-10 membered heteroary1, 4-10 membered heterocycloalkyl, C6-10 aryl-C1-4 alkyl-, C3-10 cycloalkyl-CiR alkyl-, (5-10 membered heteroary1)-CiR alkyl-, (4-10 membered heterocycloalkyl)-CiR alkyl-, CN, OH, NH2, NO2, NHOR, OR, SR, C(C1)R OR, C(C1)NR R OR, C(C1)NR S(0) R OR, OC(C1)R OR, C(=NR C1)R OR, C(=NR C1)NR R R OR, H, C1-4 haloalkyl, C2-6 haloalkoxy, C3-10 cycloalkyl, 5-10 membered heterocyclic, C6-10 aryl-C1-4 alkyl-, C3-10 cycloalkyl-CiR alkyl-, (5-10 membered heteroary1)-CiR alkyl-, (4-10 membered heterocycloalkyl)-CiR alkyl-, (6-10 membered heteroary1)-CiR alkyl- and (4-10 membered heterocycloalkyl)-CiR alkyl- of R are each further optionally substituted with 1, 2, or 3 independently selected R substituents;

each R is independently selected from H, C1-6 alkyl, C1-4 haloalkyl, C2-6 alkenyl, C2-6 alkynyl, C6-10 aryl, C3-10 cycloalkyl, 5-10 membered heteroary1, 4-10 membered heterocycloalkyl, C6-10 aryl-C1-4 alkyl-, C3-10 cycloalkyl-CiR alkyl-, (5-10 membered heteroary1)-CiR alkyl- and (4-10 membered heterocycloalkyl)-CiR alkyl- of R are each optionally substituted with 1, 2, 3, or 4 independently selected R substituents;

each R is independently selected from C1-4 alkyl, C1-4 haloalkyl, C2-6 alkenyl, C2-6 alkynyl, C6-10 aryl, C3-10 cycloalkyl, 5-10 membered heteroary1, 4-10 membered heterocycloalkyl, C6-10 aryl-C1-4 alkyl-, C3-10 cycloalkyl-CiR alkyl-, (5-10 membered heteroary1)-CiR alkyl- and (4-10 membered heterocycloalkyl)-CiR alkyl- of R are each optionally substituted with 1, 2, 3, or 5 independently selected R substituents;

each R is independently selected from C1-4 alkyl, C1-4 haloalkyl, C2-6 alkenyl, C2-6 alkynyl, C6-10 aryl, C3-10 cycloalkyl, 5-10 membered heteroary1, 4-10 membered heterocycloalkyl, C6-10 aryl-C1-4 alkyl-, C3-10 cycloalkyl-CiR alkyl-, (5-10 membered heteroary1)-CiR alkyl- and (4-10 membered heterocycloalkyl)-CiR alkyl- of R are each optionally substituted with 1, 2, 3, or 4 independently selected R substituents;
each \( R^i \) is independently selected from \( \text{Ci-4 alkyl, Ci-4haloalkyl, C2-6 alkenyl, C2-6 alkynyl, C6-10 aryl, C3-10 cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C6-10 aryl-Ci-4 alkyl-, C3-10 cycloalkyl-Ci-4 alkyl-, (5-10 membered heteroaryl)-Ci-4 alkyl-, (4-10 membered heterocycloalkyl)-Ci-4 alkyl-, halo, CN, NHOR, OR, SR, C(O)R, C(O)NR, NR, S, C(=CN)NR, S(O)R, S(O)2NR, NR0S(O)2NR, NR0S(O)2NR0, -P(O)R, NR, C(=NR)NR, R, S(O)2NR, (R)NR, R, \( \text{Ci-4 haloalkyl, C2-6 alkenyl, C2-6 alkynyl, C6-10 aryl, C3-10 cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C6-10 aryl-Ci-4 alkyl-, C3-10 cycloalkyl-Ci-4 alkyl-, (5-10 membered heteroaryl)-Ci-4 alkyl-, and (4-10 membered heterocycloalkyl)-Ci-4 alkyl- of \( R^8 \) are each optionally substituted with 1, 2 or 3 independently selected \( R^4 \) substituents;}

each \( R^6 \) is independently selected from \( \text{H, Ci-6 alkyl, Ci-4haloalkyl, C2-6 alkenyl, C2-6 alkynyl, C6-10 aryl, C3-10 cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C6-10 aryl-Ci-4 alkyl-, C3-10 cycloalkyl-Ci-4 alkyl-, (5-10 membered heteroaryl)-Ci-4 alkyl-, and (4-10 membered heterocycloalkyl)-Ci-4 alkyl-, wherein the Ci-6 alkyl, C2-6 alkenyl, C2-6 alkynyl, C6-10 aryl, C3-10 cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C6-10 aryl-Ci-4 alkyl-, C3-10 cycloalkyl-Ci-4 alkyl-, (5-10 membered heteroaryl)-Ci-4 alkyl- and (4-10 membered heterocycloalkyl)-Ci-4 alkyl- of \( R^8 \) are each optionally substituted with 1, 2, or 3 independently selected \( R^4 \) substituents;}

each \( R^8 \) is independently selected from \( \text{Ci-6 alkyl, Ci-6haloalkyl, C2-6 alkenyl, C2-6 alkynyl, C6-10 aryl, C3-10 cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C6-10 aryl-Ci-4 alkyl-, C3-10 cycloalkyl-Ci-4 alkyl-, (5-10 membered heteroaryl)-Ci-4 alkyl-, (4-10 membered heterocycloalkyl)-Ci-4 alkyl-, halo, CN, NHOR, OR, SR, C(O)R, C(O)NR, NR, S, C(=CN)NR, S(O)R, S(O)2NR, NR0S(O)2NR, NR0S(O)2NR0, -P(O)R, NR, C(=NR)NR, R, S(O)2NR, (R)NR, R, \( \text{Ci-6 haloalkyl, C2-6 alkenyl, C2-6 alkynyl, C6-10 aryl, C3-10 cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C6-10 aryl-Ci-4 alkyl-, C3-10 cycloalkyl-Ci-4 alkyl-, (5-10 membered heteroaryl)-Ci-4 alkyl- and (4-10 membered heterocycloalkyl)-Ci-4 alkyl- of \( R^8 \) is optionally substituted with 1, 2 or 3 independently selected \( R^4 \) substituents;}
or any two \( R^a \) substituents together with the boron, phosphorus or nitrogen atom to which
they are attached form a 4-, 5-, 6-, 7-, 8-, 9- or 10-membered heterocycloalkyl group optionally
substituted with 1, 2 or 3 independently selected \( R^b \) substituents;

each \( R^h \) is independently selected from \( C_1-6 \) alkyl, \( C_3-10 \) cycloalkyl, 4-7 membered
heterocycloalkyl, \( C_{6-10} \) aryl, 5-6 membered heteroaryl, \( C_{6-10} \) aryl-\( C_4 \) alkyl-, \( C_{3-10} \) cycloalkyl-\( C_4 \)
alkyl-, (5-6 membered heteroaryl)-\( C_4 \) alkyl-, (4-7 membered heterocycloalkyl)-\( C_4 \) alkyl-, \( C_6 \)
haloalkyl, \( C_i-e \) haloalkoxy, \( C_2-6 \) alkenyl, \( C_2-6 \) alkynyl, halo, \( C_{i-8} \), \( OR \), \( S \), \( NR \), \( C(=O)NR \),
\( C^NR^k, 0(0)O^k, C(O)N^R(S(O))_2^R, 0(0)^k, 0(0)N^R^k, NHR^k, NR^k, NR^kC(O)^R^k, NR^kC(=NR)^R^k,
NR^kC(=NR)^R^k, NRC(=NR)^R^k, NR^kC(=NR)^N^R^k, NR^kC(=NR)^N^R^k, S(O)^k, P(O)(O^k)(O^k),
-B(OH)_2, -B(0^k) \_2 \) and \( S(0)^k N^R^k \), wherein the \( C_i-e \) alkyl, \( C_2-6 \) alkenyl, \( C_2-6 \)
alkynyl, \( C_{3-10} \) cycloalkyl, 4-7 membered heterocycloalkyl, \( C_{6-10} \) aryl, 5-6 membered heteroaryl,
\( C_{6-10} \) aryl-\( C_4 \) alkyl-, \( C_{3-10} \) cycloalkyl-\( C_4 \) alkyl-, (5-6 membered heteroaryl)-\( C_4 \) alkyl-, (4-7
membered heterocycloalkyl)-\( C_4 \) alkyl- of \( R^h \) are each further optionally substituted by 1, 2, or 3
independently selected \( R^j \) substituents;

each \( R^j \) is independently selected from \( C_3-6 \) cycloalkyl, \( C_{6-10} \) aryl, 5 or 6-membered
heteroaryl, 4-7 membered heterocycloalkyl, \( C_{2-4} \) alkenyl, \( C_{2-4} \) alkynyl, halo, \( C_{1-4} \) alkyl, \( C_{1-4}
haloalkyl, \( C_{i-8} \) haloalkoxy, \( C_{1-8} \), \( NHOR \), \( 0 \), \( R^k \), \( SR^k \), \( C(0)OR^k \), \( C(0)NR^k \), \( C(0)OR^k \),
\( C(0)NR^kS(0)^k, OC(0)R^k, OC(0)NR^kR^k, NHR^k, NR^kR^k, NR^kC(0)R^k, NR^kC(=NR)R^k, NR^kC(=NR)R^k,
NR^kC(=NR)R^k, NRC(=NR)R^k, S(0)R^k, S(0)NR^kR^k, S(0)^kNR^kR^k, S(0)^kNR^kR^k, S(0)^kNR^kR^k,
S(0)^kNR^kR^k, S(0)^kNR^kR^k, S(0)^kNR^kR^k, S(0)^kNR^kR^k, S(0)^kNR^kR^k, -P(O)(O^k)(O^k),
-B(OH)_2, -B(0^k) \_2 \) and \( S(0)^k N^R^k \), wherein the \( C_{1-4} \) alkyl, \( C_{3-6} \) cycloalkyl, \( C_{i-8} \) aryl, 5- or 6-
membered heteroaryl, 4-7 membered heterocycloalkyl, \( C_{1-4} \) alkenyl, \( C_{1-4} \) alkynyl, \( C_{1-4} \) haloalkyl
and \( C_{i-8} \) haloalkoxy of \( R^j \) are each optionally substituted with 1, 2 or 3 independently selected \( R^g \)
substituents;

or two \( R^h \) groups attached to the same carbon atom of the 4- to 10-membered heterocycloalkyl
together with the boron, phosphorus or nitrogen atom to which they are attached form a \( C_{3-6}
\) cycloalkyl or 4- to 6-membered heterocycloalkyl having 1-2 heteroatoms as ring members
selected from \( O, N \) or \( S \);

or any two \( R^f \) substituents together with the boron, phosphorus or nitrogen atom to which
they are attached form a 4-, 5-, 6-, 7-, 8-, 9- or 10-membered heterocycloalkyl group optionally
substituted with 1, 2, or 3 independently selected \( R^h \) substituents;
or any two \( R^e \) substituents together with the boron, phosphorus or nitrogen atom to which they are attached form a 4-, 5-, 6-, 7-, 8-, 9- or 10-membered heterocycloalkyl group optionally substituted with 1, 2, or 3 independently selected \( R^k \) substituents;

or any two \( R^e \) substituents together with the boron, phosphorus or nitrogen atom to which they are attached form a 4-, 5-, 6-, 7-, 8-, 9- or 10-membered heterocycloalkyl group optionally substituted with 1, 2, or 3 independently selected \( R^k \) substituents;

or any two \( R^e \) substituents together with the boron, phosphorus or nitrogen atom to which they are attached form a 4-, 5-, 6-, 7-, 8-, 9- or 10-membered heterocycloalkyl group optionally substituted with 1, 2, or 3 independently selected \( R^k \) substituents, or 1, 2, or 3 independently selected \( R^g \) substituents;

or any two \( R^e \) substituents together with the boron, phosphorus or nitrogen atom to which they are attached form a 4-, 5-, 6-, 7-, 8-, 9- or 10-membered heterocycloalkyl group optionally substituted with 1, 2, or 3 independently selected \( R^k \) substituents;

or any two \( R^e \) substituents together with the boron, phosphorus or nitrogen atom to which they are attached form a 4-, 5-, 6-, 7-, 8-, 9- or 10-membered heterocycloalkyl group optionally substituted with 1, 2, or 3 independently selected \( R^k \) substituents;

5 or any two \( R^e \) substituents together with the boron, phosphorus or nitrogen atom to which they are attached form a 4-, 5-, 6-, 7-, 8-, 9- or 10-membered heterocycloalkyl group optionally substituted with 1, 2, or 3 independently selected \( R^k \) substituents, or 1, 2, or 3 independently selected \( R^g \) substituents;

6 each \( R^i, R^k, R^o \) or \( R^r \) is independently selected from \( \text{H, C}_1\text{-}4 \text{ alkyl, C}_3\text{-}6 \text{ cycloalkyl, C}_{6-10} \text{ aryl, 5 or 6-membered heteroaryl, 4-7 members heterocycloalkyl, C}_1\text{-}6 \text{ haloalkyl, C}_6\text{-}10 \text{ haloalkoxy, C}_2\text{-}4 \text{ alkenyl, and C}_2\text{-}4 \text{ alkynyl, wherein the C}_1\text{-}4 \text{ alkyl, C}_3\text{-}6 \text{ cycloalkyl, C}_{6-10} \text{ aryl, 5 or 6-membered heteroaryl, 4-7 members heterocycloalkyl, C}_2\text{-}4 \text{ alkenyl, and C}_2\text{-}4 \text{ alkynyl of R}_i, R^k, R^o \) or \( R^r \) are each optionally substituted with 1, 2, or 3 \( R^g \) substituents;

7 each \( R^g \) is independently selected from halo, \( \text{OH, CN, -COOH, NH}_2, \text{-NH-Ci-e alkyl, -N(Ci-6 alkyl)2, C}_{1-6} \text{ alkenyl, C}_{1-6} \text{ alkynyl, C}_{1-6} \text{ alkythio, C}_{1-6} \text{ halalkyl, C}_{1-6} \text{ halalkoxy, phenyl, 5-6 membered heteroaryl, 4-6 membered heterocycloalkyl and C}_{3-6} \text{ cycloalkyl, wherein the C}_{1-6} \text{ alkenyl, phenyl, C}_{3-6} \text{ cycloalkyl, 4-6 membered heterocycloalkyl, and 5-6 membered heteroaryl of R}_i \) are each optionally substituted with 1, 2, or 3 substituents selected from halo, \( \text{OH, CN, -COOH, NH}_2, \text{C}_1\text{-}4 \text{ alkenyl, C}_1\text{-}4 \text{ alkynyl, C}_1\text{-}4 \text{ halalkoxy, phenyl, C}_{3-10} \text{ cycloalkyl, 5-6 membered heteroaryl and 4-6 membered heterocycloalkyl};

8 the subscript \( m \) is an integer of \( 0, 1, 2 \) or \( 3 \);

9 the subscript \( n \) is an integer of \( 0, 1, 2 \) or \( 3 \);
each subscript q is independently an integer of 1, 2, 3 or 4; and
the subscript s is an integer of 1, 2, or 3.

In some embodiments, provided herein is a compound of Formula (I), or a

pharmaceutically acceptable salt or a stereoisomer thereof, wherein:

ring A is 5- to 14-membered heteroaryl, 4- to 14-membered heterocycloalkyl, C6-10 aryl
or C3-14 cycloalkyl, wherein the 5- to 14-membered heteroaryl and 4- to 14-membered
heterocycloalkyl each has 1-4 heteroatoms as ring members selected from B, P, N, O and S,
wherein the P, N or S atom as ring members is optionally oxidized and one or more carbon
atoms as ring members are each optionally replaced by a carbonyl group; and wherein ring A is
optionally substituted with 1, 2, 3, 4 or 5 R6 substituents;

L is a bond, -C(O)NR 13-, -NR13C(O)-, -C(R14R15)q-, -(CR14R15)q-0-, -0(CR14R15)q-, -
-NR13S02NR 13-, -NR13C(0)0-, -OC(0)NR 13 or -NR13C(0)NR 13-;

X is N or CR 17;

R3 is methyl, halo, CN or Ci-4-haloalkyl;

R4 is Ci-4 alkyl, Ci-4 alkoxy, Ci haloalkyl, Ci haloalkoxy, CN, halo, OH, -COOH, NH2,
-NHCl-alkyl or -N(Ci-4 alkyl)2;

R5 is Ci alkyl, Ci-4 alkoxy, Ci haloalkyl, Ci haloalkoxy, CN, halo, OH, -COOH, NH2,
-NHCl-alkyl or -N(Ci-4 alkyl)2;

R6, R7, R17 and R18 are each independently selected from H, halo, Ci-6 alkyl, Ci-6 alkenyl,
Ci-6 alkynyl, Ci-6 haloalkyl, Ci-6 haloalkoxy, Ci-6-iroyaryl, Ci-6 cycloalkyl, 5-14 membered
heteroaryl, 4-10 membered heterocycloalkyl, C6-10 aryl-Ci 4 alkyl-, C3-10 cycloalkyl-Ci 4 alkyl-,
(5-14 membered heteroaryl)-Ci-4 alkyl-, (4-10 membered heterocycloalkyl)-Ci-4 alkyl-, CN, N0 2,
OR3, SR3, NHOR3, C(0)R3, C(0)NR3R4, C(0)OR3, OC(0)R3, OC(0)NR3R4, NHR3, NR3R4,
NR3C(0)R3, NR3C(0)OR3, NR3C(0)NR3R4, C(=NR3R4)R3, C(=NR3R4)NR3R4, NR3C(=NR3R4)NR3R4,
NR3S02-R3, NR3S02-R3, S(0)R3, S(0)NR3R4, S(0)NR3R4, S(0)NR3R4, -P(O)(OR3)2, -B(OH)2,
-B(OH)2 and S(0)2NR3R4, wherein the Ci-4 alkyl, Ci-6 alkenyl, Ci-6 alkynyl, Ci-6 haloalkyl, Ci-6
cycloalkyl, 5-14 membered heteroaryl, 4-10 membered heterocycloalkyl,
Ci-6 aryl-Ci-4 alkyl-, C3-10 cycloalkyl, 5-14 membered heteroaryl, 4-10 membered heterocycloalkyl,
Ci-6 aryl-Ci-4 alkyl-, C3-10 cycloalkyl-Ci-4 alkyl-, (5-14 membered heteroaryl)-Ci-4 alkyl- and
(4-10 membered heterocycloalkyl)-Ci-4 alkyl- of R6, R7, R17 and R18 are each optionally substituted
with 1, 2, 3, 4 or 5 independently selected R8 substituents;

or two R8 substituents attached to the same ring carbon atom taken together with the ring
carbon atom to which they are attached form spiro Ci-6 cycloalkyl or spiro 4- to 7-membered

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heterocycloalkyl, each of which is optionally substituted with 1, 2, or 3 independently selected R
substituents;

each R₁ is independently H, Ci-6 haloalkyl or Ci-6 alkyl optionally substituted with a
substituent selected from Ci-4 alkyl, Ci-alkoxy, Ci-4 haloalkyl, Ci-4 haloalkoxy, CN, halo, OH, -
COOH, NH₂, -HCl-4 alkyl and -N(Cl-4 alkyl)₂;

R₁₄ and R₁₅ are each independently selected from H, halo, CN, OH, -COOH, C₁₋₄ alkyl,
Ci-4 alkoxy, -NHCl-4 alkyl, -N(Cl-4 alkyl)₂, Ci-4 haloalkyl, Ci-4 haloalkoxy, C₃₋₆ cycloalkyl,
phenyl, 5-6 membered heteroaryl and 4-6 membered heterocycloalkyl, wherein the Ci-4 alkyl, Ci-
4 alkoxy, Ci-4 haloalkyl, Ci-4 haloalkoxy, C₃₋₆ cycloalkyl, phenyl, 5-6 membered heteroaryl and 4-
6 membered heterocycloalkyl of R₁₄ or R₁₅ are each optionally substituted with 1, 2, or 3
independently selected R⁴ substituents;
or R₁₄ and R₁₅ taken together with the carbon atom to which they are attached form 3-, 4-, 5-
or 6-membered cycloalkyl or 3-, 4-, 5- or 6-membered heterocycloalkyl, each of which is
optionally substituted with 1 or 2 independently selected R⁵ substituents;
each R₆ is independently selected from H, CN, Ci-6 alkyl, C₁₋₄ haloalkyl, Ci₂₋₆ alkenyl, C₂₋₆
alkynyl, C₆₋₁₀ aryl, C₃₋₁₀ cycloalkyl, 5-14 membered heteroaryl, 4-14 membered heterocycloalkyl,
C₆₋₁₀ aryl-Ci-4 alkyl-, C₃₋₁₀ cycloalkyl-Ci-4 alkyl-, (5-14 membered heteroaryl)-Ci-4 alkyl-, and (4-
14 membered heterocycloalkyl)-Ci-4 alkyl-, wherein the Ci-6 alkyl, Ci₂₋₆ alkenyl, C₂₋₆ alkynyl,
C₆₋₁₀ aryl, C₃₋₁₀ cycloalkyl, 5-14 membered heteroaryl, 4-14 membered heterocycloalkyl, C₆₋₁₀ aryl-
Ci-4 alkyl-, C₃₋₁₀ cycloalkyl-Ci-4 alkyl-, (5-14 membered heteroaryl)-Ci-4 alkyl- and (4-14
membered heterocycloalkyl)-Ci-4 alkyl- of R₆ are each optionally substituted with 1, 2, 3, 4, or 5
independently selected R⁷ substituents;
each R₇ is independently selected from Ci-6 alkyl, Ci-6 haloalkyl, halo, C₆₋₁₀ aryl, 5-14
membered heteroaryl, C₃₋₁₀ cycloalkyl, 4-14 membered heterocycloalkyl, C₆₋₁₀ aryl-Ci-4 alkyl-
C₃₋₁₀ cycloalkyl-Ci-4 alkyl-, (5-14 membered heteroaryl)-Ci-4 alkyl-, (4-14 membered
heterocycloalkyl)-Ci-4 alkyl-, CN, NH₂, NHOR, O R, S R, C (O) R, C (O) NR, C (O) OR, O C (O) R,
O C (O) NR, O R, N H R, N R R, N R C (O) R, N R C (O) NR, N R C (O) OR, N R C (O) NR, N R C (O) OR,
N R C (O) NR, N R C (O) OR, N R C (O) NR, N R C (O) OR, S (O) R, S (O) R, S (O) S (O) R, N R S (O) R,
heteroaryl, C₃₋₁₀ cycloalkyl, 4-14 membered heterocycloalkyl, C₆₋₁₀ orioaryl-Ci-4 alkyl-, C₃₋₁₀
cycloalkyl-Ci-4 alkyl-, (5-14 membered heteroaryl)-Ci-4 alkyl-, and (4-14 membered
heterocycloalkyl)-Ci-4 alkyl- of R₇ are each optionally substituted with 1, 2, or 3 independently
selected R⁸ substituents;
each Rᵢ is independently selected from H, Ci-6 alkyl, Ci-6 haloalkyl, C₂-6 alkenyl, C₆-₁₀ aryl, C₃-₁₀ cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C₆-₁₀ aryl-Ci-4 alkyl-, C₃-₁₀ cycloalkyl-Ci-4 alkyl-, (5-10 membered heteroaryl)-Ci-4 alkyl-, and (4-10 membered heterocycloalkyl)-Ci-4 alkyl-, wherein the Ci-6 alkyl, Ci-6 haloalkyl, C₂-6 alkenyl, C₆-₁₀ aryl, C₃-₁₀ cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C₆-₁₀ aryl-Ci-4 alkyl-, C₃-₁₀ cycloalkyl-Ci-4 alkyl-, (5-10 membered heteroaryl)-Ci-4 alkyl- and (4-10 membered heterocycloalkyl)-Ci-4 alkyl- of Rᵢ are each optionally substituted with 1, 2 or 3 independently selected Rᵦ substituents; each Rᵦ substituent is independently selected from halo, Ci-6 alkyl, C₂-6 alkenyl, C₆-₁₀ aryl, C₃-₁₀ cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C₆-₁₀ aryl-Ci-4 alkyl-, C₃-₁₀ cycloalkyl-Ci-4 alkyl-, (5-10 membered heteroaryl)-Ci-4 alkyl-, (4-10 membered heterocycloalkyl)-Ci-4 alkyl-, CN, OH, NH₂, NO₂, NHOR ᵇ, OR ᵇ, SR ᵇ, C(0)R ᵇ, C(0)NR ᵇ, C(0)OR ᵇ, OC(0)R ᵇ, OC(0)NR ᵇ, C(=NR ᵇ)NR ᵇ, C(=NR ᵇ)NR ᵇ, S(0)R ᵇ, S(0)NR ᵇ, S(0)₂R ᵇ, N ᵇR S(0)₂R ᵇ, NO₂, heterocycloalkyl, membered P(0)(OR ᵇ)C(0)OR ᵇ, C(0)OR ᵇ, C(0)NR ᵇ, C(0)OR ᵇ, C(0)NR ᵇ, C(0)OR ᵇ, N ᵇR S(0)₂R ᵇ, N ᵇR S(0)₂R ᵇ, N ᵇR S(0)₂R ᵇ, N ᵇR S(0)₂R ᵇ, -P(0)(OR ᵇ)(OR ᵇ), -B(OH) ᵇ₂, -B(OH ᵇ)₂ and S(0) ᵇN ᵇR ᵇR ᵇ; wherein the Ci-6 alkyl, Ci-6 haloalkyl, Ci-6 haloalkoxy, C₂-6 alkenyl, C₂-6 alkenyl, C₆-₁₀ aryl, C₃-₁₀ cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C₆-₁₀ aryl-Ci-4 alkyl-, C₃-₁₀ cycloalkyl-Ci-4 alkyl-, (5-10 membered heteroaryl)-Ci-4 alkyl- and (4-10 membered heterocycloalkyl)-Ci-4 alkyl- of Rᵦ are each further optionally substituted with 1, 2, or 3 independently selected Rᵦ substituents; each Rᵦ is independently selected from H, Ci-6 alkyl, C₃-₄ haloalkyl, C₂-₆ alkenyl, C₆-₁₀ aryl, C₃-₁₀ cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C₆-₁₀ aryl-Ci-₄ alkyl-, C₃-₁₀ cycloalkyl-Ci-₄ alkyl-, (5-10 membered heteroaryl)-Ci-₄ alkyl-, and (4-10 membered heterocycloalkyl)-Ci-₄ alkyl-, wherein the Ci-6 alkyl, C₂-6 alkenyl, C₆-₁₀ aryl, C₃-₁₀ cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C₆-₁₀ aryl-Ci-₄ alkyl-, C₃-₁₀ cycloalkyl-Ci-₄ alkyl-, (5-10 membered heteroaryl)-Ci-₄ alkyl- and (4-10 membered heterocycloalkyl)-Ci-₄ alkyl- of Rᵦ are each optionally substituted with 1, 2, 3, 4, or 5 independently selected Rᵦ substituents; each Rᵦ is independently selected from C₁-₄ alkyl, C₁-₄ haloalkyl, C₂-₆ alkenyl, C₆-₁₀ aryl, C₃-₁₀ cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C₆-₁₀ aryl-Ci-₄ alkyl-, C₃-₁₀ cycloalkyl-Ci-₄ alkyl-, (5-10 membered heteroaryl)-Ci-₄ alkyl-, (4-10 membered heterocycloalkyl)-Ci-₄ alkyl-, halo, CN, NHOR ᵇ, OR ᵇ, SR ᵇ, C(0)R ᵇ, C(0)NR ᵇR ᵇ, C(0)OR ᵇ, OC(0)R ᵇ, OC(0)NR ᵇR ᵇ, NH ᵇR ᵇ, N ᵇR ᵇR ᵇ, N ᵇR C(0)R ᵇ, N ᵇR C(0)NR ᵇR ᵇ, N ᵇR C(0)OR ᵇ, C(=NR ᵇ)NR ᵇR ᵇ, N ᵇR C(=NR ᵇ)NR ᵇR ᵇ, N ᵇR S(0)₂R ᵇ, N ᵇR S(0)₂R ᵇ, N ᵇR S(0)₂R ᵇ, N ᵇR S(0)₂R ᵇ, N ᵇR S(0)₂R ᵇ, N ᵇR S(0)₂R ᵇ, N ᵇR S(0)₂R ᵇ, N ᵇR S(0)₂R ᵇ, N ᵇR S(0)₂R ᵇ, N ᵇR S(0)₂R ᵇ, N ᵇR S(0)₂R ᵇ, N ᵇR S(0)₂R ᵇ, N ᵇR S(0)₂R ᵇ, N ᵇR S(0)₂R ᵇ, N ᵇR S(0)₂R ᵇ, N ᵇR S(0)₂R ᵇ, N ᵇR S(0)₂R ᵇ, N ᵇR S(0)₂R ᵇ, N ᵇR S(0)₂R ᵇ, N ᵇR S(0)₂R ᵇ, N ᵇR S(0)₂R ᵇ, N ᵇR S(0)₂R ᵇ, N ᵇR S(0)₂R ᵇ, N ᵇR S(0)₂R ᵇ, N ᵇR S(0)₂R ᵇ,
NR³(0)₂NR⁴R⁵, -P(0)R³g, -P(0)(ORg)(ORg), -B(OH)₂, -B(OR)₂ and S(0)₂NR³g; wherein
the Ci-4 alkyl, Ci-4 haloalkyl, C₆-₁₀ alkyl, C₂₆ alkyl, C₆-₁₀ cycloalkyl, 5-10
membered heteroaryl, 4-10 membered heterocycloalkyl, C₆-₁₀ aryl-Ci-4 alkyl-, C₃-₁₀ cycloalkyl-
C₁₄ alkyl-, (5-10 membered heteroaryl)-Ci-4 alkyl-, and (4-10 membered heterocycloalkyl)-Ci-4
alkyl- of R¹ are each optionally substituted with 1, 2, 3, 4, or 5 independently selected R²
substituents;
each R² is independently selected from C₁₄ alkyl, Ci-₄ haloalkyl, C₂₆ alkyl, C₂₆
alkynyl, C₆-₁₀ aryl, C₃-₁₀ cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl,
C₆-₁₀ aryl-Ci-4 alkyl-, C₃-₁₀ cycloalkyl-Ci-4 alkyl-, (5-10 membered heteroaryl)-Ci-4 alkyl-, (4-10
membered heterocycloalkyl)-Ci-₄ alkyl-, halo, CN, NHOR, OR, SR, C(O)R, C(O)NR R', C(=NR)R'
R', C(=NR)NR R', C(=NOH)NR R', S(0)R, S(O)R, S(O)₂R, R', R S(O)₂R', R', S(O)R',
R²⁻S(0)₂NR²R², -P(0)R²R², -P(0)(OR²)(OR²), -B(OH)₂, -B(OR²)₂ and S(O)₂NR²R², wherein
the Ci-4 alkyl, Ci-₄ haloalkyl, C₂₆ alkyl, C₂₆ alkynyl, C₆-₁₀ aryl, C₃-₁₀ cycloalkyl, 5-10
membered heteroaryl, 4-10 membered heterocycloalkyl, C₆-₁₀ aryl-Ci-4 alkyl-, C₃-₁₀ cycloalkyl-
C₁₄ alkyl-, (5-10 membered heteroaryl)-Ci-4 alkyl-, and (4-10 membered heterocycloalkyl)-Ci-4
alkyl- of R³ are each optionally substituted with 1, 2 or 3 independently selected R⁴ substituents;
each R⁴ is independently selected from H, Ci-₆ alkyl, Ci-₄ haloalkyl, C₂₆ alkyl, C₂₆
alkynyl, C₆-₁₀ aryl, C₃-₁₀ cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl,
C₆-₁₀ aryl-Ci-4 alkyl-, C₃-₁₀ cycloalkyl-Ci-4 alkyl-, (5-10 membered heteroaryl)-Ci-4 alkyl-, and (4-
10 membered heterocycloalkyl)-Ci-₄ alkyl-, wherein the Ci-6 alkyl, C₂₆ alkyl, C₂₆ alkynyl, C₆-
₁₀ aryl, C₃-₁₀ cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C₆-₁₀ aryl-
C₁₄ alkyl-, C₃-₁₀ cycloalkyl-Ci-4 alkyl-, (5-10 membered heteroaryl)-Ci-4 alkyl- and (4-10
membered heterocycloalkyl)-Ci-₄ alkyl- of R⁵ are each optionally substituted with 1, 2, or 3
independently selected R⁶ substituents;
each R⁶ is independently selected from Ci-₆ alkyl, Ci-₄ haloalkyl, C₂₆ alkyl, C₂₆
alkynyl, C₆-₁₀ aryl, C₃-₁₀ cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl,
C₆-₁₀ aryl-Ci-4 alkyl-, C₃-₁₀ cycloalkyl-Ci-4 alkyl-, (5-10 membered heteroaryl)-Ci-4 alkyl-, (4-10
membered heterocycloalkyl)-Ci-₄ alkyl-, halo, CN, NHOR, OR, SR, C(O)R, C(O)NR R', C(=NR)R'
R²⁻S(0)₂NR²R², -P(0)R²R², -P(0)(OR²)(OR²), -B(OH)₂, -B(OR²)₂ and S(O)₂NR²R², wherein
the Ci-6 alkyl, Ci-₄ haloalkyl, C₂₆ alkyl, C₂₆ alkynyl, C₆-₁₀ aryl, C₃-₁₀ cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C₆-₁₀ aryl-Ci-4
alkyl-, C₃-₁₀ cycloalkyl-Ci-4 alkyl-, (5-10 membered heteroaryl)-Ci-4 alkyl-, and (4-10
membered heterocycloalkyl)-Ci-₄ alkyl- of R⁷ are each optionally substituted with 1, 2, or 3
independently selected R⁸ substituents;
alkyl-, C₃₋₁₀ cycloalkyl-C₄₋₁₀ alkyl-, (5-10 membered heteroaryl)-C₁₋₄ alkyl- and (4-10 membered heterocycloalkyl)-C₁₋₄ alkyl- of Rₚ is optionally substituted with 1, 2 or 3 independently selected Rₗ substituents;

or any two Rₗ substituents together with the boron, phosphorus or nitrogen atom to which they are attached form a 4-, 5-, 6-, 7-, 8-, 9- or 10-membered heterocycloalkyl group optionally substituted with 1, 2 or 3 independently selected Rₗ substituents;

each Rₜ is independently selected from C₁₋₆ cycloalkyl, C₅₋₁₀ aryl, C₆₋₁₀ heteroaryl, C₆₋₁₀ aryl-C₁₋₄ alkyl-, C₃₋₁₀ cycloalkyl-C₁₋₄ alkyl-, (5-6 membered heteroaryl)-C₁₋₄ alkyl-, (4-10 membered heterocycloalkyl)-C₁₋₄ alkyl-, C₁₋₆ haloalkyl, C₂₋₆ alkenyl, C₂₋₆ cycloalkyl-C₁₋₄ alkyl- optionally substituted with 1, 2 or 3 independently selected Rₚ substituents;

or two Rₚ groups attached to the same carbon atom of the 4- to 10-membered heterocycloalkyl taken together with the carbon atom to which they are attached form a C₃₋₆ cycloalkyl or 4- to 6-membered heterocycloalkyl having 1-2 heteroatoms as ring members selected from O, N or S;

or any two Rₘ substituents together with the boron, phosphorus or nitrogen atom to which they are attached form a 4-, 5-, 6-, 7-, 8-, 9- or 10-membered heterocycloalkyl group optionally substituted with 1, 2 or 3 independently selected Rₜ substituents;
or any two \( R^k \) substituents together with the boron, phosphorus or nitrogen atom to which they are attached form a 4-, 5-, 6-, 7-, 8-, 9- or 10-membered heterocycloalkyl group optionally substituted with 1, 2, or 3 independently selected \( R^h \) substituents;

- or any two \( R^g \) substituents together with the boron, phosphorus or nitrogen atom to which they are attached form a 4-, 5-, 6-, 7-, 8-, 9- or 10-membered heterocycloalkyl group optionally substituted with 1, 2, or 3 independently selected \( R^h \) substituents;

- or any two \( R^i \) substituents together with the boron, phosphorus or nitrogen atom to which they are attached form a 4-, 5-, 6-, 7-, 8-, 9- or 10-membered heterocycloalkyl group optionally substituted with 1, 2, or 3 independently selected \( R^h \) substituents, or 1, 2, or 3 independently selected \( R^g \) substituents;

- or any two \( R^j \) substituents together with the boron, phosphorus or nitrogen atom to which they are attached form a 4-, 5-, 6-, 7-, 8-, 9- or 10-membered heterocycloalkyl group optionally substituted with 1, 2, or 3 independently selected \( R^h \) substituents;

- or any two \( R^k \) substituents together with the boron, phosphorus or nitrogen atom to which they are attached form a 4-, 5-, 6-, 7-, 8-, 9- or 10-membered heterocycloalkyl group optionally substituted with 1, 2, or 3 independently selected \( R^h \) substituents;

- or any two \( R^l \) substituents together with the boron, phosphorus or nitrogen atom to which they are attached form a 4-, 5-, 6-, 7-, 8-, 9- or 10-membered heterocycloalkyl group optionally substituted with 1, 2, or 3 independently selected \( R^h \) substituents;

- each \( \text{R}^i, \text{R}^j, \text{R}^k, \text{R}^l, \text{R}^m \) is independently selected from \( \text{H}, \text{Cl}-4 \text{ alkyl}, \text{C}_{3-6} \text{ cycloalkyl}, \text{C}_{6-10} \text{ aryl}, 5 \text{ or } 6\text{-membered heteroaryl, } 4-7 \text{ membered heterocycloalkyl, } \text{Ci}-6 \text{ haloalkoyl, } \text{Ci}-6 \text{ haloalkoxy, } \text{C}_{2-4} \text{ alkenyl, and } \text{C}_{2-4} \text{ alkynyl, wherein the } \text{Ci}-4 \text{ alkyl, } \text{C}_{3-6} \text{ cycloalkyl, } \text{C}_{6-10} \text{ aryl, } 5 \text{ or } 6\text{-membered heteroaryl, } 4-7 \text{ membered heterocycloalkyl, } \text{C}_{2-4} \text{ alkenyl, and } \text{C}_{2-4} \text{ alkynyl of } \text{R}^i, \text{R}^j, \text{R}^k, \text{R}^l, \text{R}^m \) substituents;

- each \( \text{R}^m \) is independently selected from halo, \( \text{OH}, \text{CN}, \text{-COOH}, \text{NH}_2, \text{-NH-Cl}-e \text{ alkyl, } \text{-N(\text{Cl}-6 \text{ alky})}_2, \text{Cl}-6 \text{ alky}, \text{Cl}-6 \text{ alkoxy, } \text{Cl}-6 \text{ alkylthio, } \text{Cl}-6 \text{ haloalkoyl, } \text{Cl}-6 \text{ haloalkoxy, } \text{phenyl, } 5-6 \text{ membered heteroaryl, } 4-6 \text{ membered heterocycloalkyl and } \text{C}_{3-6} \text{ cycloalkyl, wherein the } \text{Ci}-6 \text{ alkyl, phenyl, } \text{C}_{3-6} \text{ cycloalkyl, } 4-6 \text{ membered heterocycloalkyl, and } 5-6 \text{ membered heteroaryl of } \text{R}^m \) are each optionally substituted with 1, 2, or 3 substituents selected from halo, \( \text{OH}, \text{CN}, \text{-COOH}, \text{NH}_2, \text{Cl}-4 \text{ alkyl, } \text{Cl}-4 \text{ alkoxy, } \text{Cl}-4 \text{ haloalkoyl, } \text{Cl}-4 \text{ haloalkoxy, } \text{phenyl, } \text{C}_{3-10} \text{ cycloalkyl, } 5-6 \text{ membered heteroaryl and } 4-6 \text{ membered heterocycloalkyl;}

- the subscript \( m \) is an integer of 0, 1, 2 or 3;

- the subscript \( n \) is an integer of 0, 1, 2 or 3;
each subscript $q$ is independently an integer of 1, 2, 3 or 4; and
the subscript $s$ is an integer of 1, 2, or 3.

In some embodiments, provided herein is a compound of Formula (I), or a
pharmaceutically acceptable salt or a stereoisomer thereof, wherein:

ring A is 5- to 14-membered heteroaryl, 4- to 14-membered heterocycloalkyl, C$_{6-10}$ aryl or C$_{3-14}$ cycloalkyl, wherein the 5- to 14-membered heteroaryl and 4- to 14-membered heterocycloalkyl each has 1-4 heteroatoms as ring members selected from B, P, N, O and S, wherein the P, N or S atom as ring members is optionally oxidized and one or more carbon atoms as ring members are each optionally replaced by a carbonyl group; and wherein ring A is optionally substituted with 1, 2, 3, 4 or 5 $R^6$ substituents;

$L$ is a bond, -C(0)NR$_{13-}$, -NR$_{15}$C(0) -, O, -(CR$_{14}$R$^{15}$)$_q$-, -(CR$_{14}$R$^{15}$)$_q$O-, -O( CR$_{14}$R$^{15}$)$_q$-, -NR$_{13-}$, -(CR$_{14}$R$^{15}$)$_q$NR$_{13-}$, -NR$_{15}$-(CR$_{14}$R$^{15}$)$_q$-, -CH=CH-, ≡C=C-, -SO$_2$NR$_{13-}$, -NR$_{15}$S$_{02}$NR$_{2-}$, -NR$_{15}$S$_{02}$NR$_{13-}$, -NR$_{15}$C(0)0-, -OC(0)NR$_{13}$ or -NR$_{15}$C(0)NR$_{13-}$;

$X$ is N or CR$_{17}$;

$R^3$ is methyl, halo, CN or Ci-4haloalkyl;

$R^4$ is Ci-4 alkyl, Ci-4 alkoxy, CM haloalkyl, CM haloalkoxy, CN, halo, OH, -COOH, NH$_2$, -NHCl-alkyl or -N(Ci-4 alkyl)$_2$;

$R^5$ is CM alkyl, Ci-4 alkoxy, CM haloalkyl, CM haloalkoxy, CN, halo, OH, -COOH, NH$_2$, -NHCl-alkyl or -N(CM alkyl)$_2$;

$R^6$, $R^7$, $R^17$ and $R^{18}$ are each independently selected from H, halo, Ci-6 alkyl, C$_{2-6}$ alkenyl, C$_{2-4}$ alkynyl, Ci-6 haloalkyl, Ci-6 haloalkoxy, C$_{6-10}$-iroyl, C$_{3-10}$ cycloalkyl, 5-14 membered heteroaryl, 4-10 membered heterocycloalkyl, C$_{6-10}$ aryl-Ci-4 alkyl-, C$_{3-10}$ cycloalkyl-Ci-4 alkyl-, (5-14 membered heteroaryl)-Ci-4 alkyl-, (4-10 membered heterocycloalkyl)-Ci-4 alkyl-, CN, N0$_2$;

OR$_a$, SR$_a$, NHOR$_a$, C(0)R$_a$, C(0)NR$_a$, C(0)OR$_a$, OC(0)R$_a$, OC(0)NR$_a$, NHR$_a$, NR$_a$R$_a$,

NR$_a$C(0)R$_a$, NR$_a$C(0)OR$_a$, NR$_a$C(0)NR$_a$, NR$_a$OR$_a$, C(=NR$_a$)R$_a$, C(=NR$_a$)NR$_a$R$_a$, NR$_a$C(=NR$_a$)NR$_a$R$_a$,

NR$_a$S(0)R$_a$, NR$_a$S(0)R$_a$, NR$_a$S(0)$_2$NR$_a$R$_a$, S(0)R$_a$, S(0)NR$_a$R$_a$, S(0)$_2$R$_a$, S(0)$_2$R$_a$, P(0)OR$_a$, B(OH)$_2$, B(OR)$_2$ and S(0)$_2$NR$_a$R$_a$, wherein the Ci-e alkyl, C$_{2-6}$ alkenyl, C$_{2-6}$ alkynyl, C$_{6-10}$ aryl, C$_{3-10}$ cycloalkyl, 5-14 membered heteroaryl, 4-10 membered heterocycloalkyl, C$_{6-10}$ aryl-Ci-4 alkyl-, C$_{3-10}$ cycloalkyl-Ci-4 alkyl-, (5-14 membered heteroaryl)-Ci-4 alkyl- and (4-10 membered heterocycloalkyl)-Ci-4 alkyl- of R$^6$, R$^7$, R$^{17}$ and R$^{18}$ are each optionally substituted with 1, 2, 3, 4 or 5 independently selected R$^b$ substituents;

or two R$^b$ substituents attached to the same ring carbon atom taken together with the ring carbon atom to which they are attached form spiro C$_{3-6}$ cycloalkyl or spiro 4- to 7-membered
heterocycloalkyl, each of which is optionally substituted with 1, 2, or 3 independently selected R^f substituents;

each R^{13} is independently H, Cl-6 haloalkyl or Cl-6 alkyl optionally substituted with a substituent selected from Cl-4 alkyl, Cl-4 haloxy, Cl-4 haloalkyl, Cl-4 haloalkoxy, CN, halo, OH, -COOH, NH_2, -NHC(O)-alkyl and -N(Cl-4 alkyl)_2;

R^{14} and R^{15} are each independently selected from H, halo, CN, OH, -COOH, C_1-4 alkyl, Cl-4 haloxy, -NHC(O)-alkyl, -N(Cl-4 alkyl)_2, Cl-4 haloalkyl, Cl-4 haloalkoxy, C_3-6 cycloalkyl, phenyl, 5-6 membered heteroaryl and 4-6 membered heterocycloalkyl, wherein the Cl-4 alkyl, Cl-4 haloxy, Cl-4 haloalkyl, Cl-4 haloalkoxy, C_3-6 cycloalkyl, phenyl, 5-6 membered heteroaryl and 4-6 membered heterocycloalkyl of R^{14} or R^{15} are each optionally substituted with 1, 2, or 3 independently selected R^g substituents;

or R^{14} and R^{15} taken together with the carbon atom to which they are attached form 3-, 4-, 5- or 6-membered cycloalkyl or 3-, 4-, 5- or 6-membered heterocycloalkyl, each of which is optionally substituted with 1 or 2 independently selected R^g substituents;

each R^a is independently selected from H, CN, Cl-6 alkyl, C_1-4 haloalkyl, C_2-6 alkenyl, C_2-6 alkynyl, C_6-10 aryl, C_3-10 cycloalkyl, 5-14 membered heteroaryl, 4-14 membered heterocycloalkyl, C_6-10 aryl-Cl-4 alkyl-, C_3-10 cycloalkyl-Cl-4 alkyl-, (5-14 membered heteroaryl)-Cl-4 alkyl-, and (4-14 membered heterocycloalkyl)-Cl-4 alkyl-, wherein the Cl-6 alkyl, C_2-6 alkenyl, C_2-6 alkynyl, C_6-10 aryl, C_3-10 cycloalkyl, 5-14 membered heteroaryl, 4-14 membered heterocycloalkyl, C_6-10 aryl-Cl-4 alkyl-, C_3-10 cycloalkyl-Cl-4 alkyl-, (5-14 membered heteroaryl)-Cl-4 alkyl- and (4-14 membered heterocycloalkyl)-Cl-4 alkyl- of R^a are each optionally substituted with 1, 2, 3, 4, or 5 independently selected R^d substituents;

each R^d is independently selected from Cl-6 alkyl, Cl-6 haloalkyl, halo, C_6-iloaryl, 5-14 membered heteroaryl, C_3-10 cycloalkyl, 4-14 membered heterocycloalkyl, C_6-10 aryl-Cl-4 alkyl-, C_3-10 cycloalkyl-Cl-4 alkyl-, (5-14 membered heteroaryl)-Cl-4 alkyl-, (4-14 membered heterocycloalkyl)-Cl-4 alkyl-, CN, NH_2, NHOR, O R, S R, C(O)R, C(O)NR, R OR, OC(O)R, OCN(R), NHR, N R, N R C(O)R, N R C(O)NR, N R C(O)OR, C(=NR) R, C(=NHC(O)) R, N R C(O)C(=NOH)NR, N R C(O)C(=NHC(O))NR, R OR, S(0) R, S(0) OR, R OR, N R S(O) R, N R S(O) R, N R S(O) R, -P(O) R, -P(O) OR, -(OR) OR, -(OR) OR, -(OR) OR, -(OR) OR, -(OR) OR, -(OR) OR, -(OR) OR, -(OR) OR, -(OR) OR, -(OR) OR, -(OR) OR, -(OR) OR, -(OR) OR, -(OR) OR, -(OR) OR, -(OR) OR, -(OR) OR, -(OR) OR, -(OR) OR, -(OR) OR, -(OR) OR, -(OR) OR, -(OR) OR,
each R is independently selected from H, C1-6 alkyl, C1-6 haloalkyl, C2-6 alkenyl, C6-10 aryl, C3-10 cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C6-10 aryl-C1-4 alkyl-, C3-10 cycloalkyl-C1-4 alkyl-, (5-10 membered heteroaryl)-C1-4 alkyl-, and (4-10 membered heterocycloalkyl)-C1-4 alkyl-, wherein the C1-6 alkyl, C1-6 haloalkyl, C2-6 alkenyl, C6-10 aryl, C3-10 cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C6-10 aryl-C1-4 alkyl-, C3-10 cycloalkyl-C1-4 alkyl-, (5-10 membered heteroaryl)-C1-4 alkyl- and (4-10 membered heterocycloalkyl)-C1-4 alkyl- of R are each optionally substituted with 1, 2 or 3 independently selected R substituents;

each R substituent is independently selected from halo, C1-6 alkyl, C2-6 alkenyl, C2-6 alkynyl, C1-6 haloalkoxy, C6-10 aryl, C3-10 cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C6-10 aryl-C1-4 alkyl-, C3-10 cycloalkyl-C1-4 alkyl-, (5-10 membered heteroaryl)-C1-4 alkyl-, and (4-10 membered heterocycloalkyl)-C1-4 alkyl-, wherein the C1-6 alkyl, C1-6 haloalkyl, C2-6 alkenyl, C6-10 aryl, C3-10 cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C6-10 aryl-C1-4 alkyl-, C3-10 cycloalkyl-C1-4 alkyl-, C3-10 cycloalkyl-C1-4 alkyl- and (4-10 membered heterocycloalkyl)-C1-4 alkyl- of R are each further optionally substituted with 1, 2, or 3 independently selected R substituents;

each R is independently selected from H, C1-6 alkyl, C1-4 haloalkyl, C2-6 alkenyl, C2-6 alkynyl, C6-10 aryl, C3-10 cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C6-10 aryl-C1-4 alkyl-, C3-10 cycloalkyl-C1-4 alkyl-, (5-10 membered heteroaryl)-C1-4 alkyl-, and (4-10 membered heterocycloalkyl)-C1-4 alkyl-, wherein the C1-6 alkyl, C2-6 alkenyl, C2-6 alkynyl, C6-10 aryl, C3-10 cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C6-10 aryl-C1-4 alkyl-, C3-10 cycloalkyl-C1-4 alkyl-, C3-10 cycloalkyl-C1-4 alkyl- and (4-10 membered heterocycloalkyl)-C1-4 alkyl- of R are each optionally substituted with 1, 2, 3, 4, or 5 independently selected R substituents;

each R is independently selected from C1-4 alkyl, C1-4 haloalkyl, C2-6 alkenyl, C2-6 alkynyl, C6-10 aryl, C3-10 cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C6-10 aryl-C1-4 alkyl-, C3-10 cycloalkyl-C1-4 alkyl-, (5-10 membered heteroaryl)-C1-4 alkyl-, (4-10 membered heterocycloalkyl)-C1-4 alkyl-, halo, CN, NHOR, OR, SR, C(0)R, C(0)NR R, C(=NR)R, C(=NR)2 R, P(0)OR, -B(OH) 2, -B(OR) 2 and S(0)NR R; wherein the C1-6 alkyl, C1-6 haloalkyl, C2-6 alkenyl, C2-6 alkynyl, C6-10 aryl, C3-10 cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C6-10 aryl-C1-4 alkyl-, C3-10 cycloalkyl-C1-4 alkyl- and (4-10 membered heterocycloalkyl)-C1-4 alkyl- of R are each optionally substituted with 1, 2, 3, 4, or 5 independently selected R substituents;
NR³(0)_2NR°R°, -P(0)R³g, -P(0)(OR°)(OR°), -B(OH)₂, -B(OR°)₂ and S(0)_2NR°R°; wherein
the Ci-4 alkyl, Ci-4 haloalkyl, C₂₋₆ alkynyl, C₂₋₁₀ aryalkyl, C₅₋₁₀ cycloalkyl, 5-10
membered heteroaryl, 4-10 membered heterocycloalkyl, C₆₋₁₀ aryl-Ci-4 alkyl-, C₁₋₁₀
cycloalkyl-Ci₁₄ alkyl-, (5-10 membered heteroaryl)-Ci-4 alkyl-, and (4-10 membered heterocycloalkyl)-Ci-4
alkyl- of R" are each optionally substituted with 1, 2, 3, 4, or 5 independently selected R"n
substituents;

each R"n is independently selected from C₁₋₁₀ alkyl, Ci-4 haloalkyl, C₂₋₆ alkynyl, C₂₋₁₀
aryalkyl, C₅₋₁₀ cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl,
C₆₋₁₀ aryalkyl, C₅₋₁₀ cycloalkyl-Ci₁₄ alkyl-, (5-10 membered heteroaryl)-Ci-4 alkyl-, (5-10
membered heterocycloalkyl)-Ci₁₄ alkyl-, halo, CN, NHOR ₀, OR°, SR°, C(O)R°, C(O)NR°R°,
C(O)R°, OC(0)R°, OC(0)NR°R°, NHR°, NR°R°, NR°C(O)R°, NR°C(O)NR°R°, NR°C(O)OR°,
C(=NR°)NR°R°, NR°C(=NR°)NR°OR°, S(O)R°, S(O)NR°R°, S(O)₂R°, NR°S(O)₂R°,
NR°S(0)_₂NR°R°, -P(0)R³g, -P(0)(OR°)(OR°), -B(OH)₂, -B(OR°)₂ and S(O)_₂NR°R°, wherein
the Ci-4 alkyl, Ci-4 haloalkyl, C₂₋₆ alkynyl, C₂₋₁₀ aryalkyl, C₆₋₁₀ aryalkyl, C₅₋₁₀
cycloalkyl, C₅₋₁₀ aryalkyl, C₅₋₁₀ cycloalkyl-Ci₁₄ alkyl-, (5-10 membered heteroaryl)-Ci-4 alkyl-, and (4-10
membered heterocycloalkyl)-Ci-4 alkyl- of R"n are each optionally substituted with 1, 2 or 3
independently selected R"n substitutes;

each R" is independently selected from H, Ci-6 alkyl, Ci-6 haloalkyl, C₂₋₆ alkynyl, C₂₋₁₀
aryalkyl, C₆₋₁₀ aryalkyl, C₅₋₁₀ cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl,
C₆₋₁₀ aryalkyl-Ci₁₄ alkyl-, C₁₋₁₀ cycloalkyl-Ci₁₄ alkyl-, (5-10 membered heteroaryl)-Ci-4 alkyl-, (4-10
membered heterocycloalkyl)-Ci-4 alkyl-, wherein the Ci-6 alkyl, C₂₋₆ alkynyl, C₂₋₁₀ aryalkyl,
C₆₋₁₀ aryalkyl, C₅₋₁₀ cycloalkyl-Ci₁₄ alkyl-, (5-10 membered heteroaryl)-Ci-4 alkyl-, and (4-10
membered heterocycloalkyl)-Ci-4 alkyl- of R" are each optionally substituted with 1, 2, or 3
independently selected R" substitutes;

each R° is independently selected from Ci-6 alkyl, Ci-6 haloalkyl, C₂₋₆ alkynyl, C₂₋₁₀
aryalkyl, C₆₋₁₀ aryalkyl, C₅₋₁₀ cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl,
C₆₋₁₀ aryalkyl-Ci₁₄ alkyl-, C₁₋₁₀ cycloalkyl-Ci₁₄ alkyl-, (5-10 membered heteroaryl)-Ci-4 alkyl-, (4-10
membered heterocycloalkyl)-Ci₁₄ alkyl-, halo, CN, NHOR ₀, OR°, SR°, C(O)R°, C(O)NR°R°,
C(O)R°, OC(0)R°, OC(0)NR°R°, NHR°, NR°R°, NR°C(O)R°, NR°C(O)NR°R°, NR°C(O)OR°,
C(=NR°)NR°R°, NR°C(=NR°)NR°OR°, S(O)R°, S(O)NR°R°, S(O)₂R°, NR°S(O)₂R°,
NR°S(0)_₂NR°R°, -P(0)R³g, -P(0)(OR°)(OR°), -B(OH)₂, -B(OR°)₂ and S(O)_₂NR°R°, wherein
the Ci-6 alkyl, Ci-6 haloalkyl, C₂₋₆ alkynyl, C₂₋₁₀ aryalkyl, C₆₋₁₀ aryalkyl, C₅₋₁₀
cycloalkyl, C₅₋₁₀ aryalkyl, C₅₋₁₀ cycloalkyl-Ci₁₄ alkyl-, (5-10 membered heteroaryl)-Ci-4 alkyl- and (4-10
membered heterocycloalkyl)-Ci-4 alkyl- of R° are each optionally substituted with 1, 2, or 3
independently selected R° substitutes;
alky-, C_3-10 cycloalkyl-Ci-4 alkyl-, (5-10 membered heteroaryl)-Ci-4 alkyl- and (4-10 membered heterocycloalkyl)-Ci-4 alkyl- of R is optionally substituted with 1, 2 or 3 independently selected R^a substituents;

or any two R^a substituents together with the boron, phosphorus or nitrogen atom to which they are attached form a 4-, 5-, 6-, 7-, 8-, 9- or 10-membered heterocycloalkyl group optionally substituted with 1, 2 or 3 independently selected R^b substituents;

each R^b is independently selected from Ci-6 alkyl, C_3-10 cycloalkyl, 4-7 membered heterocycloalkyl, C_6-10 aryl, 5-6 membered heteroaryl, C_6-10 aryl-Ci-4 alkyl-, C_3-10 cycloalkyl-Ci-4 alkyl-, (5-6 membered heteroaryl)-Ci-4 alkyl-, (4-7 membered heterocycloalkyl)-Ci-4 alkyl-, Ci-6 haloalkyl, Ci-e haloalkoxy, C_2-6 alkenyl, C_2-6 alkynyl, halo, CN, OR, SR, NHOR, C(O)R, C^aNR^a, 0(0)OR, 0(0)N R^1R^1, NHR^a, NR^1R^1, N R^1C(O)R^1, N R^1C(O)N R^1R^1, N R^1C(O)OR^1, C(=NR^a)NR^1R^1, NR^1C^aNRONR^a, S(0)Φ^-, S(0)R, S(0)(0)R, S(0)Φ^2, S(0)N R^1R^1, -B(OH)_2, -B(OR)_2 and S(0)Ν R^1R^1, wherein the Ci-6 alkyl, C_2-6 alkenyl, C_2-6 alkynyl, C_3-10 cycloalkyl, 4-7 membered heterocycloalkyl, C_6-10 aryl, 5-6 membered heteroaryl, C_6-10 aryl-Ci-4 alkyl-, C_3-10 cycloalkyl-Ci-4 alkyl-, (4-7 membered heterocycloalkyl)-Ci-4 alkyl- of R^b are each further optionally substituted by 1, 2 or 3 independently selected R^i substituents;

each R^i is independently selected from C_3-5 cycloalkyl, C_6-10 aryl, 5 or 6-membered heteroaryl, 4-7 membered heterocycloalkyl, C_2-4 alkenyl, C_2-4 alkynyl, halo, C_1-4 alkyl, C_1-4 haloalkyl, C M haloalkoxy, CN, NHOR, OR^k, SR^k, C(O)R^k, C(O)OR^k, OC(O)R^k, OC(O)NR^k, NHR^k, N R^kR^k, N R^kC(O)R^k, N R^kC(O)NR^k, N R^kC(O)OR^k, C(=NR^k)NR^k R^k, N R^kC(=NR^k)NR^k R^k, S(0)Φ^-, S(0)R, S(0)Φ^2, S(0)Ν R^1R^1, -B(OH)_2, -B(OR)_2 and S(0)Ν R^1R^1, wherein the C M alkyl, C_3-6 cycloalkyl, C_6-10 aryl, 5- or 6-membered heteroaryl, 4-7 membered heterocycloalkyl, C_2-4 alkenyl, C_2-4 alkynyl, C_1-4 haloalkyl and C M haloalkoxy of R^i are each optionally substituted with 1, 2 or 3 independently selected R^a substituents;

or two R^b groups attached to the same carbon atom of the 4- to 10-membered heterocycloalkyl taken together with the carbon atom to which they are attached form a C_3-6 cycloalkyl or 4- to 6-membered heterocycloalkyl having 1-2 heteroatoms as ring members selected from O, N or S;

or any two R^c substituents together with the boron, phosphorus or nitrogen atom to which they are attached form a 4-, 5-, 6-, 7-, 8-, 9- or 10-membered heterocycloalkyl group optionally substituted with 1, 2, or 3 independently selected R^b substituents;
or any two $R^k$ substituents together with the boron, phosphorus or nitrogen atom to which they are attached form a 4-, 5-, 6-, 7-, 8-, 9- or 10-membered heterocycloalkyl group optionally substituted with 1, 2, or 3 independently selected $R^b$ substituents;

or any two $R^k$ substituents together with the boron, phosphorus or nitrogen atom to which they are attached form a 4-, 5-, 6-, 7-, 8-, 9- or 10-membered heterocycloalkyl group optionally substituted with 1, 2, or 3 independently selected $R^b$ substituents;

or any two $R^k$ substituents together with the boron, phosphorus or nitrogen atom to which they are attached form a 4-, 5-, 6-, 7-, 8-, 9- or 10-membered heterocycloalkyl group optionally substituted with 1, 2, or 3 independently selected $R^b$ substituents;

or any two $R^k$ substituents together with the boron, phosphorus or nitrogen atom to which they are attached form a 4-, 5-, 6-, 7-, 8-, 9- or 10-membered heterocycloalkyl group optionally substituted with 1, 2, or 3 independently selected $R^b$ substituents;

or any two $R^k$ substituents together with the boron, phosphorus or nitrogen atom to which they are attached form a 4-, 5-, 6-, 7-, 8-, 9- or 10-membered heterocycloalkyl group optionally substituted with 1, 2, or 3 independently selected $R^b$ substituents;

or any two $R^k$ substituents together with the boron, phosphorus or nitrogen atom to which they are attached form a 4-, 5-, 6-, 7-, 8-, 9- or 10-membered heterocycloalkyl group optionally substituted with 1, 2, or 3 independently selected $R^b$ substituents;

or any two $R^f$ substituents together with the boron, phosphorus or nitrogen atom to which they are attached form a 4-, 5-, 6-, 7-, 8-, 9- or 10-membered heterocycloalkyl group optionally substituted with 1, 2, or 3 independently selected $R^b$ substituents;

or any two $R^f$ substituents together with the boron, phosphorus or nitrogen atom to which they are attached form a 4-, 5-, 6-, 7-, 8-, 9- or 10-membered heterocycloalkyl group optionally substituted with 1, 2, or 3 independently selected $R^b$ substituents;

or any two $R^f$ substituents together with the boron, phosphorus or nitrogen atom to which they are attached form a 4-, 5-, 6-, 7-, 8-, 9- or 10-membered heterocycloalkyl group optionally substituted with 1, 2, or 3 independently selected $R^b$ substituents;

or any two $R^f$ substituents together with the boron, phosphorus or nitrogen atom to which they are attached form a 4-, 5-, 6-, 7-, 8-, 9- or 10-membered heterocycloalkyl group optionally substituted with 1, 2, or 3 independently selected $R^b$ substituents;

or any two $R^f$ substituents together with the boron, phosphorus or nitrogen atom to which they are attached form a 4-, 5-, 6-, 7-, 8-, 9- or 10-membered heterocycloalkyl group optionally substituted with 1, 2, or 3 independently selected $R^b$ substituents;

or any two $R^f$ substituents together with the boron, phosphorus or nitrogen atom to which they are attached form a 4-, 5-, 6-, 7-, 8-, 9- or 10-membered heterocycloalkyl group optionally substituted with 1, 2, or 3 independently selected $R^b$ substituents;

each $R^i$, $R^j$, $R^o$ or $R^f$ is independently selected from H, Ci-4 alkyl, C3-6 cycloalkyl, C6-10 aryl, 5 or 6-membered heteroaryl, 4-7 membered heterocycloalkyl, Ci-6 haloalkyl, Ci-6 haloalkoxy, C2-4 alkenyl, and C2-4 alkynyl, wherein the C1-4 alkyl, C3-6 cycloalkyl, C6-10 aryl, 5 or 6-membered heteroaryl, 4-7 membered heterocycloalkyl, C2-4 alkenyl, and C2-4 alkynyl of $R^i$, $R^j$, $R^o$ or $R^f$ are each optionally substituted with 1, 2 or 3 $R^g$ substituents;

each $R^g$ is independently selected from halo, OH, CN, -COOH, NH2, -NH-Ci-e alkyl, - N(Ci-6 alky)2, Ci-6 alkyl, Ci-6 alkoxy, Ci-6 alkylthio, Ci-6 haloalkyl, Ci-6 haloalkoxy, phenyl, 5-6 membered heteroaryl, 4-6 membered heterocycloalkyl and C3-6 cycloalkyl, wherein the Ci-6 alkyl, phenyl, C3-6 cycloalkyl, 4-6 membered heterocycloalkyl, and 5-6 membered heteroaryl of $R^g$ are each optionally substituted with 1, 2, or 3 substituents selected from halo, OH, CN, -COOH, NH2, Ci-4 alkyl, Ci-4 alkoxy, Ci-4 haloalkyl, Ci-4 haloalkoxy, phenyl, C3-10 cycloalkyl, 5-6 membered heteroaryl and 4-6 membered heterocycloalkyl;

the subscript $m$ is an integer of 0, 1, 2 or 3;
the subscript $n$ is an integer of 0, 1, 2 or 3;
each subscript $q$ is independently an integer of 1, 2, 3 or 4; and the subscript $s$ is an integer of 1, 2, or 3.
In some embodiments, provided herein is a compound of Formula (I):

![Chemical Structure](image)

or a pharmaceutically acceptable salt or a stereoisomer thereof, wherein:

- **ring A** is 5- to 14-membered heteroaryl, 4- to 14-membered heterocycloalkyl, C$_6$-C$_{10}$ aryl or C$_3$-C$_{14}$ cycloalkyl, wherein the 5- to 14-membered heteroaryl and 4- to 14-membered heterocycloalkyl each has 1-4 heteroatoms as ring members selected from N, O and S, wherein the N or S atom as ring members is optionally oxidized and one or more carbon atoms as ring members are each optionally replaced by a carbonyl group; and wherein ring A is optionally substituted with 1, 2, 3, 4 or 5 R$^6$ substituents;

- **L** is a bond, -C(0)NR$_{13}$, -NR$_{13}$C(0)-, O, -(CR$_{14}$R$_{15}$)$_q$-, -(CR$_{14}$R$_{15}$)$_q$0-, -0(CR$_{14}$R$_{15}$)$_q$-, -NR$_{13}$, -(CR$_{14}$R$_{15}$)$_q$-NR$_{13}$, -NR$_{13}$-(CR$_{14}$R$_{15}$)$_q$-, -CH=CH-, —C≡C—, -SO$_2$NR$_{13}$, -NR$_{13}$S0$_2$-, -NR$_{13}$SO$_2$NR$_{13}$, -NR$_{13}$C(0)0-, -OC(0)NR$_{13}$ or -NR$_{13}$C(0)NR$_{13}$;

- **X** is N or CR$_{17}$;

- **R$^3$** is methyl, halo, CN or C$_4$ haloalkyl;

- **R$^4$** is C$_4$ alkyl, C$_4$ alkoxy, C$_4$ haloalkyl, C$_4$ haloalkoxy, CN, halo, OH, -COOH, NH$_2$, -NHCl$_4$ alkyl or-N(Ci-4 alkyl)$_2$;

- **R$^5$** is C$_4$ alkyl, C$_4$ alkoxy, C$_4$ haloalkyl, C$_4$ haloalkoxy, CN, halo, OH, -COOH, NH$_2$, -NHCl$_4$ alkyl or-N(Ci-4 alkyl)$_2$;

- **R$^6$**, **R$^7$**, **R$^{17}$** and **R$^{18}$** are each independently selected from H, halo, C$_6$-C$_{10}$ alkyl, C$_2$-C$_6$ alkenyl, C$_2$-C$_6$ alkynyl, C$_6$-C$_{10}$ haloalkyl, C$_6$-C$_{10}$ haloalkoxy, C$_6$-C$_{10}$ aryl, C$_3$-C$_{10}$ cycloalkyl, 5-14 membered heteroaryl, 4-10 membered heterocycloalkyl, C$_6$-C$_{10}$ aryl-C$_4$ alkyl-, C$_3$-C$_{10}$ cycloalkyl-C$_4$ alkyl-, (5-14 membered heteroaryl)-C$_4$ alkyl-, (4-10 membered heterocycloalkyl)-C$_4$ alkyl-, CN, N0$_2$, OR$_3$, SR$_3$, NHOR$_3$, C(0)R$_3$, C(0)NR$_3$R$_3$, C(0)OR$_3$A, OC(0)R$_3$, OC(0)NR$_3$R$_3$, NHN$_R$A, N(R$_3$)A, NR$_3$A, NR$_3$C(0)R$_3$, NR$_3$C(0)NR$_3$R$_3$, C(=NR$_3$)R$_3$, C(=NR$_3$)NR$_3$R$_3$, NR=C(=NR$_3$)NR$_3$R$_3$, NR$_3$S(0)R$_3$, NR$_3$S(0)R$_3$, NR$_3$SO$_2$R$_3$, S(0)R$_3$, S(0)NR$_3$R$_3$, S(0)$_2$R$_3$, and S(0)$_2$NR$_3$R$_3$, wherein the C$_6$-C$_{10}$ alkyl, C$_2$-C$_6$ alkenyl, C$_2$-C$_6$ alkynyl, C$_6$-C$_{10}$ aryl, C$_3$-C$_{10}$ cycloalkyl, 5-14 membered heteroaryl, 4-10 membered heterocycloalkyl, C$_6$-C$_{10}$ aryl-C$_4$ alkyl-, C$_3$-C$_{10}$ cycloalkyl-C$_4$ alkyl-, (5-14 membered heteroaryl)-C$_4$ alkyl- and (4-10 membered heterocycloalkyl)-C$_4$ alkyl- of R$^6$.
R^7, R^17 and R^18 are each optionally substituted with 1, 2, 3, 4 or 5 independently selected R^b substituents;

or two R^6 substituents attached to the same ring carbon atom taken together with the ring carbon atom to which they are attached form spiro C3-6 cycloalkyl or spiro 4- to 7-membered heterocycloalkyl, each of which is optionally substituted with 1, 2, or 3 independently selected R^f substituents;

each R^13 is independently H, Ci-6 haloalkyl or Ci-6 alkyl optionally substituted with a substituent selected from C1-4 alkyl, Ci-4 alkoxy, C1-4 haloalkyl, C1-4 haloalkoxy, CN, halo, OH, -COOH, NH2, -NHG-4 alkyl and -N(Ci-4 alkyl)2;

R^14 and R^15 are each independently selected from H, halo, CN, OH, -COOH, Ci-4 alkyl, Ci-4 alkoxy, -NHC1-4 alkyl, -NHG-4 alkyl, C1-4 haloalkyl, C1-4 haloalkoxy, C3-6 cycloalkyl, phenyl, 5-6 membered heteroaryl and 4-6 membered heterocycloalkyl, wherein the Ci-4 alkyl, Ci-4 alkoxy, C1-4 haloalkyl, C1-4 haloalkoxy, C3-6 cycloalkyl, phenyl, 5-6 membered heteroaryl and 4-6 membered heterocycloalkyl of R^14 or R^15 are each optionally substituted with 1, 2, or 3 independently selected R^g substituents;

or R^14 and R^13 taken together with the carbon atom to which they are attached form 3-, 4-, 5- or 6-membered cycloalkyl or 3-, 4-, 5- or 6-membered heterocycloalkyl, each of which is optionally substituted with 1 or 2 independently selected R^h substituents;

each R^i is independently selected from H, CN, Ci-6 alkyl, C1-4 haloalkyl, C2-6 alkenyl, C6-10 aryl, C3-10 cycloalkyl, 5-14 membered heteroaryl, 4-14 membered heterocycloalkyl, C6-10 aryl-Ci-4 alkyl-, C3-10 cycloalkyl-Ci-4 alkyl-, (5-14 membered heteroaryl)-Ci-4 alkyl-, and (4-14 membered heterocycloalkyl)-Ci-4 alkyl-, wherein the Ci-6 alkyl, C2-6 alkenyl, C6-10 aryl, C3-10 cycloalkyl, 5-14 membered heteroaryl, 4-14 membered heterocycloalkyl, C6-10 aryl-Ci-4 alkyl-, C3-10 cycloalkyl-Ci-4 alkyl-, (5-14 membered heteroaryl)-Ci-4 alkyl- and (4-14 membered heterocycloalkyl)-Ci-4 alkyl- of R^i are each optionally substituted with 1, 2, 3, 4, or 5 independently selected R^d substituents;

each R^d is independently selected from Ci-6 alkyl, Ci-6 haloalkyl, halo, C6-10 aryl, 5-14 membered heteroaryl, C3-10 cycloalkyl, 4-14 membered heterocycloalkyl, C6-10 aryl-Ci-4 alkyl-, C3-10 cycloalkyl-Ci-4 alkyl-, (5-14 membered heteroaryl)-Ci-4 alkyl-, (4-14 membered heterocycloalkyl)-Ci-4 alkyl-, CN, NH2, NHOR e, OR e, SR e, C(0)NR e, C(0)OR e, OC(0)R e, OC(0)NR e, OR e, NHR e, NR e, OR e, NAcC(0)R e, NR e, N AcC(0)NR e, OR e, N AcC(0)OR e, C(=NR e)NR e, NR e, C(=NOH)NR e, NR e, C(=NCN)NR e, S(0)R e, S(0)NR e, S(0) OR e, NR e, S(0) OR e, NR e, S(0) OR e, NR e, S(0) OR e, NR e, S(0) OR e, NR e, S(0) OR e, NR e, S(0) OR e, NR e, S(0) OR e, and S(0) OR e, wherein the Ci-e alkyl, Ci-6 haloalkyl, C6-10 aryl, 5-14 membered heteroaryl, C3-10 cycloalkyl, 4-14 membered heteroaryl, C3-10 cycloalkyl, 4-14 membered heterocycloalkyl.
heterocycloalkyl, C₆₋₁₀ aryl-C₄-alkyl-, C₃₋₁₀ cycloalkyl-C₄ alkyl-, (5-14 membered heteroaryl)-C₄ alkyl-, and (4-14 membered heterocycloalkyl)-C₄ alkyl- of R^d are each optionally substituted with 1, 2, or 3 independently selected R^f substituents;

each R^e is independently selected from H, Ci-6 alkyl, Ci-6 haloalkyl, C₂-6 alkenyl, C₂-6 alkynyl, C₆₋₁₀ aryl, C₃₋₁₀ cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C₆₋₁₀ aryl-C₄-alkyl-, C₃₋₁₀ cycloalkyl-C₄ alkyl-, (5-10 membered heteroaryl)-C₄ alkyl-, and (4-10 membered heterocycloalkyl)-C₄ alkyl-, wherein the Ci-6 alkyl, Ci-6 haloalkyl, C₂-6 alkenyl, C₂-6 alkynyl, C₆₋₁₀ aryl, C₃₋₁₀ cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C₆₋₁₀ aryl-C₄-alkyl-, C₃₋₁₀ cycloalkyl-C₄ alkyl-, (5-10 membered heteroaryl)-C₄ alkyl- and (4-10 membered heterocycloalkyl)-C₄ alkyl- of R^e are each optionally substituted with 1, 2 or 3 independently selected R^f substituents;

each R^b substituent is independently selected from halo, Ci-6 alkyl, C₂-6 alkenyl, C₂-6 alkynyl, Ci-6 haloalkyl, Ci-6 haloalkoxy, C₆₋₁₀ aryl, C₃₋₁₀ cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C₆₋₁₀ aryl-C₄-alkyl-, C₃₋₁₀ cycloalkyl-C₄ alkyl-, (5-10 membered heteroaryl)-C₄ alkyl-, (4-10 membered heterocycloalkyl)-C₄ alkyl-, CN, OH, NH₂, NO₂, NHOR, OR, SR, C(0)R₂, C(0)NR₂, C(0)OR₂, COC(0)R₂, CO(NR₂)R₂, C(=NR₂)NR₂, NR₂C(=NR₂)NR₂, NR₂C(O)R₂, NR₂C(O)OR₂, NR₂C(O)NR₂, NR₂S(O)OR₂, NR₂S(O)₂NR₂, NR₂S(O)₂NR₂, NR₂S(O)₂NR₂, S(0)OR₂, S(0)OR₂ and S(0)₂NR₂;

wherein the Ci-6 alkyl, Ci-6 haloalkyl, Ci-6 haloalkoxy, C₂-6 alkenyl, C₂-6 alkynyl, C₆₋₁₀ aryl, C₃₋₁₀ cycloalkyl, 5-10 membered heteroaryl, C₆₋₁₀ aryl-C₄-alkyl-, C₃₋₁₀ cycloalkyl-C₄ alkyl-, (5-10 membered heteroaryl)-C₄ alkyl- and (4-10 membered heterocycloalkyl)-C₄ alkyl- are each further optionally substituted with 1, 2 or 3 independently selected R^d substituents;

each R^c is independently selected from H, Ci-6 alkyl, Ci-4 haloalkyl, C₂-6 alkenyl, C₂-6 alkynyl, C₆₋₁₀ aryl, C₃₋₁₀ cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C₆₋₁₀ aryl-C₄-alkyl-, C₃₋₁₀ cycloalkyl-C₄ alkyl-, (5-10 membered heteroaryl)-C₄ alkyl-, and (4-10 membered heterocycloalkyl)-C₄ alkyl-, wherein the Ci-6 alkyl, C₂-6 alkenyl, C₂-6 alkynyl, C₆₋₁₀ aryl, C₃₋₁₀ cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C₆₋₁₀ aryl-C₄-alkyl-, C₃₋₁₀ cycloalkyl-C₄ alkyl-, (5-10 membered heteroaryl)-C₄ alkyl- and (4-10 membered heterocycloalkyl)-C₄ alkyl- of R^c are each optionally substituted with 1, 2, 3, 4, or 5 independently selected R^f substituents;
membered heterocycloalkyl)-C{1-4}alkyl-, halo, CN, NHOR R°, OR R°, SR R°, C(o)R R°, C(o)NR R°R°, C(o)OR R°, OC(o)R°, OC(o)NR R°R°, NHR R°, NR R°R°, NR2R°, C(=NR R°)NR R°R°, NR2C(o)R°, NR2C(o)OR R°, C(=NR R°)NR R°R°, NR2C(o)R°, OR R°, SR R°, S(o)OR R°, S(o)OB R°, S(o)2R°, NR R°S(o)2R°, and S(o)2NR R°R°; wherein the Ci-e alkyl, Ci-haloalkyl, C2-6 alkenyl, C2-6
5 alkynyl, C6-10 aryl, C3-10 cycloalkyl, 5-10 membered heteroarenyl, 4-10 membered heterocycloalkyl, C6-10 aryl-Ci 4 alkyl-, C3-10 cycloalkyl-Ci 4 alkyl-, (5-10 membered heteroarylyl)-Ci 4 alkyl-, and (4-10 membered heterocycloalkyl)-Ci 4 alkyl- of Rf are each optionally substituted with 1, 2, 3, 4, or 5 independently selected Rg substituents;

each Rg is independently selected from C1-4 alkyl, Ci-4 haloalkyl, C2-6 alkenyl, C2-6
10 alkynyl, C6-10 aryl, C3-10 cycloalkyl, 5-10 membered heteroarenyl, 4-10 membered heterocycloalkyl, C6-10 aryl-Ci 4 alkyl-, C3-10 cycloalkyl-Ci 4 alkyl-, (5-10 membered heteroarenyl)-Ci 4 alkyl-, (4-10 membered heterocycloalkyl)-Ci 4 alkyl-, halo, CN, NHOR R°, OR R°, SR R°, C(o)R R°, C(o)NR R°R°, C(o)OR R°, OC(o)R°, OC(o)NR R°R°, NHR R°, NR R°R°, NR2R°, NR2C(o)R°, NR2C(o)OR R°, C(=NR R°)NR R°R°, NR2C(o)R°, OR R°, SR R°, S(o)OR R°, S(o)OB R°, S(o)2R°, NR R°S(o)2R°, and S(o)2NR R°R°, wherein the Ci-m alkyl, Ci-4 haloalkyl, C2-6 alkenyl, C2-6
15 alkynyl, C6-10 aryl, C3-10 cycloalkyl, 5-10 membered heteroarenyl, 4-10 membered heterocycloalkyl, C6-10 aryl-Ci 4 alkyl-, C3-10 cycloalkyl-Ci 4 alkyl-, (5-10 membered heteroarenyl)-Ci 4 alkyl-, and (4-10 membered heterocycloalkyl)-Ci 4 alkyl- of Rg are each optionally substituted with 1, 2 or 3 independently selected Rh substituents;

each Rh is independently selected from H, Ci-6 alkyl, Ci-6 haloalkyl, C2-6 alkenyl, C2-6
20 alkynyl, C6-10 aryl, C3-10 cycloalkyl, 5-10 membered heteroarenyl, 4-10 membered heterocycloalkyl, C6-10 aryl-Ci 4 alkyl-, C3-10 cycloalkyl-Ci 4 alkyl-, (5-10 membered heteroarenyl)-Ci 4 alkyl-, and (4-10 membered heterocycloalkyl)-Ci 4 alkyl-, wherein the Ci-6 alkyl, C2-6 alkenyl, C2-6 alkynyl, C6-10 aryl, C3-10 cycloalkyl, 5-10 membered heteroarenyl, 4-10 membered heterocycloalkyl, C6-10 aryl-Ci 4 alkyl-, C3-10 cycloalkyl-Ci 4 alkyl-, (5-10 membered heteroarenyl)-Ci 4 alkyl- and (4-10 membered heterocycloalkyl)-Ci 4 alkyl- of Rh are each optionally substituted with 1, 2, or 3 independently selected Rj substituents;

each Rj is independently selected from Ci-6 alkyl, Ci-6 haloalkyl, C2-6 alkenyl, C2-6
25 alkynyl, C6-10 aryl, C3-10 cycloalkyl, 5-10 membered heteroarenyl, 4-10 membered heterocycloalkyl, C6-10 aryl-Ci 4 alkyl-, C3-10 cycloalkyl-Ci 4 alkyl-, (5-10 membered heteroarenyl)-Ci 4 alkyl-, (4-10 membered heterocycloalkyl)-Ci 4 alkyl-, halo, CN, NHOR R°, OR R°, SR R°, C(o)R R°, C(o)NR R°R°, C(o)OR R°, OC(o)R°, OC(o)NR R°R°, NHR R°, NR R°R°, NR2R°, NR2C(o)R°, NR2C(o)OR R°, C(=NR R°)NR R°R°, NR2C(o)R°, OR R°, SR R°, S(o)OR R°, S(o)OB R°, S(o)2R°, NR R°S(o)2R°, and S(o)2NR R°R°, wherein the Ci-e alkyl, Ci-e
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haloalkyl, C2-6 alkenyl, C2-6 alknyl, C6-10 aryl, C3-10 cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C6-10 aryl-C1-4 alkyl-, C3-10 cycloalkyl-Ci-4 alkyl-, (5-10 membered heteroaryl)-Ci-4 alkyl- and (4-10 membered heterocycloalkyl)-Ci-4 alkyl- of Rp is optionally substituted with 1, 2 or 3 independently selected R³ substituents;

or any two R⁴ substituents together with the nitrogen atom to which they are attached form a 4-, 5-, 6-, 7-, 8-, 9- or 10-membered heterocycloalkyl group optionally substituted with 1, 2 or 3 independently selected R⁵ substituents;

each R⁶ is independently selected from Cycloalkyl, C6-10 aryl, 5-6 membered heteroaryl, C6-10 aryl-C4 alkyl-, C6-10 cycloalkyl-Ci-4 alkyl-, (5-6 membered heteroaryl)-Ci-4 alkyl-, (4-7 membered heterocycloalkyl)-Ci-4 alkyl-, Ci-6 haloalkoxy, C2-6 alkenyl, C2-6 alknyl, halo, CN, OR¹, Sr, NHOR¹, C(0)R¹, C(0)NR¹, 0(0)R¹, 0(0)R¹, OC(0)NR¹R¹, NHAr¹, NR²R¹, NR²C(0)R¹, N R³C(0) N R³R¹, NR³C(0)OR¹, C(=NR⁴)NR¹R¹, NR³C(0)NR¹R¹, S(0)R¹, S(0)N R³R¹, S(0)N R³R¹, NR³O²R¹, N R⁴S(0)²N R⁴R¹, and S(0)²N R⁴R¹, wherein the Ci-e alkyl, C2-6 alkenyl, C2-6 alknyl, C3-10 cycloalkyl, 4-7 membered heterocycloalkyl, C6-10 aryl, 5-6 membered heteroaryl, C6-10 aryl-C4 alkyl-, C3-10 cycloalkyl-C4 alkyl-, (5-6 membered heteroaryl)-C1-4 alkyl-, (4-7 membered heterocycloalkyl)-Ci-4 alkyl- of R³ are each further optionally substituted by 1, 2, or 3 independently selected R⁷ substituents;

each R⁸ is independently selected from C3-6 cycloalkyl, C6-10 aryl, 5 or 6-membered heteroaryl, 4-7 membered heterocycloalkyl, C2-4 alkenyl, C2-4 alknyl, halo, C1-4 alkyl, C1-4 halooalkoxy, CN, NHOR k, OR k, Sr k, C(0)R k, C(0)NR kR k, C(0)OR k, OC(0)R k, OC(0)NR kR k, NHkR k, NR kR k, NR kC(0)R k, NR kC(0)NR kR k, NR kC(0)OR k, C(=NR k)NR kR k, NR kC(=NR k)NR kR k, S(0)R k, S(0)NR kR k, S(0)NR kR k, S(0)NR kS(0)²R k, NR kS(0)²NR kR, and S(0)²NR kR k, wherein the C1-4 alkyl, C3-6 cycloalkyl, C6-10 aryl, 5- or 6-membered heteroaryl, 4-7 membered heterocycloalkyl, C2-4 alkenyl, C2-4 alknyl, C1-4 halooalkoxy and Ci-4halooalkoxy of R⁹ are each optionally substituted with 1, 2 or 3 independently selected R⁹ substituents;

or two R⁸ groups attached to the same carbon atom of the 4- to 10-membered heterocycloalkyl taken together with the carbon atom to which they are attached form a C3-6 cycloalkyl or 4- to 6-membered heterocycloalkyl having 1-2 heteroatoms as ring members selected from O, N or S;

or any two R⁹ substituents together with the nitrogen atom to which they are attached form a 4-, 5-, 6-, 7-, 8-, 9- or 10-membered heterocycloalkyl group optionally substituted with 1, 2, or 3 independently selected R⁹ substituents;
or any two R^6 substituents together with the nitrogen atom to which they are attached
form a 4-, 5-, 6-, 7-, 8-, 9- or 10-membered heterocycloalkyl group optionally substituted with 1,
2, or 3 independently selected R^h substituents;

or any two R^R substituents together with the nitrogen atom to which they are attached
form a 4-, 5-, 6-, 7-, 8-, 9- or 10-membered heterocycloalkyl group optionally substituted with 1,
2, or 3 independently selected R^h substituents;

or any two R^r substituents together with the nitrogen atom to which they are attached
form a 4-, 5-, 6-, 7-, 8-, 9- or 10-membered heterocycloalkyl group optionally substituted with 1,
2, or 3 independently selected R^h substituents, or 1, 2, or 3 independently selected R^g
substituents;

or any two R^k substituents together with the nitrogen atom to which they are attached
form a 4-, 5-, 6-, 7-, 8-, 9- or 10-membered heterocycloalkyl group optionally substituted with 1,
2, or 3 independently selected R^h substituents, or 1, 2, or 3 independently selected R^g
substituents;

or any two R^s substituents together with the nitrogen atom to which they are attached
form a 4-, 5-, 6-, 7-, 8-, 9- or 10-membered heterocycloalkyl group optionally substituted with 1,
2, or 3 independently selected R^h substituents;

or any two R^t substituents together with the nitrogen atom to which they are attached
form a 4-, 5-, 6-, 7-, 8-, 9- or 10-membered heterocycloalkyl group optionally substituted with 1,
2, or 3 independently selected R^h substituents;

each R^l, R^k, R^o or R^t is independently selected from H, Ci-4 alkyl, C_3-6 cycloalkyl, C_6-10
aryl, 5 or 6-membered heteroaryl, 4-7 membered heterocycloalkyl, Ci-6 haloalkyl, Ci-6
haloalkoxy, C_2-4 alkenyl, and C_2-4 alkynyl, wherein the Ci-4 alkyl, C_3-6 cycloalkyl, C_6-10 aryl, 5 or
6-membered heteroaryl, 4-7 membered heterocycloalkyl, C_2-4 alkenyl, and C_2-4 alkynyl of R^l, R^k,
R^o or R^t are each optionally substituted with 1, 2 or 3 R^g substituents;

each R^s is independently selected from halo, OH, CN, -COOH, NH_2, -NH-Ci-e alkyl, -
N(Ci-6 alkyl)2, Ci-6 alkyl, Ci-6 haloalkyl, C_3-6 alkylthio, Ci-6 haloalkyl, Ci-6 haloalkoxy, phenyl, 5-6
membered heteroaryl, 4-6 membered heterocycloalkyl and C_3-6 cycloalkyl, wherein the Ci-6 alkyl,
phenyl, C_3-6 cycloalkyl, 4-6 membered heterocycloalkyl, and 5-6 membered heteroaryl of R^g are
each optionally substituted with 1, 2, or 3 substituents selected from halo, OH, CN, -COOH,
NH_2, Ci-4 alkyl, Ci-4 haloalkyl, Ci-4 haloalkoxy, phenyl, C_3-10 cycloalkyl, 5-6
membered heteroaryl and 4-6 membered heterocycloalkyl;

the subscript m is an integer of 0, 1, 2 or 3;

the subscript n is an integer of 0, 1, 2 or 3;
each subscript q is independently an integer of 1, 2, 3 or 4; and
the subscript s is an integer of 1, 2, or 3.

In some embodiments, provided herein is a compound of Formula (I), or a
pharmacologically acceptable salt or a stereoisomer thereof, wherein:

ring A is 5- to 14-membered heteroaryl, 4- to 14-membered heterocycloalkyl, C_6-10 aryl
or C_3-14 cycloalkyl, wherein the 5- to 14-membered heteroaryl and 4- to 14-membered
heterocycloalkyl each has 1-4 heteroatoms as ring members selected from N, O and S, wherein
the N or S atom as ring members is optionally oxidized and one or more carbon atoms as ring
members are each optionally replaced by a carbonyl group; and wherein ring A is optionally
substituted with 1, 2, 3, 4 or 5 R^6 substituents;

R^3 is methyl, halo, CN or haloalkyl;
R^4 is C_1-4 alkyl, C_1-4 alkoxy, C_1-4 haloalkyl, C_1-4 haloalkoxy, CN, halo, OH, -COOH, NH_2,
-NHC_1-4 alkyl or -N(CM_1-4 alkyl)_2;
R^5 is C_1-4 alkyl, C_1-4 alkoxy, C_1-4 haloalkyl, C_1-4 haloalkoxy, CN, halo, OH, -COOH, NH_2,
-NHC_1-4 alkyl or -N(CM_1-4 alkyl)_2;
R^6, R^7, R^17 and R^18 are each independently selected from H, halo, C_1-6 alkyl, C_2-6 alkenyl,
C_2-6 alkynyl, C_1-6 halocycloalkyl, C_1-6 haloalkoxy, C_1-6-aryl, C_3-10 cycloalkyl, 5-14 membered
heteroaryl, 4-10 membered heterocycloalkyl, C_6-10 aryl-C_1-4 alkyl-, C_3-10 cycloalkyl-C_1-4 alkyl-
(5-14 membered heteroaryl)-C_1-4 alkyl-, (4-10 membered heterocycloalkyl)-C_1-4 alkyl-, CN, N0,
OR^a, SR^a, NHOR^a, C(0)R^a, C(0)OR^a, C(0)NR^a, a, OC(0)R^a, OC(0)NR^a, a, NHR^a, a, NR^aR^a,
NR^aC(0)R^a, NR^aC(0)OR^a, NR^aC(0)NR^a, a, C(=NR^a)R^a, C(=NR^a)NR^a, a, NR^aC(=NR^a)NR^aR^a,
NR^aS(0)R^a, NR^aS(0)NR^aR^a, S(0)R^a, S(0)NR^aR^a, S(0)NR^aR^a, and S(0)NR^aR^a,
wherein the C_1-6 alkyl, C_2-6 alkenyl, C_2-6 alkynyl, C_6-10 aryl, C_3-10 cycloalkyl, 5-14 membered
heteroaryl, 4-10 membered heterocycloalkyl, C_6-10 aryl-C_1-4 alkyl-, C_3-10 cycloalkyl-C_1-4 alkyl-
(5-14 membered heteroaryl)-C_1-4 alkyl- and (4-10 membered heterocycloalkyl)-C_1-4 alkyl- of R^6,
R^7, R^17 and R^18 are each optionally substituted with 1, 2, 3, 4 or 5 independently selected R^b
substituents;
or two R^b substituents attached to the same ring carbon atom taken together with the ring
carbon atom to which they are attached form spiro C_3-6 cycloalkyl or spiro 4- to 7-membered
heterocycloalkyl, each of which is optionally substituted with 1, 2, or 3 independently selected R\textsuperscript{f} substituents;

each R\textsuperscript{13} is independently H, Cl-6 haloalkyl or Cl-6 alkyl optionally substituted with a substituent selected from Cl-4 alkyl, Cl-4 alkoxy, Cl-4 haloalkyl, Cl-4 haloalkoxy, CN, halo, OH, -COOH, NH\textsubscript{2}, -NHCl-4 alkyl and -N(Cl-4 alkyl)\textsubscript{2};

R\textsuperscript{14} and R\textsuperscript{15} are each independently selected from H, halo, CN, OH, -COOH, C\textsubscript{1-4} alkyl, Cl-4 alkoxy, -NHCl-4 alkyl, -N(Cl-4 alkyl)\textsubscript{2}, Cl-4 haloalkyl, Cl-4 haloalkoxy, C\textsubscript{3-6} cycloalkyl, phenyl, 5-6 membered heteroaryl and 4-6 membered heterocycloalkyl, wherein the Cl-4 alkyl, Cl-4 alkoxy, Cl-4 haloalkyl, Cl-4 haloalkoxy, C\textsubscript{3-6} cycloalkyl, phenyl, 5-6 membered heteroaryl and 4-6 membered heterocycloalkyl of R\textsuperscript{14} or R\textsuperscript{15} are each optionally substituted with 1, 2, or 3 independently selected R\textsuperscript{9} substituents;

or R\textsuperscript{14} and R\textsuperscript{15} taken together with the carbon atom to which they are attached form 3-, 4-, 5- or 6-membered cycloalkyl or 3-, 4-, 5- or 6-membered heterocycloalkyl, each of which is optionally substituted with 1 or 2 independently selected R\textsuperscript{8} substituents;

each R\textsuperscript{a} is independently selected from H, CN, Cl-6 alkyl, C\textsubscript{1-4} haloalkyl, Cl-6 alkenyl, Cl-6 alkynyl, C\textsubscript{6-10} aryl, C\textsubscript{3-10} cycloalkyl, 4-14 membered heteroaryl, 4-14 membered heterocycloalkyl, C\textsubscript{6-10} aryl-Cl-4 alkyl-, C\textsubscript{3-10} cycloalkyl-Cl-4 alkyl-, (5-14 membered heteroaryl)-Cl-4 alkyl-, and (4-14 membered heterocycloalkyl)-Cl-4 alkyl-, wherein the Cl-6 alkyl, Cl-6 alkenyl, Cl-6 alkynyl, C\textsubscript{6-10} aryl, C\textsubscript{3-10} cycloalkyl, 5-14 membered heteroaryl, 4-14 membered heterocycloalkyl, C\textsubscript{6-10} aryl-Cl-4 alkyl-, C\textsubscript{3-10} cycloalkyl-Cl-4 alkyl-, (5-14 membered heteroaryl)-Cl-4 alkyl- and (4-14 membered heterocycloalkyl)-Cl-4 alkyl- of R\textsuperscript{a} are each optionally substituted with 1, 2, 3, 4, or 5 independently selected R\textsuperscript{d} substituents;

each R\textsuperscript{d} is independently selected from Cl-6 alkyl, Cl-6 haloalkyl, halo, C\textsubscript{6-10} aryl, 5-14 membered heteroaryl, C\textsubscript{3-10} cycloalkyl, 4-14 membered heterocycloalkyl, C\textsubscript{6-10} aryl-Cl-4 alkyl-, C\textsubscript{3-10} cycloalkyl-Cl-4 alkyl-, (5-14 membered heteroaryl)-Cl-4 alkyl-, (4-14 membered heterocycloalkyl)-Cl-4 alkyl-, CN, NH\textsubscript{2}, NHOR \textsuperscript{c}, OR \textsuperscript{c}, SR \textsuperscript{c}, C(=0)R \textsuperscript{c}, C(=0)NR \textsuperscript{d}R \textsuperscript{e}, O(C(=0))R \textsuperscript{f}, OC(=0)NR \textsuperscript{g}R \textsuperscript{h}, NH heterocycloalkyl)-Cl-4 alkyl-, (5-14 membered heteroaryl)-Cl-4 alkyl-, (4-14 membered heterocycloalkyl)-Cl-4 alkyl-, (5-14 membered heteroaryl)-Cl-4 alkyl-, (4-14 membered heterocycloalkyl)-Cl-4 alkyl- of Cl-6 alkyl, Cl-6 haloalkyl, C\textsubscript{6-10} aryl, 5-14 membered heteroaryl, C\textsubscript{3-10} cycloalkyl, 4-14 membered heterocycloalkyl, C\textsubscript{6-10} aryl-Cl-4 alkyl-, C\textsubscript{3-10} cycloalkyl-Cl-4 alkyl-, (5-14 membered heteroaryl)-Cl-4 alkyl-, (4-14 membered heterocycloalkyl)-Cl-4 alkyl- of Cl-6 alkyl, Cl-6 haloalkyl, halo, C\textsubscript{6-10} aryl, 5-14 membered heteroaryl, C\textsubscript{3-10} cycloalkyl, 4-14 membered heterocycloalkyl, C\textsubscript{6-10} aryl-Cl-4 alkyl-,
each $R^a$ is independently selected from $H$, $C_{1-6}$ alkyl, $C_{6-10}$ aryl, $C_{3-10}$ cycloalkyl, $5\text{-}10$ membered heteroaryl, $4\text{-}10$ membered heterocycloalkyl, $C_{6-10}$ aryl-$C_4$ alkyl-, $C_{3-10}$ cycloalkyl-$C_4$ alkyl-, (5-10 membered heteroaryl)-$C_4$ alkyl-, and (4-10 membered heterocycloalkyl)-$C_4$ alkyl-, wherein the $C_6$ alkyl, $C_{6-10}$ alkyl, $C_{2-6}$ alkenyl, $C_{3-10}$ cycloalkyl, $5\text{-}10$ membered heteroaryl, $4\text{-}10$ membered heterocycloalkyl, $C_{6-10}$ aryl-$C_4$ alkyl-, $C_{3-10}$ cycloalkyl-$C_4$ alkyl-, (5-10 membered heteroaryl)-$C_4$ alkyl- and (4-10 membered heterocycloalkyl)-$C_4$ alkyl- of $R^a$ are each optionally substituted with 1, 2 or 3 independently selected $R^f$ substituents;

each $R^b$ substituent is independently selected from halo, $C_6$ alkyl, $C_{2-6}$ alkenyl, $C_{2-6}$ alkynyl, $C_{6-10}$ aryl, $C_{6-10}$ cycloalkyl, $5\text{-}10$ membered heteroaryl, $4\text{-}10$ membered heterocycloalkyl, $C_{6-10}$ aryl-$C_4$ alkyl-, $C_{3-10}$ cycloalkyl-$C_4$ alkyl-, (5-10 membered heteroaryl)-$C_4$ alkyl-, (4-10 membered heterocycloalkyl)-$C_4$ alkyl- of $R^b$ are each further optionally substituted with 1, 2, or 3 independently selected $R^d$ substituents;

$C_{3-10}$ cycloalkyl, $5\text{-}10$ membered heteroaryl, $4\text{-}10$ membered heterocycloalkyl, $C_{6-10}$ aryl-$C_4$ alkyl-, $C_{3-10}$ cycloalkyl-$C_4$ alkyl-, (5-10 membered heteroaryl)-$C_4$ alkyl- and (4-10 membered heterocycloalkyl)-$C_4$ alkyl- of $R^c$ are each optionally substituted with 1, 2, 3, 4, or 5 independently selected $R^f$ substituents;

each $R^d$ is independently selected from halo, $C_{1-4}$ haloalkyl, $C_{2-6}$ alkenyl, $C_{2-6}$ alkenyl, $C_{6-10}$ aryl, $C_{3-10}$ cycloalkyl, $5\text{-}10$ membered heteroaryl, $4\text{-}10$ membered heterocycloalkyl, $C_{6-10}$ aryl-$C_4$ alkyl-, $C_{3-10}$ cycloalkyl-$C_4$ alkyl-, (5-10 membered heteroaryl)-$C_4$ alkyl-, and (4-10 membered heterocycloalkyl)-$C_4$ alkyl-, wherein the $C_6$ alkyl, $C_{6-10}$ alkyl, $C_{2-6}$ alkenyl, $C_{6-10}$ aryl, $C_{3-10}$ cycloalkyl, $5\text{-}10$ membered heteroaryl, $4\text{-}10$ membered heterocycloalkyl, $C_{6-10}$ aryl-$C_4$ alkyl-, $C_{3-10}$ cycloalkyl-$C_4$ alkyl-, (5-10 membered heteroaryl)-$C_4$ alkyl- and (4-10 membered heterocycloalkyl)-$C_4$ alkyl- of $R^c$ are each optionally substituted with 1, 2, 3, 4, or 5 independently selected $R^f$ substituents;
NR₄⁺, and S₂NR₃⁺; wherein the R alkyl, Ci-4 haloalkyl, C₂-6 alkenyl, C₂-6 alkynyl, C₆-₁₀ aryl, C₃-₁₀ cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C₆-₁₀ aryl-Ci-₄ alkyl-, C₃-₁₀ cycloalkyl-Ci-₄ alkyl-, (5-10 membered heteroaryl)-Ci-₄ alkyl-, and (4-10 membered heterocycloalkyl)-Ci-₄ alkyl- of Rⁿ are each optionally substituted with 1, 2, 3, 4, or 5 independently selected Rⁿ substituents;

each Rⁿ is independently selected from Cl-₄ alkyl, Cl₂-₄ haloalkyl, C₂-₆ alkenyl, C₂-₆ alkynyl, C₆⁻₁₀ aryl, C₃⁻₁₀ cycloalkyl, 5⁻₁₀ membered heteroaryl, 4⁻₁₀ membered heterocycloalkyl, C₆⁻₁₀ aryl-Ci-₄ alkyl-, C₃⁻₁₀ cycloalkyl-Ci-₄ alkyl-, (5⁻₁₀ membered heteroaryl)-Ci-₄ alkyl-, (4⁻₁₀ membered heterocycloalkyl)-Ci-₄ alkyl-, halo, CN, NHOR, OR, SR, C(O)R, C(O)NR, OR₉, C(=NOR)N=O, N=O, C(O)=N=O, NR=O, NR²=O, NR²C(O)=O, NR²C(O)=O, OR, OR₉, OR₉=O, OR₉², OR₉²=O, wherein the R alkyl, Ci-₄ haloalkyl, C₂-₆ alkenyl, C₂-₆ alkynyl, C₆⁻₁₀ aryl, C₃⁻₁₀ cycloalkyl, 5⁻¹₀ membered heteroaryl, 4⁻¹₀ membered heterocycloalkyl, C₆⁻₁₀ aryl-Ci-₄ alkyl-, C₃⁻₁₀ cycloalkyl-Ci-₄ alkyl-, (5⁻¹₀ membered heteroaryl)-Ci-₄ alkyl-, and (4⁻¹₀ membered heterocycloalkyl)-Ci-₄ alkyl- of Rⁿ are each optionally substituted with 1, 2 or 3 independently selected Rⁿ substituents;

each Rⁿ is independently selected from H, Cl⁻₁₀ alkyl, Cl₂⁻₄ haloalkyl, C₂⁻₆ alkenyl, C₂⁻₆ alkynyl, C₆⁻₁₀ aryl, C₃⁻₁₀ cycloalkyl, 5⁻₁₀ membered heteroaryl, 4⁻₁₀ membered heterocycloalkyl, C₆⁻₁₀ aryl-Ci-₄ alkyl-, C₃⁻₁₀ cycloalkyl-Ci-₄ alkyl-, (5⁻₁₀ membered heteroaryl)-Ci-₄ alkyl-, and (4⁻¹₀ membered heterocycloalkyl)-Ci-₄ alkyl-, wherein the C⁻₁₀ alkyl, Cl⁻₄ haloalkyl, C₂⁻₆ alkenyl, C₂⁻₆ alkynyl, C₆⁻₁₀ aryl, C₃⁻₁₀ cycloalkyl, 5⁻₁₀ membered heteroaryl, 4⁻₁₀ membered heterocycloalkyl, C₆⁻₁₀ aryl-Ci-₄ alkyl-, C₃⁻₁₀ cycloalkyl-Ci-₄ alkyl-, (5⁻₁₀ membered heteroaryl)-Ci-₄ alkyl-, and (4⁻¹₀ membered heterocycloalkyl)-Ci-₄ alkyl- of Rⁿ are each optionally substituted with 1, 2, or 3 independently selected Rⁿ substituents;

each Rⁿ is independently selected from Cl⁻₁₀ alkyl, Cl₂⁻₄ haloalkyl, C₂⁻₆ alkenyl, C₂⁻₆ alkynyl, C₆⁻₁₀ aryl, C₃⁻₁₀ cycloalkyl, 5⁻₁₀ membered heteroaryl, 4⁻₁₀ membered heterocycloalkyl, C₆⁻₁₀ aryl-Ci-₄ alkyl-, C₃⁻₁₀ cycloalkyl-Ci-₄ alkyl-, (5⁻₁₀ membered heteroaryl)-Ci-₄ alkyl-, (4⁻₁₀ membered heterocycloalkyl)-Ci-₄ alkyl-, halo, CN, NHOR, OR, SR, C(O)R, C(O)NR, OR₉, C(=NOR)N=O, N=O, C(O)=N=O, NR=O, NR²=O, NR²C(O)=O, NR²C(O)=O, OR, OR₉, OR₉², OR₉²=O, wherein the C⁻₁₀ alkyl, Cl⁻₄ haloalkyl, C₂⁻₆ alkenyl, C₂⁻₆ alkynyl, C₆⁻₁₀ aryl, C₃⁻₁₀ cycloalkyl, 5⁻₁₀ membered heteroaryl, 4⁻₁₀ membered heterocycloalkyl, C₆⁻₁₀ aryl-Ci-₄ alkyl-, C₃⁻₁₀ cycloalkyl-Ci-₄ alkyl-, (5⁻₁₀ membered heteroaryl)-Ci-₄ alkyl-, and (4⁻¹₀ membered heterocycloalkyl)-Ci-₄ alkyl- of Rⁿ are each optionally substituted with 1, 2, or 3 independently selected Rⁿ substituents;
heteroaryl)-C1-4 alkyl- and (4-10 membered heterocycloalkyl)-C1-4 alkyl- of R p is optionally substituted with 1, 2 or 3 independently selected R h substituents;

or any two R x substituents together with the nitrogen atom to which they are attached form a 4-, 5-, 6-, 7-, 8-, 9- or 10-membered heterocycloalkyl group optionally substituted with 1, 2 or 3 independently selected R h substituents;

each R h is independently selected from C1-6 alkyl, C3-10 cycloalkyl, 4-7 membered heterocycloalkyl, C6-10 aryl, 5-6 membered heteroaryl, C6-10 aryl-C1-4 alkyl-, C3-10 cycloalkyl-C1-4 alkyl-, (5-6 membered heteroaryl)-C1-4 alkyl-, (4-7 membered heterocycloalkyl)-C1-4 alkyl-, C1-6 haloalkyl, C1=C1 haloalkoxy, C2-6 alkenyl, C2-6 alkylnyl, halo, CN, OR, SR, NHOR, C(0)R, O(O)NR, C(0)OR, C(0)NR, NHR, S(0)R, N(R)C(0)R i, N(R)C(0)NR, N(R)2R, N(R)S(0)R, N(R)S(0)NR, N(R)2S(0)R, and S(0)2NRR, wherein the C1=C1 alkyl, C2-6 alkenyl, C2-6 alkylnyl, C3-10 cycloalkyl, 4-7 membered heterocycloalkyl, C6-10 aryl, 5-6 membered heteroaryl, C6-10 aryl-C1-4 alkyl-, C3-10 cycloalkyl-C1-4 alkyl-, (5-6 membered heteroaryl)-C1-4 alkyl-, (4-7 membered heterocycloalkyl)-C1-4 alkyl- of R h are each further optionally substituted by 1, 2, or 3 independently selected R i substituents;

each R i is independently selected from C3-6 cycloalkyl, C6-10 aryl, 5 or 6-membered heteroaryl, 4-7 membered heterocycloalkyl, C2-4 alkenyl, C2-4 alkylnyl, halo, C1-4 alkyl, C1-4 haloalkyl, C1=C1 haloalkoxy, CN, NHOR R k, C(0)R k, C(0)OR k, C(0)NR k R k, C(0)NR k OR k, OC(0)NR k R k, NHR k, NR k R k, NR k C(0)R k, NR k C(0)NR k R k, NR k C(0)OR k, C(0)NR k R k, NR k C(0)NR k R k, S(0)NR k R k, S(0)NR k S(0)NR k R k, S(0)2R k, NR k S(0)2R k, NR k S(0)2R k, and S(0)2NR k R k, wherein the C1-4 alkyl, C3-6 cycloalkyl, C6-10 aryl, 5- or 6-membered heteroaryl, 4-7 membered heterocycloalkyl, C2-4 alkenyl, C2-4 alkylnyl, C1-4 haloalkyl and C1=C1 haloalkoxy of R i are each optionally substituted with 1, 2 or 3 independently selected R f substituents;

or two R h groups attached to the same carbon atom of the 4- to 10-membered heterocycloalkyl taken together with the carbon atom to which they are attached form a C3-6 cycloalkyl or 4- to 6-membered heterocycloalkyl having 1-2 heteroatoms as ring members selected from O, N or S;

or any two R x substituents together with the nitrogen atom to which they are attached form a 4-, 5-, 6-, 7-, 8-, 9- or 10-membered heterocycloalkyl group optionally substituted with 1, 2, or 3 independently selected R h substituents;

or any two R e substituents together with the nitrogen atom to which they are attached form a 4-, 5-, 6-, 7-, 8-, 9- or 10-membered heterocycloalkyl group optionally substituted with 1, 2, or 3 independently selected R h substituents;
or any two $R^8$ substituents together with the nitrogen atom to which they are attached form a 4-, 5-, 6-, 7-, 8-, 9- or 10-membered heterocycloalkyl group optionally substituted with 1, 2, or 3 independently selected $R^h$ substituents;

or any two $R^1$ substituents together with the nitrogen atom to which they are attached form a 4-, 5-, 6-, 7-, 8-, 9- or 10-membered heterocycloalkyl group optionally substituted with 1, 2, or 3 independently selected $R^h$ substituents;

or any two $R^k$ substituents together with the nitrogen atom to which they are attached form a 4-, 5-, 6-, 7-, 8-, 9- or 10-membered heterocycloalkyl group optionally substituted with 1, 2, or 3 independently selected $R^h$ substituents;

or any two $R^2$ substituents together with the nitrogen atom to which they are attached form a 4-, 5-, 6-, 7-, 8-, 9- or 10-membered heterocycloalkyl group optionally substituted with 1, 2, or 3 independently selected $R^h$ substituents;

or any two $R^f$ substituents together with the nitrogen atom to which they are attached form a 4-, 5-, 6-, 7-, 8-, 9- or 10-membered heterocycloalkyl group optionally substituted with 1, 2, or 3 independently selected $R^h$ substituents;

each $R^1$, $R^8$, $R^o$ or $R^f$ is independently selected from H, Ci-4 alkyl, C$_3$-6 cycloalkyl, C$_{6-10}$ aryl, 5 or 6-membered heteroaryl, 4-7 membered heterocycloalkyl, Ci-6 haloalkyl, Ci-6 haloalkoxy, C$_2$-4 alkenyl, and C$_2$-4 alkynyl, wherein the Ci-4 alkyl, C$_3$-6 cycloalkyl, C$_{6-10}$ aryl, 5 or 6-membered heteroaryl, 4-7 membered heterocycloalkyl, C$_2$-4 alkenyl, and C$_2$-4 alkynyl of $R^1$, $R^k$, $R^o$ or $R^f$ are each optionally substituted with 1, 2 or 3 $R^8$ substituents;

each $R^8$ is independently selected from halo, OH, CN, -COOH, NH$_2$, -NH-Ci-e alkyl, -N(Ci-6 alkyl)$_2$, Ci-6 alkyl, Ci-6 alkoxy, C$_{1-6}$ alkythio, Ci-6 haloalkyl, Ci-6 haloalkoxy, phenyl, 5-6 membered heteroaryl, 4-6 membered heterocycloalkyl and C$_3$-6 cycloalkyl, wherein the Ci-6 alkyl, phenyl, C$_3$-6 cycloalkyl, 4-6 membered heterocycloalkyl, and 5-6 membered heteroaryl of $R^8$ are each optionally substituted with 1, 2, or 3 substituents selected from halo, OH, CN, -COOH, NH$_2$, Ci-4 alkyl, C$_1$-4 alkoxy, C$_1$-4 haloalkyl, C$_1$-4 haloalkoxy, phenyl, C$_3$-10 cycloalkyl, 5-6 membered heteroaryl and 4-6 membered heterocycloalkyl;

the subscript $m$ is an integer of 0, 1, 2 or 3;

the subscript $n$ is an integer of 0, 1, 2 or 3;

each subscript $q$ is independently an integer of 1, 2, 3 or 4; and

the subscript $s$ is an integer of 1, 2, or 3.

In some embodiments, provided herein is a compound of Formula (I), or a pharmaceutically acceptable salt or a stereoisomer thereof, wherein:
ring A is 5- to 14-membered heteroaryl, 4- to 14-membered heterocycloalkyl, C_{6-10} aryl or C_{3-14} cycloalkyl, wherein the 5- to 14-membered heteroaryl and 4- to 14-membered heterocycloalkyl each has 1-4 heteroatoms as ring members selected from N, O and S, wherein the N or S atom as ring members is optionally oxidized and one or more carbon atoms as ring members are each optionally replaced by a carbonyl group; and wherein ring A is optionally substituted with 1, 2, 3, 4 or 5 R^6 substituents:

L is a bond, \(-\text{C}(0)\text{NR}^{13-}\), \(-\text{NR}^{13}\text{C}(0)\text{R}^{13-}\), \(\text{O}^{13-}\), \(\text{N}^{13}(\text{CR}^{14}\text{R}^{15})^{q}_{2}^{13}\), \(-\text{O}(\text{CR}^{14}\text{R}^{15})^{q}_{4}^{13}\), \(-\text{NR}^{13}(\text{CR}^{14}\text{R}^{15})^{q}_{4}^{13}\), \(-\text{CH}^{13-}\text{CH}^{13-}\), \(-\text{C}^{13}=\text{C}^{13-}\), \(-\text{SO}^{2}\text{NR}^{13-}\), \(-\text{NR}^{13}\text{SO}^{2}_{2}^{13-}\), \(-\text{NR}^{13}\text{C}(0)\text{R}^{13-}\), \(-\text{OC}(0)\text{NR}^{13-}\) or \(-\text{NR}^{13}\text{C}(0)\text{NR}^{13-}\);

X is N or CR^{17};

R^3 is methyl, halo, CN or Ci-4haloalkyl;

R^4 is Ci-4 alkyl, Ci-4 alkoxy, C_{M} haloalkyl, C_{M} haloalkoxy, CN, halo, OH, -COOH, NH_{2}, -NHCl_{4} alkyl or -N(Ci-4 alkyl);^2;

R^5 is C_{M} alkyl, Ci-4 alkoxy, C_{M} haloalkyl, C_{M} haloalkoxy, CN, halo, OH, -COOH, NH_{2}, -NHCl_{4} alkyl or -N(CM alkyl)^2;

R^6, R^7, R^{17} and R^{18} are each independently selected from H, halo, Ci-6 alkyl, C_{3-6} alkenyl, C_{3-6} alkynyl, Ci-6 haloalkyl, Ci-6 haloalkoxy, C_{6-10} cycloalkyl, 5-14 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-Ci-4 alkyl-^1, C_{3-10} cycloalkyl-Ci-4 alkyl-, (5-14 membered heteroaryl)-Ci-4 alkyl-, (4-10 membered heterocycloalkyl)-Ci-4 alkyl-, CN, N, O,

OR^a, SR^a, NHOR^a, C(0)R^a, C(0)NR^a, C(0)OR^a, OC(0)R^a, OC(0)NR^a, NR^a, NR-R^{a},

NR^{b}C(0)R^a, NR^{b}N(0)NR^{b}R^{a}, C(=\text{NR}^{b})R^{a}, C(=\text{NR}^{b})\text{NR}^{b}R^{a}, \text{NR}^{b}C(=\text{NR}^{b})\text{NR}^{b}R^{a}, \text{NR}^{b}S(0)R^{a}, \text{NR}^{b}S(0)_{2}^{b}R^{a}, \text{NR}^{b}S(0)_{2}^{b}NR^{b}R^{a}, \text{S}(0)R^{a}, \text{S}(0)NR^{b}R^{a}, \text{S}(0)_{2}^{b}R^{a}, \text{S}(0)_{2}^{b}NR^{b}R^{a},

wherein the Ci-6 alkyl, C_{3-6} alkenyl, C_{3-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-14 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-Ci-4 alkyl-, C_{3-10} cycloalkyl-Ci-4 alkyl-, (5-14 membered heteroaryl)-Ci-4 alkyl- and (4-10 membered heterocycloalkyl)-Ci-4 alkyl- of R^6, R^7, R^{17} and R^{18} are each optionally substituted with 1, 2, 3, 4 or 5 independently selected R^b substituents;

or two R^6 substituents attached to the same ring carbon atom taken together with the ring carbon atom to which they are attached form spiro C_{3-6} cycloalkyl or spiro 4- to 7-membered heterocycloalkyl, each of which is optionally substituted with 1, 2, or 3 independently selected R^f substituents;

each R^{13} is independently H, Ci-6 haloalkyl or Ci-6 alkyl optionally substituted with a substituent selected from Ci-4 alkyl, Ci-4 alkoxy, C_{M} haloalkyl, Ci-4 haloalkoxy, CN, halo, OH, -COOH, NH_{2}, -NHCl_{4} alkyl and -N(CM alkyl);^2;
R\textsuperscript{14} and R\textsuperscript{15} are each independently selected from H, halo, CN, OH, -COOH, C\textsubscript{1-4} alkyl, Ci-4 alkoxy, -NHCi-4 alkyl, -N(Ci-4 alkyl\textsubscript{2}, Ci-4 haloalkyl, Ci-4 haloalkoxy, C\textsubscript{3-6} cycloalkyl, phenyl, 5-6 membered heteroaryl and 4-6 membered heterocycloalkyl, wherein the Ci-4 alkyl, Ci-4 alkoxy, Ci-4 haloalkyl, Ci-4 haloalkoxy, C\textsubscript{3-6} cycloalkyl, phenyl, 5-6 membered heteroaryl and 4-6 membered heterocycloalkyl of R\textsuperscript{14} or R\textsuperscript{15} are each optionally substituted with 1, 2, or 3 independently selected R\textsuperscript{8} substituents;

or R\textsuperscript{14} and R\textsuperscript{15} taken together with the carbon atom to which they are attached form 3-, 4-, 5- or 6-membered cycloalkyl or 3-, 4-, 5- or 6-membered heterocycloalkyl, each of which is optionally substituted with 1 or 2 independently selected R\textsuperscript{8} substituents;

each R\textsuperscript{2} is independently selected from H, CN, Ci-6 alkyl, Ci-4 haloalkyl, C\textsubscript{2-6} alkenyl, C\textsubscript{6-10} aryl, C\textsubscript{3-10} cycloalkyl, 5-14 membered heteroaryl, 4-14 membered heterocycloalkyl, C\textsubscript{6-10} aryl-Ci-4 alkyl, C\textsubscript{3-10} cycloalkyl-Ci-4 alkyl, (5-14 membered heteroaryl)-Ci-4 alkyl, and (4-14 membered heterocycloalkyl)-Ci-4 alkyl, wherein the Ci-6 alkyl, C\textsubscript{2-6} alkenyl, C\textsubscript{6-10} aryl, C\textsubscript{3-10} cycloalkyl, 5-14 membered heteroaryl, 4-14 membered heterocycloalkyl, C\textsubscript{6-10} aryl-Ci-4 alkyl, C\textsubscript{3-10} cycloalkyl-Ci-4 alkyl, (5-14 membered heteroaryl)-Ci-4 alkyl- and (4-14 membered heterocycloalkyl)-Ci-4 alkyl- of R\textsuperscript{2} are each optionally substituted with 1, 2, 3, 4, or 5 independently selected R\textsuperscript{d} substituents;

each R\textsuperscript{d} is independently selected from Ci-6 alkyl, Ci-6 haloalkyl, halo, C\textsubscript{6-10} aryl, 5-14 membered heteroaryl, C\textsubscript{3-10} cycloalkyl, 4-14 membered heterocycloalkyl, C\textsubscript{6-10} aryl-Ci-4 alkyl, C\textsubscript{3-10} cycloalkyl-Ci-4 alkyl, (5-14 membered heteroaryl)-Ci-4 alkyl, (4-14 membered heterocycloalkyl)-Ci-4 alkyl, CN, NH\textsubscript{2}, NHOR\textsuperscript{6}, OR\textsuperscript{5}, SR\textsuperscript{5}, C(0)R\textsuperscript{5}, C(0)NR\textsuperscript{5}, C(0)OR\textsuperscript{5}, OC(0)R\textsuperscript{5}, OC(0)NR\textsuperscript{5}, NHR\textsuperscript{5}, NR\textsuperscript{5}R\textsuperscript{5}, NHC(0)R\textsuperscript{5}, NR\textsuperscript{5}C(0)NR\textsuperscript{5}, NR\textsuperscript{5}C(0)OR\textsuperscript{5}, C(=NR\textsuperscript{5})NR\textsuperscript{5}R\textsuperscript{5}, NR\textsuperscript{5}C(=NR\textsuperscript{5})NR\textsuperscript{5}R\textsuperscript{5}, NR\textsuperscript{5}C(=NOH)NR\textsuperscript{5}R\textsuperscript{5}, NR\textsuperscript{5}C(=NCN)NR\textsuperscript{5}R\textsuperscript{5}, S(0)R\textsuperscript{5}, S(0)R\textsuperscript{5}S(0)R\textsuperscript{5}, S(0)NR\textsuperscript{5}R\textsuperscript{5}, S(0)NR\textsuperscript{5}R\textsuperscript{5}, and S(0)NR\textsuperscript{5}R\textsuperscript{5}, wherein the Ci-e alkyl, Ci-6 haloalkyl, C\textsubscript{6-10} aryl, 5-14 membered heteroaryl, C\textsubscript{3-10} cycloalkyl, 4-14 membered heterocycloalkyl, C\textsubscript{6-10} aryl-Ci-4 alkyl, C\textsubscript{3-10} cycloalkyl-Ci-4 alkyl, (5-14 membered heteroaryl)-Ci-4 alkyl- and (4-14 membered heterocycloalkyl)-Ci-4 alkyl- of R\textsuperscript{2} are each optionally substituted with 1, 2, or 3 independently selected R\textsuperscript{f} substituents;

each R\textsuperscript{f} is independently selected from H, Ci-6 alkyl, Ci-6 haloalkyl, C\textsubscript{2-6} alkenyl, C\textsubscript{6-10} aryl, C\textsubscript{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C\textsubscript{6-10} aryl-Ci-4 alkyl, C\textsubscript{3-10} cycloalkyl-Ci-4 alkyl, (5-10 membered heteroaryl)-Ci-4 alkyl- and (4-10 membered heterocycloalkyl)-Ci-4 alkyl- wherein the Ci-6 alkyl, Ci-6 haloalkyl, C\textsubscript{2-6} alkenyl, C\textsubscript{6-10} aryl, C\textsubscript{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C\textsubscript{6-10} aryl-Ci-4 alkyl, C\textsubscript{3-10} cycloalkyl-Ci-4 alkyl, (5-10 membered heteroaryl)-
Ci-4 alkyl- and (4-10 membered heterocycloalkyl)-Ci-4 alkyl- of R are each optionally substituted with 1, 2 or 3 independently selected R substituents;

each R substituent is independently selected from halo, Ci-6 alkyl, C2-6 alkenyl, C2-6 alkynyl, Ci-6 haloalkyl, Ci-6 haloalkoxy, C6-10 aryl, C3-10 cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C6-10 aryl-Ci-4 alkyl-, C3-10 cycloalkyl-Ci-4 alkyl-, (5-10 membered heterocycloalkyl)-Ci-4 alkyl-, (4-10 membered heterocycloalkyl)-Ci-4 alkyl-, CN, OH, NH2, NO2, NHOR\(^5\), OR\(^5\), SR\(^5\), C(0)R\(^5\), C(0)NR\(^5\), C(0)OR\(^5\), OC(0)R\(^5\), OC(0)NR - R\(^5\), C(=NR\(^5\))NR\(^5\), N\(^5\)R\(^5\), C(=NR\(^5\))NR\(^5\), NHR\(^5\), NR\(^2\)R\(^5\), NR\(^2\)C(0)R\(^5\), NR\(^2\)C(0)OR\(^5\), NR\(^2\)C(0)NR - R\(^5\), NR\(^2\)S(0)R\(^5\), NR\(^2\)S(0)R\(^2\)R\(^5\), NR\(^2\)S(0)R\(^2\)R\(^5\), S(0)OR\(^5\), S(0)NR - R\(^5\), S(0)NR - R\(^5\) and S(0)NR - R\(^5\); wherein the Ci-6 alkyl, Ci-6 haloalkyl, Ci-6 haloalkoxy, C2-6 alkenyl, C2-6 alkynyl, C6-10 aryl, C3-10 cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C6-10 aryl-Ci-4 alkyl-, C3-10 cycloalkyl-Ci-4 alkyl-, (5-10 membered heteroaryl)-Ci-4 alkyl- and (4-10 membered heterocycloalkyl)-Ci-4 alkyl- of R are each further optionally substituted with 1, 2, or 3 independently selected R substituents;

each R is independently selected from H, Ci-6 alkyl, Ci-6 haloalkyl, C2-6 alkenyl, C2-6 alkynyl, C6-10 aryl, C3-10 cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C6-10 aryl-Ci-4 alkyl-, C3-10 cycloalkyl-Ci-4 alkyl-, (5-10 membered heteroaryl)-Ci-4 alkyl- and (4-10 membered heterocycloalkyl)-Ci-4 alkyl- wherein the Ci-6 alkyl, C2-6 alkenyl, C2-6 alkynyl, C6-10 aryl, C3-10 cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C6-10 aryl-Ci-4 alkyl-, C3-10 cycloalkyl-Ci-4 alkyl-, (5-10 membered heteroaryl)-Ci-4 alkyl- and (4-10 membered heterocycloalkyl)-Ci-4 alkyl- of R are each optionally substituted with 1, 2, 3, 4, or 5 independently selected R substituents;

each R is independently selected from C1-4 alkyl, C1-4 haloalkyl, C2-6 alkenyl, C2-6 alkynyl, C6-10 aryl, C3-10 cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C6-10 aryl-Ci-4 alkyl-, C3-10 cycloalkyl-Ci-4 alkyl-, (5-10 membered heteroaryl)-Ci-4 alkyl- and (4-10 membered heterocycloalkyl)-Ci-4 alkyl- wherein the Ci-6 alkyl, C2-6 alkenyl, C2-6 alkynyl, C6-10 aryl, C3-10 cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C6-10 aryl-Ci-4 alkyl-, C3-10 cycloalkyl-Ci-4 alkyl-, (5-10 membered heteroaryl)-Ci-4 alkyl- and (4-10 membered heterocycloalkyl)-Ci-4 alkyl- of R are each optionally substituted with 1, 2, 3, 4, or 5 independently selected R substituents;
each R is independently selected from Cl-4 alkyl, Cl-4 haloalkyl, C-6 alkyl, C-2 alkynyl, C-3-10 cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C-6-10 aryl-Ci-4 alkyl-, C-3-10 cycloalkyl-Ci-4 alkyl-, (5-10 membered heteroaryl)-Ci-4 alkyl-, (4-10 membered heterocycloalkyl)-Ci-4 alkyl-, halo, CN, NHOR, OR, SR, C(O)R, C(O)NR, R, C(=NR)NR, OC(O)R, OC(NR)R, NHR, NR, NRC(O)R, NRRC(O)NR, NRC(O)OR, C(=NR)NR, NHC(O)NR, S(=O)NR, S(O)NR, S(O)SR, S(O)2N, wherein the C alkyl, Cl-4 haloalkyl, C-2 alkynyl, C-6 alkyl, C-6-10 aryl, C-3-10 cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C-6-10 aryl-Ci-4 alkyl-, C-3-10 cycloalkyl-Ci-4 alkyl-, (5-10 membered heteroaryl)-Ci-4 alkyl-, and (4-10 membered heterocycloalkyl)-Ci-4 alkyl- of R are each optionally substituted with 1, 2 or 3 independently selected R substituents;

each R is independently selected from H, Cl-6 alkyl, Cl-4 haloalkyl, C-2-6 alkynyl, C-6-10 aryl, C-3-10 cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C-6-10 aryl-Ci-4 alkyl-, C-3-10 cycloalkyl-Ci-4 alkyl-, (5-10 membered heteroaryl)-Ci-4 alkyl-, and (4-10 membered heterocycloalkyl)-Ci-4 alkyl-, wherein the Cl-6 alkyl, C-2-6 alkynyl, C-6-10 aryl, C-3-10 cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C-6-10 aryl-Ci-4 alkyl-, C-3-10 cycloalkyl-Ci-4 alkyl-, (5-10 membered heteroaryl)-Ci-4 alkyl- and (4-10 membered heterocycloalkyl)-Ci-4 alkyl- of R are each optionally substituted with 1, 2, or 3 independently selected R substituents;

each R is independently selected from Cl-6 alkyl, Cl-6 haloalkyl, C-2-6 alkynyl, C-6-10 aryl, C-3-10 cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C-6-10 aryl-Ci-4 alkyl-, C-3-10 cycloalkyl-Ci-4 alkyl-, (5-10 membered heteroaryl)-Ci-4 alkyl-, (4-10 membered heterocycloalkyl)-Ci-4 alkyl-, halo, CN, NHOR, OR, SR, C(O)R, C(O)NR, R, C(=NR)NR, OC(O)R, OC(NR)R, NHR, NR, NRC(O)R, NRRC(O)NR, NRC(O)OR, C(=NR)NR, NHC(O)NR, S(=O)NR, S(O)NR, S(O)SR, S(O)2N, wherein the Cl-e alkyl, Cl-e haloalkyl, C-2-6 alkynyl, C-6-10 aryl, C-3-10 cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C-6-10 aryl-Ci-4 alkyl-, C-3-10 cycloalkyl-Ci-4 alkyl-, (5-10 membered heteroaryl)-Ci-4 alkyl- and (4-10 membered heterocycloalkyl)-Ci-4 alkyl- of R is optionally substituted with 1, 2 or 3 independently selected R substituents;
or any two R substituents together with the nitrogen atom to which they are attached form a 4-, 5-, 6-, 7-, 8-, 9- or 10-membered heterocycloalkyl group optionally substituted with 1, 2 or 3 independently selected R substituents;
each R^h is independently selected from C_i-6 alkyl, C_3-10 cycloalkyl, 4-7 membered heterocycloalkyl, C_6-10 aryl, 5-6 membered heteroaryl, C_6-10 aryl-Ci-4 alkyl-, C_3-10 cycloalkyl-Ci-4 alkyl-, (5-6 membered heteroaryl)-Ci-4 alkyl-, (4-7 membered heterocycloalkyl)-Ci-4 alkyl-, Ci-6 haloalkyl, Ci-chaloalkoxy, C_2-6 alkenyl, C_2-6 alkylnyl, halo, CN, OR^1, SR^1, NHOR^1, C(O)R^1, C(O)NR^1, 0(0)NR^1, 00(0)NR^1, NHR^1, NR^1R^1, NRC(O)R^1, NRC(O)NR^1, NRC(O)NR^1, NR'C(O)OR^1, C(=NR^1)NR^1R^1, NR'C=ONRONR^1R^1, S(0)^a, S(0)NR^1R^1, S(0)2NR^1R^1, NR^1S(0)2NR^1R^1, and S(0)2NR^1R^1, wherein the Ci-e alkyl, C_2-6 alkenyl, C_2-6 alkylnyl, C_3-10 cycloalkyl, 4-7 membered heterocycloalkyl, C_6-10 aryl, 5-6 membered heteroaryl, C_6-10 aryl-Ci-4 alkyl-, C_3-10 cycloalkyl-Ci-4 alkyl-, (5-6 membered heteroaryl)-C_i-4 alkyl-, (4-7 membered heterocycloalkyl)-Ci-4 alkyl- of R^h are each further optionally substituted by 1, 2, or 3 independently selected R^j substituents;

each R^j is independently selected from C_3-6 cycloalkyl, C_6-10 aryl, 5 or 6-membered heteroaryl, 4-7 membered heterocycloalkyl, C_2-4 alkenyl, C_2-4 alkylnyl, halo, C_i-4 alkyl, C_i-4 haloalkyl, Ci-chaloalkoxy, CN, NHOR^k, 0 R^k, SR^k, C(O)R^k, C(O)NR^k, C(O)OR^k, OC(0)NR^k, kR^k, NHR^k, NR^kR^k, NR^kC(O)R^k, NR^kC(O)NR^k, NR^kC(O)OR^k, C(=NR^k)NR^kR^k, NR^kC(=NR^k)NR^kR^k, S(0)R^k, S(0)NR^kR^k, S(0)2NR^kR^k, NR^kS(0)2NR^kR^k, and S(0)NR^kR^k, wherein the C_i-4 alkyl, C_3-6 cycloalkyl, C_6-10 aryl, 5- or 6-membered heteroaryl, 4-7 membered heterocycloalkyl, C_2-4 alkenyl, C_2-4 alkylnyl, C_i-4 haloalkyl and Ci-chaloalkoxy of R^j are each optionally substituted with 1, 2 or 3 independently selected R^g substituents;

or two R^h groups attached to the same carbon atom of the 4- to 10-membered heterocycloalkyl taken together to form a C_3-6 cycloalkyl or 4- to 6-membered heterocycloalkyl having 1-2 heteroatoms as ring members selected from O, N or S;

or any two R^c substituents together with the nitrogen atom to which they are attached form a 4-, 5-, 6-, 7-, 8-, 9- or 10-membered heterocycloalkyl group optionally substituted with 1, 2, or 3 independently selected R^h substituents;

or any two R^e substituents together with the nitrogen atom to which they are attached form a 4-, 5-, 6-, 7-, 8-, 9- or 10-membered heterocycloalkyl group optionally substituted with 1, 2, or 3 independently selected R^h substituents;

or any two R^f substituents together with the nitrogen atom to which they are attached form a 4-, 5-, 6-, 7-, 8-, 9- or 10-membered heterocycloalkyl group optionally substituted with 1, 2, or 3 independently selected R^h substituents;
or any two \( R^1 \) substituents together with the nitrogen atom to which they are attached form a 4-, 5-, 6-, 7-, 8-, 9- or 10-membered heterocycloalkyl group optionally substituted with 1, 2, or 3 independently selected \( R^9 \) substituents;

or any two \( R^k \) substituents together with the nitrogen atom to which they are attached form a 4-, 5-, 6-, 7-, 8-, 9- or 10-membered heterocycloalkyl group optionally substituted with 1, 2, or 3 independently selected \( R^9 \) substituents;

or any two \( R^s \) substituents together with the nitrogen atom to which they are attached form a 4-, 5-, 6-, 7-, 8-, 9- or 10-membered heterocycloalkyl group optionally substituted with 1, 2, or 3 independently selected \( R^h \) substituents;

or any two \( R^t \) substituents together with the nitrogen atom to which they are attached form a 4-, 5-, 6-, 7-, 8-, 9- or 10-membered heterocycloalkyl group optionally substituted with 1, 2, or 3 independently selected \( R^h \) substituents;

each \( R^1, R^k, R^s \) or \( R^t \) is independently selected from \( H, \text{Ci}-4 \) alkyl, \( C_3-6 \) cycloalkyl, \( C_6-10 \) aryl, 5 or 6-membered heteroaryl, 4-7 membered heterocycloalkyl, \( \text{Ci}-6 \) haloalkyl, \( \text{Ci}-6 \) halalkoxy, \( \text{C}_2-4 \) alkenyl, and \( \text{C}_2-4 \) alkynyl, wherein the \( \text{Ci}-4 \) alkyl, \( C_3-6 \) cycloalkyl, \( C_6-10 \) aryl, 5 or 6-membered heteroaryl, 4-7 membered heterocycloalkyl, \( \text{C}_2-4 \) alkenyl, and \( \text{C}_2-4 \) alkynyl of \( R^1, R^k, R^s \) are each optionally substituted with 1, 2 or 3 \( R^9 \) substituents;

each \( R^s \) is independently selected from halo, \( \text{OH}, \text{CN}, -\text{COOH}, \text{NH}_2, -\text{NH-Ci-e alkyl}, -\text{N(Ci-6 alkyl)}_2, \text{Ci}-6 \) alkyl, \( \text{Ci}-6 \) alkoxy, \( \text{C}_1-6 \) alkylthio, \( \text{Ci}-6 \) haloalkyl, \( \text{Ci}-6 \) haloalkoxy, \( \text{phenyl}, 5-6 \) membered heteroaryl, \( \text{C}_3-6 \) cycloalkyl, \( \text{C}_3-6 \) cycloalkyl, \( \text{C}_6-10 \) aryl, 4-6 membered heterocycloalkyl, and \( \text{C}_3-6 \) cycloalkyl, wherein the \( \text{Ci}-6 \) alkyl, \( \text{phenyl}, \text{C}_3-6 \) cycloalkyl, \( \text{C}_3-6 \) cycloalkyl, \( \text{C}_6-10 \) aryl, and 5-6 membered heteroaryl of \( R^k \) are each optionally substituted with 1, 2, or 3 substituents selected from halo, \( \text{OH}, \text{CN}, -\text{COOH}, \text{NH}_2, \text{Ci-4 alkyl}, \text{C}_1-4 \) alkoxy, \( \text{C}_1-4 \) haloalkyl, \( \text{C}_1-4 \) haloalkoxy, \( \text{phenyl}, \text{C}_3-10 \) cycloalkyl, 5-6 membered heteroaryl and 4-6 membered heterocycloalkyl;

the subscript \( m \) is an integer of 0, 1, 2 or 3;

the subscript \( n \) is an integer of 0, 1, 2 or 3;

each subscript \( q \) is independently an integer of 1, 2, 3 or 4; and

the subscript \( s \) is an integer of 1, 2, or 3.

In some embodiments, provided herein is a compound of Formula (I), or a pharmaceutically acceptable salt or a stereoisomer thereof, wherein:

ring \( A \) is 5- to 14-membered heteroaryl, 4- to 14-membered heterocycloalkyl, \( C_6-10 \) aryl or \( C_3-10 \) cycloalkyl, wherein the 5- to 10-membered heteroaryl and 4- to 11-membered heterocycloalkyl each has 1-4 heteroatoms as ring members selected from \( N, O \) and \( S \), wherein
the N or S atom as ring members is optionally oxidized and one or more carbon atoms as ring members are each optionally replaced by a carbonyl group; and wherein ring A is optionally substituted with 1, 2, 3, 4 or 5 independently selected R^6 substituents;

L is a bond, -C(0)NR^13-, -NR^13C(0)-, O, -(CR^14R^15)q-, -(CR^14R^15)q0-, -O(CR^14R^15)q-, -NR^13-, -(CR^14R^15)q-NR^13-, -NR^13-(CR^14R^15)q-, -CH=CH-, —C≡C—, -SO2NR^13-, -NR^13S0^2-, -NR^15S0^2-, or -NR^13C(0)NR^11-;

X is N or CR^17;

R^3 is methyl, halo, CN or C1-4haloalkyl;

R^4 is C1-4 alkyl, C1-4 alkoxy, C1-4 haloalkyl, C1-4 haloalkoxy, CN, halo, OH, -COOH, NH_2,

-NHCi-4 alkyl or -N(CM alkyl)_2;

R^5 is C1-4 alkyl, C1-4 alkoxy, C1-4 haloalkyl, C1-4 haloalkoxy, CN, halo, OH, -COOH, NH_2,

-NHCi-4 alkyl or N(Ci-4 alkyl)_{2};

R^6, R^7, R^17 and R^18 are each independently selected from H, halo, C1-6 alkyl, C2-6 alkenyl,

C2-6 alkynyl, C1-6 haloalkyl, C1-6 haloalkoxy, C1-6 alkoxy, C3-10 cycloalkyl, 5-14 membered heteroaryl, 4-10 membered heterocycloalkyl, C6-10 aryl-C1-4 alkyl-, C1-10 cycloalkyl-C1-4 alkyl-,

(5-14 membered heteroaryl)-C1-4 alkyl-, (4-10 membered heterocycloalkyl)-C1-4 alkyl-, CN, N0_{2},

OR_{a}, OR_{a}, NHOR_{a}, C(0)R_{a}, C(0)NR_{a}R_{a}, C(0)OR_{a}, OC(0)R_{a}, OC(0)NR_{a}R_{a}, NHR_{a}, NR_{a}R_{a},

NR_{a}C(0)R_{a}, NR_{a}C(0)OR_{a}, NR_{a}C(0)NR_{a}R_{a}, C(=NR_{a})R_{a}, C(=NR_{a})NR_{a}R_{a}, NR_{a}C(=NR_{a})NR_{a}R_{a},

NR_{a}S(0)R_{a}, NR_{a}S(0)_{2}R_{a}, NR_{a}S(0)_{2}NR_{a}R_{a}, S(0)R_{a}, S(0)NR_{a}R_{a}, S(0)_{2}R_{a}, and S(0)_{2}NR_{a}R_{a},

wherein the C1-6 alkyl, C2-6 alkenyl, C2-6 alkynyl, C3-10 aryl, C1-10 cycloalkyl, 5-14 membered heteroaryl, 4-10 membered heterocycloalkyl, C6-10 aryl-C1-4 alkyl-, C1-10 cycloalkyl-C1-4 alkyl-,

(5-14 membered heteroaryl)-C1-4 alkyl- and (4-10 membered heterocycloalkyl)-C1-4 alkyl- of R^6,

R^7, R^17 and R^18 are each optionally substituted with 1, 2, 3, 4 or 5 independently selected R^b substituents;

each R^13 is independently H, C1-6 haloalkyl or C1-6 alkyl optionally substituted with a substituent selected from C1-4 alkyl, C1-4 alkoxy, C1-4 haloalkyl, C1-4 haloalkoxy, CN, halo, OH, -COOH, NH_2,

-NHCi-4 alkyl and -N(CM alkyl)_{2};

R^14 and R^15 are each independently selected from H, halo, CN, OH, -COOH, C1-4 alkyl,

C1-4 alkoxy, -NHCi-4 alkyl, -N(Ci-4 alkyl)_{2}, C1-4 haloalkyl, C1-4 haloalkoxy, C3-6 cycloalkyl,

phenyl, 5-6 membered heteroaryl and 4-6 membered heterocycloalkyl, wherein the C1-4 alkyl, C1-4 alkoxy, C1-4 haloalkyl, C1-4 haloalkoxy, C3-6 cycloalkyl, phenyl, 5-6 membered heteroaryl and 4-6 membered heterocycloalkyl of R^14 or R^15 are each optionally substituted with 1, 2, or 3 independently selected independently selected R^b substituents;
or R\textsuperscript{14} and R\textsuperscript{15} taken together with the carbon atom to which they are attached form 3-, 4-, 5- or 6-membered cycloalkyl or 3-, 4-, 5- or 6-membered heterocycloalkyl, each of which is optionally substituted with 1 or 2 independently selected R\textsuperscript{8} substituents;

each R\textsuperscript{8} is independently selected from H, CN, Ci-6 alkyl, Ci-haloalkyl, C2-6 alkenyl, C2-6 alkynyl, C6-10 aryl, C3-10 cycloalkyl, 5-14 membered heteroaryl, 4-14 membered heterocycloalkyl, C6-10 aryl-Ci-4 alkyl-, C3-10 cycloalkyl-Ci-4 alkyl-, (5-14 membered heteroaryl)-Ci-4 alkyl-, and (4-14 membered heterocycloalkyl)-Ci-4 alkyl-, wherein the Ci-6 alkyl, C2-6 alkenyl, C2-6 alkynyl, C6-10 aryl, C3-10 cycloalkyl, 5-14 membered heteroaryl, 4-14 membered heterocycloalkyl, C6-10 aryl-Ci-4 alkyl-, C3-10 cycloalkyl-Ci-4 alkyl-, (5-14 membered heteroaryl)-Ci-4 alkyl- and (4-14 membered heterocycloalkyl)-Ci-4 alkyl- of R\textsuperscript{8} are each optionally substituted with 1, 2, 3, or 5 independently selected R\textsuperscript{d} substituents;

each R\textsuperscript{d} is independently selected from Ci-6 alkyl, Ci-haloalkyl, halo, C6-10 aryl, 5-14 membered heteroaryl, C3-10 cycloalkyl, 4-14 membered heterocycloalkyl, C6-10 aryl-Ci-4 alkyl-, C3-10 cycloalkyl-Ci-4 alkyl-, (5-14 membered heteroaryl)-Ci-4 alkyl-, (4-14 membered heterocycloalkyl)-Ci-4 alkyl-, (5-14 membered heteroaryl)-Ci-4 alkyl- and (4-14 membered heterocycloalkyl)-Ci-4 alkyl- of R\textsuperscript{d} are each optionally substituted with 1, 2, or 3 independently selected R\textsuperscript{8} substituents;

each R\textsuperscript{e} is independently selected from H, Ci-6 alkyl, Ci-haloalkyl, C2-6 alkenyl, C2-6 alkynyl, C6-10 aryl, C3-10 cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C6-10 aryl-Ci-4 alkyl-, C3-10 cycloalkyl-Ci-4 alkyl-, (5-10 membered heteroaryl)-Ci-4 alkyl-, and (4-10 membered heterocycloalkyl)-Ci-4 alkyl-, wherein the Ci-6 alkyl, Ci-haloalkyl, C2-6 alkenyl, C2-6 alkynyl, C6-10 aryl, C3-10 cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C6-10 aryl-Ci-4 alkyl-, C3-10 cycloalkyl-Ci-4 alkyl-, (5-10 membered heteroaryl)-Ci-4 alkyl- and (4-10 membered heterocycloalkyl)-Ci-4 alkyl- of R\textsuperscript{e} are each optionally substituted with 1, 2 or 3 independently selected R\textsuperscript{9} substituents;

each R\textsuperscript{b} substituent is independently selected from halo, Ci-6 alkyl, C2-6 alkenyl, C2-6 alkynyl, Ci-6 haloalkyl, Ci-haloalkoxy, C6-10 aryl, C3-10 cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C6-10 aryl-Ci-4 alkyl-, C3-10 cycloalkyl-Ci-4 alkyl-, (5-10 membered heteroaryl)-Ci-4 alkyl-, (4-10 membered heterocycloalkyl)-Ci-4 alkyl-
NO2, NHOR, OR, SR, C(0)R, C(0)NR2, C(0)OR, OC(0)R, OC(0)NR2, C(=NR)NR2, NHR, NRR2, N... C-ι ο aryl-Ci-4 alkyl-, C3-10 cycloalkyl, 5-10 membered heterocycloalkyl, C6-10 aryl-Ci-4 alkyl-, C3-10 cycloalkyl-Ci-4 alkyl-, (5-10 membered heteroaryl)-Ci-4 alkyl-and (4-10 membered heterocycloalkyl)-Ci-4 alkyl-of R8 are each further optionally substituted with 1, 2, or 3 independently selected R4 substituents;

each R5 is independently selected from H, Ci-6 alkyl, C1-4 haloalkyl, C2-6 alkenyl, C2-6 alkynyl, C6-10 aryl, C3-10 cycloalkyl, 5-10 membered heterocycloalkyl, C6-10 aryl-Ci-4 alkyl-, C3-10 cycloalkyl-Ci-4 alkyl-, (5-10 membered heteroaryl)-Ci-4 alkyl-, and (4-10 membered heterocyclusalkyl)-Ci-4 alkyl-, wherein the Ci-6 alkyl, Ci-6 haloalkyl, Ci-6 halalkoxy, C2-6 alkenyl, C2-6 alkynyl, C6-10 aryl, C3-10 cycloalkyl, 5-10 membered heterocycloalkyl, C6-10 aryl-Ci-4 alkyl-, C3-10 cycloalkyl-Ci-4 alkyl-, (5-10 membered heteroaryl)-Ci-4 alkyl- and (4-10 membered heterocycloalkyl)-Ci-4 alkyl-of R8 are each optionally substituted with 1, 2, 3, 4, or 5 independently selected R6 substituents;

or any two R2 substituents together with the nitrogen atom to which they are attached form a 4-, 5-, 6-, 7-, 8-, 9- or 10-membered heterocycloalkyl group optionally substituted with 1, 2 or 3 independently selected R6 substituents;

or any two R5 substituents together with the nitrogen atom to which they are attached form a 4-, 5-, 6-, 7-, 8-, 9- or 10-membered heterocycloalkyl group optionally substituted with 1, 2, or 3 independently selected R6 substituents;

or any two R6 substituents together with the nitrogen atom to which they are attached form a 4-, 5-, 6-, 7-, 8-, 9- or 10-membered heterocycloalkyl group optionally substituted with 1, 2, or 3 independently selected R6 substituents;

each R6 is independently selected from Ci-6 alkyl, C3-10 cycloalkyl, 4-7 membered heterocycloalkyl, C6-10 aryl, 5-6 membered heteroaryl, C6-10 aryl-Ci-4 alkyl-, C3-10 cycloalkyl-Ci-4 alkyl-, (5-6 membered heterocycloalkyl)-Ci-4 alkyl-, (4-7 membered heterocycloalkyl)-Ci-4 alkyl-, Ci-6 haloalkyl, Ci-e haloalkoxy, C2-6 alkenyl, C2-6 alkynyl, halo, CN, OR1, S(0)NR2, NHOR i, C(O)R1, C(O)NR2, C(O)O, C(O)N R'R2, NHR i, NR'R2, NRC(0)R1, NRC(0)NR2, NRC(0)O R1, S(0)N R'R2, S(0)NR2, S(0)O R1, S(0)O NR2, S(0)OR1, S(0)NR2, S(0)O NR2 R1, and S(0)O R1 R2, wherein the Ci-e alkyl, C2-6 alkenyl, C2-6 alkynyl, C3-10 cycloalkyl, 4-7 membered heterocycloalkyl, C6-10 aryl, 5-6 membered heteroaryl, C6-10 aryl-Ci-4 alkyl-, C3-10 cycloalkyl-Ci-4 alkyl-, (5-6 membered heteroaryl)-C 1-4 alkyl-.
heterocycloalkyl)-Cl alkyl- of R^k are each further optionally substituted by 1, 2, or 3 independently selected R_i substituents;

each R_j is independently selected from C_3-C_6 cycloalkyl, C_{6-10} aryl, 5 or 6-membered heteroaryl, 4-7 membered heterocycloalkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl, halo, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 haloalkoxy, CN, NHOR, OR^k, SR^k, C_(1-6)NR^k, C_(1-6)OR^k, OC(=NR^k)OR^k, OC(=O)OR^k, NHR^k, NR^kC(=O)R^k, NHC(=O)R^k, NH_2, the heterocycloalkyl membered 4-6 ring members are each further optionally substituted by 1, 2, or 3 independently selected N, O and S, wherein the N or S atom as ring members is optionally oxidized and one or more carbon atoms as ring substituents; wherein:

each of R^1 and R^k is independently selected from H, C_1-C_4 alkyl, C_3-C_6 cycloalkyl, C_{6-10} aryl, 5 or 6-membered heteroaryl, 4-7 membered heterocycloalkyl, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, C_2-C_4 alkenyl, and C_2-C_4 alkynyl, wherein the C_1-C_4 alkyl, C_3-C_6 cycloalkyl, C_{6-10} aryl, 5 or 6-membered heteroaryl, 4-7 membered heterocycloalkyl, C_2-C_4 alkenyl, and C_2-C_4 alkynyl of R^1 or R^k are each optionally substituted with 1, 2 or 3 independently selected R^8 substituents;

each R^k is independently selected from halo, OH, CN, -COOH, NH_2, -NH-Ci-alkyl, -N(Ci-alkyl)_2, C_3-C_6 alkyl, C_3-C_6 alkoxy, C_{1-6} alkythio, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, phenyl, 5-6 membered heteroaryl, 4-6 membered heterocycloalkyl and C_3-C_6 cycloalkyl, wherein the C_1-C_6 alkyl, phenyl, C_3-C_6 cycloalkyl, 4-6 membered heterocycloalkyl, and 5-6 membered heteroaryl of R^k are each optionally substituted with 1, 2, or 3 substituents selected from halo, OH, CN, -COOH, NH_2, C_1-C_4 alkyl, C_1-C_4 alkoxy, C_1-C_4 haloalkyl, C_1-C_4 haloalkoxy, phenyl, C_3-C_10 cycloalkyl, 5-6 membered heteroaryl and 4-6 membered heterocycloalkyl;

the subscript m is an integer of 0, 1, 2 or 3;

the subscript n is an integer of 0, 1, 2 or 3;

each subscript q is independently an integer of 1, 2, 3 or 4; and

the subscript s is an integer of 1, 2, or 3.

In some embodiments, provided herein is a compound of Formula (I), or a pharmaceutically acceptable salt or a stereoisomer thereof, wherein:

ring A is 5- to 10-membered heteroaryl, 4- to 11-membered heterocycloalkyl, C_{6-10} aryl or C_{3-10} cycloalkyl, wherein the 5- to 10-membered heteroaryl and 4- to 11-membered heterocycloalkyl each has 1-4 heteroatoms as ring members selected from N, O and S, wherein the N or S atom as ring members is optionally oxidized and one or more carbon atoms as ring
members are each optionally replaced by a carbonyl group; and wherein ring A is optionally substituted with 1, 2, 3, 4 or 5 $R^6$ substituents;

$L$ is a bond, -C(0)NR$^{13-}$, -NR$^{13-}$C(0)-, O, -(CR$^{14}$R$^{15}$)$_q$-, -(CR$^{14}$R$^{15}$)$_q$0-, -0(CR$^{14}$R$^{15}$)$_q$-, -NR$^{13-}$, -(CR$^{14}$R$^{15}$)$_q$-NR$^{13-}$, -NR$^{13-}$C(0)R$^{15}$-, -CH=CH-, ---C= C=, -SO$^{13-}$, -NR$^{13-}$SO$^{2-}$,

$X$ is N or CR$^{17}$;

$R^3$ is methyl, halo, CN or CCl$^3$haloalkyl;

$R^4$ is C$^4$-alkyl, C$^4$-alkoxy, C$^M$ haloalkyl, C$^M$ haloalkoxy, CN, halo, OH, -COOH, NH$_2$,
-NHCl$^4$ alkyl or-N(C$^4$-alkyl)$_2$;

$R^5$ is C$^M$ alkyl, C$^M$ alkoxy, C$M$ haloalkyl, C$M$ haloalkoxy, CN, halo, OH, -COOH, NH$_2$,
-NHCl$^4$ alkyl or-N(C$^4$-alkyl)$_2$;

$R^6$, R$^7$, R$^{17}$ and R$^{18}$ are each independently selected fromH, halo, C$^6$-alkyl, C$^2$-alkenyl,
C$^2$-$^6$ alkynyl, C$^6$-haloalkyl, C$^6$-haloalkoxy, C$^6$-$^4$-ary1, c$^3$-$^10$ cycloalkyl, 5-14 membered heteroaryl, 4-10 membered heterocycloalkyl, C$^6$-$^10$ aryl-C$^4$-alkyl-, c$^3$-$^10$ cycloalkyl-C$^4$-alkyl-, (5-14 membered heteroaryl)-C$^4$ alkyl-, (4-10 membered heterocycloalkyl)-C$^4$ alkyl-, CN, N0$_2$,
OR$^2$, SR$^2$, NHOR$^3$, C(0)R$^4$, C(0)NR$^2$R$^5$, C(0)OR$^4$, OC(0)R$^5$, OC(0)NR$^2$R$^5$, NR$^2$R$^5$, NR$^2$C(0)R$^5$, NR$^2$C(0)OR$^5$, NRC(0)NR$^2$R$^5$, NR$^2$C(0)NR$^2$R$^5$, NRC(0)NR$^2$R$^5$, NR$^2$S(0)R$^5$, NR$^2$S(0)R$^5$, NR$^2$S(0)R$^5$, NR$^2$S(0)R$^5$, S(0)R$^5$, S(0)NR$^2$R$^5$, S(0)NR$^2$R$^5$, S(0)NR$^2$R$^5$, and S(0)NR$^2$R$^5$, wherein the C$^6$-alkyl, C$^2$-$^6$ alkenyl, C$^2$-$^6$ alkynyl, C$^6$-$^10$ aryl, c$^3$-$^10$ cycloalkyl, 5-14 membered heteroaryl, 4-10 membered heterocycloalkyl, C$^6$-$^10$ aryl-C$^4$-alkyl-, c$^3$-$^10$ cycloalkyl-C$^4$-alkyl-, (5-14 membered heteroaryl)-C$^4$ alkyl- and (4-10 membered heterocycloalkyl)-C$^4$ alkyl- of R$^6$, R$^7$, R$^{17}$ and R$^{18}$ are each optionally substituted with 1, 2, 3, 4 or 5 $R^b$ substituents;

or two $R^b$ substituents attached to the same ring carbon atom taken together with the ring carbon atom to which they are attached form spiro C$^6$-$^6$ cycloalkyl or spiro 4- to 7-membered heterocycloalkyl, each of which is optionally substituted with 1, 2, or 3 independently selected $R^f$ substituents;

each R$^{13}$ is independently H, C$^6$-$^6$ haloalkyl or C$^6$-alkyl optionally substituted with a substituent selected from C$^M$ alkyl, C$^1$-$^4$ alkoxy, C$^M$ haloalkyl, C$^1$-$^4$ haloalkoxy, CN, halo, OH, -COOH, NH$_2$, -NHCl$^4$ alkyl and -N(C$^4$-alkyl)$_2$;

R$^{14}$ and R$^{15}$ are each independently selected from H, halo, CN, OH, -COOH, C$^M$ alkyl, C$^M$ alkoxy, -NHCl$^4$ alkyl, -N(C$^4$-alkyl)$_2$, C$^1$-$^4$ haloalkyl, C$^M$ haloalkoxy, C$^3$-$^6$ cycloalkyl, phenyl, 5-6 membered heteroaryl and 4-6 membered heterocycloalkyl, wherein the C$^1$-$^4$ alkyl, C$^4$ alkoxy, C$^M$ haloalkyl, C$^1$-$^4$ haloalkoxy, C$^3$-$^6$ cycloalkyl, phenyl, 5-6 membered heteroaryl and 4-
6 membered heterocycloalkyl of R\textsuperscript{14} or R\textsuperscript{15} are each optionally substituted with 1, 2, or 3 independently selected R\textsuperscript{8} substituents;

or R\textsuperscript{14} and R\textsuperscript{15} taken together with the carbon atom to which they are attached form 3-, 4-, 5-, or 6-membered cycloalkyl or 3-, 4-, 5- or 6-membered heterocycloalkyl, each of which is optionally substituted with 1 or 2 R\textsuperscript{9} substituents;

each R\textsuperscript{8} is independently selected from H, CN, Ci-6 alkyl, Ci-4 haloalkyl, C2-6 alkenyl, C2-6 alkynyl, C\textsubscript{6-10} aryl, C\textsubscript{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C\textsubscript{6-10} aryl-Ci-4 alkyl-, C\textsubscript{3-10} cycloalkyl-Ci-4 alkyl-, (5-10 membered heteroaryl)-Ci-4 alkyl-, and (4-10 membered heterocycloalkyl)-Ci-4 alkyl-, wherein the Ci-6 alkyl, C2-6 alkenyl, C2-6 alkynyl, C\textsubscript{6-10} aryl, C\textsubscript{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C\textsubscript{6-10} aryl-Ci-4 alkyl-, C\textsubscript{3-10} cycloalkyl-Ci-4 alkyl-, (5-10 membered heteroaryl)-Ci-4 alkyl- and (4-10 membered heterocycloalkyl)-Ci-4 alkyl- of R\textsuperscript{8} are each optionally substituted with 1, 2, 3, 4, or 5 R\textsuperscript{d} substituents;

each R\textsuperscript{d} is independently selected from Ci-6 alkyl, Ci-6 haloalkyl, halo, C\textsubscript{6-10} aryl, 5-10 membered heteroaryl, C\textsubscript{3-10} cycloalkyl, 4-10 membered heterocycloalkyl, C\textsubscript{6-10} aryl-Ci-4 alkyl-, C\textsubscript{3-10} cycloalkyl-Ci-4 alkyl-, (5-10 membered heteroaryl)-Ci-4 alkyl-, (4-10 membered heterocycloalkyl)-Ci-4 alkyl-, CN, NH\textsubscript{2}, NHOR, OR, SR, C(0)R, C(0)NR, R, C(0)OR, R, OC(0)R, OC(0)NR, NHNR, NR, NR\textsubscript{2}, NR\textsubscript{2}C(0)R, NR\textsubscript{2}C(0)NR, R, NR\textsubscript{2}C(0)OR, R, C(=NR)NR, NR\textsubscript{2}C(=NR)NR, R, NR\textsubscript{2}C(=NOH)NR, R, NR\textsubscript{2}C(=NCN)NR, R, S(0)R, R, S(0)NR, S(0)R\textsubscript{2}, NR\textsubscript{2}S(0)R\textsubscript{2}, NR\textsubscript{2}S(0)S(0)NR\textsubscript{2}, and S(0)S(0)NR\textsubscript{2}, wherein the Ci-e alkyl, Ci-6haloalkyl, C\textsubscript{6-10} aryl, 5-10 membered heteroaryl, C\textsubscript{3-10} cycloalkyl, 4-10 membered heterocycloalkyl, C\textsubscript{6-10} aryl-Ci-4 alkyl-, C\textsubscript{3-10} cycloalkyl-Ci-4 alkyl-, (5-10 membered heteroaryl)-Ci-4 alkyl- and (4-10 membered heterocycloalkyl)-Ci-4 alkyl- of R\textsuperscript{d} are each optionally substituted with 1, 2, or 3 independently selected R\textsuperscript{f} substituents;

each R\textsuperscript{f} is independently selected from H, Ci-6 alkyl, Ci-6 haloalkyl, C2-6 alkenyl, C2-6 alkynyl, C\textsubscript{6-10} aryl, C\textsubscript{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C\textsubscript{6-10} aryl-Ci-4 alkyl-, C\textsubscript{3-10} cycloalkyl-Ci-4 alkyl-, (5-10 membered heteroaryl)-Ci-4 alkyl-, and (4-10 membered heterocycloalkyl)-Ci-4 alkyl-, wherein the Ci-6 alkyl, Ci-6 halalkyl, C2-6 alkenyl, C2-6 alkynyl, C\textsubscript{6-10} aryl, C\textsubscript{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C\textsubscript{6-10} aryl-Ci-4 alkyl-, C\textsubscript{3-10} cycloalkyl-Ci-4 alkyl-, (5-10 membered heteroaryl)-Ci-4 alkyl- and (4-10 membered heterocycloalkyl)-Ci-4 alkyl- of R\textsuperscript{f} are each optionally substituted with 1, 2 or 3 independently selected R\textsuperscript{g} substituents;
10 membered heterocycloalkyl, C<sub>6-10</sub> ary1-C<sub>1-4</sub> alkyl-, C<sub>3-10</sub> cycloalkyl-Ci-4 alkyl-, (5-10 membered heteroaryl)-Ci-4 alkyl-, (4-10 membered heterocycloalkyl)-Ci-4 alkyl-, CN, OH, NH<sub>2</sub>, NO<sub>2</sub>, NHOR<sup>ε</sup>, OR<sup>ε</sup>, SR<sup>ε</sup>, C(0)R<sup>ε</sup>, C(0)NR<sup>ε</sup>, C(0)OR<sup>ε</sup>, OC(0)NR<sup>ε</sup>, OC(0)OR<sup>ε</sup>, C(=NR)<sup>ε</sup>R<sup>R°</sup>, NR<sup>R°</sup>C(=NR)<sup>ε</sup>R<sup>R°</sup>, NHR<sup>ε</sup>, NR<sup>R°</sup>R<sup>R°</sup>, NR<sup>R°</sup>C(0)R<sup>ε</sup>, NR<sup>R°</sup>C(0)OR<sup>ε</sup>, NR<sup>R°</sup>C(0)NR<sup>ε</sup>, NR<sup>R°</sup>S(0)R<sup>R°</sup>, NR<sup>R°</sup>S(0)<sub>2</sub>R<sup>R°</sup>, NR<sup>R°</sup>S(0)R<sup>R°</sup>R<sup>R°</sup>, S(0)R<sup>ε</sup>, S(0)NR<sup>ε</sup>R<sup>R°</sup>, S(0)<sub>2</sub>R<sup>R°</sup>, and S(0)<sub>2</sub>NR<sup>R°</sup>R<sup>R°</sup>;
5 wherein the Ci-6 alkyl, Ci-6 haloalkyl, Ci-6 haloalkoxy, C<sub>2-6</sub> alkynyl, C<sub>6-10</sub> aryl, C<sub>3-10</sub> cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C<sub>6-10</sub> aryl-C<sub>1-4</sub> alkyl-, C<sub>3-10</sub> cycloalkyl-Ci-4 alkyl-, (5-10 membered heteroaryl)-Ci-4 alkyl-and (4-10 membered heterocycloalkyl)-Ci-4 alkyl-of R<sup>ε</sup> are each further optionally substituted with 1, 2, or 3 independently selected R<sup>d</sup> substituents;
10 each R<sup>d</sup> is independently selected from H, Ci-6 alkyl, C<sub>1-4</sub> haloalkyl, C<sub>2-6</sub> alkeny1, C<sub>2-6</sub> alkenyl, C<sub>6-10</sub> aryl, C<sub>3-10</sub> cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C<sub>6-10</sub> aryl-C<sub>1-4</sub> alkyl-, C<sub>3-10</sub> cycloalkyl-Ci-4 alkyl-, (5-10 membered heteroaryl)-Ci-4 alkyl-, and (4-10 membered heterocycloalkyl)-Ci-4 alkyl-, wherein the Ci-6 alkyl, C<sub>2-6</sub> alkeny1, C<sub>6-10</sub> aryl, C<sub>3-10</sub> cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C<sub>6-10</sub> aryl-C<sub>1-4</sub> alkyl-, C<sub>3-10</sub> cycloalkyl-Ci-4 alkyl-, (5-10 membered heteroaryl)-Ci-4 alkyl-and (4-10 membered heterocycloalkyl)-Ci-4 alkyl-of R<sup>d</sup> are each optionally substituted with 1, 2, 3, 4, or 5 R<sup>f</sup> substituents;
15 each R<sup>f</sup> is independently selected from Ci-4 alkyl, C<sub>1-4</sub> haloalkyl, C<sub>2-6</sub> alkeny1, C<sub>2-6</sub> alkenyl, C<sub>6-10</sub> aryl, C<sub>3-10</sub> cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C<sub>6-10</sub> aryl-Ci-4 alkyl-, C<sub>3-10</sub> cycloalkyl-Ci-4 alkyl-, (5-10 membered heteroaryl)-Ci-4 alkyl-, (4-10 membered heterocycloalkyl)-Ci-4 alkyl-, halO, CN, NHOR<sup>ε</sup>, OR<sup>ε</sup>, SR<sup>ε</sup>, C(0)R<sup>ε</sup>, C(0)NR<sup>ε</sup>, C(0)OR<sup>ε</sup>, C(=NR)<sup>ε</sup>R<sup>R°</sup>, NR<sup>R°</sup>C(=NR)<sup>ε</sup>R<sup>R°</sup>, NHR<sup>ε</sup>, NR<sup>R°</sup>R<sup>R°</sup>, NR<sup>R°</sup>C(0)R<sup>ε</sup>, NR<sup>R°</sup>C(0)OR<sup>ε</sup>, NR<sup>R°</sup>C(0)NR<sup>ε</sup>, NR<sup>R°</sup>S(0)R<sup>R°</sup>, NR<sup>R°</sup>S(0)<sub>2</sub>R<sup>R°</sup>, NR<sup>R°</sup>S(0)R<sup>R°</sup>R<sup>R°</sup>, S(0)R<sup>ε</sup>, S(0)NR<sup>ε</sup>R<sup>R°</sup>, S(0)<sub>2</sub>R<sup>R°</sup>, and S(0)<sub>2</sub>NR<sup>R°</sup>R<sup>R°</sup>;
20 wherein the C<sub>1-4</sub> alkyl, C<sub>1-4</sub> haloalkyl, C<sub>2-6</sub> alkeny1, C<sub>2-6</sub> alkenyl, C<sub>6-10</sub> aryl, C<sub>3-10</sub> cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C<sub>6-10</sub> aryl-Ci-4 alkyl-, C<sub>3-10</sub> cycloalkyl-Ci-4 alkyl-, (5-10 membered heteroaryl)-Ci-4 alkyl-, (4-10 membered heterocycloalkyl)-Ci-4 alkyl-, halO, CN, NHOR<sup>0</sup>, OR<sup>0</sup>, SR<sup>0</sup>, C(0)R<sup>0</sup>, C(0)NR<sup>R°</sup><sub>0</sub>, C(0)OR<sup>0</sup>, OC(0)R<sup>0</sup>, OC(0)NR<sup>R°</sup><sub>0</sub>, NR<sup>R°</sup>R<sup>0</sup>, NR<sup>R°</sup>C(0)R<sup>0</sup>, NR<sup>R°</sup>C(0)NR<sup>R°</sup><sub>0</sub>, NR<sup>R°</sup>C(0)OR<sup>0</sup>, NR<sup>R°</sup>
C(=NR°)NR°R°, NR°(=NR°)NR°R°, S(0)R°, S(0)NR°R°, S(0)2R°, NR°S(0)2R°,
NR°S(O)NR°R°, and S(0)2NR°R°, wherein the C M alkyl, C M haloalkyl, C2-6 alkenyl, C2-6 alkynyl, C6-10 aryl, C3-10 cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl,
c6-10 aryl-Ci alky-, C3-10 cycloalkyl-Ci alky-, (5-10 membered heteroaryl)-Ci alky-, and (4-10
membered heterocycloalkyl)-Ci alky- of R° are each optionally substituted with 1, 2 or 3
independently selected R° substituents;

each R° is independently selected from H, Ci-6 alkyl, Ci-haloalkyl, C2-6 alkenyl, C2-6
alkynyl, C6-10 aryl, C3-10 cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl,
C6-10 aryI-Ci alky-, C3-10 cycloalkyl-Ci alky-, (5-10 membered heteroaryl)-Ci alky-, and (4-10
membered heterocycloalkyl)-Ci alky-, wherein the Ci-6 alkyl, C2-6 alkenyl, C2-6 alkynyl, C6-
10 aryl, C3-10 cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C6-10 aryI-
Ci alky-, C3-10 cycloalkyl-Ci alky-, (5-10 membered heteroaryl)-Ci alky- and (4-10
membered heterocycloalkyl)-Ci alky- of R° are each optionally substituted with 1, 2, or 3 R°
substituents;

each R° is independently selected from Ci-6 alkyl, Ci-haloalkyl, C2-6 alkenyl, C2-6
alkynyl, C6-10 aryl, C3-10 cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl,
C6-10 aryI-Ci alky-, C3-10 cycloalkyl-Ci alky-, (5-10 membered heteroaryl)-Ci alky-, (4-10
membered heterocycloalkyl)-Ci alky-, halo, CN, NHOR, OR, SR, C(0)R, C(0)NR, R',
C(0)OR, OC(0)R, OC(0)NR'R, NHR, NR'R', NR'C(0)R, NR'C(0)NR'R, NR'C(0)OR, Ci-
alkyl, Ci-6 alkyl, C2-6 alkenyl, C2-6 alkynyl, C6-10 aryl, C3-10 cycloalkyl, 5-10 membered heteroaryl, 4-10
membered heterocycloalkyl, C6-10 aryI-Ci alky-, C3-10 cycloalkyl-Ci alky-, (5-10 membered heteroaryl)-
Ci alky- and (4-10 membered heterocycloalkyl)-Ci alky- of R° is optionally
substituted with 1, 2 or 3 R° substituents;

or any two R° substituents together with the nitrogen atom to which they are attached
form a 4-, 5-, 6-, 7-, 8-, 9- or 10-membered heterocycloalkyl group optionally substituted with 1,
2 or 3 R° substituents;

each R° is independently selected from Ci-6 alkyl, C3-10 cycloalkyl, 4-7 membered
heterocycloalkyl, C6-10 aryl, 5-6 membered heteroaryl, C6-10 aryl-Ci alky-, C3-10 cycloalkyl-Ci alky-
-, (5-6 membered heteroaryl)-Ci alky-, (4-7 membered heterocycloalkyl)-Ci alky-,
Ci-haloalkoxy, C2-6 alkynyl, C2-6 alkenyl, halo, CN, OR, S(0), NHOR, C(0)R, C(0)OR,
OC(0)R, OC(0)NR'R, NHR, NR'R, NR'C(0)R, NR'C(0)NR'R, NR'C(0)OR, Ci-
alkyl, Ci-6 alkyl, C2-6 alkenyl, C2-6 alkynyl, halo, CN, OR, S(0), NHOR, C(0)R, C(0)OR,
OC(0)R, OC(0)NR'R, NHR, NR'R, NR'C(0)R, NR'C(0)NR'R, NR'C(0)OR, Ci-
alkyl, Ci-6 alkyl, C2-6 alkenyl, C2-6 alkynyl, halo, CN, OR, S(0), NHOR, C(0)R, C(0)OR,
OC(0)R, OC(0)NR'R, NHR, NR'R, NR'C(0)R, NR'C(0)NR'R, NR'C(0)OR, Ci-
alkyl, Ci-6 alkyl, C2-6 alkenyl, C2-6 alkynyl, halo, CN, OR, S(0), NHOR, C(0)R, C(0)OR,
OC(0)R, OC(0)NR'R, NHR, NR'R, NR'C(0)R, NR'C(0)NR'R, NR'C(0)OR, Ci-
alkyl, Ci-6 alkyl, C2-6 alkenyl, C2-6 alkynyl, halo, CN, OR, S(0), NHOR, C(0)R, C(0)OR,
NR²S(0)²NR¹R¹, and S(O)₂NR¹NR¹, wherein the Ci-e alkyl, C2-6 alkenyl, C2-6 alkynyl, C₃-₁₀
cycloalkyl, 4-7 membered heterocycloalkyl, C₆-₁₀ aryl, 5-6 membered heteroaryl, C₆-₁₀ aryl-Ci-4
alkyl-, C₃-₁₀ cycloalkyl-Ci-4 alkyl-, (5-6 membered heteroaryl)-C₁-₄ alkyl-, (4-7 membered
heterocycloalkyl)-Ci-4 alkyl- of R₂ are each further optionally substituted by 1, 2, or 3 R¹
substituents;

  each R is independently selected from C₃-₆ cycloalkyl, C₆-₁₀ aryl, 5 or 6-membered
heteroaryl, 4-7 membered heterocycloalkyl, C₂-₄ alkenyl, C₂-₄ alkynyl, halo, C₁-₄ alkyl, C₁-₄
haloalkyl, CN, NHOR², OR², SR², C(0)R², C(0)NR²R², C(0)OR²R², OC(O)R², OC(O)NR²R²,
NHR², NₗR²R², NₗC(0)R², NₗC(0)NR²R², NₗR²C(0)NR²R², NₗR²C(0)OR²R², C(=NR²)NR²R²,
NR²C(=NR²)NR²R², S(O)R², S(O)NR²R², S(O)₂R², NR²S(O)₂R², NR²S(O)₂NR²R², and
S(O)₂NR²R², wherein the C₁-₄ alkyl, C₃-₆ cycloalkyl, C₆-₁₀ aryl, 5- or 6-membered heteroaryl, 4-6
membered heterocycloalkyl, C₂-₄ alkenyl, C₂-₄ alkynyl, C₁-₄ haloalkyl, and C₁-₄ haloalkoxy of R³
are each optionally substituted with 1, 2 or 3 independently selected R⁴ substituents;

  or two R² groups attached to the same carbon atom of the 4- to 10-membered
heterocycloalkyl taken together with the carbon atom to which they are attached form a C₃-₆
cycloalkyl or 4- to 6-membered heterocycloalkyl having 1-2 heteroatoms as ring members
selected from O, N or S;

  or any two R² substituents together with the nitrogen atom to which they are attached
form a 4-, 5-, 6-, or 7-membered heterocycloalkyl group optionally substituted with 1, 2, or 3
independently selected R² substituents;

  or any two R² substituents together with the nitrogen atom to which they are attached
form a 4-, 5-, 6-, or 7-membered heterocycloalkyl group optionally substituted with 1, 2, or 3
independently selected R³ substituents;

  or any two R³ substituents together with the nitrogen atom to which they are attached
form a 4-, 5-, 6-, or 7-membered heterocycloalkyl group optionally substituted with 1, 2, or 3
independently selected R⁴ substituents;

  or any two R¹ substituents together with the nitrogen atom to which they are attached
form a 4-, 5-, 6-, or 7-membered heterocycloalkyl group optionally substituted with 1, 2, or 3
independently selected R² substituents, or 1, 2, or 3 independently selected R² substituents;

  or any two R³ substituents together with the nitrogen atom to which they are attached
form a 4-, 5-, 6-, or 7-membered heterocycloalkyl group optionally substituted with 1, 2, or 3
independently selected R³ substituents, or 1, 2, or 3 independently selected R³ substituents;
or any two \( R^s \) substituents together with the nitrogen atom to which they are attached form a 4-, 5-, 6-, or 7-membered heterocycloalkyl group optionally substituted with 1, 2, or 3 independently selected \( R^b \) substituents;

or any two \( R^t \) substituents together with the nitrogen atom to which they are attached form a 4-, 5-, 6-, or 7-membered heterocycloalkyl group optionally substituted with 1, 2, or 3 independently selected \( R^b \) substituents;

each \( R^1, R^2, R^5 \) or \( R^t \) is independently selected from \( H, C_1-4 \) alkyl, \( C_5-6 \) cycloalkyl, \( C_6-10 \) aryl, 5 or 6-membered heteroaryl, 4-7 membered heterocycloalkyl, \( C_5-6 \) haloalkyl, \( C_6-6 \) halalkoxy, \( C_2-4 \) alkenyl, and \( C_2-4 \) alkynyl, wherein the \( C_1-4 \) alkyl, \( C_5-6 \) cycloalkyl, \( C_6-10 \) aryl, 5 or 6-membered heteroaryl, 4-7 membered heterocycloalkyl, \( C_2-4 \) alkenyl, and \( C_2-4 \) alkynyl of \( R^1, R^2, R^5 \) or \( R^t \) are each optionally substituted with 1, 2 or 3 \( R^g \) substituents;

each \( R^g \) is independently selected from halo, \( O\), \( C_1-4 \) alkyl, \( C_5-6 \) haloalkoxy, \( C_1-6 \) alkythio, \( C_6-6 \) haloalkyl, \( C_6-6 \) haloalkoxy, \( C_1-6 \) haloalkyl, \( C_6-6 \) haloalkoxy, \( C_3-6 \) cycloalkyl, 4-6 membered heterocycloalkyl and \( C_3-6 \) cycloalkyl, wherein the \( C_1-6 \) alkyl, \( C_3-6 \) cycloalkyl, 4-6 membered heterocycloalkyl, and 5-6 membered heteroaryl of \( R^g \) are each optionally substituted with 1, 2, or 3 substituents selected from halo, \( O\), \( C_1-4 \) alkyl, \( C_1-4 \) alkenoxy, \( C_1-4 \) alkynyl, \( C_1-4 \) haloalkyl, \( C_1-4 \) haloalkoxy, \( C_3-10 \) cycloalkyl, 5-6 membered heteroaryl and 4-6 membered heterocycloalkyl;

the subscript \( m \) is an integer of 0, 1, 2 or 3;

the subscript \( n \) is an integer of 0, 1, 2 or 3;

each subscript \( q \) is independently an integer of 1, 2, 3 or 4; and

the subscript \( s \) is an integer of 1, 2, or 3.

In some embodiments, provided herein is a compound of Formula (I) or a pharmaceutically acceptable salt or a stereoisomer thereof, wherein:

ring \( A \) is 5- to 10-membered heteroaryl, 4- to 11-membered heterocycloalkyl, \( C_6-10 \) aryl or \( C_3-10 \) cycloalkyl, wherein the 5- to 10-membered heteroaryl and 4- to 11-membered heterocycloalkyl each has 1-4 heteroatoms as ring members selected from \( N \), \( O \) and \( S \), wherein the \( N \) or \( S \) atom as ring members is optionally oxidized and one or more carbon atoms as ring members are each optionally replaced by a carbonyl group; and wherein ring \( A \) is optionally substituted with 1, 2, 3, 4 or 5 \( R^6 \) substituents;

\( L \) is a bond, \(-\text{C}(0)\text{NR}^{13}-\), \(-\text{NR}^{13}\text{C}(0)-\), \(-\text{O}-(\text{CR}^{14}\text{R}^{15})_{q^0}-\), \(-\text{CR}^{14}\text{R}^{15})_{q^0}-\), \(-\text{COOH}\), \(-\text{NH}-(\text{CR}^{14}\text{R}^{15})_{q^0}-\), \(-\text{CHCH}_2\), \(-\text{C}^(+)-\), \(-\text{SO}_2\text{NR}^{13}-\), \(-\text{NR}^{13}\text{SO}_2\), \(-\text{NR}^{13}\text{C}(0)\text{NR}^{13}-\), or \(-\text{NR}^{13}\text{C}(0)\text{NR}^{13}-\).
X is N or CR^{17};
R^3 is methyl, halo, CN or Ci-4-haloalkyl;
R^4 is Ci-4 alkyl, Ci-4 alkoxy, C_M haloalkyl, C_M haloalkoxy, CN, halo, OH, -COOH, NH_2, -NHCI_4 alkyl or -N(Ci-4 alkyl)_2;
R^5 is C_M alkyl, C_M alkoxy, C_M haloalkyl, C_M haloalkoxy, CN, halo, OH, -COOH, NH_2, -NHCI_4 alkyl or -N(Ci-4 alkyl)_2;
R^6, R^7, R^{17} and R^{18} are each independently selected from H, halo, Ci-6 alkyl, C_2-6 alkenyl, C_2-6 alkylnyl, Ci-6 haloalkyl, Ci-6 haloalkoxy, C_6-10 aryl, C_3-10 cycloalkyl, 5-14 membered heteroaryl, 4-10 membered heterocycloalkyl, C_6-10 aryl-Ci-4 alkyl-, C_3-10 cycloalkyl-Ci-4 alkyl-, (5-14 membered heteroaryl)-Ci-4 alkyl-, (4-10 membered heterocycloalkyl)-Ci-4 alkyl-, CN, N0_2, OR^a, SR^a, NHOR^a, C(0)R^a, C(0)NR^aR^a, C(0)OR^a, OC(0)R^a, OC(0)NR^aR^a, NHR^a, NR^aR^a, NR^aC(0)R^a, NR^aC(0)OR^a, NR^aC(0)NR^aR^a, C(=NR^a)R^a, C(=NR^a)NR^aR^a, NR^aC(=NR^a)NR^aR^a, NR^aS(0)R^a, NR^aS(0)NR^aR^a, S(0)R^a, S(0)NR^aR^a, S(0)NR^aR^a, and S(0)NR^aR^a, wherein the Ci-6 alkyl, C_2-6 alkenyl, C_2-6 alkylnyl, C_6-10 aryl, C_3-10 cycloalkyl, 5-14 membered heteroaryl, 4-10 membered heterocycloalkyl, C_6-10 aryl-Ci-4 alkyl-, C_3-10 cycloalkyl-Ci-4 alkyl-, (5-14 membered heteroaryl)-Ci-4 alkyl- and (4-10 membered heterocycloalkyl)-Ci-4 alkyl- of R^6 are each optionally substituted with 1, 2, 3, 4 or 5 R^b substituents;

or two R^6 substituents attached to the same ring carbon atom taken together with the ring carbon atom to which they are attached form spiro C_3-6 cycloalkyl or spiro 4- to 7-membered heterocycloalkyl, each of which is optionally substituted with 1, 2, or 3 independently selected R^f substituents;

each R^{13} is independently H, Ci-6 haloalkyl or Ci-6 alkyl optionally substituted with a substituent selected from C_M alkyl, Ci-4 alkoxy, C_M haloalkyl, Ci-4 haloalkoxy, CN, halo, OH, -COOH, NH_2, -NHCI_4 alkyl and -N(Ci-M alkyl)_2;
R^14 and R^15 are each independently selected from H, halo, CN, OH, -COOH, C_M alkyl, C_M alkoxy, -NHCI_4 alkyl, -N(Ci-4 alkyl)_2, Ci-4 haloalkyl, C_M haloalkoxy, C_3-6 cycloalkyl, phenyl, 5-6 membered heteroaryl and 4-6 membered heterocycloalkyl, wherein the Ci-4 alkyl, Ci-4 alkoxy, C_M haloalkyl, Ci-4 haloalkoxy, C_3-6 cycloalkyl, phenyl, 5-6 membered heteroaryl and 4-6 membered heterocycloalkyl of R^14 or R^15 are each optionally substituted with 1, 2, or 3 independently selected R^9 substituents;
or R^14 and R^15 taken together with the carbon atom to which they are attached form 3-, 4-, 5- or 6-membered cycloalkyl or 3-, 4-, 5- or 6-membered heterocycloalkyl, each of which is optionally substituted with 1 or 2 R^4 substituents;
each R^a is independently selected from H, CN, C1-6 alkyl, C1-6 haloalkyl, C2-6 alkenyl, C6-10 aryl, C1-6 haloalkyl, C1-6 cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C6-10 aryl-C1-4 alkyl-, C1-6 cycloalkyl-C1-4 alkyl-, (5-10 membered heteroaryl)-C1-4 alkyl-, and (4-10 membered heterocycloalkyl)-C1-4 alkyl-, wherein the C1-6 alkyl, C2-6 alkenyl, C6-10 aryl, C1-6 cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C6-10 aryl-C1-4 alkyl-, C1-6 cycloalkyl-C1-4 alkyl-, (5-10 membered heteroaryl)-C1-4 alkyl- and (4-10 membered heterocycloalkyl)-C1-4 alkyl- of R^a are each optionally substituted with 1, 2, 3, 4, or 5 R^d substituents;

each R^d is independently selected from C1-6 alkyl, C1-6 haloalkyl, halo, C6-10 aryl, 5-10 membered heteroaryl, C1-6 cycloalkyl, 4-10 membered heterocycloalkyl, C6-10 aryl-C1-4 alkyl-, C1-6 cycloalkyl-C1-4 alkyl-, (5-10 membered heteroaryl)-C1-4 alkyl-, (4-10 membered heterocycloalkyl)-C1-4 alkyl-, CN, NH2, NHOR, O, OR, SR, C(0)R, C(0)NR R, C(0)OR, OC(0)R, OC(0)NR R, NHR, NRR R, NR R C(0)R, NR R C(0)NR R, NR R C(0)OR R, C(NR R)NR R, NR R C(=NOH)NR R, NR R C(N=NCN)NR R, S(0)R,

S(0)NR R, S(0)2R, NRR S(0)R, NR R S(0)2R, S(0)2NR R, and S(0)2S(0)2R, wherein the C1-6 alkyl, C1-6 haloalkyl, C6-10 aryl, 5-10 membered heteroaryl, C3-10 cycloalkyl, 4-10 membered heterocycloalkyl, C6-10 aryl-C1-4 alkyl-, C1-3 cycloalkyl-C1-4 alkyl-, (5-10 membered heteroaryl)-C1-4 alkyl-, and (4-10 membered heterocycloalkyl)-C1-4 alkyl- of R^d are each optionally substituted with 1, 2, or 3 independently selected R^f substituents;

each R^f is independently selected from H, C1-6 alkyl, C1-6 haloalkyl, C2-6 alkenyl, C2-6 alkynyl, C6-10 aryl, C1-6 cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C6-10 aryl-C1-4 alkyl-, C1-6 cycloalkyl-C1-4 alkyl-, (5-10 membered heteroaryl)-C1-4 alkyl-, (4-10 membered heterocycloalkyl)-C1-4 alkyl-, CN, OH, NH2, NO2, NHOR, O, OR, SR, C(0)R, C(0)NR R, C(0)OR, OC(0)R, OC(0)NR R, C(NR R)NR R, NR R C(=NOH)NR R, NR R C(N=NCN)NR R, S(0)R,

S(0)NR R, S(0)2R, NRR S(0)R, NR R S(0)2R, S(0)2NR R, and S(0)2S(0)2R, wherein the C1-6 alkyl, C1-6 haloalkyl, C6-10 aryl, 5-10 membered heteroaryl, C3-10 cycloalkyl, 4-10 membered heterocycloalkyl, C6-10 aryl-C1-4 alkyl-, C1-3 cycloalkyl-C1-4 alkyl-, (5-10 membered heteroaryl)-C1-4 alkyl-, and (4-10 membered heterocycloalkyl)-C1-4 alkyl- of R^f are each optionally substituted with 1, 2 or 3 independently selected R^g substituents;

each R^g substituent is independently selected from halo, C1-6 alkyl, C2-6 alkenyl, C2-6 alkynyl, C1-6 haloalkyl, C1-6 haloalkoxy, C6-10 aryl, C3-10 cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C6-10 aryl-C1-4 alkyl-, C1-3 cycloalkyl-C1-4 alkyl-, (5-10 membered heteroaryl)-C1-4 alkyl-, (4-10 membered heterocycloalkyl)-C1-4 alkyl-, CN, OH, NH2, NO2, NHOR, O, OR, SR, C(0)R, C(0)NR R, C(0)OR, OC(0)R, OC(0)NR R, C(NR R)NR R, NR R C(=NOH)NR R, NR R C(N=NCN)NR R, S(0)R,

S(0)NR R, S(0)2R, NRR S(0)R, NR R S(0)2R, S(0)2NR R, and S(0)2S(0)2R, wherein the C1-6 alkyl, C1-6 haloalkyl, C6-10 aryl, 5-10 membered heteroaryl, C3-10 cycloalkyl, 4-10 membered heterocycloalkyl, C6-10 aryl-C1-4 alkyl-, C1-3 cycloalkyl-C1-4 alkyl-, (5-10 membered heteroaryl)-C1-4 alkyl-, and (4-10 membered heterocycloalkyl)-C1-4 alkyl- of R^g are each optionally substituted with 1, 2 or 3 independently selected R^h substituents;
wherein the Ci-6 alkyl, Ci-6 haloalkyl, Ci-6 haloalkoxy, C2-6 alkenyl, C2-6 alkynyl, C6-10 aryl, C3-10
cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C6-10 aryl-Ci-4 alkyl-,
c3-10 cycloalkyl-Ci 4 alkyl-, (5-10 membered heteroaryl)-Ci 4 alkyl- and (4-10 membered
heterocycloalkyl)-Ci 4 alkyl- of R8 are each further optionally substituted with 1, 2, or 3
independently selected R f substituents;

each R f is independently selected from H, Ci-6 alkyl, C1-4 haloalkyl, C2-6 alkenyl, C2-6
alkynyl, C6-10 aryl, C 3-10 cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl,
C6-10 aryl-Ci-4 alkyl-, C 3-10 cycloalkyl-Ci 4 alkyl-, (5-10 membered heteroaryl)-Ci 4 alkyl-,
and (4-10 membered heterocycloalkyl)-Ci 4 alkyl-, wherein the Ci-6 alkyl, C2-6 alkenyl, C2-6
alkynyl, C6-10 aryl, C 3-10 cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl,
C6-10 aryl-Ci-4 alkyl-, C 3-10 cycloalkyl-Ci 4 alkyl-, (5-10 membered heteroaryl)-Ci 4 alkyl- and
(4-10 membered heterocycloalkyl)-Ci 4 alkyl- of R f are each optionally substituted with 1, 2, 3, 4, or 5
R g substituents;

each R g is independently selected from C1-4 alkyl, C1-4 haloalkyl, C2-6 alkenyl, C2-6
alkynyl, C6-10 aryl, C 3-10 cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl,
C6-10 aryl-Ci-4 alkyl-, C 3-10 cycloalkyl-Ci 4 alkyl-, (5-10 membered heteroaryl)-Ci 4 alkyl-,
(4-10 membered heterocycloalkyl)-Ci 4 alkyl- of R f are each optionally substituted with 1, 2, 3, 4, or 5
R g substituents;

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10 membered heterocycloalkyl)-Ci-4 alkyl- of R^8 are each optionally substituted with 1, 2 or 3 independently selected R^8 substituents;

   each R^8 is independently selected from H, Ci-6 alkyl, Ci-6 haloalkyl, C2-6 alkenyl, C2-6 alkynyl, C6-10 aryl, C3-10 cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C6-10 aryl-Ci-4 alkyl-, C3-10 cycloalkyl-Ci-4 alkyl-, (5-10 membered heteroaryl)-Ci-4 alkyl-, and (4-10 membered heterocycloalkyl)-Ci-4 alkyl-, wherein the Ci-6 alkyl, C2-6 alkenyl, C2-6 alkynyl, C6-10 aryl, C3-10 cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C6+10 aryl-Ci-4 alkyl-, C3-10 cycloalkyl-Ci-4 alkyl-, (5-10 membered heteroaryl)-Ci-4 alkyl- and (4-10 membered heterocycloalkyl)-Ci-4 alkyl- of R^8 are each optionally substituted with 1, 2, or 3 R^p substituents;

   each R^p is independently selected from Ci-6 alkyl, Ci-6 haloalkyl, C2-6 alkenyl, C2-6 alkynyl, C6-10 aryl, C3-10 cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C6+10 aryl-Ci-4 alkyl-, C3-10 cycloalkyl-Ci-4 alkyl-, (5-10 membered heteroaryl)-Ci-4 alkyl-, (4-10 membered heterocycloalkyl)-Ci-4 alkyl-, halogen, CN, NHOR, OR, SR, C(O)R, C(=O)NR, haloalkoxy, 1, 2, or 3 R^q substituents; wherein the Ci-6 alkyl, C2-6 alkenyl, C2-6 alkynyl, C6-10 aryl, C3-10 cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C6+10 aryl-Ci-4 alkyl-, C3-10 cycloalkyl-Ci-4 alkyl-, (5-10 membered heteroaryl)-Ci-4 alkyl- and (4-10 membered heterocycloalkyl)-Ci-4 alkyl- of R^p is optionally substituted with 1, 2 or 3 R^q substituents;

   or any two R^a substituents together with the nitrogen atom to which they are attached form a 4-, 5-, 6-, 7-, 8-, 9- or 10-membered heterocycloalkyl group optionally substituted with 1, 2 or 3 R^b substituents;

   each R^b is independently selected from Ci-6 alkyl, C3-10 cycloalkyl, 4-7 membered heterocycloalkyl, C6+10 aryl, 5-6 membered heteroaryl, C6+10 aryl-Ci-4 alkyl-, C3-10 cycloalkyl-Ci-4 alkyl-, (5-6 membered heteroaryl)-Ci-4 alkyl-, 4-7 membered heterocycloalkyl, C6+10 aryl-Ci-4 alkyl-, C3-10 cycloalkyl-Ci-4 alkyl-, (5-6 membered heteroaryl)-C1+4 alkyl-, (4-7 membered heteroaryl)-C1+4 alkyl-.
heterocycloalkyl)-Ci-4 alkyl- of R^h are each further optionally substituted by 1, 2, or 3 R^i substituents;

each R^j is independently selected from C\textsubscript{3-6} cycloalkyl, C\textsubscript{6-10} aryl, 5 or 6-membered heteroaryl, 4-7 membered heterocycloalkyl, C\textsubscript{2-4} alkenyl, C\textsubscript{2-4} alkynyl, halo, C\textsubscript{1-4} alkyl, C\textsubscript{1-4} haloalkyl, CN, NHOR \textsuperscript{k}, OR\textsuperscript{k}, SR\textsuperscript{k}, C(\textsuperscript{0})R\textsuperscript{k}, C(\textsuperscript{0})NR\textsuperscript{k}R\textsuperscript{k}, C(\textsuperscript{0})OR\textsuperscript{k}, OC(\textsuperscript{0})R\textsuperscript{k}, OCN(\textsuperscript{0})R\textsuperscript{k}, NHR \textsuperscript{k}, NR\textsuperscript{k}R\textsuperscript{k}, NR\textsuperscript{k}C(\textsuperscript{0})R\textsuperscript{k}, N\textsuperscript{R}C(\textsuperscript{0})NR\textsuperscript{R}R\textsuperscript{k}, N\textsuperscript{R}C(\textsuperscript{0})OR\textsuperscript{k}, C(=NR \textsuperscript{k})NR \textsuperscript{k}R\textsuperscript{k}, N\textsuperscript{R}C(=NR \textsuperscript{k})NR \textsuperscript{k}R\textsuperscript{k}, S(\textsuperscript{0})R\textsuperscript{k}, S(\textsuperscript{0})NR\textsuperscript{k}R\textsuperscript{k}, S(\textsuperscript{0})\textsuperscript{2}R\textsuperscript{k}, N\textsuperscript{R}S(\textsuperscript{0})\textsuperscript{2}R\textsuperscript{k}, N\textsuperscript{R}S(\textsuperscript{0}) \textsuperscript{2}NR\textsuperscript{k}R\textsuperscript{k}, and 
S(\textsuperscript{0})\textsuperscript{2}NR \textsuperscript{k}R\textsuperscript{k}, wherein the C\textsubscript{1-4} alkyl, C\textsubscript{3-6} cycloalkyl, C\textsubscript{6-10} aryl, 5- or 6-membered heteroaryl, 4-6 membered heterocycloalkyl, C\textsubscript{2-4} alkenyl, C\textsubscript{2-4} alkynyl, C\textsubscript{1-4} haloalkyl, and Ci-4 haloalkoxy of R^j are each optionally substituted with 1, 2 or 3 independently selected R^g substituents; or two R^h groups attached to the same carbon atom of the 4- to 10-membered heterocycloalkyl taken together with the carbon atom to which they are attached form a C\textsubscript{3-6} cycloalkyl or 4- to 6-membered heterocycloalkyl having 1-2 heteroatoms as ring members selected from O, N or S; or any two R^c substituents together with the nitrogen atom to which they are attached form a 4-, 5-, 6-, or 7-membered heterocycloalkyl group optionally substituted with 1, 2, or 3 independently selected R^b substituents;
or any two R^c substituents together with the nitrogen atom to which they are attached form a 4-, 5-, 6-, or 7-membered heterocycloalkyl group optionally substituted with 1, 2, or 3 independently selected R^b substituents;
or any two R^b substituents together with the nitrogen atom to which they are attached form a 4-, 5-, 6-, or 7-membered heterocycloalkyl group optionally substituted with 1, 2, or 3 independently selected R^b substituents;
or any two R^b substituents together with the nitrogen atom to which they are attached form a 4-, 5-, 6-, or 7-membered heterocycloalkyl group optionally substituted with 1, 2, or 3 independently selected R^b substituents;
each R₁, R₅, R° or R⁹ is independently selected from H, C₁-4 alkyl, C₅₋₉ cycloalkyl, C₆₋₁₀ aryl, 5 or 6-membered heteroaryl, 4-7 membered heterocycloalkyl, C₁-6 haloalkyl, C₁-6 haloalkoxy, C₂-4 alkenyl, and C₂-4 alkylnyl, wherein the C₁-4 alkyl, C₅₋₉ cycloalkyl, C₆₋₁₀ aryl, 5 or 6-membered heteroaryl, 4-7 membered heterocycloalkyl, C₂-4 alkenyl, and C₂-4 alkylnyl of R₁, R₅,

R° or R⁹ are each optionally substituted with 1, 2 or 3 R⁸ substituents;

each R⁸ is independently selected from halo, OH, CN, -COOH, NH₂, -NH-Ci-6 alkyl, -N(Ci-6 alkyl)₂, C₁-6 alkyl, C₁-6 alkoxy, C₁-6 alkythio, C₁-6 haloalkyl, C₁-6 haloalkoxy, phenyl, 5-6 membered heteroaryl, 4-6 membered heterocycloalkyl and C₃-₆ cycloalkyl, wherein the C₁-6 alkyl, phenyl, C₃-₆ cycloalkyl, 4-6 membered heterocycloalkyl, and 5-6 membered heteroaryl of R⁸ are each optionally substituted with 1, 2, or 3 substituents selected from halo, OH, CN, -COOH, NH₂, C₁-4 alkyl, C₁-4 alkoxy, C₁-4 haloalkyl, C₁-4 haloalkoxy, phenyl, C₃₋₁₀ cycloalkyl, 5-6 membered heteroaryl and 4-6 membered heterocycloalkyl;

the subscript m is an integer of 0, 1, 2 or 3;

the subscript n is an integer of 0, 1, 2 or 3;

the subscript p is an integer of 1, 2, 3 or 4;

each subscript q is independently an integer of 1, 2, 3 or 4; and

the subscript s is an integer of 1, 2, or 3.

In some embodiments, any two R¹ substituents together with the nitrogen atom to which they are attached form a 4-, 5-, 6-, 7-, 8-, 9- or 10-membered heterocycloalkyl group optionally substituted with 1, 2, or 3 independently selected R⁹ substituents;
or any two R₅ substituents together with the nitrogen atom to which they are attached form a 4-, 5-, 6-, 7-, 8-, 9- or 10-membered heterocycloalkyl group optionally substituted with 1, 2, or 3 independently selected R⁹ substituents.

In some embodiments, provided herein is a compound of Formula (I) or a pharmaceutically acceptable salt or a stereoisomer thereof, wherein (1) when L is -C(0)NH-, ring A is not 4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridin-2-yl; (2) when L is a bond, ring A is not [1,2,4]triazolo[1,5-a]pyridin-2-yl; (3) when L is a bond, ring A is not 2-benzoxazolyl; and (4) when L is -C(0)NH-, ring A is not 2-pyridyl.

In some embodiments, provided herein is a compound of Formula (I) or a pharmaceutically acceptable salt or a stereoisomer thereof, wherein (1) when L is -C(0)NH-, ring A is not 4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridin-2-yl; (2) when L is a bond, ring A is not [1,2,4]triazolo[1,5-a]pyridin-2-yl; (3) when L is a bond, ring A is not 2-benzoxazolyl; or (4) when L is -C(0)NH-, ring A is not 2-pyridyl.
In some embodiments, provided herein is a compound of Formula (la):

or a pharmaceutically acceptable salt or a stereoisomer thereof, wherein:

R^17 is H, C1-4 alkyl, C1-4 alkoxy, \textit{c} M haloalkyl, \textit{c} M haloalkoxy, CN, halo, OH, -COOH, NH2, -NH\textit{c}i\textit{4} alkyl or -N(Ci\textit{4} alkyl)2, wherein the C1-4 alkyl and C1-4 alkoxy are each optionally substituted with 1 or 2 substituents independently selected from CN, halo and -C(0)NH2;

one of R^1 and R^2 is -(CR^8R^9)_p-NR^10 for the other is H, \textit{c} M alkyl, \textit{c} M alkoxy, \textit{c} M haloalkyl, \textit{c} M haloalkoxy, CN, halo, OH, -COOH, NH2, -NH\textit{c}i\textit{4} alkyl or -N(Ci\textit{4} alkyl)2, wherein the C1-4 alkyl and C1-4 alkoxy of R^1 or R^2 is optionally substituted with 1 or 2 substituents independently selected from \textit{c} M alkoxy, \textit{c} M haloalkyl, \textit{c} M haloalkoxy, CN, halo, OH, -COOH, -C(0)NH2, \textit{c} M haloalkyl, \textit{c} M haloalkoxy, CN, halo, OH, -COOH, -C(0)NH2 for the other is H, \textit{c} M alkyl, \textit{c} M alkoxy, \textit{c} M haloalkyl, \textit{c} M haloalkoxy, CN, halo, OH, -COOH, NH2, -NH\textit{c}i\textit{4} alkyl or -N(Ci\textit{4} alkyl)2, wherein the C1-4 alkyl and C1-4 alkoxy are each optionally substituted with 1 or 2 substituents independently selected from CN, halo or -C(0)NH2;

R^7 is H, \textit{c} M alkyl, \textit{c} M alkoxy, \textit{c} M haloalkyl, \textit{c} M haloalkoxy, CN, halo, OH, -COOH, NH2, -NH\textit{c}i\textit{4} alkyl or -N(Ci\textit{4} alkyl)2, wherein the C1-4 alkyl and C1-4 alkoxy of R^1 or R^2 is optionally substituted with 1 or 2 substituents independently selected from CN, halo or -C(0)NH2;

R^8 and R^9 are each independently selected from H, halo, CN, OH, -COOH, \textit{c} M alkyl, C1-4 alkoxy, -NH\textit{c}i\textit{4} alkyl, -N(C1-4 alkyl)2, \textit{c} M haloalkyl, \textit{c} M haloalkoxy, C3-6 cycloalkyl, phenyl, 5-6 membered heteroaryl and 4-6 membered heterocycloalkyl, wherein the C1-4 alkoxy, C1-4 haloalkyl, C1-4 haloalkoxy, C3-6 cycloalkyl, phenyl, 5-6 membered heteroaryl and 4-6 membered heterocycloalkyl of R^8 or R^9 are each optionally substituted with 1, 2 or 3 independently selected R^4 substituents;

or R^8 and R^9 taken together with the carbon atom to which they are attached form 3-, 4-, 5- or 6-membered cycloalkyl or 4-, 5-, 6- or 7-membered heterocycloalkyl, each of which is optionally substituted with 1 or 2 R^9 substituents;

or R^8 and R^10 taken together with the atoms to which they are attached form 4-, 5-, 6- or 7-membered heterocycloalkyl, having zero to one additional heteroatoms as ring members selected from O, N or S, wherein the 4-, 5-, 6- or 7-membered heterocycloalkyl formed by R^8 and R^10 are each optionally substituted with 1 or 2 R^9 substituents;

R^10 and R^11 are each independently selected from H, C1-6 alkyl, C1-6 haloalkyl, C3-6 cycloalkyl, C6-10 aryl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C6-10 aryl-Ci-
alkyl-, C₃-6 cycloalkyl-Ci - 4 alkyl-, (5-10 membered heteroaryl)-Ci - 4 alkyl-, (4-10 membered heterocycloalkyl)-Ci - 4 alkyl-, -C(=O)R®, -C(=O)OR®, -C(=O)NR₂R®, -SO₂R® and -SO₂NR'R®;

wherein the C3-6 alkyl, C6-10 aryl, C3-6 cycloalkyl, C6-10 aryl-C1-4 alkyl-, C3-6 cycloalkyl-C1-4 alkyl-, (5-10 membered heteroaryl)-Ci - 4 alkyl-, and (4-10 membered heterocycloalkyl)-Ci - 4 alkyl- of R₁₀ or R¹¹ are each optionally substituted with 1, 2, or 3 independently selected R³ substituents;

or R¹₀ and R¹¹ taken together with the nitrogen atom to which they are attached form 4-, 5-, 6-, 7-, 8-, 9-, 10-, or 11-membered heterocycloalkyl, wherein the 4-11-membered heterocycloalkyl is each optionally substituted with 1, 2 or 3 R² substituents;

R¹² is H, C1-4 alkyl, C₃ alkoxy, C₃ haloalkyl, C₃ haloalkoxy, CN, halo, OH, -COOH, NH₂,
-NH-Ci-4 alkyl or -N(Ci-4 alkyl)₂; and

the subscript p is an integer of 1, 2, 3 or 4.

In some embodiments, provided herein is a compound of Formula (1a), or a

pharmaceutically acceptable salt or a stereoisomer thereof, wherein:

R¹ is H, C₃ alkyl, C₃ alkoxy, C₃ haloalkyl, C₃ haloalkoxy, CN, halo, OH, -COOH, NH₂, -NH-Ci-4 alkyl or -N(Ci-4 alkyl)₂, wherein the C1-4 alkyl and C1-4 alkoxy are each optionally substituted with 1 or 2 substituents independently selected from CN, halo and -C(=O)NH₂;

one of R¹ and R² is -(CR₈R₉)ₚ-NR₁₀R¹¹ and the other is H, C₃ alkyl, C₃ alkoxy, C₃ haloalkyl, C₃ haloalkoxy, CN, halo, OH, -COOH, C(=O)NH₂, NH₂, -NH-Ci-4 alkyl and -N(Ci-4 alkyl)₂;

R² is H, C₃ alkyl, C₃ alkoxy, C₃ haloalkyl, C₃ haloalkoxy, CN, halo, OH, -COOH, NH₂, -NH-Ci-4 alkyl or -N(Ci-4 alkyl)₂, wherein the C1-4 alkyl and C1-4 alkoxy of R¹ or R² is optionally substituted with 1 or 2 substituents independently selected from C₃ alkoxy, C₃ haloalkyl, C₃ haloalkoxy, CN, halo, OH, -COOH, C(=O)NH₂, C(=O)NH₂, -NH-Ci-4 alkyl and -N(Ci-4 alkyl)₂;

R⁸ and R⁹ are each independently selected from H, halo, CN, OH, -COOH, C₃ alkyl, C₁-4 alkoxy, -NH-Ci-4 alkyl, -N(Ci-4 alkoxy)₂, C₃ haloalkyl, C₃ haloalkoxy, C₃-6 cycloalkyl, phenyl, 5-6 membered heteroaryl and 4-6 membered heterocycloalkyl, wherein the C₃ alkyl, C₁-4 alkoxy, C₁-4 haloalkyl, C₁-4 haloalkoxy, C₃-6 cycloalkyl, phenyl, 5-6 membered heteroaryl and 4-6 membered heterocycloalkyl of R⁸ or R⁹ are each optionally substituted with 1, 2 or 3 independently selected R⁴ substituents;
or $R^8$ and $R^9$ taken together with the carbon atom to which they are attached form 3-, 4-, 5- or 6-membered cycloalkyl or 4-, 5-, 6- or 7-membered heterocycloalkyl, each of which is optionally substituted with 1 or 2 $R^8$ substituents;

or $R^8$ and $R^{10}$ taken together with the atoms to which they are attached form 4-, 5-, 6- or 7-membered heterocycloalkyl, having zero to one additional heteroatoms as ring members selected from O, N or S, wherein the 4-, 5-, 6- or 7-membered heterocycloalkyl formed by $R^8$ and $R^{10}$ are each optionally substituted with 1 or 2 $R^8$ substituents;

$R^{10}$ and $R^{11}$ are each independently selected from H, Ci-6 alkyl, Ci-6haloalkyl, C$_3$-6 cycloalkyl, C$_6$-10 aryl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C$_6$-10 aryl-Ci-4 alkyl-, C$_3$-6 cycloalkyl-Ci-4 alkyl-, (5-10 membered heteroaryl)-Ci-4 alkyl-, (4-10 membered heterocycloalkyl)-Ci-4 alkyl-, -(C(0))R, -(C(0))OR, -(C(0))NR$_3$g, -SO$_2$R and -SO$_2$ NR$_3$g, wherein the Ci-6 alkyl, Ci-6haloalkyl, C$_3$-6 cycloalkyl, C$_6$-10 aryl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C$_6$-10 aryl-C$_4$ alkyl-, C$_3$-6 cycloalkyl-C$_4$ alkyl-, (5-10 membered heteroaryl)-Ci-$_4$ alkyl-, and (4-10 membered heterocycloalkyl)-Ci-$_4$ alkyl- of $R^{10}$ or $R^{11}$ are each optionally substituted with 1, 2, or 3 independently selected $R^d$ substituents;

or $R^{10}$ and $R^{11}$ taken together with the nitrogen atom to which they are attached form 4-, 5-, 6-, 7-, 8-, 9-, 10-, or 11-membered heterocycloalkyl, wherein the 4-11 membered heterocycloalkyl is each optionally substituted with 1, 2 or 3 $R^d$ substituents; and $R^{12}$ is H, Ci-4 alkyl, Ci-4 alkoxy, C$_M$ haloalkyl, Ci-4 haloalkoxy, CN, halo, OH, -COOH, NH$_2$, -NHCi-4 alkyl or -N(Ci-4 alkyl)$_2$.

In some embodiments, the compound provided herein is a compound having Formula (II):

![Formula (II)](image)

or a pharmaceutically acceptable salt or a stereoisomer thereof.

In some embodiments, the compound provided herein is a compound having Formula (IIa):
or a pharmaceutically acceptable salt or a stereoisomer thereof.

In some embodiments, the compound provided herein is a compound having Formula (IIa-1):

or a pharmaceutically acceptable salt or a stereoisomer thereof, wherein:

- ring A is 5- to 10-membered heteroaryl, 4- to 11-membered heterocycloalkyl or C_{6-10} aryl, wherein the 5- to 10-membered heteroaryl and 4- to 11-membered heterocycloalkyl each has 1-4 heteroatoms as ring members selected from N, O and S, wherein the N or S atom as ring members is optionally oxidized and one or more carbon atoms as ring members are each optionally replaced by a carbonyl group; and wherein ring A is optionally substituted with 1, 2 or 3 R^6 substituents; L is a bond, -C(0)NH-, -NH- or -OCH2-, wherein the carbonyl group in the -C(0)NH- linkage or the oxygen atom in the -OCH2- linkage is attached to ring A; and X is CH or N.

In some embodiments, the compound provided herein is a compound having Formula (IIa-2):

or a pharmaceutically acceptable salt or a stereoisomer thereof.

In some embodiments, the compound provided herein is a compound having Formula (lib):
or a pharmaceutically acceptable salt or a stereoisomer thereof.

In some embodiments, the compound provided herein is a compound having Formula (Iib):

or a pharmaceutically acceptable salt or a stereoisomer thereof, wherein:

X^1, X^2, X^3, X^4, X^5 and X^6 are each independently N or CH, with the proviso that X^1, X^5 and X^6 are not simultaneously N;

R_{13} is H or Ci-4 alkyl; and

the subscript r is an integer of 1, 2 or 3.

In some embodiments, the compound provided herein is a compound having Formula (Iic-1):

or a pharmaceutically acceptable salt or a stereoisomer thereof.

In some embodiments, R_{13} is H.

In some embodiments, the compound provided herein is a compound having Formula (Iid):

or a pharmaceutically acceptable salt or a stereoisomer thereof, wherein:

R_{13} is H or Ci-4 alkyl;
R\textsuperscript{19} is H, Ci-6 alkyl, Ci-4 haloalkyl, C2-6 alkenyl, C2-6 alkynyl, C\textsubscript{6}-ioaryl, C\textsubscript{3}-10
cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C\textsubscript{6}-io aryl-Ci-4 alkyl-
, C\textsubscript{3}-10 cycloalkyl-Ci-4 alkyl-, (5-10 membered heteroaryl)-Ci-4 alkyl-, or (4-10 membered
heterocycloalkyl)-Ci-4 alkyl-, wherein the Ci-6 alkyl, C2-6 alkenyl, C2-6 alkynyl, C\textsubscript{6}-io aryl, C\textsubscript{3}-
to cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C\textsubscript{6}-io aryl-Ci-4
alkyl-, C\textsubscript{3}-10 cycloalkyl-Ci-4 alkyl-, (5-10 membered heteroaryl)-Ci-4 alkyl- and (4-10
membered heterocycloalkyl)-Ci-4 alkyl- of R\textsuperscript{i8} are each optionally substituted with 1, 2, or 3
R\textsuperscript{b} substituents; and

the subscript t is an integer of 0, 1 or 2.

In some embodiments, the compound provided herein is a compound having Formula
(IId-1):

\[
\text{(IId-1)}
\]

or a pharmaceutically acceptable salt or a stereoisomer thereof.

In some embodiments, the compound provided herein is a compound having Formula
(He):

\[
\text{(He)}
\]

or a pharmaceutically acceptable salt or a stereoisomer thereof.

In some embodiments, the compound provided herein is a compound having Formula (Ilf):

\[
\text{(Ilf)}
\]

or a pharmaceutically acceptable salt or a stereoisomer thereof.

In some embodiments, the compound provided herein is a compound having Formula
(III):
or a pharmaceutically acceptable salt or a stereoisomer thereof.

In some embodiments, the compound provided herein is a compound having Formula (IIIa):

or a pharmaceutically acceptable salt or a stereoisomer thereof.

In some embodiments, the compound provided herein is a compound having Formula (IIIb):

or a pharmaceutically acceptable salt or a stereoisomer thereof.

In some embodiments, provided herein are compounds having Formula (IV):

or a pharmaceutically acceptable salt or a stereoisomer thereof, wherein the subscript $r$ is 1, 2, 3, 4 or 5. In some embodiments, $X$ is N or CH. In one embodiment, ring A is pyridyl, for example, 2-pyridyl. In some embodiments, the subscript $n$ is 0, 1 or 2 and each $R^5$ is independently C1-4 alkyl, C1-4 alkoxy, C1-4 haloalkyl, C1-4 haloalkoxy, CN, halo, OH, -COOH, NH2, -NHC1-4 alkyl or -N(C1-4 alkyl)2. In certain instances, $R^5$ is halo or C1-4 alkyl. In some embodiments, the subscript $m$ is 0. In some embodiments, the subscript $r$ is 1 or 2. In some embodiments, $R^{12}$ is H, C1-4 alkyl, C1-4 alkoxy, C1-4 haloalkyl, C1-4 haloalkoxy, CN, halo, -
COOH, NH2, -NHCl-4 alkyl or -N(Cl-4 alkyl)2. In one embodiment, R2 is H. In some embodiments, the subscript p is 1 and R8 and R9 are each H. In one embodiment, R10 is H. In some embodiments, R8 and R10 taken together form 4- to 6-membered heterocycloalkyl, optionally substituted with 1 or 2 R8 substituents. In some embodiments, R10 and R11 taken together form 4- to 6-membered heterocycloalkyl, optionally substituted with 1 or 2 R9 substituents.

In some embodiments, provided herein are compounds having Formula (V):

![Formula V](image)

or a pharmaceutically acceptable salt or a stereoisomer thereof, wherein the subscript r is 1, 2, 3, 4 or 5, the other variables of Formula (V) are as defined in any embodiment disclosed herein. In some embodiments, the subscript r is 1 or 2.

In some embodiments, provided herein are compounds having Formula (VI):

![Formula VI](image)

or a pharmaceutically acceptable salt or a stereoisomer thereof, wherein the subscript r is 1, 2, 3, 4 or 5, the other variables of Formula (VI) are as defined in any embodiment disclosed herein. In some embodiments, the subscript r is 1 or 2.

In some embodiments, provided herein are compounds having Formula (Vila) or (VIIb):

![Formula Vila or VIIb](image)
or a pharmaceutically acceptable salt or a stereoisomer thereof, wherein the subscript \( r \) is 1, 2, 3, 4 or 5, the other variables of Formula (VIIa) or (VIIb) are as defined in any embodiment disclosed herein. In some embodiments, the subscript \( r \) is 1 or 2.

In some embodiments, provided herein are compounds having Formula (VIIa) or (VIIb):

or a pharmaceutically acceptable salt or a stereoisomer thereof, wherein the subscript \( r \) is 1, 2, 3, 4 or 5, the other variables of Formula (VIIa) or (VIIb) are as defined in any embodiment disclosed herein. In some embodiments, the subscript \( r \) is 1 or 2.

In some embodiments, ring A is 5- to 14-membered heteroaryl, 4- to 14-membered heterocycloalkyl or \( \text{C}_{6-10} \) aryl, wherein the 5- to 14-membered heteroaryl and 4- to 14-membered heterocycloalkyl each has 1-4 heteroatoms as ring members selected from N, O and S, wherein the N or S atom as ring members is optionally oxidized and one or more carbon atoms as ring members are each optionally replaced by a carbonyl group; and wherein ring A is optionally substituted with 1, 2, 3, or 4 \( \text{R}^6 \) substituents. In some embodiments, ring A is 5- to 14-membered heteroaryl or 4- to 14-membered heterocycloalkyl, wherein the 5- to 14-membered heteroaryl and 4- to 14-membered heterocycloalkyl each has 1-4 heteroatoms as ring members selected from N, O and S, wherein the N or S atom as ring members is optionally oxidized and one or more carbon atoms as ring members are each optionally replaced by a carbonyl group;
and wherein ring A is optionally substituted with 1, 2, or 3 \( R^6 \) substituents. In some embodiments, ring A is is 5- to 14-membered heteroaryl, wherein the 5- to 14-membered heteroaryl has 1-4 heteroatoms as ring members selected from N, O and S, wherein the N or S atom as ring members is optionally oxidized and one or more carbon atoms as ring members are each optionally replaced by a carbonyl group; and wherein ring A is optionally substituted with 1, 2, or 3 \( R^6 \) substituents. In some embodiments, ring A is is 4- to 14-membered heterocycloalkyl, wherein the 4- to 14-membered heterocycloalkyl has 1-4 heteroatoms as ring members selected from N, O and S, wherein the N or S atom as ring members is optionally oxidized and one or more carbon atoms as ring members are each optionally replaced by a carbonyl group; and wherein ring A is optionally substituted with 1, 2, or 3 \( R^6 \) substituents. In some embodiments, ring A is selected from:

\[
\begin{align*}
\text{attachment to } L.
\end{align*}
\]

In some embodiments, ring A is selected from:
wherein each subscript $r$ is an integer of 1, 2, 3, 4 or 5; and the wavy line indicates the point of attachment to L.

In some embodiments, ring A is selected from:

wherein each subscript $r$ is an integer of 1, 2, 3, 4 or 5; and the wavy line indicates the point of attachment to L.

In some embodiments, ring A is selected from:

wherein each subscript $r$ is an integer of 1, 2, 3, 4 or 5; and the wavy line indicates the point of attachment to L.

In some embodiments, ring A is selected from:
In some embodiments, ring A is selected from:

\[ \text{\textbf{I}} \]

wherein each subscript \( r \) is an integer of 1, 2, 3, 4 or 5; \( R^6 \) is C6 alkyl; and the wavy line indicates the point of attachment to L.

In some embodiments, ring A is 2-pyridyl, optionally substituted with 1, 2, 3, or 4 independently selected \( R^6 \) substituents.

In some embodiments, ring A is selected from:

\[ \text{\textbf{II}} \]

wherein each subscript \( r \) is an integer of 1, 2, 3, 4 or 5; and the wavy line indicates the point of attachment to L.
In some embodiments, L is a bond, -C(0)NR\textsuperscript{13}-, -(CR\textsuperscript{14}R\textsuperscript{15})\textsuperscript{q}O-, -0 (CR\textsuperscript{14}R\textsuperscript{15})\textsuperscript{q}O-, -0 (CR\textsuperscript{14}R\textsuperscript{15})q\textsuperscript{13}-, -NR\textsuperscript{13}-, or -CH=CH-. In some embodiments, L is a bond, -C(0)NR\textsuperscript{13}-, -N R\textsuperscript{13}C(0)-, -(CR\textsuperscript{14}R\textsuperscript{15})\textsuperscript{q}O-, -0 (CR\textsuperscript{14}R\textsuperscript{15})\textsuperscript{q}O-, -0 (CR\textsuperscript{14}R\textsuperscript{15})q\textsuperscript{13}-, or -NR\textsuperscript{13}-. In some embodiments, L is a bond, -C(0)NR\textsuperscript{13}-, -N R\textsuperscript{13}C(0)-, -NR\textsuperscript{13}-, or -CH=CH-. In some embodiments, L is a bond, -NH-, -CH=CH- or -C(0)NH-, wherein the carbonyl group in the -C(0)NH- linkage is attached to ring A. In some embodiments, L is a bond. In some embodiments, L is -C(0)NR\textsuperscript{13}- (e.g., -C(0)NH-), wherein the carbonyl group is attached to ring A. In some embodiments, L is a bond, -NR\textsuperscript{13}-, -(CR\textsuperscript{14}R\textsuperscript{15})qO-, -0 (CR\textsuperscript{14}R\textsuperscript{15})\textsuperscript{q}O-, -(CR\textsuperscript{14}R\textsuperscript{15})qNR\textsuperscript{13}- or -NR\textsuperscript{13}-(CR\textsuperscript{14}R\textsuperscript{15})q-, wherein the subscript q is 1, 2 or 3. In certain instances, R\textsuperscript{14} and R\textsuperscript{15} are each independently H or Ci-4 alkyl. In other instances, R\textsuperscript{14} and R\textsuperscript{15} taken together form C\textsubscript{3,6} cycloalkyl or 4-6-membered heterocycloalkyl, each of which is optionally substituted with 1 or 2 R\textsuperscript{9} substituents.

In some embodiments, L is a bond. In some embodiments, L is -NR\textsuperscript{13}. In certain instances, R\textsuperscript{13} is H or Ci-4 alkyl.

In some embodiments, L is -CH2O- or -OCH2-.

In some embodiments, L is -NR\textsuperscript{13}CH2- or -CH2NR\textsuperscript{13}. In certain instances, R\textsuperscript{13} is H or Ci-4 alkyl.

In some embodiments, L is -C(0)NH-.

In some embodiments, L is -NH-.

In some embodiments, the subscript m is 0, 1, or 2. In some embodiments, the subscript m is 0 or 1. In some embodiments, the subscript m is 0.

In some embodiments, R\textsuperscript{5} is Ci-4 alkyl, Ci-4alkoxy, Ci-4 haloalkyl, Ci-4 haloalkoxy, CN, halo, or OH. In some embodiments, R\textsuperscript{5} is Ci-4 alkyl, Ci-4alkoxy, CN, halo, or OH. In some embodiments, R\textsuperscript{5} is Ci-4 alkyl or halo. In some embodiments, R\textsuperscript{5} is Ci-4 alkyl (e.g., methyl). In some embodiments, R\textsuperscript{5} is halo (e.g., Cl).

In some embodiments, the subscript n is an integer of 0, 1, or 2. In some embodiments, the subscript n is an integer of 1 or 2. In some embodiments, the subscript n is an integer of 1.
In some embodiments, the subscript \( n \) is 1 and \( R^5 \) is halo or Ci-4 alkyl. In some embodiments, the subscript \( n \) is 1 and \( R^5 \) is halo. In some embodiments, the subscript \( n \) is 1 and \( R^5 \) is Ci-4 alkyl.

In some embodiments, \( R^3 \) is methyl, halo, or CN. In some embodiments, \( R^3 \) is methyl. In some embodiments, \( R^3 \) is halo (e.g., CI). In some embodiments, \( R^3 \) is CN. In some embodiments, \( R^3 \) is methyl, CN or Cl.

In some embodiments, \( R^{12} \) is H, Ci-4 alkyl, Ci-4 alkoxy, Ci-4 haloalkyl, Ci-4 haloalkoxy, CN, halo, or OH. In some embodiments, \( R^{12} \) is H, halo, CN, Ci-4 alkyl or Ci-4 alkoxy. In some embodiments, \( R^{12} \) is H, halo, or Ci-4 alkoxy. In some embodiments, \( R^{12} \) is H.

In some embodiments, \( R^7 \) is H, Ci-4 alkyl, Ci-4 alkoxy, Ci-4 haloalkyl, Ci-4 haloalkoxy, CN, halo, or OH, wherein the Ci-4 alkyl and Ci-4 alkoxy are each optionally substituted with 1 or 2 substituents independently selected from CN, halo and -C(0)NH2. In some embodiments, \( R^7 \) is H, halo, CN, Ci-4 alkyl, Ci-4 alkoxy or Ci-4 haloalkoxy, wherein the Ci-4 alkyl and Ci-4 alkoxy of \( R^7 \) are each optionally substituted with CN. In some embodiments, \( R^7 \) is H, halo, CN, or Ci-4 alkoxy. In some embodiments, \( R^7 \) is H or Ci-4 alkyl. In some embodiments, \( R^7 \) is H.

In some embodiments, one of \( R^1 \) and \( R^2 \) is \( -(CR^8R^9)_pNR^{10}R^{11} \) and the other is H, Ci-4 alkyl, Ci-4 alkoxy, Ci-4 haloalkyl, Ci-4 haloalkoxy, CN, halo, or OH, wherein the Ci-4 alkyl and Ci-4 alkoxy of \( R^1 \) or \( R^2 \) is optionally substituted with 1 or 2 substituents independently selected from Ci-4 alkyl, Ci-4 haloalkyl, Ci-4 haloalkoxy, CN, halo, and OH. In some embodiments, one of \( R^1 \) and \( R^2 \) is \( -(CR^8R^9)_pNR^{10}R^{11} \) and the other is H, Ci-4 alkyl, Ci-4 alkoxy, Ci-4 haloalkyl, or Ci-4 haloalkoxy. In some embodiments, one of \( R^1 \) and \( R^2 \) is \( -(CR^8R^9)_pNR^{10}R^{11} \) and the other is H or Ci-4 alkyl. In some embodiments, one of \( R^1 \) and \( R^2 \) is \( -(CR^8R^9)_pNR^{10}R^{11} \) and the other is H.

In some embodiments, \( R^2 \) is H.

In some embodiments, \( R^1 \) is H.

In some embodiments, \( R^2 \), \( R^7 \) and \( R^{12} \) are each H.

In some embodiments, \( R^3 \) and \( R^5 \) are each independently halo, methyl or CN.

In some embodiments, the subscript \( p \) is an integer of 1, 2, or 3. In some embodiments, the subscript \( p \) is an integer of 1 or 2. In some embodiments, the subscript \( p \) is 1.

In some embodiments, \( R^8 \) and \( R^9 \) are each independently selected from H, halo, CN, OH, -COOH, Ci M alkyl, Ci M alkoxy, -NHCi-4 alkyl, -N(Ci M alkyl)\(_2\), Ci M haloalkyl, and Ci M haloalkoxy, wherein the Ci M alkyl, Ci-4 alkoxy, Ci-4 haloalkyl, and Ci M haloalkoxy of \( R^8 \) or \( R^9 \) are each optionally substituted with 1 or 2 independently selected R\(_8\) substituents. In some embodiments, \( R^8 \) and \( R^9 \) are each independently selected from H, halo, CN, Ci M alkyl, and Ci M alkoxy, wherein the Ci M alkyl and Ci-4 alkoxy of \( R^8 \) or \( R^9 \) are each optionally substituted with 1
or 2 independently selected R8 substituents. In some embodiments, R8 and R9 are each independently selected from H and C1-4 alkyl. In some embodiments, R8 is H. In some embodiments, R9 is H.

In some embodiments, R8 and R9 are each H.

In some embodiments, R10 and R11 are each independently selected from H, C1-4 alkyl, and C1-5 haloalkyl, wherein the C1-4 alkyl and C1-5 haloalkyl of R10 or R11 are each optionally substituted with 1, 2, or 3 independently selected Rf substituents;

or R10 and R11 taken together with the nitrogen atom to which they are attached form 4-, 5-, 6- or 7-membered heterocycloalkyl, wherein the 4-, 5-, 6- or 7-membered heterocycloalkyl is optionally substituted with 1, 2 or 3 Rb substituents.

In some embodiments, R10 and R11 are each independently selected from H and C1-4 alkyl optionally substituted with 1 or 2 independently selected Rf substituents;

or R10 and R11 taken together with the nitrogen atom to which they are attached form 4-, 5-, 6- or 7-membered heterocycloalkyl, wherein the 4-, 5-, 6- or 7-membered heterocycloalkyl is optionally substituted with 1, 2 or 3 Rb substituents.

In some embodiments, R10 and R11 are each independently selected from H and C1-4 alkyl optionally substituted with 1 or 2 independently selected Rf substituents. In some embodiments, R10 and R11 taken together with the nitrogen atom to which they are attached form 4-, 5-, 6- or 7-membered heterocycloalkyl, wherein the 4-, 5-, 6- or 7-membered heterocycloalkyl is optionally substituted with 1, 2 or 3 Rb substituents.

In some embodiments, R10 is H.

In some embodiments, R11 is 2-hydroxyethyl, [1-(hydroxymethyl)cyclopropyl]methyl, [1-(hydroxymethyl)cyclobutyl]methyl or 2-(dimethylamino)-2-oxo-ethyl.

In some embodiments, R11 is 1-hydroxy-2-propyl, 2-carboxy ethyl, or 2-

hydroxycyclopentyl.

In some embodiments, -NR10R11 is (2-hydroxyethyl)amino, 3-hydroxypyrrolidin-l -yl, (R)-3-hydroxypyrrolidin-l-yl, (S)- 3-hydroxypyrrolidin-l -yl, 3-carboxyprrrolidin-l -yl, (R)-3-carboxyprrrolidin-l-yl, (S)-3-carboxyprrrolidin-l -yl, 3-carboxyazetidin-l -yl, (S)-3-carboxyazetidin-l-yl, (Kj-3-carboxyazetidin-l-yl, 2-carboxy-l-piperidinyl, (R)-2-carboxy-l-piperidinyl, (S)- 2-carboxy-l-piperidinyl, 2-oxooxazolidin-3-yl, [1-(hydroxymethyl)cyclopropyl]methylamino, [1-(hydroxymethyl)cyclobutyl]methylamino, [2-(dimethylamino)-2-oxo-ethyl]amino, 3-(dimethylaminocarbonyl)pyrrolidin-l -yl, (R)-3-(dimethylaminocarbonyl)pyrrolidin-l -yl, 2-hydroxypropylamino, 2-hydroxy-2-methylpropylamino, or 3-methyl-3-carboxyprrrolidin-l -yl.
In some embodiments, \(-NR^{10}R^{11}\) is (2-hydroxyethyl)amino, 3-hydroxypyrrolidin-1-yl, 3-carboxypyrrolidin-1-yl, 3-carboxyazetidin-1-yl, S(\(\beta\))-3-carboxyazetidin-1-yl, (R)-3-carboxyazetidin-1-yl, 2-carboxy-1-piperidinyl, 2-oxooxazolidin-3-yl, 2-(hydroxymethyl)cyclopentyl)methylamino, [1-(hydroxymethyl)cyclobutyl]methylamino or [2-(dimethylamino)-2-oxoethyl]amino.

In some embodiments, \(-NR^{10}R^{11}\) is (2-hydroxyethyl)amino, 3-hydroxypyrrolidin-1-yl, 3-carboxypyrrolidin-1-yl, 3-carboxyazetidin-1-yl, S(\(\beta\))-3-carboxyazetidin-1-yl, (R)-3-carboxyazetidin-1-yl, 2-carboxy-1-piperidinyl, 2-oxooxazolidin-3-yl, [1-(hydroxymethyl)cyclopentyl)methylamino, [1-(hydroxymethyl)cyclobutyl]methylamino, [2-(dimethylamino)-2-oxoethyl]amino, 3-(dimethylaminocarbonyl)pyrrolidin-1-yl, 2-hydroxypropylamino, 2-hydroxy-2-methylpropylamino, or 3-methyl-3-carboxypyrrolidin-1-yl.

In some embodiments, \(-NR^{10}R^{11}\) is (2-hydroxyethyl)amino, 3-hydroxypyrrolidin-1-yl, 3-carboxypyrrolidin-1-yl, 3-carboxyazetidin-1-yl, 2-carboxy-1-piperidinyl, 2-oxooxazolidin-3-yl, [1-(hydroxymethyl)cyclobutyl]methylamino, [1-(hydroxymethyl)cyclobutyl]methylamino or [2-(dimethylamino)-2-oxoethyl]amino.

In some embodiments, \(-NR^{10}R^{11}\) is 1-pyrrolidinyl, (3-carboxy-3-methyl)pyrrolidin-1-yl, (R)-(3-carboxy-3-methyl)pyrrolidin-1-yl, (R)-(3-carboxy-3-methyl)pyrrolidin-1-yl, (S)-(3-carboxy-3-methyl)pyrrolidin-1-yl, (S)-(3-carboxy-3-methyl)pyrrolidin-1-yl, (R)-(3-hydroxy-3-methyl)pyrrolidin-1-yl, (S)-(3-hydroxy-3-methyl)pyrrolidin-1-yl, (2-hydroxycyclopentyl)amino, (IR,2S)-2-hydroxycyclopentyl)amino, (IR,2R)-2-hydroxycyclopentyl)amino, (IR,2S)-2-hydroxycyclopentyl)amino, (IR,2R)-2-hydroxycyclopentyl)amino, 2-carboxyethylamino, 3-(carboxymethyl)pyrrolidin-1-yl, or 5-carboxy-2-azabicyclo[2.2.1]heptan-2-yl.

In some embodiments, X is N or CR\(^{17}\), wherein R\(^{17}\) is H, C\(_4\) alkyl, C\(_4\) alkoxy, C\(_4\) haloalkyl, C\(_4\) haloalkoxy, CN, or halo. In some embodiments, X is N or CR\(^{17}\), wherein R\(^{17}\) is H or C\(_4\) alkyl. In some embodiments, X is N or CH. In some embodiments, X is CR\(^{17}\) (e.g., CH).

In some embodiments, R\(^6\), R\(^7\), R\(^{17}\) and R\(^{18}\) are each independently selected from H, halo, C\(_6\) alkyl, C\(_2\) alkynyl, C\(_2\) alkoxy, C\(_6\) haloalkyl, C\(_1\) haloalkoxy, C\(_6\) aryl, C\(_3\) cycloalkyl, 5-14 membered heterocyclic, 4-10 membered heteroalkyl, C\(_6\) aryl-C\(_4\) alky-, C\(_3\) cycloalkyl-C\(_1\) alky-, (5-14 membered heteroaryl)-C\(_4\) alky-, (4-10 membered heterocycloalkyl)-C\(_4\) alky-, CN, OR\(^2\), C(\(\beta\))O \(^R\), C(\(\beta\))NR \(^R\), C(\(\beta\))OR \(^R\), OC(\(\beta\))R \(^R\), OC(\(\beta\))NR \(^R\), NHR \(^R\), NR\(^2\)R\(^R\), NR\(^2\)C(\(\beta\))OR \(^R\), and NR\(^3\)C(\(\beta\))OR \(^R\), wherein the C\(_6\) alkyl, C\(_2\) alkenyl, C\(_2\) alkynyl, C\(_6\) aryl, C\(_3\) cycloalkyl, 5-14 membered heteroaryl, 4-10 membered heterocycloalkyl, C\(_6\) aryl-C\(_4\) alky-.
aryl-C₄ alkyl-, C₃-10 cycloalkyl-C₄ alkyl-, (5-14 membered heteroaryl)-C₄ alkyl- and (4-10 membered heterocycloalkyl)-C₄ alkyl- of R⁶, R⁷, R¹⁷ and R¹⁸ are each optionally substituted with 1, 2, or 3 independently selected Rᵇ substituents.

In some embodiments, R⁶, R⁷, R¹⁷ and R¹⁸ are each independently selected from H, halo, C₆ alkyl, C₂-6 alkenyl, C₂-6 alkynyl, (5-14 membered heteroaryl), 4-10 membered heterocycloalkyl, (5-14 membered heteroaryl)-C₄ alkyl-, (4-10 membered heterocycloalkyl)-C₄ alkyl-, 4-10 membered heterocycloalkyl, (5-14 membered heteroaryl)-C₄ alkyl- and (4-10 membered heterocycloalkyl)-C₄ alkyl- of R⁶, R⁷, R¹⁷ and R¹⁸ are each optionally substituted with 1, 2, or 3 independently selected Rᵇ substituents.

In some embodiments, R⁶, R⁷, R¹⁷ and R¹⁸ are each independently selected from H, halo, C₆ alkyl, (5-14 membered heteroaryl)-C₄ alkyl-, (4-10 membered heterocycloalkyl)-C₄ alkyl-, CN, OR, C(O)R, C(O)NR₂, C(O)OR, NHR, NR₂, NR=C(O)R, and NR=C(O)OR, wherein the Ci-e alkyl, C₂-6 alkenyl, C₂-6 alkynyl, 5-14 membered heteroaryl, 4-10 membered heterocycloalkyl, (5-14 membered heteroaryl)-C₄ alkyl- and (4-10 membered heterocycloalkyl)-C₄ alkyl- of R⁶, R⁷, R¹⁷ and R¹⁸ are each optionally substituted with 1, 2, or 3 independently selected Rᵇ substituents.

In some embodiments, R⁶ is H, C₆ alkyl, (3-carboxypyrrolidin-1-yl)methyl, (R)-(3-carboxypyrrolidin-1-yl)methyl, (S)-(3-carboxypyrrolidin-1-yl)methyl, (3-hydroxypyrrolidin-1-yl)methyl, (R)-(3-hydroxypyrrolidin-1-yl)methyl, (2-hydroxyethylamino)methyl, (2-hydroxy-2-methylpropylamino)methyl, 2-(dimethylamino)ethanoyl, 2-(3-carboxyazetidin-1-yl)ethanoyl, (R)-2-(3-carboxyazetidin-1-yl)ethanoyl, (S)-2-(3-carboxyazetidin-1-yl)ethanoyl, 2-(2-carboxypiperidin-1-yl)ethanoyl, (R)-2-(2-carboxypiperidin-1-yl)ethanoyl, (S)-2-(2-carboxypiperidin-1-yl)ethanoyl, 2-(3-carboxypyrrolidin-1-yl)ethanoyl, (S)-2-(3-carboxypyrrolidin-1-yl)ethanoyl, (R)-2-(3-carboxypyrrolidin-1-yl)ethanoyl, (5-cyanopyridin-3-yl)methoxy, halo or CN.

In some embodiments, R⁶ is (4-carboxycyclohexyl)methyl, trans-(4-carboxycyclohexyl)methyl, cis-(4-carboxycyclohexyl)methyl, 1-carboxy-2-propyl, (R)-1-carboxy-2-propyl, (S)-1-carboxy-2-propyl, (4-carboxy-4-methylcyclohexyl)methyl, 2-pyrrolidinyl, 2-(3-hydroxypyrrolidin-1-yl)acetyl, 2-(3-hydroxypyrrolidin-1-yl)acetyl, 2-(2-hydroxyethyl)(methyl)amino)acetyl, (4-carboxycyclohexyl)ethyl, 4-carboxycyclohexyl, 4-carboxy-4-methylcyclohexyl, dimethylglycyl, or N-ethyl-N-methylglycyl.

In some embodiments, each Rₘ is independently selected from H, CN, C₆ alkyl, C₄ haloalkyl, C₂-6 alkenyl, C₂-6 alkynyl, 5-14 membered heteroaryl, 4-14 membered
heterocycloalkyl, (5-14 membered heteroaryl)-Ci-4 alkyl-, and (4-14 membered heterocycloalkyl)-Ci-4 alkyl-, wherein the Ci-6 alkyl, C2-6 alkenyl, C2-6 alkynyl, 5-14 membered heteroaryl, 4-14 membered heterocycloalkyl, (5-14 membered heteroaryl)-Ci-4 alkyl- and (4-14 membered heterocycloalkyl)-Ci-4 alkyl- of R^a are each optionally substituted with 1, 2, or 3 independently selected R^d substituents. In some embodiments, each R^a is independently selected from H, CN, Ci-6 alkyl, 5-14 membered heteroaryl, 4-14 membered heterocycloalkyl, (5-14 membered heteroaryl)-Ci-4 alkyl-, and (4-14 membered heterocycloalkyl)-Ci-4 alkyl-, wherein the Ci-6 alkyl, 5-14 membered heteroaryl, 4-14 membered heterocycloalkyl, (5-14 membered heteroaryl)-Ci-4 alkyl- and (4-14 membered heterocycloalkyl)-Ci-4 alkyl- of R^a are each optionally substituted with 1 or 2 independently selected R^d substituents. In some embodiments, each R^d is independently selected from H, CN, Ci-6 alkyl, (5-14 membered heteroaryl)-Ci-4 alkyl-, and (4-14 membered heterocycloalkyl)-Ci-4 alkyl-, wherein the Ci-6 alkyl, (5-14 membered heteroaryl)-Ci-4 alkyl- and (4-14 membered heterocycloalkyl)-Ci-4 alkyl- of R^a are each optionally substituted with 1 or 2 independently selected R^d substituents.

In some embodiments, each R^d is independently selected from H, CN, NH2, OR^e, C(0)R^e, C(0)NR^e, C(0)OR^e, OC(0)R^e, OC(0)NR^e, NHR^e, NR^eR^e, and NR^eC(0)R^e, wherein the Ci-6 alkyl of R^d are each optionally substituted with 1 or 2 independently selected R^f substituents. In some embodiments, each R^d is independently selected from Ci-6 alkyl, CN, NH2, OR^e, C(0)R^e, C(0)NR^e, C(0)OR^e, NHR^e, or NR^eR^e.

In some embodiments, each R^e is independently selected from H, Ci-6 alkyl, Ci-6 haloalkyl, C2-6 alkenyl, and C2-6 alkynyl. In some embodiments, each R^e is independently selected from H and Ci-6 alkyl.

In some embodiments, each R^b substituent is independently selected from halo, Ci-6 alkyl, C2-6 alkenyl, C2-6 alkynyl, Ci-6 haloalkyl, Ci-6 haloalkoxy, C6-10 aryl, C3-10 cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C6-10 aryl-Ci-4 alkyl-, C3-10 cycloalkyl-Ci-4 alkyl-, (5-10 membered heteroaryl)-Ci-4 alkyl-, (4-10 membered heterocycloalkyl)-Ci-4 alkyl-, CN, OH, NH2, OR^e, C(0)R^e, C(0)NR^e, C(0)OR^e, OC(0)R^e, OC(0)NR^e, NHR^e, NR^eR^e, and NR^eC(0)R^e; wherein the Ci-6 alkyl, Ci-6 haloalkyl, Ci-6 haloalkoxy, C2-6 alkenyl, C2-6 alkynyl, C6-10 aryl, C3-10 cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C6-10 aryl-Ci-4 alkyl-, C3-10 cycloalkyl-Ci-4 alkyl-, (5-10 membered heteroaryl)-Ci-4 alkyl- and (4-10 membered heterocycloalkyl)-Ci-4 alkyl- of R^b are each further optionally substituted with 1 or 2 independently selected R^d substituents. In some embodiments, each R^b substituent is independently selected from halo, Ci-6 alkyl, C2-6 alkenyl, C2-6 alkynyl, Ci-6 haloalkyl, Ci-6 haloalkoxy, CN, OH, NH2, OR^e, C(0)R^e, C(0)NR^e, C(0)OR^e, NHR^e, and NR^eR^e; wherein the
Cl-6 alkyl, Cl-6 haloalkyl, Cl-6 haloalkoxy, C2-6 alkenyl, and C2-6 alkynyl of R are each further optionally substituted with 1 or 2 independently selected R5 substituents. In some embodiments, each R5 substituent is independently selected from halo, Cl-6 alkyl, C2-6 alkenyl, C2-6 alkynyl, CN, OH, NH2, OR, C(=O)R, C(=O)NR, C(=O)OR, C(=O)NR, and NR3C(=O)R; wherein the Cl-6 alkyl, C2-6 alkenyl, and C2-6 alkynyl of R5 are each further optionally substituted with 1 or 2 independently selected R6 substituents.

In some embodiments, each R5 is independently selected from H, Cl-6 alkyl, Cl-4 haloalkyl, C2-6 alkenyl, and C2-6 alkynyl, wherein the Cl-6 alkyl, C2-6 alkenyl, and C2-6 alkynyl of R5 are each optionally substituted with 1 or 2 independently selected R6 substituents. In some embodiments, each R5 is independently selected from H and Cl-6 alkyl optionally substituted with 1 or 2 independently selected R6 substituents.

In some embodiments, each R6 is independently selected from Cl-4 alkyl, C1-4 haloalkyl, C2-6 alkenyl, C2-6 alkynyl, halo, CN, OR, C(=O)R, C(=O)NR, C(=O)OR, OC(=O)R, OC(=O)NR, OC(=O)OR, and NR3C(=O)R; wherein the C1 alkyl, C4 haloalkyl, C2-6 alkenyl, and C2-6 alkynyl of R6 are each optionally substituted with 1 or 2 independently selected R7 substituents. In some embodiments, each R6 is independently selected from C1-4 alkyl, halo, and OR.

In some embodiments, each R7 is independently selected from H, Cl-6 alkyl, Cl-4 haloalkyl, C2-6 alkenyl, and C2-6 alkynyl, wherein the Cl-6 alkyl, C2-6 alkenyl, and C2-6 alkynyl of R7 are each optionally substituted with 1 or 2 independently selected R8 substituents. In some embodiments, each R7 is independently selected from H and Cl-6 alkyl.

In some embodiments, provided herein is a compound of Formula (I) or (Ia), or a pharmaceutically acceptable salt or a stereoisomer thereof, wherein:

ring A is 5- to 10-membered heteroaryl, 4- to 11-membered heterocycloalkyl, or C6+aryl, wherein the 5- to 10-membered heteroaryl and 4- to 11-membered heterocycloalkyl each has 1-4 heteroatoms as ring members selected from N, O and S, wherein the N or S atom as ring members is optionally oxidized and one or more carbon atoms as ring members are each optionally replaced by a carbonyl group; and wherein ring A is optionally substituted with 1, 2 or 3 R6 substituents;

L is a bond, -C(=O)NR, -NRC(=O), -CR(=O)R, -CR(=O)R, -CR(=O)R, -CN, -CN, or CH=CH-;
X is N or CR\(^1\), wherein R\(^1\) is H, Ci-4 alkyl, Ci-4 alkoxy, Ci-4 haloalkyl, Ci-4 haloalkoxy, CN, halo, or OH, wherein the Ci-4 alkyl and Ci-4 alkoxy are each optionally substituted with 1 or 2 substituents independently selected from CN, halo and -C(0)NH2;

one of R\(^1\) and R\(^2\) is -(CR\(^8\)R\(^9\))p-NR\(^{10}\)R\(^{11}\) and the other is H, C\(_\text{M}\) alkyl, Ci-4 alkoxy, Ci-4 haloalkyl, Ci-4 haloalkoxy, CN, halo, or OH, wherein the Ci-4 alkyl and Ci-4 alkoxy of R\(^1\) or R\(^2\) is optionally substituted with 1 or 2 substituents independently selected from Ci-4 alkoxy, Ci-4 haloalkyl, Ci-4 haloalkoxy, CN, halo, and OH;

R\(^3\) is methyl, halo, CN or Ci-4 haloalkyl;

R\(^4\) is Ci-4 alkyl, Ci-4 alkoxy, or Ci-4 haloalkyl;

R\(^5\) is Ci-4 alkyl, Ci-4 alkoxy, Ci-4 haloalkyl, Ci-4 haloalkoxy, CN, halo, or OH;

each R\(^6\) is independently selected from H, halo, Ci-6 alkyl, C\(_2\)6 alknenyl, C\(_2\)6 alkynyl, Ci-6 haloalkyl, C\(_4\)6 haloalkoxy, 5-14 membered heteroaryl, 4-10 membered heterocycloalkyl, (5-14 membered heteroaryl)-Ci \(_\text{M}\) alkyl-, (4-10 membered heterocycloalkyl)-Ci \(_\text{M}\) alkyl-, CN, NO\(_2\), OR\(^a\), C(O)R\(^a\), C(O)NR\(^a\), C(O)OR\(^a\), OC(O)NR\(^a\), OC(O)OR\(^a\), NHR\(^a\), NR\(^a\)R\(^a\), NR\(^a\)C(O)R\(^a\), or NR\(^a\)C(O)OR\(^a\), wherein the Ci-4 alkyl, C\(_2\)6 alknenyl, C\(_2\)6 alkynyl, 5-14 membered heteroaryl, 4-10 membered heterocycloalkyl, (5-14 membered heteroaryl)-Ci \(_\text{M}\) alkyl- and (4-10 membered heterocycloalkyl)-Ci \(_\text{M}\) alkyl- of R\(^6\) are each optionally substituted with 1, 2, or 3 R\(^b\) substituents;

R\(^7\) is H, Ci-4 alkyl, Ci-4 alkoxy, Ci-4 haloalkyl, Ci-4 haloalkoxy, CN, halo, or OH;

R\(^8\) and R\(^9\) are each independently selected from H, halo, CN, OH, -COOH, C\(_\text{M}\) alkyl, Ci-4 alkoxy, -NH Ci-4 alkyl, -N (Ci-4 alkyl)\(_2\), and Ci-4 haloalkyl;

R\(^10\) and R\(^11\) are each independently selected from H, Ci-6 alkyl, Ci-6 haloalkyl, -C(O)R\(^8\), -C(O)OR\(_g\), and -C(O)NR\(_{3g}\). wherein the Ci-4 alkyl and Ci-4 haloalkyl of R\(^10\) or R\(^11\) are each optionally substituted with 1 or 2 independently selected R\(^f\) substituents;

or R\(^10\) and R\(^11\) taken together with the nitrogen atom to which they are attached form 4-, 5-, 6- or 7-membered heterocycloalkyl, wherein the 4-, 5-, 6- or 7-membered heterocycloalkyl is optionally substituted with 1, 2 or 3 R\(^b\) substituents;

R\(^12\) is H, C\(_\text{M}\) alkyl, Ci-4 alkoxy, C\(_\text{M}\) haloalkyl, Ci-4 haloalkoxy, CN, halo, or OH;

each R\(^13\) is independently H, Ci-6 haloalkyl or Ci-6 alkyl;

R\(^14\) and R\(^15\) are each independently selected from H, halo, or C\(_\text{M}\) alkyl;

each R\(^a\) is independently selected from H, CN, Ci-6 alkyl, Ci-4 haloalkyl, C\(_2\)6 alknenyl, C\(_2\)6 alkynyl, (5-14 membered heteroaryl)-Ci \(_\text{M}\) alkyl-, and (4-14 membered heterocycloalkyl)-Ci \(_\text{M}\) alkyl-, wherein the Ci-6 alkyl, C\(_2\)6 alknenyl, C\(_2\)6 alkynyl, (5-14 membered heteroaryl)-Ci-4 alkyl- and (4-14 membered heterocycloalkyl)-Ci \(_\text{M}\) alkyl- of R\(^a\) are each optionally substituted with 1, 2, 3 or independently selected R\(^d\) substituents;
each R^d is independently selected from Ci-6 alkyl, Ci-6 haloalkyl, halo, CN, NH2, OR^e, C(0)R^e, C(0)NR^R^e, C(0)OR^e, OC(0)R^e, OC(0)NR^R^e, NHR^e, NR^R^e, and NR^C(0)R^e;

each R^e is independently selected from H, Ci-6 alkyl, Ci-6 haloalkyl, C2-6 alkenyl, and C2-6 alkyynl;

each R^b substituent is independently selected from halo, Ci-6 alkyl, Ci-6 haloalkyl, C6 haloalkoxy, CN, OH, NH2, NO2, OR^c, C(0)R^c, C(0)NR^R^c, C(0)OR^c, OC(0)R^c, OC(0)NR^R^c, C(=NR)^cNR^R^c, N R^C(=NR)^cNR^R^c, NHR^c, NR^R^c, NR^C(0)R^c, and NR^C(0)OR^c; wherein the Ci-4 alkyl, C1-4 haloalkyl, and C1-4 haloalkoxy of R^b are each further optionally substituted with 1 or 2 independently selected R^d substituents;

each R^c is independently selected from H, Ci-6 alkyl, C1-4 haloalkyl, C2-6 alkenyl, C2-6 alkynyl, C6-10 aryl, C3-10 cycloalkyl, C6-10 aryl-C1-4 alkyl-, and C3-10 cycloalkyl-C1-4 alkyl-, wherein the Ci-6 alkyl, C2-6 alkenyl, C2-6 alkynyl, C6-10 aryl, C3-10 cycloalkyl, C6-10 aryl-C1-4 alkyl-, and C3-10 cycloalkyl-C1-4 alkyl- of R^c are each optionally substituted with 1, 2, or 3 R^f substituents;

each R^f is independently selected from C1-4 alkyl, C1-4 haloalkyl, C2-6 alkenyl, C2-6 alkynyl, halo, CN, OR^g, C(0)R^g, C(0)NR^R^g, C(0)OR^g, OC(0)R^g, OC(0)NR^R^g, NHR^g, NR^R^g, NR^C(0)R^g, and NR^C(0)OR^g;

each R^g is independently selected from H, Ci-6 alkyl, C1-4 haloalkyl, C2-6 alkenyl, and C2-6 alkynyl;

each R^h is independently selected from Ci-6 alkyl, Ci-6 haloalkyl, Ci-6 haloalkoxy, C2-6 alkenyl, C2-6 alkynyl, halo, CN, OR^i, C^oR^i, C(0)NR^R^i, C(0)OR^i, OC(0)R^i, OC(0)NR^R^i, NHR^i, NR^R^i, NR^O)^i, and NR^C(0)OR^i, wherein the Ci-e alkyl, C2-6 alkenyl, and C2-6 alkynyl of R^h are each further optionally substituted by 1, 2, or 3 R^j substituents;

each R^j is independently selected from C2-4 alkeny, C2-4 alkyln, halo, C1-4 alkyl, C1-4 haloalkyl, and CN;

or any two R^c substituents together with the nitrogen atom to which they are attached form a 4-, 5-, 6-, or 7-membered heterocycloalkyl group optionally substituted with 1, 2, or 3 independently selected R^b substituents;

each R^l is independently selected from H, C1-4 alkyl, Ci-6 haloalkyl, Ci-6 haloalkoxy, C2-4 alkenyl, and C2-4 alkynyl;

the subscript m is an integer of 0, 1, or 2;

the subscript n is an integer of 0, 1, or 2; and

the subscript p is an integer of 1, 2, or 3.
In some embodiments, provided herein is a compound of Formula (I) or (Ia), or a pharmaceutically acceptable salt or a stereoisomer thereof, wherein:

ring A is 5- to 10-membered heteroaryl or 4- to 11-membered heterocycloalkyl, wherein the 5- to 10-membered heteroaryl and 4- to 11-membered heterocycloalkyl each has 1-4 heteroatoms as ring members selected from N, O and S, wherein the N or S atom as ring members is optionally oxidized and one or more carbon atoms as ring members are each optionally replaced by a carbonyl group; and wherein ring A is optionally substituted with 1, 2 or 3 R^6 substituents;

L is a bond, -C(0)NR^13-, -NR^13C(0)-, -NR^13-, or CH=CH-;

X is N or CR^17, wherein R^17 is H, Ci-4 alkyl, Ci-4 alkoxy, Ci-4 haloalkyl, Ci-4 haloalkoxy, CN, halo, or OH, wherein the Ci-4 alkyl and Ci-4 alkoxy are each optionally substituted with 1 or 2 substituents independently selected from CN, halo, and -C(0)NH2;

one of R^1 and R^2 is -(CR^8R^9)_p-NR^10R^11 and the other is H, CM alkyl, CM alkoxy, CM haloalkyl, Ci-4 haloalkoxy, CN, halo, or OH, wherein the CM alkyl and Ci-4 alkoxy of R^1 or R^2 is optionally substituted with 1 or 2 substituents independently selected from Ci-4 alkoxy, CM haloalkyl, C16 haloalkoxy, CN, halo, and OH;

R^3 is methyl, halo, CN or Ci-4 haloalkyl;

R^4 is Ci-4 alkyl, Ci-4 alkoxy, or CM haloalkyl;

R^5 is Ci-4 alkyl, Ci-4 alkoxy. CM haloalkyl, Ci-4 haloalkoxy, CN, halo, or OH;

each R^6 is independently selected from H, halo, Ci-6 alkyl, C26 alkenyl, C26 alkynyl, Ci-6 haloalkyl, C16 haloalkoxy, 5-14 membered heteroaryl, 4-10 membered heterocycloalkyl, (5-14 membered heteroaryl)-Ci-4 alkyl-, (4-10 membered heterocycloalkyl)-Ci-4 alkyl-, CN, NO2, OR^a, C(0)R^a, C(0)NR^aR^a, C(0)OR^a, OC(0)R^a, OC(0)NR^aR^a, NH^aR^a, NR^aR^a, NR^aC(0)R^a, or NR^aC(0)OR^a, wherein the Ci-e alkyl, C26 alkenyl, C26 alkynyl, 5-14 membered heteroaryl, 4-10 membered heterocycloalkyl, (5-14 membered heteroaryl)-Ci-4 alkyl- and (4-10 membered heterocycloalkyl)-Ci-4 alkyl- of R^6 are each optionally substituted with 1, 2, or 3 R^b substituents;

R^7 is H, Ci-4 alkyl, CM alkoxy, C14 haloalkyl, CM haloalkoxy, CN, halo, or OH;

R^8 and R^9 are each independently selected from H, halo, CN, OH, -COOH, CM alkyl, Ci-4 alkoxy, -NHCi-4 alkyl, -N(CM alkyl)2, and Ci-4 haloalkyl;

R^10 and R^11 are each independently selected from H, Ci-6 alkyl, Ci-6 haloalkyl, -(C(0)R^8, -C(0)OR^8, and -(C(0)NR^8R^8, wherein the Ci-e alkyl and Ci-e haloalkyl of R^10 or R^11 are each optionally substituted with 1 or 2 independently selected R^f substituents;
or R^{10} and R^{11} taken together with the nitrogen atom to which they are attached form 4-, 5-, 6- or 7-membered heterocycloalkyl, wherein the 4-, 5-, 6- or 7-membered heterocycloalkyl is optionally substituted with 1, 2 or 3 R^h substituents;

R^{12} is H, Ci-4 alkyl, Ci-4 alkoxy, Ci-4 haloalkyl, Ci-4 haloalkoxy, CN, halo, or OH;
each R^{13} is independently H, Ci-6 haloalkyl or Ci-6 alkyl;
each R^a is independently selected from H, CN, Ci-6 alkyl, Ci-4 haloalkyl, C2-6 alkenyl, and C2-6 alkynyl;
each R^d is independently selected from Ci-6 alkyl, Ci-6 haloalkyl, halo, CN, NH2, OR^e, C(0)R^e, C(0)NR^e, C(0)OR^e, OC(0)R^e, OC(0)NR^e, NHR^e, NR^eR^e, and NR^eC(0)R^e;
each R^e is independently selected from H, Ci-6 alkyl, Ci-6 haloalkyl, C2-6 alkenyl, and C2-6 alkynyl;
each R^b substituent is independently selected from halo, Ci-6 alkyl, Ci-6 haloalkyl, Ci-6 haloalkoxy, CN, OH, NH2, NO2, OR^e, C(0)R^e, C(0)NR^e, C(0)OR^e, OC(0)R^e, OC(0)NR^e, C(=NR^e)NR^eR^e, C(=NR^e)NR^eR^e, NHR^e, NR^eR^e, NR^eC(0)R^e, and NR^eC(0)OR^e; wherein the Ci-4 alkyl, Ci-4 haloalkyl, and C1-4 haloalkoxy of R^b are each further optionally substituted with 1 or 2 independently selected R^d substituents;
each R^c is independently selected from H, Ci-6 alkyl, Ci-4 haloalkyl, C2-6 alkenyl, C2-6 alkynyl, C6-10 aryl, C3-10 cycloalkyl, C6-10 aryl-Ci-4 alkyl-, and C3-10 cycloalkyl-Ci-4 alkyl-, wherein the Ci-6 alkyl, C2-6 alkenyl, C2-6 alkynyl, C6-10 aryl, C3-10 cycloalkyl, C6-10 aryl-Ci-4 alkyl-, and C3-10 cycloalkyl-Ci-4 alkyl- of R^c are each optionally substituted with 1, 2, or 3 R^f substituents;
each R^f is independently selected from C1-4 alkyl, C1-4 haloalkyl, C2-6 alkenyl, C2-6 alkynyl, halo, CN, OR^g, C(0)R^g, C(0)NR^g, C(0)OR^g, OC(0)R^g, OC(0)NR^g, NHR^g, NR^gR^g, NR^gC(0)R^g, and NR^gC(0)OR^g;
each R^g is independently selected from H, Ci-6 alkyl, Ci-4 haloalkyl, C2-6 alkenyl, and C2-6 alkynyl;
each R^h is independently selected from Ci-6 alkyl, Ci-6 haloalkyl, Ci-6 haloalkoxy, C2-6 alkenyl, C2-6 alkynyl, halo, CN, OR^i, C^AR^i, C(0)NR^i, C(0)OR^i, OC(0)R^i, OC(0)NR^i, NHR^i, NR^iR^i, NR^iC(0)R^i, and NR^iC(0)OR^i; wherein the Ci-e alkyl, C2-6 alkenyl, and C2-6 alkynyl of R^h are each further optionally substituted by 1, 2, or 3 R^i substituents;
each R^i is independently selected from C2-4 alkenyl, C2-4 alkynyl, halo, C1-4 alkyl, C1-4 haloalkyl, and CN;
or any two R^c substituents together with the nitrogen atom to which they are attached form a 4-, 5-, 6-, or 7-membered heterocycloalkyl group optionally substituted with 1, 2, or 3 independently selected R^h substituents;
each \( R^1 \) is independently selected from H, C\(_{\text{i-4}}\) alkyl, C\(_{\text{i-6}}\) haloalkyl, C\(_{\text{i-6}}\) haloalkoxy, C\(_{\text{2-4}}\) alkenyl, and C\(_{\text{2-4}}\) alkynyl;

the subscript \( m \) is an integer of 0, 1, or 2;
the subscript \( n \) is an integer of 0, 1, or 2; and
the subscript \( p \) is an integer of 1, 2, or 3.

In some embodiments provided herein is a compound of Formula (I) or (Ia), or a pharmaceutically acceptable salt or a stereoisomer thereof, wherein:

the 5- to 10-membered heteroaryl and 4- to 11-membered heterocycloalkyl each has 1-4 heteroatoms as ring members selected from N, O and S, wherein the N or S atom as ring members is optionally oxidized and one or more carbon atoms as ring members are each optionally replaced by a carbonyl group; and wherein ring A is optionally substituted with 1, 2 or 3 \( R^6 \) substituents;

\( L \) is a bond, -C(0)NR\(^{13}\) or -NR\(^{15}\)C(0)-;
\( X \) is CR\(^{17}\), wherein \( R^7 \) is H or C\(_{\text{M}}\) alkyl;
one of \( R^1 \) and \( R^2 \) is -(CR\(^8\)R\(^9\))\(_p\)NR\(^{10}\)R\(^{11}\) and the other is H, C\(_{\text{M}}\) alkyl, or C\(_{\text{M}}\) alkoxy;
\( R^3 \) is methyl, or halo;
\( R^4 \) is C\(_{\text{i-4}}\) alkyl or C\(_{\text{i-4}}\) alkoxy;
\( R^5 \) is C\(_{\text{i-4}}\) alkyl, C\(_{\text{i-4}}\) alkoxy, or halo;
each \( R^6 \) is independently selected from H, halo, C\(_{\text{i-6}}\) alkyl, C\(_{\text{2-6}}\) alkenyl, C\(_{\text{2-6}}\) alkynyl, 5-14
membered heteroaryl, 4-10 membered heterocycloalkyl, (5-14 membered heteroaryl)-C\(_{\text{i-4}}\) alkyl-, and (4-10 membered heterocycloalkyl)-C\(_{\text{i-4}}\) alkyl-, wherein the C\(_{\text{i-6}}\) alkyl, C\(_{\text{2-6}}\) alkenyl, C\(_{\text{2-6}}\) alkynyl, 5-14 membered heteroaryl, 4-10 membered heterocycloalkyl, (5-14 membered heteroaryl)-C\(_{\text{i-4}}\) alkyl- and (4-10 membered heterocycloalkyl)-C\(_{\text{i-4}}\) alkyl- of \( R^6 \) are each optionally substituted with 1, 2, or 3 \( R^b \) substituents;
\( R^7 \) is H or C\(_{\text{i-4}}\) alkyl;
\( R^8 \) and \( R^9 \) are each independently selected from H and C\(_{\text{i-4}}\) alkyl;
\( R^{10} \) and \( R^{11} \) are each independently selected from H and C\(_{\text{i-6}}\) alkyl optionally substituted with 1 or 2 independently selected \( R^f \) substituents;
or \( R^{10} \) and \( R^{11} \) taken together with the nitrogen atom to which they are attached form 4-, 5-, 6- or 7-membered heterocycloalkyl, wherein the 4-, 5-, 6- or 7-membered heterocycloalkyl is optionally substituted with 1, 2 or 3 \( R^b \) substituents;
\( R^{12} \) is H or C\(_{\text{M}}\) alkyl;
each R$^{13}$ is independently H or Ci-6 alkyl;
each R$^{b}$ substituent is independently selected from halo, Ci-6 alkyl, OH, NH$_2$, C(0)OR, C(0)NR, and NHR;
each R$^{c}$ is independently selected from H, Ci-6 alkyl, C2-6 alkenyl, C2-6 alkynyl, C3-10 cycloalkyl, and C3-10 cycloalkyl-C4 alkyl-, wherein the Ci-6 alkyl, C2-6 alkenyl, C2-6 alkynyl, C3-10 cycloalkyl, and C3-10 cycloalkyl-C4 alkyl- of R$^{c}$ are each optionally substituted with 1 or 2 R$^{f}$ substituents;
each R$^{f}$ is independently selected from C1-4 alkyl, C2-6 alkenyl, C2-6 alkynyl, halo, OR, and C(0)OR;
each R$^{g}$ is independently selected from H and Ci-6 alkyl;
each R$^{h}$ is independently selected from Ci-6 alkyl, C2-6 alkenyl, C2-6 alkynyl, halo, CN, OR, and 0(0)0$^{a}$;
or any two R$^{c}$ substituents together with the nitrogen atom to which they are attached form a 4-, 5-, 6-, or 7-membered heterocycloalkyl group optionally substituted with 1, 2, or 3 independently selected R$^{b}$ substituents;
each R$^{i}$ is independently selected from H and C1-4 alkyl;
the subscript m is an integer of 0 or 1;
the subscript n is an integer of 0 or 1; and
the subscript p is an integer of 1 or 2.

In some embodiments provided herein is a compound of Formula (I) or (Ia), or a pharmaceutically acceptable salt or a stereoisomer thereof, wherein:
ring A is 5- to 10-membered heteroaryl, wherein the 5- to 10-membered heteroaryl has 1-4 heteroatoms as ring members selected from N, O and S, wherein the N or S atom as ring members is optionally oxidized and one or more carbon atoms as ring members are each optionally replaced by a carbonyl group; and wherein ring A is optionally substituted with 1 or 2 R$^{6}$ substituents;
L is a bond, -C(0)NR$_{13}$ or -NR$_{13}$C(0)-;
X is CR$_{17}$, wherein R$_{17}$ is H;
one of R$^{4}$ and R$^{5}$ is -(CR$_{8}$R$_{9}$)$_{p}$-NR$_{10}$R$_{11}$ and the other is H;
R$^{3}$ is methyl or halo;
R$^{4}$ is Ci-4 alkyl or C1-4 alkoxy;
R$^{5}$ is Ci-4 alkyl or halo;
each R^6 is independently selected from H, C_{1-6} alkyl, and (4-10 membered heterocycloalkyl)-C_{1-4} alkyl- of R^6 are each optionally substituted with 1 or 2 R^b substituents;
R^7 is H;
R^8 and R^9 are each independently selected from H and C_{1-4} alkyl;
R^{10} and R^{11} are each independently selected from H and C_{1-4} alkyl optionally substituted with 1 or 2 independently selected R^f substituents;
or R^{10} and R^{11} taken together with the nitrogen atom to which they are attached form 4-, 5-, 6- or 7-membered heterocycloalkyl, wherein the 4-, 5-, 6- or 7-membered heterocycloalkyl is optionally substituted with 1, 2 or 3 R^b substituents;
R^{12} is H;
R^{13} is H;
each R^b substituent is independently selected from OH, C(0)OR^c, NHR^c, and NR^cR^c;
each R^c is independently selected from H, C_{1-4} alkyl, and C_{3-10} cycloalkyl, wherein the C_{1-6} alkyl, and C_{3-10} cycloalkyl of R^c are each optionally substituted with 1 or 2 R^f substituents;
each R^f is independently selected from OR^g, and C(0)OR^g;
R^g is H;
each R^h is independently selected from OR^1 and C(0)OR^c;
or any two R^c substituents together with the nitrogen atom to which they are attached form a 4-, 5-, 6-, or 7-membered heterocycloalkyl group optionally substituted with 1, 2, or 3 independently selected R^b substituents;
R^j is H;
the subscript m is an integer of 0 or 1;
the subscript n is an integer of 0 or 1; and
the subscript p is an integer of 1 or 2.

In some embodiments provided herein is a compound of Formula (I) or (Ia), or a pharmaceutically acceptable salt or a stereoisomer thereof, wherein:
ring A is 5- to 10-membered heteroaryl or 4- to 11-membered heterocycloalkyl, wherein the 5- to 10-membered heteroaryl and 4- to 11-membered heterocycloalkyl each has 1-4 heteroatoms as ring members selected from N, O and S, wherein the N or S atom as ring members is optionally oxidized and one or more carbon atoms as ring members are each optionally replaced by a carbonyl group; and wherein ring A is optionally substituted with 1, 2 or 3 R^6 substituents;
L is a bond, -C(0)NR 13-, -NR 13-, or -NR 13C(0)-;
X is CR 17, wherein R 17 is H or C M alkyl;
one of R 1 and R 2 is -(CR 8R 9)p-NR 10R 11 and the other is H, C M alkyl, or C M alkoxy;
R 3 is methyl, or halo;
R 4 is Ci-4 alkyl or C M alkoxy;
R 5 is Ci-4 alkyl, Ci-4 alkoxy, or halo;
each R 6 is independently selected from H, halo, Ci-6 alkyl, C2-6 alkenyl, C2-6 alkynyl, 5-14 membered heteroaryl, 4-10 membered heterocycloalkyl, (5-14 membered heteroaryl)-Ci-4 alkyl-, and (4-10 membered heterocycloalkyl)-Ci-4 alkyl-, wherein the Ci-6 alkyl, C2-6 alkenyl, C2-6 alkynyl, 5-14 membered heteroaryl, 4-10 membered heterocycloalkyl, (5-14 membered heteroaryl)-Ci-4 alkyl- and (4-10 membered heterocycloalkyl)-Ci-4 alkyl- of R 6 are each optionally substituted with 1, 2, or 3 R 8 substituents;
R 7 is H or C M alkyl;
R 8 and R 9 are each independently selected from H and C M alkyl;
R 10 and R 11 are each independently selected from H and Ci-6 alkyl optionally substituted with 1 or 2 independently selected R 1 substituents;
or R 10 and R 11 taken together with the nitrogen atom to which they are attached form 4-, 5-, 6- or 7-membered heterocycloalkyl, wherein the 4-, 5-, 6- or 7-membered heterocycloalkyl is optionally substituted with 1, 2 or 3 R 8 substituents;
R 12 is H or C M alkyl;
each R 13 is independently H or Ci-6 alkyl;
each R 8 substituent is independently selected from halo, Ci-6 alkyl, OH, NH2, C(0)OR 5, NHR 5, and NR-R 5;
each R 5 is independently selected from H, Ci-6 alkyl, C2-6 alkenyl, C2-6 alkynyl, C3-10 cycloalkyl, and C3-10 cycloalkyl-Ci-4 alkyl-, wherein the Ci-6 alkyl, C2-6 alkenyl, C2-6 alkynyl, C3-10 cycloalkyl, and C3-10 cycloalkyl-Ci-4 alkyl- of R 5 are each optionally substituted with 1 or 2 R 1 substituents;
each R 1 is independently selected from C M alkyl, C2-6 alkenyl, C2-6 alkynyl, halo, OR 8, and C(0)OR 8;
each R 8 is independently selected from H and Ci-6 alkyl;
each R 8 is independently selected from Ci-6 alkyl, C2-6 alkenyl, C2-6 alkynyl, halo, CN, OR 1, and C(0)OR 1;
or any two R\textsuperscript{5} substituents together with the nitrogen atom to which they are attached form a 4-, 5-, 6-, or 7-membered heterocycloalkyl group optionally substituted with 1, 2, or 3 independently selected R\textsuperscript{8} substituents;

- each R\textsuperscript{1} is independently selected from H and Ci-4 alkyl;
- the subscript m is an integer of 0 or 1;
- the subscript n is an integer of 0 or 1; and
- the subscript p is an integer of 1 or 2.

In some embodiments provided herein is a compound of Formula (I) or (la), or a pharmaceutically acceptable salt or a stereoisomer thereof, wherein:

- ring A is 5- to 10-membered heteroaryl, wherein the 5- to 10-membered heteroaryl has 1-4 heteroatoms as ring members selected from N, O and S, wherein the N or S atom as ring members is optionally oxidized and one or more carbon atoms as ring members are each optionally replaced by a carbonyl group; and wherein ring A is optionally substituted with 1 or 2 R\textsuperscript{6} substituents;
  - L is a bond, \(-\text{C}(\text{O})\text{NR}^\text{13}\), \(-\text{NR}^\text{13}\), or \(-\text{NR}^\text{13}\text{C}(\text{O})\);  
  - X is CR\textsuperscript{17}, wherein R\textsuperscript{17} is H;  
  - one of R\textsuperscript{1} and R\textsuperscript{2} is \(-\text{(CR}^\text{8}R^\text{9})_p\text{NR}^{10}R^{11}\) and the other is H;  
  - R\textsuperscript{3} is methyl, or halo;
  - R\textsuperscript{4} is Ci-4 alkyl or Ci-4 alkoxy;
  - R\textsuperscript{5} is Ci-4 alkyl or halo;
  - each R\textsuperscript{6} is independently selected from H, Ci-6 alkyl, and (4-10 membered heterocycloalkyl)-Ci-4 alkyl-, wherein the Ci-6 alkyl and (4-10 membered heterocycloalkyl)-Ci-4 alkyl- of R\textsuperscript{6} are each optionally substituted with 1 or 2 R\textsuperscript{8} substituents;
  - R\textsuperscript{7} is H;
  - R\textsuperscript{8} and R\textsuperscript{9} are each independently selected from H and Ci-4 alkyl;
  - R\textsuperscript{10} and R\textsuperscript{11} are each independently selected from H and Ci-6 alkyl optionally substituted with 1 or 2 independently selected R\textsuperscript{12} substituents;
- or R\textsuperscript{10} and R\textsuperscript{11} taken together with the nitrogen atom to which they are attached form 4-, 5-, 6- or 7-membered heterocycloalkyl, wherein the 4-, 5-, 6- or 7-membered heterocycloalkyl is optionally substituted with 1, 2 or 3 R\textsuperscript{8} substituents;
  - R\textsuperscript{12} is H;
  - R\textsuperscript{13} is H;
  - each R\textsuperscript{8} substituent is independently selected from OH, C(\text{O})OR \textsuperscript{c}, NHR \textsuperscript{c}, and NR\textsuperscript{c}R\textsuperscript{c}.
each \( R^6 \) is independently selected from \( H, \text{Ci-6 alkyl, and C}_{3-10} \) cycloalkyl, wherein the Ci-6 alkyl, and \( \text{C}_{3-10} \) cycloalkyl of \( R^6 \) are each optionally substituted with 1 or 2 \( R^1 \) substituents;
each \( R^f \) is independently selected from \( OR^g \) and \( C(0)OR^g \);
\( R^g \) is \( H \);
each \( R^h \) is independently selected from \( OR^1 \) and \( C(0)OR^1 \);
or any two \( R^5 \) substituents together with the nitrogen atom to which they are attached form a \( 4-, 5-, 6-, \) or 7-membered heterocycloalkyl group optionally substituted with 1, 2, or 3 independently selected \( R^h \) substituents;
\( R^1 \) is \( H \);
the subscript \( m \) is an integer of 0 or 1;
the subscript \( n \) is an integer of 0 or 1; and
the subscript \( p \) is an integer of 1 or 2.

It is further appreciated that certain features of the invention, which are, for clarity, described in the context of separate embodiments, can also be provided in combination in a single embodiment (while the embodiments are intended to be combined as if written in multiply dependent form). Conversely, various features of the invention which are, for brevity, described in the context of a single embodiment, can also be provided separately or in any suitable subcombination. Thus, it is contemplated as features described as embodiments of the compounds of Formula (I) can be combined in any suitable combination.

At various places in the present specification, certain features of the compounds are disclosed in groups or in ranges. It is specifically intended that such a disclosure include each and every individual subcombination of the members of such groups and ranges. For example, the term "Ci-6 alkyl" is specifically intended to individually disclose (without limitation) methyl, ethyl, \( \text{C}_3 \) alkyl, \( \text{C}_4 \) alkyl, \( \text{C}_5 \) alkyl and \( \text{C}_6 \) alkyl.

The term "n-membered," where \( n \) is an integer, typically describes the number of ring-forming atoms in a moiety where the number of ring-forming atoms is \( n \). For example, piperidinyl is an example of a 6-membered heterocycloalkyl ring, pyrazolyl is an example of a 5-membered heteroaryl ring, pyridyl is an example of a 6-membered heteroaryl ring and 1,2,3,4-tetrahydro-naphthalene is an example of a 10-membered cycloalkyl group.

At various places in the present specification, variables defining divalent linking groups may be described. It is specifically intended that each linking substituent include both the forward and backward forms of the linking substituent. For example, \( -NR(CR'R^")_n \) includes both \( -NR(CR'R^")_nR^" \) and \( -R^"_nNR^- \) and is intended to disclose each of the forms
individually. Where the structure requires a linking group, the Markush variables listed for that group are understood to be linking groups. For example, if the structure requires a linking group and the Markush group definition for that variable lists "alkyl" or "aryl" then it is understood that the "alkyl" or "aryl" represents a linking alkylene group or areylene group, respectively.

The term "substituted" means that an atom or group of atoms formally replaces hydrogen as a "substituent" attached to another group. The term "substituted", unless otherwise indicated, refers to any level of substitution, e.g., mono-, di-, tri-, tetra- or penta-substitution, where such substitution is permitted. The substituents are independently selected, and substitution may be at any chemically accessible position. It is to be understood that substitution at a given atom is limited by valency. It is to be understood that substitution at a given atom results in a chemically stable molecule. The phrase "optionally substituted" means unsubstituted or substituted. The term "substituted" means that a hydrogen atom is removed and replaced by a substituent. A single divalent substituent, e.g., oxo, can replace two hydrogen atoms.

The term "C<sub>n-m</sub>" indicates a range which includes the endpoints, wherein n and m are integers and indicate the number of carbons. Examples include C<sub>1-4</sub>, C<sub>1-6</sub> and the like.

The term "alkyl," employed alone or in combination with other terms, refers to a saturated hydrocarbon group that may be straight-chained or branched. The term "C<sub>n-m</sub> alkyl," refers to an alkyl group having n to m carbon atoms. An alkyl group formally corresponds to an alkane with one C-H bond replaced by the point of attachment of the alkyl group to the remainder of the compound. In some embodiments, the alkyl group contains from 1 to 6 carbon atoms, from 1 to 4 carbon atoms, from 1 to 3 carbon atoms, or 1 to 2 carbon atoms. Examples of alkyl moieties include, but are not limited to, chemical groups such as methyl, ethyl, ft-propyl, isopropyl, w-butyl, tert-butyl, isobutyl, sec-butyl; higher homologs such as 2-methyl-1-butyl, w-pentyl, 3-pentyl, w-hexyl, 1,2,2-trimethylpropyl and the like.

The term "alkenyl," employed alone or in combination with other terms, refers to a straight-chain or branched hydrocarbon group corresponding to an alkyl group having one or more double carbon-carbon bonds. An alkenyl group formally corresponds to an alkene with one C-H bond replaced by the point of attachment of the alkenyl group to the remainder of the compound. The term "C<sub>n-m</sub> alkenyl" refers to an alkenyl group having n to m carbons. In some embodiments, the alkenyl moiety contains 2 to 6, 2 to 4, or 2 to 3 carbon atoms. Example alkenyl groups include, but are not limited to, ethenyl, w-propenyl, isopropenyl, n-butenyl, sec-butenyl and the like.
The term "alkynyl," employed alone or in combination with other terms, refers to a straight-chain or branched hydrocarbon group corresponding to an alkyl group having one or more triple carbon-carbon bonds. An alkynyl group formally corresponds to an alkyne with one C-H bond replaced by the point of attachment of the alkyne group to the remainder of the compound. The term "C\textsubscript{n}-m alkynyl" refers to an alkynyl group having n to m carbons.

Example alkynyl groups include, but are not limited to, ethynyl, propyn-1-yl, propyn-2-yl and the like. In some embodiments, the alkynyl moiety contains 2 to 6, 2 to 4, or 2 to 3 carbon atoms.

The term "alkylene," employed alone or in combination with other terms, refers to a divalent alkyl linking group. An alkyne group formally corresponds to an alkane with two C-H bond replaced by points of attachment of the alkyne group to the remainder of the compound. The term "C\textsubscript{n}-m alkyne" refers to an alkyne group having n to m carbon atoms. Examples of alkyne groups include, but are not limited to, ethan-1,2-diyl, propan-1,3-diyl, butan-1,2-diyl, butan-1,3-diyl, butan-1,2-diyl, 2-methyl-propan-1,3-diyl and the like.

The term "alkoxy," employed alone or in combination with other terms, refers to a group of formula -O-alkyl, wherein the alkyl group is as defined above. The term "C\textsubscript{n}-m alkoxy" refers to an alkoxy group, the alkyl group of which has n to m carbons. Example alkoxy groups include methoxy, ethoxy, propoxy (e.g., w-propoxy and isopropoxy), i-butoxy and the like. In some embodiments, the alkyl group has 1 to 6, 1 to 4, or 1 to 3 carbon atoms.

The term "alkylthio," employed alone or in combination with other terms, refers to a group of formula -S-alkyl, wherein the alkyl group is as defined above. The term "C\textsubscript{n}-m alkylthio" refers to an alkylthio group, the alkyl group of which has n to m carbons. Example alkylthio groups include methylthio, ethylthio, etc. In some embodiments, the alkyl group of the alkylthio group has 1 to 6, 1 to 4, or 1 to 3 carbon atoms.

The term "amino," employed alone or in combination with other terms, refers to a group of formula -NH\textsubscript{2}.

The term "carbonyl", employed alone or in combination with other terms, refers to a -C(=0)- group, which also may be written as C(O).

The term "cyano" or "nitrile" refers to a group of formula -C=\textsubscript{N}, which also may be written as -CN.

The terms "halo" or "halogen", used alone or in combination with other terms, refers to fluoro, chloro, bromo and iodo. In some embodiments, "halo" refers to a halogen atom selected from F, Cl, or Br. In some embodiments, halo groups are F.
The term "haloalkyl," employed alone or in combination with other terms, refers to an alkyl group in which one or more of the hydrogen atoms has been replaced by a halogen atom. The term "Cn-m-haloalkyl" refers to a Cn-m-alkyl group having n to m carbon atoms and from at least one up to \(2(n \text{ to } m+1)\) halogen atoms, which may either be the same or different. In some embodiments, the haloalkyl group has 1 to 6 or 1 to 4 carbon atoms. Example haloalkyl groups include CF3, C2F5, CHF2, CCh, CHCh, C2C15 and the like. In some embodiments, the haloalkyl group is a fluoroalkyl group.

The term "haloalkoxy," employed alone or in combination with other terms, refers to a group of formula -O-haloalkyl, wherein the haloalkyl group is as defined above. The term "Cn-m-haloalkoxy" refers to a haloalkoxy group, the haloalkyl group of which has n to m carbons. Example haloalkoxy groups include trifluoromethoxy and the like. In some embodiments, the haloalkoxy group has 1 to 6, 1 to 4, or 1 to 3 carbon atoms.

The term "oxo" refers to an oxygen atom as a divalent substituent, forming a carbonyl group when attached to carbon, or attached to a heteroatom forming a sulfoxide or sulfone group, or an N-oxide group. In some embodiments, heterocyclic groups may be optionally substituted by 1 or 2 oxo (=O) substituents.

The term "sulfido" refers to a sulfur atom as a divalent substituent, forming a thiocarbonyl group (C=S) when attached to carbon.

The term "aromatic" refers to a carbocycle or heterocycle having one or more polyunsaturated rings having aromatic character (i.e., having \((4n + 2)\) delocalized \(\pi\) (pi) electrons where n is an integer).

The term "aryl," employed alone or in combination with other terms, refers to an aromatic hydrocarbon group, which may be monocyclic or polycyclic (e.g., having 2 fused rings). The term "Cn-m-aryl" refers to an aryl group having from n to m ring carbon atoms. Aryl groups include, e.g., phenyl, naphthyl, indanyl, indenyl and the like. In some embodiments, aryl groups have from 6 to about 10 carbon atoms. In some embodiments aryl groups have 6 carbon atoms. In some embodiments aryl groups have 10 carbon atoms. In some embodiments, the aryl group is phenyl. In some embodiments, the aryl group is naphthyl.

The term "heteroatom" used herein is meant to include boron, phosphorus, sulfur, oxygen and nitrogen.
The term "heteroaryl" or "heteroaromatic," employed alone or in combination with other terms, refers to a monocyclic or polycyclic aromatic heterocycle having at least one heteroatom ring member selected from boron, phosphorus, sulfur, oxygen and nitrogen. In some embodiments, the heteroaryl ring has 1, 2, 3 or 4 heteroatom ring members independently selected from nitrogen, sulfur and oxygen. In some embodiments, any ring-forming N in a heteroaryl moiety can be an N-oxide. In some embodiments, the heteroaryl has 5-14 ring atoms including carbon atoms and 1, 2, 3 or 4 heteroatom ring members independently selected from nitrogen, sulfur and oxygen. In some embodiments, the heteroaryl has 5-14, or 5-10 ring atoms including carbon atoms and 1, 2, 3 or 4 heteroatom ring members independently selected from nitrogen, sulfur and oxygen. In some embodiments, the heteroaryl has 5-6 ring atoms and 1 or 2 heteroatom ring members independently selected from nitrogen, sulfur and oxygen. In some embodiments, the heteroaryl is a five-membered or six-membered heteroaryl ring. In other embodiments, the heteroaryl is an eight-membered, nine-membered or ten-membered fused bicyclic heteroaryl ring. Example heteroaryl groups include, but are not limited to, pyridinyl (pyridyl), pyrimidinyl, pyrazinyl, pyridazinyl, pyrrolyl, pyrazolyl, azolyl, oxazolyl, thiazolyl, imidazolyl, furanyl, thiophenyl, pyridyl, pyrazinyl, pyridazinyl, pyrazolyl, azolyl, oxazolyl, thiazolyl, imidazolyl, furanyl, thiophenyl, quinolinyl, isoquinolinyl, naphthyridinyl (including 1,2-, 1,3-, 1,4-, 1,5-, 1,6-, 1,7-, 1,8-, 2,3- and 2,6-naphthyridine), indolyl, benzothiophenyl, benzofuranyl, benzisoxazolyl, imidazo[1,2-Z]thiazolyl, purinyl, and the like.

A five-membered heteroaryl ring is a heteroaryl group having five ring atoms wherein one or more (e.g., 1, 2 or 3) ring atoms are independently selected from N, O and S. Exemplary five-membered ring heteroaryls include thienyl, furyl, pyrrolyl, imidazolyl, thiazolyl, oxazolyl, pyrazolyl, isothiazolyl, isoaxazolyl, 1,2,3-triazolyl, tetrazolyl, 1,2,3-thiadiazolyl, 1,2,3-oxadiazolyl, 1,2,4-triazolyl, 1,2,4-thiadiazolyl, 1,2,4-oxadiazolyl, 1,3,4-triazolyl, 1,3,4-thiadiazolyl and 1,3,4-oxadiazolyl.

A six-membered heteroaryl ring is a heteroaryl group having six ring atoms wherein one or more (e.g., 1, 2 or 3) ring atoms are independently selected from N, O and S. Exemplary six-membered ring heteroaryls are pyridyl, pyrazinyl, pyrimidinyl, triazinyl and pyridazinyl.

The term "cycloalkyl," employed alone or in combination with other terms, refers to a non-aromatic hydrocarbon ring system (monocyclic, bicyclic or polycyclic), including cyclized alkyl and alkenyl groups. The term "cₙ₋ₘ cycloalkyl" refers to a cycloalkyl that has n to m ring member carbon atoms. Cycloalkyl groups can include mono- or polycyclic (e.g.,
having 2, 3 or 4 fused rings) groups and spirocycles. Cycloalkyl groups can have 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, or 14 ring-forming carbons \( (C_{3-14}) \). In some embodiments, the cycloalkyl group has 3 to 14 members, 3 to 10 members, 3 to 6 ring members, 3 to 5 ring members, or 3 to 4 ring members. In some embodiments, the cycloalkyl group is monocyclic. In some embodiments, the cycloalkyl group is monomeric or bicyclic. In some embodiments, the cycloalkyl group is a \( C_{3-6} \) monocyclic cycloalkyl group. Ring-forming carbon atoms of a cycloalkyl group can be optionally oxidized to form an oxo or sulfido group. Cycloalkyl groups also include cycloalkylidene derivatives. In some embodiments, cycloalkyl is cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or cycloheptyl. Also included in the definition of cycloalkyl are moieties that have one or more aromatic rings fused \( (i.e., \) having a bond in common with) to the cycloalkyl ring, \( e.g., \) benzo or thiienyl derivatives of cyclopentane, cyclohexane and the like. A cycloalkyl group containing a fused aromatic ring can be attached through any ring-forming atom including a ring-forming atom of the fused aromatic ring. Examples of cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclopentenyl, cyclohexenyl, cyclohexadienyl, cycloheptatrienyl, norbornyl, norpinyl, norcamyl, bicyclo[1.1.1]pentanyl, bicyclo[2.1.1]hexanyl, and the like. In some embodiments, the cycloalkyl group is cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl.

The term "heterocycloalkyl," employed alone or in combination with other terms, refers to a non-aromatic ring or ring system, which may optionally contain one or more alkenylene groups as part of the ring structure, which has at least one heteroatom ring member independently selected from boron, nitrogen, sulfur oxygen and phosphorus, and which has 4-14 ring members, 4-10 ring members, 4-7 ring members, or 4-6 ring members. Included within the term "heterocycloalkyl" are monocyclic 4-, 5-, 6- and 7-membered heterocycloalkyl groups. Heterocycloalkyl groups can include mono- or bicyclic or polycyclic \( (e.g., \) having two or three fused or bridged rings) ring systems or spirocycles. In some embodiments, the heterocycloalkyl group is a monocyclic group having 1, 2 or 3 heteroatoms independently selected from nitrogen, sulfur and oxygen. Ring-forming carbon atoms and heteroatoms of a heterocycloalkyl group can be optionally oxidized to form an oxo or sulfido group or other oxidized linkage \( (e.g., \) C(O), S(O), C(S) or S(O) \( _2 \), N-oxide \( etc. \)) or a nitrogen atom can be quaternized. The heterocycloalkyl group can be attached through a ring-forming carbon atom or a ring-forming heteroatom. In some embodiments, the heterocycloalkyl group contains 0 to 3 double bonds. In some embodiments, the heterocycloalkyl group contains 0 to 2 double bonds. Also included in the definition of heterocycloalkyl are moieties that have one or more aromatic rings fused \( (i.e., \) having a bond
in common with) to the heterocycloalkyl ring, e.g., benzo or thienyl derivatives of piperidine, morpholine, azepine, etc. A heterocycloalkyl group containing a fused aromatic ring can be attached through any ring-forming atom including a ring-forming atom of the fused aromatic ring. Examples of heterocycloalkyl groups include azetidinyl, azepanyl, dihydrobenzofuranyl, dihydrofuranyl, dihydropyranyl, morpholino, 3-oxa-9-
5 azaspiro[5.5]undecanyl, 1-oxa-8-azaspiro[4.5]decanyl, piperidinyl, piperazinyl, oxopiperazinyl, pyranyl, pyrrolidinyl, quinuclidinyl, tetrahydrofuranyl, tetrahydropyranyl, 1,2,3,4-tetrahydroquinolinyl, tropanyl, tetrahydrothiazolopyridinyl (e.g., 4,5,6,7-
10 tetrahydrothiazolo[5,4-c]pyridin-2-yl) and thiomorpholino.

The term "arylalkyl," employed alone or in combination with other terms, refers to an aryl-(alkylene)- group where aryl and alkylene are as defined herein. An example arylalkyl group is benzyl.

The term "heteroarylalkyl," employed alone or in combination with other terms, refers to an heteroaryl-(alkylene)- group, where heteroaryl and alkylene are as defined herein. An example heteroarylalkyl group is pyridylmethyl.

The term "cycloalkylalkyl," employed alone or in combination with other terms, refers to a cycloalkyl-(alkylene)- group, where cycloalkyl and alkylene are as defined herein. An example cycloalkylalkyl group is cyclopropylmethyl.

The term "heterocycloalkylalkyl," employed alone or in combination with other terms, refers to a heterocycloalkyl-(alkylene)- group, where heterocycloalkyl and alkylene are as defined herein. An example heterocycloalkylalkyl group is azetidinylmethyl.

At certain places, the definitions or embodiments refer to specific rings (e.g., an azetidine ring, a pyridine ring, etc.). Unless otherwise indicated, these rings can be attached to any ring member provided that the valency of the atom is not exceeded. For example, an azetidine ring may be attached at any position of the ring, whereas an azetidin-3-yl ring is attached at the 3-position.

The compounds described herein can be asymmetric (e.g., having one or more stereocenters). All stereoisomers, such as enantiomers and diastereomers, are intended unless otherwise indicated. Compounds of the present invention that contain asymmetrically substituted carbon atoms can be isolated in optically active or racemic forms. Methods on how to prepare optically active forms from optically inactive starting materials are known in the art, such as by resolution of racemic mixtures or by stereoselective synthesis. Many geometric isomers of olefins, C≡N double bonds and the like can also be present in the compounds described herein, and all such stable isomers are contemplated in the present
invention. *Cis* and *trans* geometric isomers of the compounds of the present invention are
described and may be isolated as a mixture of isomers or as separated isomeric forms.

Resolution of racemic mixtures of compounds can be carried out by any of numerous methods known in the art. One method includes fractional recrystallization using a chiral resolving acid which is an optically active, salt-forming organic acid. Suitable resolving agents for fractional recrystallization methods are, *e.g.*, optically active acids, such as the D and L forms of tartaric acid, diacetyltartaric acid, dibenzoyltartaric acid, mandelic acid, malic acid, lactic acid or the various optically active camphorsulfonic acids such as β-camphorsulfonic acid. Other resolving agents suitable for fractional crystallization methods include stereoisomerically pure forms of α-methylbenzylamine (e.g., *S* and *R* forms, or diastereomerically pure forms), 2-phenylglycinol, norephedrine, ephedrine, *N*-methylephedrine, cyclohexylethylamine, 1,2-diaminocyclohexane and the like.

Resolution of racemic mixtures can also be carried out by elution on a column packed with an optically active resolving agent (e.g., dinitrobenzoylphenylglycine). Suitable elution solvent composition can be determined by one skilled in the art.

In some embodiments, the compounds of the invention have the (*R*)-configuration. In other embodiments, the compounds have the (*S*)-configuration. In compounds with more than one chiral centers, each of the chiral centers in the compound may be independently (*R*) or (*S*), unless otherwise indicated.

Compounds of the invention also include tautomeric forms. Tautomeric forms result from the swapping of a single bond with an adjacent double bond together with the concomitant migration of a proton. Tautomeric forms include prototropic tautomers which are isomeric protonation states having the same empirical formula and total charge. Example prototropic tautomers include ketone - enol pairs, amide - imidic acid pairs, lactam - lactim pairs, enamine - imine pairs, and annular forms where a proton can occupy two or more positions of a heterocyclic system, e.g., 1\(H\)- and 3\(H\)-imidazole, 1\(H\)-, 2\(H\)- and 4\(H\)- 1,2,4-triazole, 1\(H\)- and 2\(H\)- isoindole and 1\(H\)- and 2\(H\)-pyrazole. Tautomeric forms can be in equilibrium or stericly locked into one form by appropriate substitution.

Compounds of the invention can also include all isotopes of atoms occurring in the intermediates or final compounds. Isotopes include those atoms having the same atomic number but different mass numbers. For example, isotopes of hydrogen include tritium and deuterium. One or more constituent atoms of the compounds of the invention can be replaced or substituted with isotopes of the atoms in natural or non-natural abundance. In some
embodiments, the compound includes at least one deuterium atom. For example, one or more hydrogen atoms in a compound of the present disclosure can be replaced or substituted by deuterium. In some embodiments, the compound includes two or more deuterium atoms. In some embodiments, the compound includes 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12 deuterium atoms. Synthetic methods for including isotopes into organic compounds are known in the art.

The term, "compound," as used herein is meant to include all stereoisomers, geometric isomers, tautomers and isotopes of the structures depicted. The term is also meant to refer to compounds of the inventions, regardless of how they are prepared, e.g., synthetically, through biological process (e.g., metabolism or enzyme conversion), or a combination thereof.

All compounds, and pharmaceutically acceptable salts thereof, can be found together with other substances such as water and solvents (e.g., hydrates and solvates) or can be isolated. When in the solid state, the compounds described herein and salts thereof may occur in various forms and may, e.g., take the form of solvates, including hydrates. The compounds may be in any solid state form, such as a polymorph or solvate, so unless clearly indicated otherwise, reference in the specification to compounds and salts thereof should be understood as encompassing any solid state form of the compound.

In some embodiments, the compounds of the invention, or salts thereof, are substantially isolated. By "substantially isolated" is meant that the compound is at least partially or substantially separated from the environment in which it was formed or detected. Partial separation can include, e.g., a composition enriched in the compounds of the invention. Substantial separation can include compositions containing at least about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 90%, at least about 95%, at least about 97%, or at least about 99% by weight of the compounds of the invention, or salt thereof.

The phrase "pharmaceutically acceptable" is employed herein to refer to those compounds, materials, compositions and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

The expressions, "ambient temperature" and "room temperature," as used herein, are understood in the art, and refer generally to a temperature, e.g., a reaction temperature, that is
about the temperature of the room in which the reaction is carried out, e.g., a temperature from about 20 °C to about 30 °C.

The present invention also includes pharmaceutically acceptable salts of the compounds described herein. The term "pharmaceutically acceptable salts" refers to derivatives of the disclosed compounds wherein the parent compound is modified by converting an existing acid or base moiety to its salt form. Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic residues such as amines; alkali or organic salts of acidic residues such as carboxylic acids; and the like. The pharmaceutically acceptable salts of the present invention include the non-toxic salts of the parent compound formed, e.g., from non-toxic inorganic or organic acids. The pharmaceutically acceptable salts of the present invention can be synthesized from the parent compound which contains a basic or acidic moiety by conventional chemical methods. Generally, such salts can be prepared by reacting the free acid or base forms of these compounds with a stoichiometric amount of the appropriate base or acid in water or in an organic solvent, or in a mixture of the two; generally, non-aqueous media like ether, ethyl acetate, alcohols (e.g., methanol, ethanol, iso-propanol or butanol) or acetonitrile (MeCN) are preferred. Lists of suitable salts are found in Remington's Pharmaceutical Sciences, 17th Ed., (Mack Publishing Company, Easton, 1985), p. 1418. Berge et al., J. Pharm. Sci., 1977, 66(1), 1-19 and in Stahl et al., Handbook of Pharmaceutical Salts: Properties, Selection, and Use, (Wiley, 2002). In some embodiments, the compounds described herein include the N-oxide forms.

II. Synthesis

Compounds of the invention, including salts thereof, can be prepared using known organic synthesis techniques and can be synthesized according to any of numerous possible synthetic routes, such as those in the Schemes below.

The reactions for preparing compounds of the invention can be carried out in suitable solvents which can be readily selected by one of skill in the art of organic synthesis. Suitable solvents can be substantially non-reactive with the starting materials (reactants), the intermediates or products at the temperatures at which the reactions are carried out, e.g., temperatures which can range from the solvent's freezing temperature to the solvent's boiling temperature. A given reaction can be carried out in one solvent or a mixture of more than one solvent. Depending on the particular reaction step, suitable solvents for a particular reaction step can be selected by the skilled artisan.

Reactions can be monitored according to any suitable method known in the art. For example, product formation can be monitored by spectroscopic means, such as nuclear magnetic resonance spectroscopy (e.g., 3/4 or 13C), infrared spectroscopy, spectrophotometry (e.g., UV-visible), mass spectrometry or by chromatographic methods such as high performance liquid chromatography (HPLC) or thin layer chromatography (TLC).

The Schemes below provide general guidance in connection with preparing the compounds of the invention. One skilled in the art would understand that the preparations shown in the Schemes can be modified or optimized using general knowledge of organic chemistry to prepare various compounds of the invention.

Compounds of Formula I can be synthesized using a process shown in Scheme 1. In Scheme 1, a suitable halo (Hal^-)-substituted [4,4.0] aromatic heterocycle 1-1 is reacted with a suitable halo (Hal^-)-substituted aniline 1-2 to produce compound 1-3 under standard SNAr conditions using an acid such as, but not limited to, sulfuric acid, or base such as, but not limited to, potassium tert-butoxide. Compounds of formula 1-3 may also be synthesized under standard metal catalyzed cross-coupling reaction conditions (such as Buchwald-Hartwig coupling reaction, e.g., in the presence of a palladium catalyst (e.g., [(4,5-bis(diphenylphosphino)-9,9-dimethylxanthene)-2-(2’-amino-1’-biphenyl)]palladium(II) methanesulfonate) and a base (e.g., cesium carbonate)). Then the aromatic halide 1-3 can be reacted with a suitable coupling reagent 1-4 (where M is, e.g., -BOH2) to provide the product of formula I under standard metal catalyzed cross-coupling reaction conditions (such as Suzuki coupling reaction, e.g., in the presence of a palladium catalyst (e.g., [1,1’-bis(diphenylphosphino)ferrocene]dichloropalladium(II)) and a base (e.g., a bicarbonate or a carbonate base)).
Compounds of formula II can be synthesized using a process shown in Scheme 2. A suitable halo (Hal\(^{-}\)-substituted [4.4.0] aromatic heterocycle 2-1 can be reacted with a suitable halo (Hal\(^{2}\))-substituted aniline 2-2 to produce formula 2-3 under SNAr conditions using an acid such as, but not limited to, sulfuric acid, or base such as, but not limited to, potassium tert-butoxide. Compounds of formula 2-3 may also be synthesized under standard metal catalyzed cross-coupling reaction conditions (such as Buchwald-Hartwig coupling reaction, e.g., in the presence of a palladium catalyst (e.g., [(4,5-bis(diphenylphosphino)-9,9-dimethylxanthene)-2-(2'-amino-1-r-biphenyl)]palladium(II) methanesulfonate) and a base (e.g., cesium carbonate)). Then the aromatic halide 2-3 is reacted with a suitable coupling reagent 2-4 (where M is, e.g., -B(OH)\(^{2}\)) to form the bi-aryl bond of formula 2-5 under standard metal catalyzed cross-coupling reaction conditions (such as Suzuki coupling reaction, e.g., in the presence of a palladium catalyst (e.g., [\(1,\Gamma\)-bis(diphenylphosphino)ferrocene]dichloropalladium(II)) and a base (e.g., a bicarbonate or a carbonate base)). The vinyl group in compound 2-5 can be oxidatively cleaved to afford an aldehyde in the presence of suitable reagents such as, but not limited to, O\(\text{SO}_4\) and Na\(\text{K}\)\(_4\). Then the compound of formula II can be obtained by a reductive animation between the aldehyde derivative and a suitable amine 2-6 in a proper solvent such as THF or DCM using
a reducing agent such as, but not limited to, sodium triacetoxyborohydride, optionally in the presence of an acid such as acetic acid or a base such as DIPEA.

Compounds of formula II can be alternatively synthesized using a process shown in Scheme 3. The vinyl group of a suitable halo (Hal*-substituted [4.4.0] aromatic heterocycle 3-1 can be oxidatively cleaved to afford an aldehyde in the presence of suitable reagents such as, but not limited to, OsO₄ and NaI₂O₄. Then the compound of formula 3-3 can be obtained by a reductive animation between the aldehyde derivative and a suitable amine 3-2 in a proper solvent such as THF or DCM using a reducing agent such as, but not limited to, sodium triacetoxyborohydride, optionally in the presence of an acid such as acetic acid or a base such as DIPEA. The compound of formula 3-5 can be synthesized by reacting formula 3-3 with a suitable halo (Hal²)-substituted aniline 3-4 under standard SNAr conditions using an acid such as, but not limited to, sulfuric acid, or base such as, but not limited to, potassium tert-butoxide. Compounds of formula 3-5 may also be synthesized under standard metal catalyzed cross-coupling reaction conditions (such as Buchwald-Hartwig coupling reaction, e.g., in the presence of a palladium catalyst (e.g., [(4,5-bis(diphenylphosphino)-9,9-dimethylxanthene)-2-(2’-amino-1,1’-biphenyl)]palladium(II) methanesulfonate) and a base (e.g., cesium carbonate)). Then the aromatic halide 3-5 is reacted with a suitable coupling reagent 3-6 (where M is, e.g., -B(OH)₂) to provide compounds of formula II under standard metal catalyzed cross-coupling reaction conditions (such as Suzuki coupling...
reaction, e.g., in the presence of a palladium catalyst (e.g., \( \left[ \text{I}, \text{Gamma}^- \right. \text{bis(diphenylphosphino)ferrocene} \left. \text{dichloropalladium(II)} \right] \) and a base (e.g., a bicarbonate or a carbonate base)).

Compounds of formula III can be synthesized using a process shown in Scheme 4. A suitable halo (Hal^+-substituted [4.4.0] aromatic heterocycle 4-1 can be reacted with a suitable halo (Hal^-)-substituted aniline 4-2 to produce a compound of formula 4-3 under standard SNAT conditions using an acid such as, but not limited to, sulfuric acid, or base such as, but not limited to, potassium tert-butoxide. Compounds of formula 4-3 may also be synthesized under standard metal catalyzed cross-coupling reaction conditions (such as Buchwald-Hartwig coupling reaction, e.g., in the presence of a palladium catalyst (e.g., \( \left[ 4.5^- \text{bis(diphenylphosphino)-9,9-dimethylxanthene} \right] \text{2-(2'}^-\text{amino-1,1'}^-\text{biphenyl}) \text{palladium(II)} \text{methanesulfonate} \) and a base (e.g., cesium carbonate)). Then the aromatic halide 4-3 can be reacted with a suitable coupling reagent 4-4 (where M is, e.g., -B(OH)2) to form the bi-aryl bond of formula 4-5 under standard metal catalyzed cross-coupling reaction conditions (such as Suzuki coupling reaction, e.g., in the presence of a palladium catalyst (e.g., \( \left[ \text{I}, \text{Gamma}^- \right. \text{bis(diphenylphosphino)ferrocene} \left. \text{dichloropalladium(II)} \right] \) and a base (e.g., a bicarbonate or a carbonate base)). The vinyl group in compound 4-5 can be oxidatively cleaved to afford an aldehyde in the presence of suitable reagents such as, but not limited to, \( \text{OSO}_4 \) and \( \text{NaK}_4 \). Then the compound of formula III is obtained by a reductive amination between the aldehyde derivative and a suitable amine 4-6 in a proper solvent such as THF or DCM using a reducing agent such as, but not limited to, sodium triacetoxyborohydride, optionally in the presence of an acid such as acetic acid or a base such as DIPEA.
Compounds of formula III can be alternatively synthesized using a process shown in Scheme 5. The vinyl group of a suitable halo (Hal^+-substituted [4,4,0] aromatic heterocycle 5-1) can be oxidatively cleaved to afford an aldehyde in the presence of suitable reagents such as, but not limited to, OsO₄ and NaIO₄. Then the compound of formula 5-3 is obtained by a reductive animation between the aldehyde derivative and a suitable amine 5-2 in a proper solvent such as THF or DCM using a reducing agent such as, but not limited to, sodium triacetoxyborohydride, optionally in the presence of an acid such as acetic acid or a base such as DIPEA. The compound of formula 5-5 can be synthesized by reacting formula 5-3 with a suitable halo (Hal^2)-substituted aniline 5-4 under standard SNAr conditions using an acid such as, but not limited to, sulfuric acid, or base such as, but not limited to, potassium tert-butoxide. Compounds of formula 5-5 may also be synthesized under standard metal catalyzed cross-coupling reaction conditions (such as Buchwald-Hartwig coupling reaction, e.g., in the presence of a palladium catalyst (e.g., [(4,5-bis(diphenylphosphino)-9,9-dimethylxanthene)-2-(2’-amino-1,1’-biphenyl)]palladium(II) methanesulfonate) and a base (e.g., cesium carbonate)). Then the aromatic halide 5-5 is reacted with a suitable coupling reagent 5-6 (where M is, e.g., -B(OH)₂) to provide compounds of formula II under standard metal catalyzed cross-coupling reaction conditions (such as Suzuki coupling reaction, e.g., in the presence of a palladium catalyst (e.g., I,Γ'-bis(diphenylphosphino)ferrocene)dichloropalladium(II)) and a base (e.g., a bicarbonate or a carbonate base)).
III. Uses of the Compounds

Compounds of the present disclosure can inhibit the activity of PD-1/PD-L1 protein/protein interaction and, thus, are useful in treating diseases and disorders associated with activity of PD-1 and the diseases and disorders associated with PD-L1 including its interaction with other proteins such as PD-1 and B7-1 (CD80). In certain embodiments, the compounds of the present disclosure, or pharmaceutically acceptable salts or stereoisomers thereof, are useful for therapeutic administration to enhance immunity in cancer, chronic infection or sepsis, including enhancement of response to vaccination. In some embodiments, the present disclosure provides a method for inhibiting the PD-1/PD-L1 protein/protein interaction. The method includes administering to an individual or a patient a compound of Formula (I) or of any of the formulas as described herein, or of a compound as recited in any of the claims and described herein, or a pharmaceutically acceptable salt or a stereoisomer thereof. The compounds of the present disclosure can be used alone, in combination with other agents or therapies or as an adjuvant or neoadjuvant for the treatment of diseases or disorders, including cancer or infection diseases. For the uses described herein, any of the compounds of the disclosure, including any of the embodiments thereof, may be used.

The compounds of the present disclosure inhibit the PD-1/PD-L1 protein/protein interaction, resulting in a PD-1 pathway blockade. The blockade of PD-1 can enhance the immune response to cancerous cells and infectious diseases in mammals, including humans. In some embodiments, the present disclosure provides treatment of an individual or a patient
in vivo using a compound of Formula (I) or a salt or stereoisomer thereof such that growth of cancerous tumors is inhibited. A compound of Formula (I) or of any of the formulas as described herein, or a compound as recited in any of the claims and described herein, or a salt or stereoisomer thereof, can be used to inhibit the growth of cancerous tumors. Alternatively, a compound of Formula (I) or of any of the formulas as described herein, or a compound as recited in any of the claims and described herein, or a salt or stereoisomer thereof, can be used in conjunction with other agents or standard cancer treatments, as described below. In one embodiment, the present disclosure provides a method for inhibiting growth of tumor cells in vitro. The method includes contacting the tumor cells in vitro with a compound of Formula (I) or of any of the formulas as described herein, or of a compound as recited in any of the claims and described herein, or of a salt or stereoisomer thereof. In another embodiment, the present disclosure provides a method for inhibiting growth of tumor cells in an individual or a patient. The method includes administering to the individual or patient in need thereof a therapeutically effective amount of a compound of Formula (I) or of any of the formulas as described herein, or of a compound as recited in any of the claims and described herein, or a salt thereof. Examples of cancers include those whose growth may be inhibited using compounds of the disclosure and cancers typically responsive to immunotherapy.

Examples of cancers that are treatable using the compounds of the present disclosure include, but are not limited to, bone cancer, pancreatic cancer, skin cancer, cancer of the head or neck, cutaneous or intraocular malignant melanoma, uterine cancer, ovarian cancer, rectal cancer, cancer of the anal region, stomach cancer, testicular cancer, uterine cancer, carcinoma of the fallopian tubes, carcinoma of the endometrium, endometrial cancer, carcinoma of the cervix, carcinoma of the vagina, carcinoma of the vulva, Hodgkin's Disease, non-Hodgkin's lymphoma, cancer of the esophagus, cancer of the small intestine, cancer of the endocrine system, cancer of the thyroid gland, cancer of the parathyroid gland, cancer of the adrenal gland, sarcoma of soft tissue, cancer of the urethra, cancer of the penis, chronic or acute leukemias including acute myeloid leukemia, chronic myeloid leukemia, acute lymphoblastic leukemia, chronic lymphocytic leukemia, solid tumors of childhood, lymphocytic lymphoma, cancer of the bladder, cancer of the kidney or urethra, carcinoma of the renal pelvis,
neoplasm of the central nervous system (CNS), primary CNS lymphoma, tumor angiogenesis, spinal axis tumor, brain stem glioma, pituitary adenoma, Kaposi's sarcoma, epidermoid cancer, squamous cell cancer, T-cell lymphoma, environmentally induced cancers including those induced by asbestos, and combinations of said cancers. The compounds of the present disclosure are also useful for the treatment of metastatic cancers, especially metastatic cancers that express PD-L1.

In some embodiments, cancers treatable with compounds of the present disclosure include melanoma (e.g., metastatic malignant melanoma), renal cancer (e.g. clear cell carcinoma), prostate cancer (e.g. hormone refractory prostate adenocarcinoma), breast cancer, colon cancer, lung cancer (e.g. non-small cell lung cancer and small cell lung cancer), squamous cell head and neck cancer, urothelial cancer (e.g. bladder and cancers with high microsatellite instability (MSI	extsuperscript{H})). Additionally, the disclosure includes refractory or recurrent malignancies whose growth may be inhibited using the compounds of the disclosure.

In some embodiments, cancers that are treatable using the compounds of the present disclosure include, but are not limited to, solid tumors (e.g., prostate cancer, colon cancer, esophageal cancer, endometrial cancer, ovarian cancer, uterine cancer, renal cancer, hepatic cancer, pancreatic cancer, gastric cancer, breast cancer, lung cancer, cancers of the head and neck, thyroid cancer, glioblastoma, sarcoma, bladder cancer, etc.), hematological cancers (e.g., lymphoma, leukemia such as acute lymphoblastic leukemia (ALL), acute myelogenous leukemia (AML), chronic lymphocytic leukemia (CLL), chronic myelogenous leukemia (CML), DLBCL, mantle cell lymphoma, Non-Hodgkin lymphoma (including relapsed or refractory NHL and recurrent follicular), Hodgkin lymphoma or multiple myeloma) and combinations of said cancers.

In some embodiments, cancers that are treatable using the compounds of the present disclosure include, but are not limited to, cholangiocarcinoma, bile duct cancer, triple negative breast cancer, rhabdomyosarcoma, small cell lung cancer, leiomyosarcoma, hepatocellular carcinoma, Ewing's sarcoma, brain cancer, brain tumor, astrocytoma, neuroblastoma, neurofibroma, basal cell carcinoma, chondrosarcoma, epithelioid sarcoma, eye cancer, Fallopian tube cancer, gastrointestinal cancer, gastrointestinal stromal tumors, hairy cell leukemia, intestinal cancer, islet cell cancer, oral cancer, mouth cancer, throat cancer, laryngeal cancer, lip cancer, mesothelioma, neck cancer, nasal cavity cancer, ocular cancer, ocular melanoma, pelvic cancer, rectal cancer, renal cell carcinoma, salivary gland cancer, sinus cancer, spinal cancer, tongue cancer, tubular carcinoma, urethral cancer, and ureteral cancer.
In some embodiments, the compounds of the present disclosure can be used to treat sickle cell disease and sickle cell anemia.

In some embodiments, diseases and indications that are treatable using the compounds of the present disclosure include, but are not limited to hematological cancers, sarcomas, lung cancers, gastrointestinal cancers, genitourinary tract cancers, liver cancers, bone cancers, nervous system cancers, gynecological cancers, and skin cancers.

Exemplary hematological cancers include lymphomas and leukemias such as acute lymphoblastic leukemia (ALL), acute myelogenous leukemia (AML), acute promyelocytic leukemia (APL), chronic lymphocytic leukemia (CLL), chronic myelogenous leukemia (CML), diffuse large B-cell lymphoma (DLBCL), mantle cell lymphoma, Non-Hodgkin lymphoma (including relapsed or refractory NHL and recurrent follicular), Hodgkin lymphoma, myeloproliferative diseases (e.g., primary myelofibrosis (PMF), polycythemia vera (PV), essential thrombocytosis (ET)), myelodysplasia syndrome (MDS), T-cell acute lymphoblastic lymphoma (T-ALL) and multiple myeloma (MM).

Exemplary sarcomas include chondrosarcoma, Ewing's sarcoma, osteosarcoma, rhabdomyosarcoma, angiosarcoma, fibrosarcoma, liposarcoma, myxoma, rhabdomyoma, rhabdosarcoma, fibroma, lipoma, hamartoma, and teratoma.

Exemplary lung cancers include non-small cell lung cancer (NSCLC), small cell lung cancer, bronchogenic carcinoma (squamous cell, undifferentiated small cell, undifferentiated large cell, adenocarcinoma), alveolar (bronchiolar) carcinoma, bronchial adenoma, chondromatous hamartoma, and mesothelioma.

Exemplary gastrointestinal cancers include cancers of the esophagus (squamous cell carcinoma, adenocarcinoma, leiomyosarcoma, lymphoma), stomach (carcinoma, lymphoma, leiomyosarcoma), pancreas (ductal adenocarcinoma, insulinoma, glucagonoma, gastrinoma, carcinoid tumors, vipoma), small bowel (adenocarcinoma, lymphoma, carcinoid tumors, Kaposi's sarcoma, leiomyoma, hemangioma, lipoma, neurofibroma, fibroma), large bowel (adenocarcinoma, tubular adenoma, villous adenoma, hamartoma, leiomyoma), and colorectal cancer.

Exemplary genitourinary tract cancers include cancers of the kidney (adenocarcinoma, Wilm's tumor [nephroblastoma]), bladder and urethra (squamous cell carcinoma, transitional cell carcinoma, adenocarcinoma), prostate (adenocarcinoma, sarcoma), and testis (seminoma, teratoma, embryonal carcinoma, teratocarcinoma, choriocarcinoma, sarcoma, interstitial cell carcinoma, fibroma, fibroadenoma, adenomatoid tumors, lipoma).
Exemplary liver cancers include hepatoma (hepatocellular carcinoma), cholangiocarcinoma, hepatoblastoma, angiosarcoma, hepatocellular adenoma, and hemangioma.

Exemplary bone cancers include, for example, osteogenic sarcoma (osteosarcoma), fibrosarcoma, malignant fibrous histiocytoma, chondrosarcoma, Ewing's sarcoma, malignant lymphoma (reticulum cell sarcoma), multiple myeloma, malignant giant cell tumor chordoma, osteochonfrorna (osteocartilaginous exostoses), benign chordoma, chondroblastoma, chondromyxofibroma, osteoid osteoma, and giant cell tumors.

Exemplary nervous system cancers include cancers of the skull (osteoma, hemangioma, granuloma, xanthoma, osteitis deformans), meninges (meningioma, meningiosarcoma, gliomatosis), brain (astrocytoma, meduoblastoma, glioma, ependymoma, germinoma (pinealoma), glioblastoma, glioblastoma multiform, oligodendrogioma, schwannoma, retinoblastoma, congenital tumors), and spinal cord (neurofibroma, meningioma, glioma, sarcoma), as well as neuroblastoma and Lhermitte-Duclos disease.

Exemplary gynecological cancers include cancers of the uterus (endometrial carcinoma), cervix (cervical carcinoma, pre-tumor cervical dysplasia), ovaries (ovarian carcinoma (serous cystadenocarcinoma, mucinous cystadenocarcinoma, unclassified carcinoma), granulosa-thecal cell tumors, Sertoli-Leydig cell tumors, dysgerminoma, malignant teratoma), vulva (squamous cell carcinoma, intraepithelial carcinoma, botryoid sarcoma (embryonal rhabdomyosarcoma), and fallopian tubes (carcinoma).

Exemplary skin cancers include melanoma, basal cell carcinoma, squamous cell carcinoma, Kaposi's sarcoma, moles dysplastic nevi, lipoma, angioma, dermatofibroma, and keloids. In some embodiments, diseases and indications that are treatable using the compounds of the present disclosure include, but are not limited to, sickle cell disease (e.g., sickle cell anemia), triple-negative breast cancer (TNBC), myelodysplasia syndromes, testicular cancer, bile duct cancer, esophageal cancer, and urothelial carcinoma.

PD-1 pathway blockade with compounds of the present disclosure can also be used for treating infections such as viral, bacteria, fungus and parasite infections. The present disclosure provides a method for treating infections such as viral infections. The method includes administering to a patient in need thereof, a therapeutically effective amount of a compound of Formula (I) or any of the formulas as described herein, a compound as recited in any of the claims and described herein, a salt thereof. Examples of viruses causing
infections treatable by methods of the present disclosure include, but are not limit to, human immunodeficiency virus, human papillomavirus, influenza, hepatitis A, B, C or D viruses, adenovirus, poxvirus, herpes simplex viruses, human cytomegalovirus, severe acute respiratory syndrome virus, ebola virus, and measles virus. In some embodiments, viruses causing infections treatable by methods of the present disclosure include, but are not limit to, hepatitis (A, B, or C), herpes virus (e.g., VZV, HSV-1, HAV-6, HSV-II, and CMV, Epstein Barr virus), adenovirus, influenza virus, flaviviruses, echovirus, rhinovirus, coxsackie virus, cornovirus, respiratory syncytial virus, mumps virus, rotavirus, measles virus, rubella virus, parovirus, vaccinia virus, HTLV virus, dengue virus, papillomavirus, molluscum virus, poliovirus, rabies virus, JC virus and arboviral encephalitis virus.

The present disclosure provides a method for treating bacterial infections. The method includes administering to a patient in need thereof, a therapeutically effective amount of a compound of Formula (I) or any of the formulas as described herein, a compound as recited in any of the claims and described herein, or a salt thereof. Non-limiting examples of pathogenic bacteria causing infections treatable by methods of the disclosure include chlamydia, rickettsial bacteria, mycobacteria, staphylococci, streptococci, pneumonococci, meningococci and conococci, klebsiella, proteus, serratia, pseudomonas, legionella, diphtheria, salmonella, bacilli, cholera, tetanus, botulism, anthrax, plague, leptospirosis, and Lyme's disease bacteria.

The present disclosure provides a method for treating fungus infections. The method includes administering to a patient in need thereof, a therapeutically effective amount of a compound of Formula (I) or any of the formulas as described herein, a compound as recited in any of the claims and described herein, or a salt thereof. Non-limiting examples of pathogenic fungi causing infections treatable by methods of the disclosure include Candida (albicans, krusei, glabrata, tropicalis, etc.), Cryptococcus neoformans, Aspergillus (fumigatus, niger, etc.), Genus Mucorales (mucor, absidia, rhizophus), Sporothrix schenckii, Blastomyces dermatitidis, Paracoccidioides brasiensis, Coccidioides immitis and Histoplasma capsulatum.

The present disclosure provides a method for treating parasite infections. The method includes administering to a patient in need thereof, a therapeutically effective amount of a compound of Formula (I) or any of the formulas as described herein, a compound as recited in any of the claims and described herein, or a salt thereof. Non-limiting examples of pathogenic parasites causing infections treatable by methods of the disclosure include Entamoeba histolytica, Balantidium coli, Naegleriaifowleri, Acanthamoeba sp., Giardia
lambia, Cryptosporidium sp., Pneumocystis carinii, Plasmodium vivax, Babesia microti, Trypanosoma brucei, Trypanosoma cruzi, Leishmania donovani, Toxoplasma gondii, and Nippostrongylus brasiliensis.

It is believed that compounds of Formula (I), or any of the embodiments thereof, may possess satisfactory pharmacological profile and promising biopharmaceutical properties, such as toxicological profile, metabolism and pharmacokinetic properties, solubility, and permeability. It will be understood that determination of appropriate biopharmaceutical properties is within the knowledge of a person skilled in the art, e.g., determination of cytotoxicity in cells or inhibition of certain targets or channels to determine potential toxicity.

The terms "individual" or "patient," used interchangeably, refer to any animal, including mammals, preferably mice, rats, other rodents, rabbits, dogs, cats, swine, cattle, sheep, horses, or primates, and most preferably humans.

The phrase "therapeutically effective amount" refers to the amount of active compound or pharmaceutical agent that elicits the biological or medicinal response in a tissue, system, animal, individual or human that is being sought by a researcher, veterinarian, medical doctor or other clinician.

As used herein, the term "treating" or "treatment" refers to one or more of (1) inhibiting the disease; e.g., inhibiting a disease, condition or disorder in an individual who is experiencing or displaying the pathology or symptomatology of the disease, condition or disorder (i.e., arresting further development of the pathology and/or symptomatology); and (2) ameliorating the disease; e.g., ameliorating a disease, condition or disorder in an individual who is experiencing or displaying the pathology or symptomatology of the disease, condition or disorder (i.e., reversing the pathology and/or symptomatology) such as decreasing the severity of disease.

In some embodiments, the compounds of the invention are useful in preventing or reducing the risk of developing any of the diseases referred to herein; e.g., preventing or reducing the risk of developing a disease, condition or disorder in an individual who may be predisposed to the disease, condition or disorder but does not yet experience or display the pathology or symptomatology of the disease.

Combination Therapies

Cancer cell growth and survival can be impacted by multiple signaling pathways. Thus, it is useful to combine different enzyme/protein/receptor inhibitors, exhibiting different preferences in the targets which they modulate the activities of, to treat such conditions.
Targeting more than one signaling pathway (or more than one biological molecule involved in a given signaling pathway) may reduce the likelihood of drug-resistance arising in a cell population, and/or reduce the toxicity of treatment.

The compounds of the present disclosure can be used in combination with one or more other enzyme/protein/receptor inhibitors or one or more therapies for the treatment of diseases, such as cancer or infections. Examples of diseases and indications treatable with combination therapies include those as described herein. Examples of cancers include solid tumors and liquid tumors, such as blood cancers. Examples of infections include viral infections, bacterial infections, fungus infections or parasite infections. For example, the compounds of the present disclosure can be combined with one or more inhibitors of the following kinases for the treatment of cancer: Akt1, Akt2, Akt3, TGF-PR, PKA, PKG, PKC, CaM-kinase, phosphorylase kinase, MEKK, ERK, MAPK, mTOR, EGFR, HER2, HER3, HER4, INS-R, IGF-1R, IR-R, PDGFrA, PDGFrP, PI3K (alpha, beta, gamma, delta), CSFIR, KIT, FLK-II, KDR/FLK-1, FLK-4, flt-1, FGFR1, FGFR2, FGFR3, FGFR4, c-Met, Ron, Sea, TRKA, TRKB, TRKC, TAM kinases (Axl, Mer, Tyro3), FLT3, VEGFR/Flt2, Flt4, EphA1, EphA2, EphA3, EphB2, EphB4, Tie2, Src, Fyn, Lck, Fgr, Btk, Fak, SYK, FRK, JAK, ABL, ALK and B-Raf. In some embodiments, the compounds of the present disclosure can be combined with one or more of the following inhibitors for the treatment of cancer or infections. Non-limiting examples of inhibitors that can be combined with the compounds of the present disclosure for treatment of cancer and infections include an FGFR inhibitor (FGFR1, FGFR2, FGFR3 or FGFR4, e.g., INCB54828, INCB62079 and INCB63904), a JAK inhibitor (JAK1 and/or JAK2, e.g., ruxolitinib, baricitinib or INCB39110), an IDO inhibitor (e.g., epacadostat, NLG919, BMS-986205), an LSD1 inhibitor (e.g., INCB59872 and INCB60003), a TDO inhibitor, a PI3K-delta inhibitor (e.g., INCB50797 and INCB50465), a PI3K-gamma inhibitor such as PI3K-gamma selective inhibitor, a Pirn inhibitor (e.g., INCB53914), a CSFIR inhibitor, a TAM receptor tyrosine kinases (Tyro-3, Axl, and Mer), an adenosine receptor antagonist (e.g., A2a/A2b receptor antagonist), an HPK1 inhibitor, an histone deacetylase inhibitor (HDAC) such as an HDAC8 inhibitor, an angiogenesis inhibitor, an interleukin receptor inhibitor, bromo and extra terminal family members inhibitors (for example, bromodomain inhibitors or BET inhibitors such as INCB54329 and INCB57643), a poly ADP ribose polymerase (PARP) inhibitor such as rucaparib, olaparib, niraparib, veliparib, or talazoparib, an arginase inhibitor (INCB01158), and an adenosine receptor antagonist or combinations thereof.
Compounds of the present disclosure can be used in combination with one or more immune checkpoint inhibitors. Exemplary immune checkpoint inhibitors include inhibitors against immune checkpoint molecules such as CD27, CD28, CD40, CD122, CD96, CD73, CD47, OX40, GITR, CSF1R, JAK, PI3K delta, PI3K gamma, TAM, arginase, CD137 (also known as 4-1BB), ICOS, A2AR, B7-H3, B7-H4, BTLA, CTLA-4, LAG3, TIM3, VISTA, PD-1, PD-L1 and PD-L2. In some embodiments, the immune checkpoint molecule is a stimulatory checkpoint molecule selected from CD27, CD28, CD40, ICOS, OX40, GITR and CD137. In some embodiments, the immune checkpoint molecule is an inhibitory checkpoint molecule selected from A2AR, B7-H3, B7-H4, BTLA, CTLA-4, IDO, KIR, LAG3, PD-1, TIM3, and VISTA. In some embodiments, the compounds provided herein can be used in combination with one or more agents selected from KIR inhibitors, TIGIT inhibitors, LAIR1 inhibitors, CD160 inhibitors, 2B4 inhibitors and TGFR beta inhibitors.

In some embodiments, the inhibitor of an immune checkpoint molecule is anti-PD1 antibody, anti-PD-L1 antibody, or anti-CTLA-4 antibody.

In some embodiments, the inhibitor of an immune checkpoint molecule is an inhibitor of PD-1, e.g., an anti-PD-1 monoclonal antibody. In some embodiments, the anti-PD-1 monoclonal antibody is nivolumab, pembrolizumab (also known as MK-3475), pidilizumab, SHR-1210, PDR001, or AMP-224. In some embodiments, the anti-PD-1 monoclonal antibody is nivolumab or pembrolizumab. In some embodiments, the anti-PD1 antibody is pembrolizumab. In some embodiments, the anti PD-1 antibody is SHR-1210.

In some embodiments, the inhibitor of an immune checkpoint molecule is an inhibitor of PD-L1, e.g., an anti-PD-L1 monoclonal antibody. In some embodiments, the anti-PD-L1 monoclonal antibody is BMS-935559, MEDI4736, MPDL3280A (also known as RG7446), or MSB0010718C. In some embodiments, the anti-PD-L1 monoclonal antibody is MPDL3280A or MEDI4736.

In some embodiments, the inhibitor of an immune checkpoint molecule is an inhibitor of CTLA-4, e.g., an anti-CTLA-4 antibody. In some embodiments, the anti-CTLA-4 antibody is ipilimumab or tremelimumab.

In some embodiments, the inhibitor of an immune checkpoint molecule is an inhibitor of LAG3, e.g., an anti-LAG3 antibody. In some embodiments, the anti-LAG3 antibody is BMS-986016, LAG525 or INCAGN2385.

In some embodiments, the inhibitor of an immune checkpoint molecule is an inhibitor of TIM3, e.g., an anti-TIM3 antibody. In some embodiments, the anti-TIM3 antibody is INCAGN2390, MBG453, or TSR-022.
In some embodiments, the inhibitor of an immune checkpoint molecule is an inhibitor of GITR, e.g., an anti-GITR antibody. In some embodiments, the anti-GITR antibody is TRX5 18, MK-4166, INCAGN1 876, MK-1248, AMG228, BMS-986156, GWN323, or MEDI1 873.

In some embodiments, the inhibitor of an immune checkpoint molecule is an inhibitor of OX40, e.g., an anti-OX40 antibody or OX40L fusion protein. In some embodiments, the anti-OX40 antibody is MEDI0562, MOXR-0916, PF-04518600, GSK3174998, or BMS-986178. In some embodiments, the OX40L fusion protein is MEDI6383.

Compounds of the present disclosure can be used in combination with one or more agents for the treatment of diseases such as cancer. In some embodiments, the agent is an alkylating agent, a proteasome inhibitor, a corticosteroid, or an immunomodulatory agent. Examples of an alkylating agent include cyclophosphamide (CY), melphalan (MEL), and bendamustine. In some embodiments, the proteasome inhibitor is carfilzomib. In some embodiments, the corticosteroid is dexamethasone (DEX). In some embodiments, the immunomodulatory agent is lenalidomide (LEN) or pomalidomide (POM).

The compounds of the present disclosure can further be used in combination with other methods of treating cancers, for example by chemotherapy, irradiation therapy, tumor-targeted therapy, adjuvant therapy, immunotherapy or surgery. Examples of immunotherapy include cytokine treatment (e.g., interferons, GM-CSF, G-CSF, IL-2), CRS-207 immunotherapy, cancer vaccine, monoclonal antibody, adoptive T cell transfer, Toll receptor agonists, STING agonists, oncolytic virotherapy and immunomodulating small molecules, including thalidomide or JAK1/2 inhibitor and the like. The compounds can be administered in combination with one or more anti-cancer drugs, such as a chemotherapeutics. Example chemotherapeutics include any of: abarelix, aldesleukin, alemtuzumab, alitretinoin, allopurinol, altretamine, anastrozole, arsenic trioxide, asparaginase, azacitidine, bevacizumab, bexarotene, baricitinib, bleomycin, bortezomib, bortezomib, busulfan intravenous, busulfan oral, calusterone, capecitabine, carboplatin, camustine, cetuximab, chlorambucil, cisplatin, cladribine, clofarabine, cyclophosphamide, cytarabine, dacarbazine, dactinomycin, dalteparin sodium, dasatinib, daunorubicin, decitabine, denileukin, denileukin difitox, dexamethasone, docetaxel, doxorubicin, dromostanolone propionate, eculizumab, epirubicin, erlotinib, estramustine, etoposide phosphate, etoposide, exemestane, fentanyl citrate, filgrastim, fioxuridine, fludarabine, fluorouracil, fulvestrant, gefitinib, gemcitabine, gemtuzumab ozogamicin, goserelin acetate, histrelin acetate, ibritumomab tiuxetan, idarubicin, ifosfamide, imatinib mesylate, interferon alfa 2a, irinotecan, lapatinib ditosylate, lenalidomide, letrozole,
leucovorin, leuprolide acetate, levamisole, lomustine, mecloretamine, megestrol acetate, melphalan, mercaptopurine, methotrexate, methoxsalen, mitomycin C, mitotane, mitoxantrone, nandrolone phenpropionate, nelfinavir, nelarabine, nolatumomab, olaparib, oxaliplatin, paclitaxel, pamidronate, panitumumab, pegasparagase, pegfilgrastim, pemetrexed disodium, pentostatin, pipobroman, plicamycin, procarbazine, quinacrine, rasburicase, rituximab, ruxolitinib, rucaparib, sorafenib, streptozocin, sunitinib, sunitinib maleate, tamoxifen, temozolomide, teniposide, testolactone, thalidomide, thioguanine, thiotepa, toremifene, tositumomab, trastuzumab, tretinoin, uracil mustard, valrubicin, vinblastine, vincristine, vinorelbine, vorinostat, niraparib, veliparib, talazoparib and zoledronate.

Other anti-cancer agent(s) include antibody therapeutics such as trastuzumab (Herceptin), antibodies to costimulatory molecules such as CTLA-4 (e.g., ipilimumab), 4-1BB (e.g., ertulimumab, utomilumab), antibodies to PD-1 and PD-L1, or antibodies to cytokines (IL-10, TGF-β, etc.). Examples of antibodies to PD-1 and/or PD-L1 that can be combined with compounds of the present disclosure for the treatment of cancer or infections such as viral, bacteria, fungus and parasite infections include, but are not limited to, nivolumab, pembrolizumab, MPDL3280A, MEDI-4736 and SHR-1210.

In some embodiments, the anti-cancer agent is an alkylating agent, a proteasome inhibitor, a corticosteroid, or an immunomodulatory agent. Examples of an alkylating agent include cyclophosphamide (CY), melphalan (MEL), and bendamustine. In some embodiments, the proteasome inhibitor is carfilzomib. In some embodiments, the corticosteroid is dexamethasone (DEX). In some embodiments, the immunomodulatory agent is lenalidomide (LEN) or pomalidomide (POM).

The compounds of Formula (I) or any of the formulas as described herein, a compound as recited in any of the claims and described herein, or salts, stereoisomers thereof can be used in combination with an immune checkpoint inhibitor for the treatment of cancer and viral infections.

Exemplary immune checkpoint inhibitors include inhibitors against immune checkpoint molecules such as CD27, CD28, CD40, CD122, CD96, CD73, CD47, OX40, GITR, CSF1R, JAK, PI3K delta, PI3K gamma, TAM, arginase, CD137 (also known as 4-1BB), ICOS, A2AR, B7-H3, B7-H4, BTLA, CTLA-4, LAG3, TIM3, VISTA, PD-1, PD-L1 and PD-L2. In some embodiments, the immune checkpoint molecule is a stimulatory checkpoint molecule selected from CD27, CD28, CD40, ICOS, OX40, GITR and CD137. In some embodiments, the immune checkpoint molecule is an inhibitory checkpoint molecule selected from A2AR, B7-H3, B7-H4, BTLA, CTLA-4, IDO, KIR, LAG3, PD-1, TIM3, and
VISTA. In some embodiments, the compounds provided herein can be used in combination with one or more agents selected from KIR inhibitors, TIGIT inhibitors, LAIR1 inhibitors, CD160 inhibitors, 2B4 inhibitors and TGFR beta inhibitors.

In some embodiments, the inhibitor of an immune checkpoint molecule is anti-PDL1 antibody, anti-PD-L1 antibody, or anti-CTLA-4 antibody.

In some embodiments, the inhibitor of an immune checkpoint molecule is an inhibitor of PD-1, e.g., an anti-PD-1 monoclonal antibody. In some embodiments, the anti-PD-1 monoclonal antibody is nivolumab, pembrolizumab (also known as MK-3475), pidilizumab, SHR-1210, PDR001, or AMP-224. In some embodiments, the anti-PD-1 monoclonal antibody is nivolumab or pembrolizumab. In some embodiments, the anti-PDL1 antibody is pembrolizumab.

In some embodiments, the inhibitor of an immune checkpoint molecule is an inhibitor of PD-L1, e.g., an anti-PD-L1 monoclonal antibody. In some embodiments, the anti-PD-L1 monoclonal antibody is BMS-935559, MEDI4736, MPDL3280A (also known as RG7446), or MSB001071 8C. In some embodiments, the anti-PD-L1 monoclonal antibody is MPDL3280A or MEDI4736.

In some embodiments, the inhibitor of an immune checkpoint molecule is an inhibitor of CTLA-4, e.g., an anti-CTLA-4 antibody. In some embodiments, the anti-CTLA-4 antibody is ipilimumab.

In some embodiments, the inhibitor of an immune checkpoint molecule is an inhibitor of LAG3, e.g., an anti-LAG3 antibody. In some embodiments, the anti-LAG3 antibody is BMS-986016 or LAG525.

In some embodiments, the inhibitor of an immune checkpoint molecule is an inhibitor of GITR, e.g., an anti-GITR antibody. In some embodiments, the anti-GITR antibody is TRX5 18 or MK-41 66.

In some embodiments, the inhibitor of an immune checkpoint molecule is an inhibitor of OX40, e.g., an anti-OX40 antibody or OX40L fusion protein. In some embodiments, the anti-OX40 antibody is MEDI0562. In some embodiments, the OX40L fusion protein is MEDI6383.

The compounds of the present disclosure can further be used in combination with one or more anti-inflammatory agents, steroids, immunosuppressants or therapeutic antibodies.

The compounds of Formula (I) or any of the formulas as described herein, a compound as recited in any of the claims and described herein, or salts thereof can be combined with another immunogenic agent, such as cancerous cells, purified tumor antigens
(including recombinant proteins, peptides, and carbohydrate molecules), cells, and cells transfected with genes encoding immune stimulating cytokines. Non-limiting examples of tumor vaccines that can be used include peptides of melanoma antigens, such as peptides of gplO0, MAGE antigens, **Trp-2**, MARTI and/or tyrosinase, or tumor cells transfected to express the cytokine GM-CSF.

The compounds of Formula (I) or any of the formulas as described herein, a compound as recited in any of the claims and described herein, or salts thereof can be used in combination with a vaccination protocol for the treatment of cancer. In some embodiments, the tumor cells are transduced to express GM-CSF. In some embodiments, tumor vaccines include the proteins from viruses implicated in human cancers such as Human Papilloma Viruses (HPV), Hepatitis Viruses (HBV and HCV) and Kaposi's Herpes Sarcoma Virus (KHSV). In some embodiments, the compounds of the present disclosure can be used in combination with tumor specific antigen such as heat shock proteins isolated from tumor tissue itself. In some embodiments, the compounds of Formula (I) or any of the formulas as described herein, a compound as recited in any of the claims and described herein, or salts thereof can be combined with dendritic cells immunization to activate potent anti-tumor responses.

The compounds of the present disclosure can be used in combination with bispecific macrocyclic peptides that target Fe alpha or Fe gamma receptor-expressing effectors cells to tumor cells. The compounds of the present disclosure can also be combined with macrocyclic peptides that activate host immune responsiveness.

The compounds of the present disclosure can be used in combination with bone marrow transplant for the treatment of a variety of tumors of hematopoietic origin.

The compounds of Formula (I) or any of the formulas as described herein, a compound as recited in any of the claims and described herein, or salts thereof can be used in combination with vaccines, to stimulate the immune response to pathogens, toxins, and self antigens. Examples of pathogens for which this therapeutic approach may be particularly useful, include pathogens for which there is currently no effective vaccine, or pathogens for which conventional vaccines are less than completely effective. These include, but are not limited to, HIV, Hepatitis (A, B, & C), Influenza, Herpes, Giardia, Malaria, Leishmania, Staphylococcus aureus, Pseudomonas Aeruginosa.

Viruses causing infections treatable by methods of the present disclosure include, but are not limited to human papillomavirus, influenza, hepatitis A, B, C or D viruses, adenovirus, poxvirus, herpes simplex viruses, human cytomegalovirus, severe acute respiratory syndrome...
virus, ebola virus, measles virus, herpes virus (e.g., VZV, HSV-1, HAV-6, HSV-II, and CMV, Epstein Barr virus), flaviviruses, echovirus, rhinovirus, coxsackie virus, coronvirus, respiratory syncytial virus, mumps virus, rotavirus, measles virus, rubella virus, parvovirus, vaccinia virus, HTLV virus, dengue virus, papillomavirus, molluscum virus, poliovirus, rabies virus, JC virus and arboviral encephalitis virus.

Pathogenic bacteria causing infections treatable by methods of the disclosure include, but are not limited to, chlamydia, rickettsial bacteria, mycobacteria, staphylococci, streptococci, pneumococci, meningococci and concocci, klebsiella, proteus, serratia, pseudomonas, legionella, diphertheria, salmonella, bacilli, cholera, tetanus, botulism, anthrax, plague, leptospirosis, and Lyme's disease bacteria.

Pathogenic fungi causing infections treatable by methods of the disclosure include, but are not limited to, Candida (albicans, krusei, glabrate, tropicalis, etc.), Cryptococcus neoformans, Aspergillus (fumigatus, niger, etc.), Genus Mucorales (mucor, absidia, rhizophus), Sporothrix schenkii, Blastomyces dermatitidis, Paracoccidioides brasiliensis, Coccidioides immitis and Histoplasma capsulatum.

Pathogenic parasites causing infections treatable by methods of the disclosure include, but are not limited to, Entamoeba histolytica, Balantidium coli, Naegleriafowleri, Acanthamoeba sp., Giardia lambia, Cryptosporidium sp., Pneumocystis carinii, Plasmodium vivax, Babesia microti, Trypanosoma brucei, Trypanosoma cruzi, Leishmania donovani, Toxoplasma gondi, and Nipponstrongylus brasiliensis.

When more than one pharmaceutical agent is administered to a patient, they can be administered simultaneously, separately, sequentially, or in combination (e.g., for more than two agents).

IV. **Formulation, Dosage Forms and Administration**

When employed as pharmaceuticals, the compounds of the present disclosure can be administered in the form of pharmaceutical compositions. Thus the present disclosure provides a composition comprising a compound of Formula (I) or any of the formulas as described herein, a compound as recited in any of the claims and described herein, or a pharmaceutically acceptable salt thereof, or any of the embodiments thereof, and at least one pharmaceutically acceptable carrier or excipient. These compositions can be prepared in a manner well known in the pharmaceutical art, and can be administered by a variety of routes, depending upon whether local or systemic treatment is indicated and upon the area to be treated. Administration may be topical (including transdermal, epidermal, ophthalmic and to
mucous membranes including intranasal, vaginal and rectal delivery), pulmonary (e.g., by
inhalation or insufflation of powders or aerosols, including by nebulizer; intratracehal or
intranasal), oral or parenteral. Parenteral administration includes intravenous, intrarterial,
subcutaneous, intraperitoneal intramuscular or injection or infusion; or intracranial, e.g.,
intrathecal or intraventricular, administration. Parenteral administration can be in the form of
a single bolus dose, or may be, e.g., by a continuous perfusion pump. Pharmaceutical
compositions and formulations for topical administration may include transdermal patches,
ointments, lotions, creams, gels, drops, suppositories, sprays, liquids and powders.
Conventional pharmaceutical carriers, aqueous, powder or oily bases, thickeners and the like
may be necessary or desirable.

This invention also includes pharmaceutical compositions which contain, as the active
ingredient, the compound of the present disclosure or a pharmaceutically acceptable salt
thereof, in combination with one or more pharmaceutically acceptable carriers or excipients.
In some embodiments, the composition is suitable for topical administration. In making the
compositions of the invention, the active ingredient is typically mixed with an excipient,
diluted by an excipient or enclosed within such a carrier in the form of, e.g., a capsule, sachet,
paper, or other container. When the excipient serves as a diluent, it can be a solid, semi-solid,
or liquid material, which acts as a vehicle, carrier or medium for the active ingredient. Thus,
the compositions can be in the form of tablets, pills, powders, lozenges, sachets, cachets,
elixirs, suspensions, emulsions, solutions, syrups, aerosols (as a solid or in a liquid medium),
ointments containing, e.g., up to 10% by weight of the active compound, soft and hard gelatin
capsules, suppositories, sterile injectable solutions and sterile packaged powders.

In preparing a formulation, the active compound can be milled to provide the
appropriate particle size prior to combining with the other ingredients. If the active compound
is substantially insoluble, it can be milled to a particle size of less than 200 mesh. If the active
compound is substantially water soluble, the particle size can be adjusted by milling to
provide a substantially uniform distribution in the formulation, e.g., about 40 mesh.

The compounds of the invention may be milled using known milling procedures such
as wet milling to obtain a particle size appropriate for tablet formation and for other
formulation types. Finely divided (nanoparticulate) preparations of the compounds of the
invention can be prepared by processes known in the art see, e.g., WO 2002/000196.

Some examples of suitable excipients include lactose, dextrose, sucrose, sorbitol,
mannitol, starches, gum acacia, calcium phosphate, alginates, tragacanth, gelatin, calcium
silicate, microcrystalline cellulose, polyvinylpyrrolidone, cellulose, water, syrup and methyl
cellulose. The formulations can additionally include: lubricating agents such as talc, magnesium stearate and mineral oil; wetting agents; emulsifying and suspending agents; preserving agents such as methyl- and propylhydroxy-benzoates; sweetening agents; and flavoring agents. The compositions of the invention can be formulated so as to provide quick, sustained or delayed release of the active ingredient after administration to the patient by employing procedures known in the art.

In some embodiments, the pharmaceutical composition comprises silicified microcrystalline cellulose (SMCC) and at least one compound described herein, or a pharmaceutically acceptable salt thereof. In some embodiments, the silicified microcrystalline cellulose comprises about 98% microcrystalline cellulose and about 2% silicon dioxide w/w.

In some embodiments, the composition is a sustained release composition comprising at least one compound described herein, or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable carrier or excipient. In some embodiments, the composition comprises at least one compound described herein, or a pharmaceutically acceptable salt thereof, and at least one component selected from microcrystalline cellulose, lactose monohydrate, hydroxypropyl methylcellulose and polyethylene oxide. In some embodiments, the composition comprises at least one compound described herein, or a pharmaceutically acceptable salt thereof, and microcrystalline cellulose, lactose monohydrate and hydroxypropyl methylcellulose. In some embodiments, the composition comprises at least one compound described herein, or a pharmaceutically acceptable salt thereof, and microcrystalline cellulose, lactose monohydrate and polyethylene oxide. In some embodiments, the composition further comprises magnesium stearate or silicon dioxide. In some embodiments, the microcrystalline cellulose is Avicel PH102™. In some embodiments, the lactose monohydrate is Fast-flo 316™. In some embodiments, the hydroxypropyl methylcellulose is hydroxypropyl methylcellulose 2208 K4M (e.g., Methocel K4 M Premier™) and/or hydroxypropyl methylcellulose 2208 K100LV (e.g., Methocel K00LV™). In some embodiments, the polyethylene oxide is polyethylene oxide WSR 1105 (e.g., Polyox WSR 1105™).

In some embodiments, a wet granulation process is used to produce the composition. In some embodiments, a dry granulation process is used to produce the composition.

The compositions can be formulated in a unit dosage form, each dosage containing from about 5 to about 1,000 mg (1 g), more usually about 100 mg to about 500 mg, of the active ingredient. In some embodiments, each dosage contains about 10 mg of the active
ingredient. In some embodiments, each dosage contains about 50 mg of the active ingredient. In some embodiments, each dosage contains about 25 mg of the active ingredient. The term "unit dosage forms" refers to physically discrete units suitable as unitary dosages for human subjects and other mammals, each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic effect, in association with a suitable pharmaceutical excipient.

The components used to formulate the pharmaceutical compositions are of high purity and are substantially free of potentially harmful contaminants (e.g., at least National Food grade, generally at least analytical grade, and more typically at least pharmaceutical grade). Particularly for human consumption, the composition is preferably manufactured or formulated under Good Manufacturing Practice standards as defined in the applicable regulations of the U.S. Food and Drug Administration. For example, suitable formulations may be sterile and/or substantially isotonic and/or in full compliance with all Good Manufacturing Practice regulations of the U.S. Food and Drug Administration.

The active compound may be effective over a wide dosage range and is generally administered in a therapeutically effective amount. It will be understood, however, that the amount of the compound actually administered will usually be determined by a physician, according to the relevant circumstances, including the condition to be treated, the chosen route of administration, the actual compound administered, the age, weight, and response of the individual patient, the severity of the patient's symptoms and the like.

The therapeutic dosage of a compound of the present invention can vary according to, e.g., the particular use for which the treatment is made, the manner of administration of the compound, the health and condition of the patient, and the judgment of the prescribing physician. The proportion or concentration of a compound of the invention in a pharmaceutical composition can vary depending upon a number of factors including dosage, chemical characteristics (e.g., hydrophobicity), and the route of administration. For example, the compounds of the invention can be provided in an aqueous physiological buffer solution containing about 0.1 to about 10% w/v of the compound for parenteral administration. Some typical dose ranges are from about 1 µg/kg to about 1 g/kg of body weight per day. In some embodiments, the dose range is from about 0.01 mg/kg to about 100 mg/kg of body weight per day. The dosage is likely to depend on such variables as the type and extent of progression of the disease or disorder, the overall health status of the particular patient, the relative biological efficacy of the compound selected, formulation of the excipient, and its
route of administration. Effective doses can be extrapolated from dose-response curves derived from in vitro or animal model test systems.

For preparing solid compositions such as tablets, the principal active ingredient is mixed with a pharmaceutical excipient to form a solid preformulation composition containing a homogeneous mixture of a compound of the present invention. When referring to these preformulation compositions as homogeneous, the active ingredient is typically dispersed evenly throughout the composition so that the composition can be readily subdivided into equally effective unit dosage forms such as tablets, pills and capsules. This solid preformulation is then subdivided into unit dosage forms of the type described above containing from, e.g., about 0.1 to about 1000 mg of the active ingredient of the present invention.

The tablets or pills of the present invention can be coated or otherwise compounded to provide a dosage form affording the advantage of prolonged action. For example, the tablet or pill can comprise an inner dosage and an outer dosage component, the latter being in the form of an envelope over the former. The two components can be separated by an enteric layer which serves to resist disintegration in the stomach and permit the inner component to pass intact into the duodenum or to be delayed in release. A variety of materials can be used for such enteric layers or coatings, such materials including a number of polymeric acids and mixtures of polymeric acids with such materials as shellac, cetyl alcohol and cellulose acetate.

The liquid forms in which the compounds and compositions of the present invention can be incorporated for administration orally or by injection include aqueous solutions, suitably flavored syrups, aqueous or oil suspensions, and flavored emulsions with edible oils such as cottonseed oil, sesame oil, coconut oil, or peanut oil, as well as elixirs and similar pharmaceutical vehicles.

Compositions for inhalation or insufflation include solutions and suspensions in pharmaceutically acceptable, aqueous or organic solvents, or mixtures thereof, and powders. The liquid or solid compositions may contain suitable pharmaceutically acceptable excipients as described supra. In some embodiments, the compositions are administered by the oral or nasal respiratory route for local or systemic effect. Compositions can be nebulized by use of inert gases. Nebulized solutions may be breathed directly from the nebulizing device or the nebulizing device can be attached to a face mask, tent, or intermittent positive pressure breathing machine. Solution, suspension, or powder compositions can be administered orally or nasally from devices which deliver the formulation in an appropriate manner.
Topical formulations can contain one or more conventional carriers. In some embodiments, ointments can contain water and one or more hydrophobic carriers selected from, e.g., liquid paraffin, polyoxyethylene alkyl ether, propylene glycol, white Vaseline, and the like. Carrier compositions of creams can be based on water in combination with glycerol and one or more other components, e.g., glycerinemenostearate, PEG-glycerinemenostearate and cetylstearyl alcohol. Gels can be formulated using isopropyl alcohol and water, suitably in combination with other components such as, e.g., glycerol, hydroxyethyl cellulose, and the like. In some embodiments, topical formulations contain at least about 0.1, at least about 0.25, at least about 0.5, at least about 1, at least about 2 or at least about 5 wt % of the compound of the invention. The topical formulations can be suitably packaged in tubes of, e.g., 100 g which are optionally associated with instructions for the treatment of the select indication, e.g., psoriasis or other skin condition.

The amount of compound or composition administered to a patient will vary depending upon what is being administered, the purpose of the administration, such as prophylaxis or therapy, the state of the patient, the manner of administration and the like. In therapeutic applications, compositions can be administered to a patient already suffering from a disease in an amount sufficient to cure or at least partially arrest the symptoms of the disease and its complications. Effective doses will depend on the disease condition being treated as well as by the judgment of the attending clinician depending upon factors such as the severity of the disease, the age, weight and general condition of the patient and the like.

The compositions administered to a patient can be in the form of pharmaceutical compositions described above. These compositions can be sterilized by conventional sterilization techniques, or may be sterile filtered. Aqueous solutions can be packaged for use as is, or lyophilized, the lyophilized preparation being combined with a sterile aqueous carrier prior to administration. The pH of the compound preparations typically will be between 3 and 11, more preferably from 5 to 9 and most preferably from 7 to 8. It will be understood that use of certain of the foregoing excipients, carriers or stabilizers will result in the formation of pharmaceutical salts.

The therapeutic dosage of a compound of the present invention can vary according to, e.g., the particular use for which the treatment is made, the manner of administration of the compound, the health and condition of the patient, and the judgment of the prescribing physician. The proportion or concentration of a compound of the invention in a pharmaceutical composition can vary depending upon a number of factors including dosage, chemical characteristics (e.g., hydrophobicity), and the route of administration. For example,
the compounds of the invention can be provided in an aqueous physiological buffer solution containing about 0.1 to about 10% w/v of the compound for parenteral administration. Some typical dose ranges are from about 1 μg/kg to about 1 g/kg of body weight per day. In some embodiments, the dose range is from about 0.01 mg/kg to about 100 mg/kg of body weight per day. The dosage is likely to depend on such variables as the type and extent of progression of the disease or disorder, the overall health status of the particular patient, the relative biological efficacy of the compound selected, formulation of the excipient, and its route of administration. Effective doses can be extrapolated from dose-response curves derived from in vitro or animal model test systems.

v. **Labeled Compounds and Assay Methods**

The compounds of the present disclosure can further be useful in investigations of biological processes in normal and abnormal tissues. Thus, another aspect of the present invention relates to labeled compounds of the invention (radio-labeled, fluorescent-labeled, etc.) that would be useful not only in imaging techniques but also in assays, both in vitro and in vivo, for localizing and quantitating PD-1 or PD-L1 protein in tissue samples, including human, and for identifying PD-L1 ligands by inhibition binding of a labeled compound. Accordingly, the present invention includes PD-1/PD-L1 binding assays that contain such labeled compounds.

The present invention further includes isotopically-substituted compounds of the disclosure. An "isotopically-substituted" compound is a compound of the invention where one or more atoms are replaced or substituted by an atom having the same atomic number but different atomic mass or mass number e.g., a different atomic mass or mass number from the atomic mass or mass number typically found in nature (i.e., naturally occurring). It is to be understood that a "radio-labeled" compound is a compound that has incorporated at least one isotope that is radioactive (e.g., radionuclide). Suitable radionuclides that may be incorporated in compounds of the present invention include but are not limited to ³H (also written as T for tritium), ¹¹C, ¹³C, ¹⁴C, ¹⁵N, ¹⁷O, ¹⁸O, ¹⁸F, ³⁵S, ³⁶Cl, ⁸²Br, ⁷⁵Br, ⁷⁶Br, ⁷⁷Br, ¹²³I, ¹²⁴I, ¹²⁵I and ¹³¹I. The radionuclide that is incorporated in the instant radio-labeled compounds will depend on the specific application of that radio-labeled compound. For example, for in vitro PD-L1 protein labeling and competition assays, compounds that incorporate ³H, ¹⁴C, ⁸²Br, ¹²⁵I, ¹³¹I, ³⁵S or will generally be most useful. For radio-imaging applications ¹¹C, ¹⁸F, ¹²⁵I, ¹²⁴I, ¹³¹I, ⁷⁵Br, ⁷⁶Br or ⁷⁷Br will generally be most useful.
It is understood that a "radio-labeled" or "labeled compound" is a compound that has incorporated at least one radionuclide. In some embodiments the radionuclide is selected from the group consisting of \( ^{3}H, ^{14}C, ^{125}I, ^{35}S \) and \(^{82}Br\). Synthetic methods for incorporating radio-isotopes into organic compounds are applicable to compounds provided herein and are well known in the art.

A radio-labeled compound of the invention can be used in a screening assay to identify and/or evaluate compounds. In general terms, a newly synthesized or identified compound (i.e., test compound) which is labeled can be evaluated for its ability to bind a PD-L1 protein by monitoring its concentration variation when contacting with the PD-L1 protein, through tracking of the labeling. For example, a test compound (radio-labeled) can be evaluated for its ability to reduce binding of another compound which is known to bind to a PD-L1 protein (i.e., standard compound). Accordingly, the ability of a test compound to compete with the standard compound for binding to the PD-L1 protein directly correlates to its binding affinity. Conversely, in some other screening assays, the standard compound is labeled and test compounds are unlabeled. Accordingly, the concentration of the labeled standard compound is monitored in order to evaluate the competition between the standard compound and the test compound, and the relative binding affinity of the test compound is thus ascertained.

**vi. Kits**

The present disclosure also includes pharmaceutical kits useful, e.g., in the treatment or prevention of diseases or disorders associated with the activity of PD-L1 including its interaction with other proteins such as PD-1 and B7-1 (CD80), such as cancer or infections, which include one or more containers containing a pharmaceutical composition comprising a therapeutically effective amount of a compound of Formula (I), or any of the embodiments thereof. Such kits can further include one or more of various conventional pharmaceutical kit components, such as, e.g., containers with one or more pharmaceutically acceptable carriers, additional containers, etc., as will be readily apparent to those skilled in the art. Instructions, either as inserts or as labels, indicating quantities of the components to be administered, guidelines for administration, and/or guidelines for mixing the components, can also be included in the kit.

The invention will be described in greater detail by way of specific examples. The following examples are offered for illustrative purposes, and are not intended to limit the invention in any manner. Those of skill in the art will readily recognize a variety of non-
critical parameters which can be changed or modified to yield essentially the same results. The compounds of the Examples have been found to inhibit the activity of PD-1/PD-L1 protein/protein interaction according to at least one assay described herein.

EXEMPLARY

Experimental procedures for compounds of the invention are provided below. Open Access Preparative LCMS Purification of some of the compounds prepared was performed on Waters mass directed fractionation systems. The basic equipment setup, protocols and control software for the operation of these systems have been described in detail in literature. See, e.g., Blom, "Two-Pump At Column Dilution Configuration for Preparative LC-MS", K. Blom, J. Combi. Chem., 2002, 4, 295-301; Blom et al, "Optimizing Preparative LC-MS Configurations and Methods for Parallel Synthesis Purification", J. Combi. Chem., 2003, 5, 670-83; and Blom et al, "Preparative LC-MS Purification: Improved Compound Specific Method Optimization", J. Combi. Chem., 2004, 6, 874-883.

Example 1: 2-(((8-((2-chloro-2'-methyl-3'-(4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)-[1,1'-biphenyl]-3-yl)amino)-l,7-naphthyridin-3-yl)methyl)amino)ethan-l-ol

\[
\text{HN} \quad \text{Cl} \quad \text{HN} \quad \text{OH}
\]

Step 1: 8-chloro-3-vinyl, 7-naphthyridine

A mixture of 3-bromo-8-chloro-1,7-naphthyridine (PharmaBlock, cat#PBLJ2743: 0.200 g, 0.821 mmol), 4,4,5,5-tetramethyl-2-vinyl-1,3,2-dioxaborolane (Aldrich, cat#663348: 153 µL, 0.904 mmol), sodium carbonate (0.174 g, 1.64 mmol) and [1,1'-bis(di-cyclohexylphosphino)ferrocene]dichloropalladium(II) (Aldrich, cat#701998: 6.2 mg, 0.0082 mmol) in tert-butyl alcohol (5.91 mL, 61.8 mmol) and water (6 mL, 300 mmol) was degassed and sealed. It was stirred at 110 °C for 2 h. The reaction mixture was cooled then extracted with ethyl acetate (3x 20 mL). The combined organic layers were washed with brine, dried over MgSO4, filtered and concentrated under reduced pressure. The crude residue was used
directly in the next step without further purification. LC-MS calculated for 
C10H8ClN2 (M+H)+: m/z = 191.0; found 191.0.

**Step 2: 8-chloro-1,7-naphthyridine-3-carbaldehyde**

![Structure of 8-chloro-1,7-naphthyridine-3-carbaldehyde]

A flask was charged with 8-chloro-3-vinyl-1,7-naphthyridine (391. mg, 2.05 mmol), 1,4-dioxane (40. mL), a stir bar and water (40. mL). To this suspension was added a 4% w/w mixture of osmium tetraoxide in water (0.84 mL, 0.132 mmol). The reaction was stirred for 5 min then sodium periodate (3.23 g, 15.11 mmol) was added and stirred for 3 h. The mixture was diluted with water (20 mL) and EtOAc (20 mL). The layers were separated and the aqueous layer was further extracted with EtOAc (2 X 20 mL). The combined organic extracts were washed with brine, dried over sodium sulfate, filtered, and concentrated in vacuo. The crude aldehyde was purified by silica gel chromatography (0 → 60% EtOAc/hexanes). LC-MS calculated for C9H6CIN2O (M+H)+: m/z = 193.0; found 192.9.

**Step 3: 2-[[8-chloro-1,7-naphthyridin-3-yl]methyl]amino]ethanol**

![Structure of 2-[[8-chloro-1,7-naphthyridin-3-yl]methyl]amino]ethanol]

A mixture of 8-chloro-1,7-naphthyridine-3-carbaldehyde (0.160 g, 0.831 mmol) and ethanolamine (Aldrich, cat#398136: 251 µL, 4.15 mmol) in methylene chloride (6 mL, 100 mmol) and N,N-diisopropylethylamine (868 µL, 4.98 mmol) was stirred at rt for 1 h. Sodium triacetoxyborohydride (0.528 g, 2.49 mmol) was carefully added in portions. The reaction was stirred at rt for 2 h. To the mixture was then carefully added sodium tetrahydroborate (157 mg, 4.15 mmol) and methanol (1 mL) and the reaction mixture was stirred overnight under nitrogen. The reaction was quenched with a saturated aqueous solution of sodium bicarbonate. The mixture was then extracted with a 3:1 mixture of chloroform/isopropyl alcohol. The combined organic layers were washed with brine, dried over sodium sulfate, then concentrated in vacuo. The crude residue was purified by column chromatography (0 → 50% methanol/DCM) and was obtained as an off white solid. LC-MS calculated for C11H13CIN3O (M+H)+: m/z = 238.1; found 238.1.
Step 4: 2-(((8-((3-bromo-2-chlorophenyl)amino)-1, 7-naphthyridin-3-yl)methyl)amino)ethan-1-ol

to a vial was added 3-bromo-2-chloroaniline (Enamine, cat# EN300-1 05778: 0.021 g, 0.101 mmol) and 2-(((8-chloro-1,7-naphthyridin-3-yl)methyl)amino)ethan-1-ol (0.020 g, 0.084 mmol). The solids were suspended in isopropanol (0.421 ml). Sulfuric acid (4.48 µl, 0.084 mmol) was added to the reaction mixture and then heated to 100 °C for 1 h. After cooling, the mixture was quenched with a saturated aqueous sodium bicarbonate solution, and extracted with 3:1 chloroform/isopropyl alcohol. The combined organic extracts were dried over magnesium sulfate, filtered, and concentrated in vacuo. The crude residue was purified using silica gel chromatography (1:1 DCM/MeOH) to afford a yellow solid. LC-MS calculated for C₁₂H₁₇BrCN₂O₂ (M+H)⁺: m/z = 407.0; found 407.2.

Step 5: tert-butyl 2-(3-chloro-2-methylphenyl)-6, 7-dihydrothiazolo[5,4-c]pyridine-5(4H)-carboxylate

to a vial was added (3-chloro-2-methylphenyl)boronic acid (Combi-blocks, cat#BB-2035: 640 mg, 3.76 mmol), tert-butyl 2-bromo-6,7-dihydro[1,3]thiazolo[5,4-c]pyridine-5(4H)-carboxylate (AstaTech, cat#AB1 021: 1000. mg, 3.133 mmol), sodium carbonate (996 mg, 9.40 mmol), tert-butyl alcohol (160 mmol), water (600 mmol) [1,1'-bis(dicyclohexylphosphino)ferrocene]dichloropalladium(II) (Aldrich, cat#701 998: 240 mg, 0.31 mmol). The mixture was sparged with nitrogen, then heated at 105°C for 1.5 h. The mixture was concentrated, dissolved with DCM, and purified using silica gel chromatography (40% EtOAc/hexanes). LC-MS calculated for C₁₈H₂₂CIN₂O₂S (M+H)⁺: m/z = 365.1; found 365.1.

Step 6: tert-butyl 2-(2-methyl-3-(4, 4, 5, 5-tetramethyl-1, 3, 2-dioxaborolan-2-yl)phenyl)-6, 7-dihydrothiazolo[5,4-c]pyridine-5(4H)-carboxylate
A mixture of tert-butyl 2-(3-chloro-2-methylphenyl)-6,7-dihydro[1,3]thiazolo[5,4-c]pyridine-5(4H)-carboxylate (261 mg, 0.715 mmol), 4,4,5,5,4',4',5',5'-octamethyl-[2,2']bi[1,3,2]dioxaborolanyl (Aldrich, cat#473294: 545 mg, 2.14 mmol), palladium acetate (6.42 mg, 0.0286 mmol), K3PO4 (455 mg, 2.14 mmol) and 2-(dicyclohexylphosphino)-2',6'-dimethoxy-1,1'-biphenyl (Strem Chemicals, cat#151143: 29.4 mg, 0.0715 mmol) in 1,4-Dioxane was degassed and stirred at rt for 16 h. The mixture was diluted with DCM, and washed with water. The organic layer was concentrated in vacuo and purified by silica-gel chromatography (5% EtOAc/DCM). LC-MS calculated for C24H34BN2O4S (M+H)+: m/z = 457.2; found 457.3.

Step 7: tert-butyl 2-(2'-chloro-3'-(3-((2-hydroxyethylamino)methyl)-1,7-naphthyridin-8-ylamino)-2-methylbiphenyl-3-yl)-6,7-dihydrothiazolo[5,4-c]pyridine-5(4H)-carboxylate

To a vial was added tert-butyl 2-(2-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-6,7-dihydrothiazolo[5,4-c]pyridine-5(4H)-carboxylate (0.013 g, 0.029 mmol), 2-((8-((3-bromo-2-chlorophenyl)amino)-1,7-naphthyridin-3-yl)methylamino)ethan-1-ol (0.008 g, 0.020 mmol), sodium carbonate (6.24 mg, 0.059 mmol), [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (1.436 mg, 1.962 µmol), 1,4-dioxane (0.346 ml), and water (0.046 ml). The mixture was degassed, sealed, and heated to 90 °C whilst stirring for 4 h. After cooling, the mixture was diluted with DCM and water. The layers were separated and the aqueous layer was further extracted. The combined organic layers were dried over magnesium sulfate, filtered, concentrated in vacuo, and purified by silica gel chromatography (MeOH/DCM). LC-MS calculated for C33H38ClN6O3S (M+H)+: m/z = 657.2; found 657.5.
Step 8: 2-((8-((2-chloro-2'-methyl-3'-((4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)-[1,1'-biphenyl]-3-yl)amino)-1,7-naphthyridin-3-yl)methyl)amino)ethan-1-ol

A vial was charged with tert-butyl 2-((2'-chloro-3'-(3-((2-hydroxyethylamino)methyl)-1,7-naphthyridin-8-ylamino)-2-methylbiphenyl-3-yl)-6,7-dihydrothiazolo[5,4-c]pyridine-5(4H)-carboxylate (13 mg, 0.020 mmol), DCM (0.4 mL) and TFA (0.010 mL, 1 mmol). The resulting mixture was stirred for 1 h, open to air. The mixture was then dissolved in MeOH and purified by prep HPLC (pH = 2, acetonitrile/water+TFA) to provide the compound as the TFA salt. LC-MS calculated for C36H50ClNeOS (M+H)⁺: m/z = 557.2; found 557.3.

Example 2: 1-(((6-(2-fluoro-3'-(3-((2-hydroxyethylamino)methyl)-1,7-naphthyridin-8-ylamino)-2'-methylbiphenyl-3-ylcarbamoyl)pyridin-3-yl)methyl)amino)cyclobutanecarboxylic acid

Step 1: 2-((8-((3-bromo-2-methylphenyl)amino)-1,7-naphthyridin-3-yl)methyl)amino)ethan-1-ol

This compound was prepared using a similar procedure as described for Example 1, Step 4 with 3-bromo-2-methylaniline (Aldrich, cat#530018) replacing 3-bromo-2-chloroaniline. The crude compound was purified using column chromatography (0 → 50% MeOH/DCM). LC-MS calculated for C38H40BrN4O (M+H)+: m/z = 387.1; found 387.2.

Step 2: 5-(dimethoxymethyl)-N-(2-fluoro-3-((4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)picolinamide
To a solution of 2-fluoro-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (Combi-Blocks, cat#PN-5021: 200 mg, 0.844 mmol) and methyl 5-(dimethoxymethyl)picolinate (Combi-Blocks, cat#QY-13 18: 196 mg, 0.928 mmol) in THF (8436 µl) was added 1.0 M potassium tert-butoxide in THF (1265 µl, 1.265 mmol) at rt. The mixture was stirred at rt for 2 h. Water and EtOAc were added, and the layers were separated. The aqueous layer was further extracted with ethyl acetate, and the combined organic layers were washed with brine, dried over magnesium sulfate, filtered, and concentrated in vacuo. The crude residue was purified using silica gel chromatography (30% EtOAc/hexanes). LC-MS calculated for C21H27BFN2O5 (M+H)+: m/z = 417.2; found 417.3.

Step 3: 5-(dimethoxymethyl)-N-(2-fluoro-3'-(3-(((2-hydroxyethyl)amino)methyl)-1,7-napthyridin-8-yl)amino)-2'-methyl-[1,1'-biphenyl]-3-yl)picolinamide

To a vial was added 5-(dimethoxymethyl)-N-(2-fluoro-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)picolinamide (0.161 g, 0.387 mmol), 2-(((8-((3-bromo-2-methylphenyl)amino)-l,7-napthyridin-3-yl)methyl)amino)ethan-1-ol (0.10 g, 0.258 mmol), sodium carbonate (0.041 g, 0.387 mmol), [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (0.019 g, 0.026 mmol), 1,4-dioxane (4.56 ml), and water (0.608 ml). The mixture was degassed, sealed, and heated to 90 °C whilst stirring for 4 h. After cooling, the mixture was diluted with DCM and water, and the layers were separated. The aqueous layer was further extracted with DCM, and the combined organic layers were dried over magnesium sulfate, filtered, and concentrated in vacuo. The crude residue was purified by silica gel chromatography (20% MeOH/DCM) to provide the desired product. LC-MS calculated for C33H34FN6O4 (M+H)+: m/z = 597.3; found 597.2.

Step 4: N-(2-fluoro-3'-(3-(((2-hydroxyethyl)amino)methyl)-1,7-napthyridin-8-yl)amino)-2'-methyl-[1,1'-biphenyl]-3-yl)-5-formylpicolinamide
To a solution of 5-(dimethoxymethyl)-N-(2-fluoro-3’-((3-(((2-hydroxyethyl)amino)methyl)-1,7-naphthyridin-8-yl)amino)-2’-methyl-[1,1'-biphenyl]-3-yl)picolinamide (0.068 g, 0.114 mmol) in DCM (1.899 ml) was added TFA (0.439 ml, 5.70 mmol). The mixture was stirred at r.t for 2 h. The mixture was concentrated and the residue was dissolved in DCM, and washed with a saturated aqueous NaHCO₃ solution. The layers were separated and the aqueous layer was further extracted with DCM. The combined organic layers were dried over magnesium sulfate, filtered and concentrated in vacuo. The crude product was used directly in the next step without further purification. LC-MS calculated for C₃₁H₂₈FN₆O₃ (M+H)⁺: m/z = 551.2; found 551.2.

**Step 5:** 1-(((6-(2-fluoro-3’-((3-(((2-hydroxyethyl)amino)methyl)-1,7-naphthyridin-8-yl)amino)-2’-methylbiphenyl-3-yl)carbamoyl)pyridin-3-yl)methyl)amino)cyclobutanecarboxylic acid

To a vial was added N-(2-fluoro-3’-((3-(((2-hydroxyethyl)amino)methyl)-1,7-naphthyridin-8-yl)amino)-2’-methyl-[1,r-biphenyl]-3-yl)-5-formylpicolinamide (0.030 g, 0.054 mmol), 1-aminocyclobutane-1-carboxylic acid (Aldrich, cat#652369: 0.019 g, 0.163 mmol), dichloromethane (0.893 ml) and triethylamine (0.016 ml, 0.115 mmol). The reaction was stirred at r.t for 2 h, then sodium triacetoxyborohydride (0.058 g, 0.272 mmol) and acetic acid (9.36 µl, 0.163 mmol) were added. The reaction was stirred for 2 h, then the mixture was diluted with methanol and purified by prep HPLC (pH = 2, acetonitrile/water+TFA) to provide the desired compound as the TFA salt. LC-MS calculated for C₃₆H₃₇FN₇O₄ (M+H)⁺: m/z = 650.3; found 650.3

**Example 3:** (S)-1-(((6-(2-fluoro-3’-((3-(((2-hydroxyethyl)amino)methyl)-1,7-naphthyridin-8-yl)amino)-2’-methyl-[1,1'-biphenyl]-3-yl)carbamoyl)pyridin-3-yl)methyl)piperidine-2-carboxylic acid
This compound was prepared using a similar procedure as described for Example 2, Step 5 with L-pipecolinic acid (Alfa Aesar, cat# L15373) replacing 1-aminocyclobutane-1-carboxylic acid. LC-MS calculated for C₃₇H₃₉FN₇O₄ (M+H)^+: m/z = 664.3; found 664.3.

**Example 4:** N-(2-fluoro-3'-(3-(((2-hydroxyethyl)amino)methyl)-1,7-naphthyridin-8-yl)amino)-2'-methyl-[1,1'-biphenyl]-3-yl)-5-(((2-hydroxyethyl)amino)methyl)picolinamide

This compound was prepared using a similar procedure as described for Example 2, Step 5 with ethanolamine (Aldrich, cat# 398136) replacing 1-aminocyclobutane-1-carboxylic acid. LC-MS calculated for C₃₃H₃₅FN₇O₃ (M+H)^+: m/z = 596.3; found 596.2.

**Example 5:** N-(2-chloro-3'-(3-(((2-hydroxyethyl)amino)methyl)-1,7-naphthyridin-8-yl)amino)-2'-methyl-[1,1'-biphenyl]-3-yl)-5-(((2-hydroxyethyl)amino)methyl)picolinamide

*Step 1:* 2-chloro-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline
4,4,5,5',4',5',5'-Octamethyl-[2,2']bi[l,3,2]dioxaborolanyl (1.48 g, 5.81 mmol), potassium acetate (0.428 g, 4.36 mmol), 3-bromo-2-chloroaniline (Enamine, cat# EN300-105778: 0.300 g, 1.453 mmol), 1,4-dioxane (7.27 ml) and [1,1’-bis(diphenylphosphino)ferrocene] dichloropalladium (II) (0.053 g, 0.073 mmol) was stirred in a closed vial flushed with argon at 110 °C for 2 h. The mixture was cooled, diluted with EtOAc, and filtered over celite. The filtrate was concentrated and purified by silica gel chromatography (20% EtOAc/hexanes). LC-MS calculated for C12H18BCINO2 (M+H)+: m/z = 254.1; found 254.1.

**Step 2: N-(2-chloro-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-5-(dimethoxymethyl)picolinamid**

![Chemical structure of the compound](image)

This compound was prepared using a similar procedure as described for Example 2, Step 2 with 2-chloro-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline replacing 2-fluoro-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline. LC-MS calculated for C21H27BCIN2O5 (M+H)+: m/z = 433.2; found 433.1.

**Step 3: N-(2-chloro-3’-(3’-((2-hydroxyethyl)amino)methyl)-1,7-naphthyridin-8-yl)amino)-2-methyl-[1,1’-biphenyl]-3-yl)-5-(dimethoxymethyl)picolinamide**

![Chemical structure of the compound](image)

This compound was prepared using a similar procedure as described for Example 2, Step 3 with N-(2-chloro-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-5-(dimethoxymethyl)picolinamide replacing 5-(dimethoxymethyl)-N-(2-fluoro-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)picolinamide. LC-MS calculated for C33H34CIN6O4 (M+H)+: m/z = 613.2; found 613.2.
Step 4: N-(2-chloro-3'-((3-(((2-hydroxyethyl)amino)methyl)-1,7-naphthyridin-8-yl)amino)-2'-methyl-[1,1'-biphenyl]-3-yl)-5-formylpicolinamide

This compound was prepared using a similar procedure as described for Example 2.

Step 4 with N-(2-chloro-3'-((3-(((2-hydroxyethyl)amino)methyl)-1,7-naphthyridin-8-yl)amino)-2'-methyl-[1,1'-biphenyl]-3-yl)-5-(dimethoxymethyl)picolinamide replacing 5-(dimethoxymethyl)-N-(2-fluoro-3'-((3-(((2-hydroxyethyl)amino)methyl)-1,7-naphthyridin-8-yl)amino)-2'-methyl-[1,1'-biphenyl]-3-yl)picolinamide. LC-MS calculated for C31H28CIN6O3 (M+H) +: m/z = 567.2; found 567.2.

Step 5: N-(2-chloro-3'-((3-(((2-hydroxyethyl)amino)methyl)-1,7-naphthyridin-8-yl)amino)-2'-methyl-[1,1'-biphenyl]-3-yl)-5-(((R)-3-hydroxypyrrolidin-1-yl)methyl)picolinamide

To a vial was added N-(2-chloro-3'-((3-(((2-hydroxyethyl)amino)methyl)-1,7-naphthyridin-8-yl)amino)-2'-methyl-[1,1'-biphenyl]-3-yl)-5-formylpicolinamide (0.015 g, 0.026 mmol), ethanolamine (Aldrich, cat# 398136: 0.0049 g, 0.163 mmol), dichloromethane (0.893 ml) and N,N-diisopropylethylamine (0.028 mL, 0.159 mmol). The reaction was stirred at rt for 2 h, then sodium triacetoxyborohydride (0.058 g, 0.272 mmol) was added. The reaction was stirred for 2 h, then the mixture was diluted with methanol and purified by prep HPLC (pH = 2, acetonitrile/water+TFA; then pH = 10, acetonitrile/water+NH₃OH). LC-MS calculated for C33H35CIN7O3 (M+H) +: m/z = 612.2; found 612.2.

Example 6: N-(2-chloro-3'-((3-(((R)-3-hydroxypyrrolidin-1-yl)methyl)-1,7-naphthyridin-8-yl)amino)-2'-methyl-[1,1'-biphenyl]-3-yl)-5-(((R)-3-hydroxypyrrolidin-1-yl)methyl)picolinamide

Step 1: N-(3-bromo-2-methylphenyl)-3-vinyl-1, 7-naphthyridin-8-amine
In a vial, 3-bromo-2-methylaniline (Aldrich, cat#53001 8: 0.931 ml, 7.55 mmol) and 8-chloro-3-vinyl-1,7-naphthyridine (Example 1, Step 1: 1.20 g, 6.29 mmol) were suspended in isopropanol (3.15 ml). Sulfuric acid (0.336 ml, 6.29 mmol) was added to the reaction mixture. The resulting mixture was heated to 100 °C for 1 h whilst stirring. The mixture was cooled, quenched with aqueous saturated sodium bicarbonate, and diluted with DCM. The layers were separated and the water layer was further extracted with DCM. The combined organic layers were dried over magnesium sulfate, filtered and concentrated in vacuo. The crude solid was purified by column chromatography (0→1% Methanol/DCM) to provide the desired compound as a yellow solid. LC-MS calculated for C13H13BrN3 (M+H)+: m/z = 340.0; found 340.1.

Step 2: 2'-chloro-2-methyl-N3-(3-vinyl-1,7-naphthyridin-8-yl)-[1,1'-biphenyl]-3,3'-diamine

To a flask was added 2-chloro-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (Example 5, Step 1: 1.414 g, 5.58 mmol), N-(3-bromo-2-methylphenyl)-3-vinyl-1,7-naphthyridin-8-amine (1.2646 g, 3.72 mmol), sodium carbonate (0.591 g, 5.58 mmol), [1,1'-bis(diphenylphosphino)ferrocene] dichloropalladium (II) (0.272 g, 0.372 mmol), 1,4-dioxane (32.8 ml), and water (4.37 ml). The mixture was degassed, sealed, and heated to 90 °C whilst stirring for 4 h. The mixture was cooled, diluted with EtOAc, and the layers were separated. The aqueous layer was further extracted with EtOAc, and the combined organic layers were washed with brine, dried of magnesium sulfate, filtered, and concentrated in vacuo. The crude residue was then purified by silica gel chromatography (20% EtOAc/hexanes) to provide the desired compound as a yellow solid. LC-MS calculated for C23H20CIN4 (M+H)+: m/z = 387.1; found 387.1.

Step 3: N-(2-chloro-2'-methyl-3'-(3-vinyl-1,7-naphthyridin-8-yl)amino)-[1,1'-biphenyl]-3-yl)-5-(dimethoxymethyl)picolinamide
To a solution of 2'-chloro-2-methyl-N3-(3-vinyl-1,7-naphthyridin-8-yl)-[1,1'-biphenyl]-3,3'-diamine (0.682 g, 1.763 mmol) and methyl 5-(dimethoxymethyl)picolinate (Combi-Blocks, cat#QY-1 318: 0.372 g, 1.763 mmol) in THF (17.63 ml) was added 1.0 M Potassium tert-butoxide in THF (2.64 ml, 2.64 mmol) at rt. The mixture was stirred at rt for 2 h. Water was added to quench the reaction. The layers were separated and the water layer was further extracted with ethyl acetate. The combined organic layers were washed with brine, dried over magnesium sulfate, filtered and concentrated in vacuo. The crude orange foam was used directly in the next step without further purification. LC-MS calculated for C32H29CIN5O3 (M+H)⁺: m/z = 566.2; found 566.3.

**Step 4:** \(N\)-(2-chloro-2'-methyl-3'-((3-vinyl-1,7-naphthyridin-8-yl)amino)-[1,1'-biphenyl]-3-yl)-5-formylpicolinamide

This compound was prepared using a similar procedure as described for Example 2, Step 4 with \(N\)-(2-chloro-2'-methyl-3'-((3-vinyl-1,7-naphthyridin-8-yl)amino)-[1,1'-biphenyl]-3-yl)-5-(dimethoxymethyl)picolinamide replacing 5-(dimethoxymethyl)-N-(2-fluoro-3'-((3-((2-hydroxyethyl)andno)methyl)-l,7-naphthyridin-8-yl)amino)-2'-methyl-[1,1'-biphenyl]-3-yl)picolinamide. LC-MS calculated for C30H23CIN5O2 (M+H)⁺: m/z = 520.2; found 520.2.

**Step 5:** \(R\)-N-(2-chloro-2'-methyl-3'-((3-vinyl-1, 7-naphthyridin-8-yl)amino)-[1,1'-biphenyl]-3-yl)-5-((3-hydroxypyrrolidin-1-yl)methyl)picolinamide
A mixture of N-(2-chloro-2'-methyl-3'-((3-vinyl-7-naphthyridin-8-yl)amino)-[1,1'-biphenyl]-3-yl)-5-formylpicolinamide (0.180 g, 0.346 mmol) and (R)-3-hydroxy pyrrolidine (Combi-Blocks, cat#AM-2005: 0.090 g, 1.038 mmol) in methylene chloride (1.73 ml) and N,N-diisopropylethylamine (0.301 ml, 1.731 mmol) was stirred at rt for 1 h. Sodium triacetoxyborohydride (0.220 g, 1.038 mmol) was carefully added in portions. The reaction was stirred at rt for 2 h. The reaction was quenched with a saturated aqueous solution of sodium bicarbonate. The mixture was then extracted with a 3:1 mixture of chloroform/IP A. The combined organic layers were washed with brine, dried over sodium sulfate, and then concentrated in vacuo. The crude residue was purified by column chromatography (0 → 20% methanol/DCM). LC-MS calculated for C34H32CIN6O2 (M+H)+: m/z = 591.2; found 591.4.

Step 6: (R)-N-(2-chloro-3'-((3-formyl-7-naphthyridin-8-yl)amino)-2'-methyl-[1,1'-biphenyl]-3-yl)-5-((3-hydroxypyrrolidin-1-yl)methyl)picolinamide

A flask was charged with (R)-N-(2-chloro-2'-methyl-3'-((3-vinyl-7-naphthyridin-8-yl)amino)-[1,1'-biphenyl]-3-yl)-5-((3-hydroxy pyrrolidine-1-yl)methyl)picolinamide (0.241 g, 0.408 mmol), 1,4-dioxane (4.5 mL) and water (2.3 mL). A 4% osmium tetroxide solution in water (0.181 ml, 0.029 mmol) was added to the reaction mixture. After 5 min of stirring, sodium periodate (0.349 g, 1.631 mmol) was added and the mixture was stirred for 3 h. The mixture was diluted with water (2 mL) and EtOAc (5 mL), and the layers were separated. The aqueous layer was further extracted with EtOAc. The combined organic extracts were washed with brine, dried over sodium sulfate, filtered, and concentrated in vacuo. The crude aldehyde was purified by silica gel chromatography (20% MeOH/DCM). LC-MS calculated for C33H30CIN6O3 (M+H)+: m/z = 593.2; found 593.1.

Step 7: N-(2-chloro-3'-((3-(((R)-3-hydroxypyrrolidin-1-yl)methyl)-7-naphthyridin-8-yl)amino)-2'-methyl-[1,1'-biphenyl]-3-yl)-5-((R)-3-hydroxy pyrrolidin-1-yl)methyl)picolinamide

To a vial was added (R)-N-(2-chloro-3'-((3-formyl-1,7-naphthyridin-8-yl)amino)-2'-methyl-[1,1'-biphenyl]-3-yl)-5-((3-hydroxy pyrrolidin-1-yl)methyl)picolinamide (0.030 g, ...
0.051 mmol), ethanolamine (Aldrich, cat#398136: 9.3 mg, 0.152 mmol), dichloromethane (0.829 ml) and N,N-diisopropylethylamine (0.053 ml, 0.303 mmol). The reaction was stirred at rt for 2 h, then sodium triacetoxyborohydride (0.054 g, 0.253 mmol) was added. The reaction was stirred for 2 h, then the mixture was diluted with methanol and purified by prep HPLC (pH = 2, acetonitrile/water+TFA) to provide the desired compound as the TFA salt. LC-MS calculated for C\textsubscript{37}H\textsubscript{39}CIN\textsubscript{7}O\textsubscript{3} (M+H)\textsuperscript{+}: m/z = 664.3; found 664.2.

**Example 7:** (R)-l-((8-((2'-chloro-3'-(5-(((R)-3-hydroxypyrrolidin-1-yl)methyl)picolinamido)-2-methyl-[1,1'-biphenyl]-3-yl)amino)-l,7-naphthyridin-3-yl)methyl)pyrrolidine-3-carboxylic acid

![Chemical Structure](image)

To a vial was added (R)-N-(2-chloro-3'-(3-formyl-1,7-naphthyridin-8-yl)amino)-2'-methyl-[1,1'-biphenyl]-3-yl)-5-((3-hydroxypyrrolidin-1-yl)methyl)picolinamide (Example 6, Step 6: 0.030 g, 0.051 mmol), (R)-pyrrolidine-3-carboxylic acid (Combi-Blocks, cat#ST-7698: 0.017 g, 0.152 mmol), dichloromethane (0.829 ml) and triethylamine (0.016 ml, 0.115 mmol). The reaction was stirred at rt for 2 h, then sodium triacetoxyborohydride (0.054 g, 0.253 mmol) and acetic acid (8.69 µl, 0.152 mmol) were added. The reaction was stirred for 2 h, then the mixture was diluted with methanol and purified by prep HPLC (pH = 2, acetonitrile/water+TFA) to provide the compound as the TFA salt. LC-MS calculated for C\textsubscript{38}H\textsubscript{39}CIN\textsubscript{7}O\textsubscript{4} (M+H)\textsuperscript{+}: m/z = 692.3; found 692.2.

**Example 8:** (R)-l-((8-((2'-chloro-3'-(5-((3-hydroxypyrrolidin-1-yl)methyl)picolinamido)-2-methyl-[1,1'-biphenyl]-3-yl)amino)-l,7-naphthyridin-3-yl)methyl)azetidine-3-carboxylic acid

![Chemical Structure](image)

This compound was prepared using a similar procedure as described for Example 7 with azetidine-3-carboxylic acid (Aldrich, cat#391131) replacing (R)-pyrrolidine-3-
carboxylic acid. LC-MS calculated for C\textsubscript{37}H\textsubscript{37}CIN\textsubscript{7}O\textsubscript{4} (M+H)\textsuperscript{+}: m/z = 678.3; found 678.3.

**Example 9**

(R)-1-\{8-(3'-((3-(((R)-3-hydroxy)pyrrolidin-1-yl)methyl)-1,7-naphthyridin-8-yl)amino)-2,2'-dimethyl-[1,1'-biphenyl]-3-yl)amino)-l',7-naphthyridin-3-yl)methyl\}pyrrolidine-3-carboxylic acid

*Step 1:* 8-((3-bromo-2-methylphenyl)amino)-1,7-naphthyridine-3-carbaldehyde

![Chemical Structure](image)

A suspension of (8-((3-bromo-2-methylphenyl)amino)-1,7-naphthyridin-3-yl) methanol (Affinity Research Chemicals, #ARI-0169: 300.0 mg, 0.872 mmol) and manganese dioxide (1515 mg, 17.43 mmol) in DCM (8716 µL) was stirred at 45 °C for 1 h. The reaction was filtered through Celite\textsuperscript{®} and the filtrate was concentrated to yield a crude residue, which was used directly in the next step without further purification. LC-MS calculated for C\textsubscript{i}eH\textsubscript{His}BrNsO (M+H)\textsuperscript{+}: m/z = 342.0; found 342.0.

*Step 2:*  \((R)-1-(8-(3-(3-hydroxy)pyrrolidin-1-yl)methyl)-1,7-naphthyridin-3-yl)\)pyrrolidine-3-ol

![Chemical Structure](image)

A mixture of 8-((3-bromo-2-methylphenyl)amino)-1,7-naphthyridine-3-carbaldehyde (0.100 g, 0.292 mmol) and (3)-3-hydroxy pyrrolidine (Combi-Blocks, #AM-2005: 0.025 g, 0.292 mmol) in 1,2-dichloroethane (1.46 ml) and \(N,N\)-diisopropylethylamine (0.051 ml, 0.292 mmol) was stirred at rt for 1 h. Sodium triacetoxyborohydride (0.093 g, 0.438 mmol) was carefully added in portions. The reaction was stirred at rt for 2 h, then quenched with a saturated aqueous solution of sodium bicarbonate. The mixture was then extracted with a 3:1 mixture of chloroform/IPA. The combined organic layers were dried over sodium sulfate, then concentrated in vacuo. The crude residue was purified by silica gel...
chromatography (0 → 30% methanol/DCM) to give the desired product. LC-MS calculated for C20H22BrN0 (M+H)⁺: m/z = 413.1; found 413.1.

**Step 3:** (8-((2-methyl-3-(4, 4, 5-tetramethyl-l, 3,2-dioxaborolan-2-yl)phenyl)amino)-l, 7-naphthyridin-3-yl)methanol

![Chemical Structure](image)

A mixture of (8-((3-bromo-2-methylphenyl)amino)-l, 7-naphthyridin-3-yl)methanol (Affinity Research Chemicals, #ARI-0169: 0.300 g, 0.872 mmol), bis(pinacolato)diboron (Aldrich, #473294: 0.266 g, 1.046 mmol), dichloro[l,1'-bis(diphenylphosphino)ferrocene]palladium (II) dichlormethane adduct (0.071 g, 0.087 mmol) and potassium acetate (0.214 g, 2.179 mmol) was charged with nitrogen and stirred at 110 °C for 2 h. The crude was diluted with DCM, and then filtered through Celite®. The filtrate was concentrated, and the resulting residue was used directly in the next step without further purification. LC-MS calculated for C22H27BN3O3 (M+H)⁺: m/z = 392.2; found 392.3.

**Step 4:** (R)-l-((8-((3'-(3-(hydroxymethyl)-l, 7-naphthyridin-8-yl)amino)-2,2'-dimethyl-[1,1'-biphenyl]-3-yl)amino)-l,7-naphthyridin-3-yl)methyl)pyrrolidin-3-ol

![Chemical Structure](image)

To a vial was added (8-((2-methyl-3-(4,4,5, 5-tetramethyl-l,3,2-dioxaborolan-2-yl)phenyl)amino)-l, 7-naphthyridin-3-yl)methanol (0.162 g, 0.414 mmol), (i?)-l-((8-((3-bromo-2-methylphenyl)amino)-l,7-naphthyridin-3-yl)methyl)pyrrolidin-3-ol (0.163 g, 0.394 mmol), 1 M aqueous sodium carbonate (0.789 mmol), [l, 1'-bis(dicyclohexylphosphino)ferrocene]-dichloropalladium (II) (0.029 g, 0.039 mmol), and 1,4-dioxane (3.48 ml). The mixture was purged with nitrogen, sealed, and heated to 90 °C whilst stirring for 2 h. The mixture was cooled, diluted with EtOAc and filtered through Celite®. The filtrate was concentrated and purified using silica gel chromatography (20% MeOH/DCM) to provide the desired compound as an orange solid. LC-MS calculated for C36H36N7O2 (M+H)⁺: m/z = 598.3; found 598.4.
Step 5: (R)-8-((3’-(3-hydroxypyrrolidin-1-yl)methyl)-1,7-naphthyridin-8-yl)amino)-2,2’-dimethyl-[1,1’-biphenyl]-3-yl)amino)-1,7-naphthyridine-3-carbaldehyde

To a solution of (i?)-1-((8-((3’-(3-(hydroxymethyl)-1,7-naphthyridin-8-yl)amino)-2,2’-dimethyl-[1,1’-biphenyl]-3-yl)amino)-1,7-naphthyridine-3-carbaldehyde (0.0715 g, 0.12 mmol) in DCM (1.20 ml) was added manganese dioxide (0.208 g, 2.392 mmol). The resulting mixture was heated at 45 °C for 30 min. After cooling, the mixture was filtered through Celite® and the filtrate was concentrated. The crude orange solid was used directly in the next step. LC-MS calculated for C36H34N7O2 (M+H)+: m/z = 596.3; found 596.5.

Step 6: (R)-1-((8-((3’-(3-(3-hydroxypyrrolidin-1-yl)methyl)-1,7-naphthyridin-8-yl)amino)-2,2’-dimethyl-[1,1’-biphenyl]-3-yl)amino)-1,7-naphthyridine-3-carboxylic acid

To a vial was added (i?)-8-((3’-(3-(3-hydroxypyrrolidin-1-yl)methyl)-1,7-naphthyridin-8-yl)amino)-2,2’-dimethyl-[1,1’-biphenyl]-3-yl)amino)-1,7-naphthyridine-3-carbaldehyde (0.013 g, 0.022 mmol), (i?)-pyrrolidine-3-carboxylic acid (Combi-Blocks, #ST-7698: 7.5 mg, 0.065 mmol), 1,2-dichloroethane (0.336 ml) and triethylamine (9.13 µl, 0.065 mmol). The reaction was stirred at rt for 2 h, then sodium triacetoxyborohydride (0.023 g, 0.109 mmol) and acetic acid (3.75 µl, 0.065 mmol) were added. The reaction was stirred for 2 h, then the mixture was diluted with methanol and purified by prep HPLC (pH = 2, acetonitrile/water+TFA) to give the desired product as the TFA salt. LC-MS calculated for C41H42N8O5 (M+H)+: m/z = 695.3; found 695.3. 34 NMR (500 MHz, DMSO) δ 10.72 (br s, 2H), 9.11 (m, 2H), 8.54 (m, 2H), 8.02 (m, 4H), 7.42 (m, 2H), 7.26 (m, 2H), 7.11 (m, 2H), 4.70 (m, 4H), 4.47 (m, 1H), 3.82 - 3.08 (m, 10H), 2.38 - 2.18 (m, 2H), 2.10 (s, 6H), 2.05 - 1.82 (m, 2H).

Example 10

(S)-1-((8-((3’-(3’-(3-hydroxypyrrolidin-1-yl)methyl)-1,7-naphthyridin-8-yl)amino)-2,2’-dimethyl-[1,1’-biphenyl]-3-yl)amino)-1,7-naphthyridine-3-carboxylic acid
This compound was prepared using similar procedures as described for Example 9 with (5)-pyrrolidine-3-carboxylic acid (Combi-Blocks, #ST-1381) replacing (i?)-pyrrolidine-3-carboxylic acid in Step 6. The reaction was diluted with MeOH and then purified by prep-HPLC (pH = 2, acetonitrile/water+TFA) to give the desired product as the TFA salt. LC-MS calculated for C41H43N8O3 (M+H)+: m/z = 695.3; found 695.3.

Example 11
(i?)-l-((8-((3'-((3-(((2-hydroxyethyl)amino)methyl)-l,7-naphthyridin-8-yl)amino)-2,2'-dimethyl-[l,l'-biphenyl]-3-yl)amino)-l,7-naphthyridin-3-yl)methyl)pyrrolidine-3-carboxylic acid

This compound was prepared using similar procedures as described for Example 9 with ethanolamine (Aldrich, #411000) replacing (i?)-3-hydroxypyrrolidine in Step 2. The reaction mixture was diluted with MeOH and then purified by prep-HPLC (pH = 6.5, acetonitrile/water+NH40Ac) to give the desired product. LC-MS calculated for C39H44N8O3 (M+H)+: m/z = 669.3; found 669.4.

Example 12
(i?)-l-((8-((3'-((3-(((5)-3-hydroxypyrrolidin-1-yl)methyl)-l,7-naphthyridin-8-yl)amino)-2,2'-dimethyl-[l,l'-biphenyl]-3-yl)amino)-l,7-naphthyridin-3-yl)methyl)pyrrolidine-3-carboxylic acid

This compound was prepared using similar procedures as described for Example 9 with (5)-3-hydroxypyrrolidine (Combi-Blocks, #SS-7948) replacing (R)-3-hydroxypyrrolidine in Step 2. The reaction was diluted with MeOH and then purified by
Example 13

(S)-1-((8-((3'-(3-(((S)-3-hydroxypyrrolidin-1-yl)methyl)-1,7-naphthyridin-8-yl)amino)-2,2'-dimethyl-[1,1'-biphenyl]-3-yl)amino)-1,7-naphthyridin-3-yl)methyl)pyrrolidine-3-carboxylic acid

This compound was prepared using similar procedures as described for Example 9 with (S)-3-hydroxypyrrolidine replacing (i?)-3-hydroxypyrrolidine in Step 2 and (S)-pyrrolidine-3-carboxylic acid replacing (i?)-pyrrolidine-3-carboxylic acid in Step 6. The reaction mixture was diluted with MeOH and then purified by prep-HPLC (pH = 2, acetonitrile/water+TFA) to give the desired product as the TFA salt. LC-MS calculated for C41H43N8O3 (M+H)^+: m/z = 695.3; found 695.4.

Example 14

1-((8-(2-chloro-3'-(1,5-dimethyl-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridine-2-carboxamido)-2'-methylbiphenyl-3-ylamino)-1,7-naphthyridin-3-yl)methyl)azetidine-3-carboxylic acid

Step 1: tert-butyl 1-methyl-6H-dihydro-IH-imidazo[4,5-c]pyridine-5(4H)-carboxylate

A solution of 1-methyl-4,5,6,7-tetrahydro-IH-imidazo[4,5-c]pyridine (Accela, cat#SY032476: 2.0 g, 14.58 mmol) and (BochO (3.38 mL, 14.58 mmol) in dichloromethane (60.0 mL) was stirred at room temperature for 1 h. The reaction was quenched with saturated
aqueous NaHCO₃ solution, and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The crude product was used for next step without further purification. LC-MS calculated for C₁₂H₂₀N₃O₂ (M+H)⁺: m/z = 238.2; found 238.2.

Step 2: 5-tert-butyl 2-methyl l-methyl-6, 7-dihydro-lH-imidazo[4, 5-c]pyridine-2, 5(4H)-dicarboxylate

To a solution of tert-butyl 1-methyl-6,7-dihydro-lH-imidazo[4,5-c]pyridine-5(4H)-dicarboxylate (Crude product from Step 1) in tetrahydrofuran (60.0 mL) was added n-Butyllithium in hexanes (2.5 M, 7.00 mL, 17.49 mmol) at -78 °C, dropwise. The reaction mixture was stirred at -78 °C for 10 min prior to the addition of methyl chloroformate (1.7 mL, 21.9 mmol). After being stirred at -78 °C for 15 min, the reaction was then quenched with saturated aqueous NaHCCb solution, and extracted with ethyl acetate, dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on a silica gel column eluting with 80% ethyl acetate in hexanes to afford the desired product. LC-MS calculated for C₁₄H₂₂N₃O₄ (M+H)⁺: m/z = 296.2; found 296.3.

Step 3: tert-butyl l-methyl-2-((2-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)carbamoyl)-l, 4.6, 7-tetrahydro-5H-imidazo[4,5-c]pyridine-5-carboxylate

Potassium tert-butoxide (0.122 mL, 0.122 mmol) was added to a solution of 5-tert-butyl 2-methyl 1-methyl-1,4,6,7-tetrahydro-5H-imidazo[4,5-c]pyridine-2,5-dicarboxylate (30 mg, 0.102 mmol) and 2-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (Combi-Blocks, cat#PN-9127: 23.68 mg, 0.102 mmol) in THF (0.2 mL). After being stirred at
rt for 2 h, the reaction mixture was quenched with water, and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over Na2SO4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on a silica gel column with ethyl acetate in hexanes (0-40%) to afford the product. LC-MS calculated for C26H38BN4O5 (M+H)⁺: m/z = 497.3; found 497.2.

Step 4: 8-chloro-3-vinyl-1,7-naphthyridine

A mixture of 3-bromo-8-chloro-1, 7-naphthyridine (PharmaBlock, cat#PBLJ2743 : 0.200 g, 0.821 mmol), 4,4,5,5-tetramethyl-2-vinyl-1,3,2-dioxaborolane (Aldrich, cat#663348: 153 µL, 0.904 mmol), sodium carbonate (0.174 g, 1.64 mmol) and [1,1’-bis(di-cyclohexylphosphino)ferrocene]dichloropalladium(II) (Aldrich, cat#701 998: 6.2 mg, 0.0082 mmol) in tert-butyl alcohol (5.91 mL, 61.8 mmol) and water (6 mL, 300 mmol) was degassed and sealed. It was stirred at 110 °C for 2 h. The reaction mixture was cooled then extracted with ethyl acetate (3x 20 mL). The combined organic layers were washed with brine, dried over MgSO4, filtered and concentrated under reduced pressure. The crude residue was used directly in the next step without further purification. LC-MS calculated for C10H8CIN2 (M+H)⁺: m/z = 191.0; found 191.0.

Step 5: N-(3-bromo-2-chlorophenyl)-3-vinyl-1,7-naphthyridin-8-amine

In a vial, 3-bromo-2-chloroaniline (Enamine, cat# EN300-1 05778 :0.476 g, 2.304 mmol) and 8-chloro-3-vinyl-1, 7-naphthyridine (0.366 g, 1.920 mmol) were suspended in isopropanol (9.60 ml). Sulfuric acid (0.102 ml, 1.920 mmol) was added to the reaction mixture. The resulting mixture was heated to 100 °C for 1 h. The mixture was cooled to rt then quenched with aqueous saturated sodium bicarbonate, and diluted with DCM. The layers were separated and the water layer was further extracted with DCM. The combined organic layers were dried over magnesium sulfate, filtered and concentrated in vacuo. The crude solid was purified by column chromatography (0→2% methanol/DCM). LC-MS calculated for C16H12BrClN (M+H)⁺: m/z = 360.0; found 360.0.
Step 6: 8-((3-bromo-2-chlorophenyl)amino)-1,7-naphthyridine-3-carbaldehyde

A flask was charged with N-(3-bromo-2-chlorophenyl)-3-vinyl-1,7-naphthyridin-8-amine (0.586 g, 1.625 mmol), 1,4-dioxane (40 mL) and water (40 mL). A 4% osmium tetroxide solution in water (0.207 ml, 0.032 mmol) was added to the reaction mixture. After 5 min, sodium periodate (1.390 g, 6.50 mmol) was added. The mixture was stirred overnight at rt. The reaction was diluted with water and ethyl acetate. The layers were separated and the aqueous layer was further extracted with EtOAc. The combined organic extracts were washed with brine, dried over sodium sulfate, filtered, and concentrated in vacuo. The crude product was purified by silica gel chromatography (0→60% EtOAc/hexanes). LC-MS calculated for C_{12}H_{10}BrClN_0 (M+H)^+: m/z = 362.0; found 362.0.

Step 7: methyl 1-((8-((3-bromo-2-chlorophenyl)amino)-1,7-naphthyridin-3-yl)methyl)azetidine-3-carboxylate

A mixture of 8-((3-bromo-2-chlorophenyl)amino)-1,7-naphthyridine-3-carbaldehyde (0.272 g, 0.750 mmol) and methyl azetidine-3-carboxylate, HCl (Combi-Blocks, cat#SS-3302:125 mg, 0.825 mmol) in methylene chloride (3.75 ml) and N,N-diisopropylethylamine (0.392 ml, 2.250 mmol) was stirred at rt for 1 h. Sodium triacetoxyborohydride (0.477 g, 2.250 mmol) was added in portions. The reaction was stirred at rt for 2 h, then sodium tetrahydroborate (0.060 ml, 1.500 mmol) and methanol (6 mL) were added carefully. After stirring overnight, the reaction was quenched with a saturated solution of sodium bicarbonate. The mixture was then extracted with a 3:1 mixture of chloroform/isopropanol. The combined organic layers were washed with brine, dried over sodium sulfate, and concentrated under reduced pressure. The crude residue was purified by column chromatography (methanol/DCM). LC-MS calculated for C_{2}OHi9BrClN_4O_2 (M+H)^+: m/z = 461.0; found 461.1.
Step 8: tert-butyl 2-((2'-chloro-3'-((3-((3-(methoxycarbonyl)azetidin-1-yl)methyl)-7-naphthyridin-8-yl)amino)-2-methyl-1,1'-biphenyl)-3-yl)carbamoyl)-1-methyl-1,4,6,7-tetrahydro-5H-imidazo[4,5-c]pyridine-5-carboxylate

To a vial was added tert-butyl 1-methyl-2-((2-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)carbamoyl)-1,4,6,7-tetrahydro-5H-imidazo[4,5-c]pyridine-5-carboxylate (Step 3: 0.037 g, 0.074 mmol), methyl l-((8-((3-bromo-2-chlorophenyl)amino)-1,7-naphthyridin-3-yl)methyl)azetidine-3-carboxylate (0.034 g, 0.074 mmol), sodium carbonate (8.58 mg, 0.081 mmol), (l,l'-bis(diphenylphosphino)ferrocene)-dichloropalladium(II) (5.39 mg, 7.36 µmol), 1,4-dioxane (0.650 ml), and water (0.087 ml). The mixture was degassed, sealed, and heated to 90 °C whilst stirring for 18 h. The mixture was cooled, diluted with water and methylene chloride, and the layers were separated. The aqueous layer was further extracted with methylene chloride and the combined organic layers were dried over MgSO4, filtered, and concentrated in vacuo. The crude residue was purified by silica gel chromatography (15% MeOH/DCM) to provide the desired product. LC-MS calculated for C40H44CIN8O5 (M+H)+: m/z = 751.3; found 751.3.

Step 9: methyl l-((8-(2-chloro-2'-methyl-3'-(l-methyl-4,5,6,7-tetrahydro-lH-imidazo[4,5-c]pyridine-2-carboxamido)biphenyl-3-ylamino)-l,7-naphthyridin-3-yl)m ethyl)azetidine-3-carboxylate

To a vial was added tert-butyl 2-((2'-chloro-3'-((3-((3-(methoxycarbonyl)azetidin-1-yl)methyl)-7-naphthyridin-8-yl)amino)-2-methyl-1,1'-biphenyl)-3-yl)carbamoyl)-1-methyl-1,4,6,7-tetrahydro-5H-imidazo[4,5-c]pyridine-5-carboxylate (0.041 g, 0.055 mmol), DCM (0.6 mL), and TFA (0.084 mL, 1.091 mmol). The reaction was stirred at rt for 1 h. The mixture was concentrated under reduced pressure, and the resulting residue was redissolved in DCM and washed with a saturated aqueous solution of sodium bicarbonate. The layers
were separated, and the organic layer was dried over MgSO₄, filtered, and concentrated under reduced pressure. The crude residue was then used directly in the next step without further purification. LC-MS calculated for C₃₆H₅₈Cl₈N₆O₅ (M+H)+: m/z = 651.3; found 651.4.

*Step 10:* methyl l-((8-(2-chloro-3’-(1,5-dimethyl-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridine-2-carboxamido)-2’-methylbiphenyl-3-ylamino)-1,7-naphthyridin-3-yl)methyl)azetidine-3-carboxylate

A mixture of methyl l-((8-((2-chloro-3’-(1-methyl-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridine-2-carboxamido)-2’-methyl-[1,1’-biphenyl]-3-yl)amino)-1,7-naphthyridin-3-yl)methyl)azetidine-3-carboxylate (0.032 g, 0.049 mmol) and 12.3 M formaldehyde in water (7.99 µl, 0.098 mmol) in methylene chloride (0.430 ml) and methanol (0.061 ml) was stirred at rt for 30 min after which time, acetic acid (0.017 ml, 0.295 mmol) and sodium triacetoxyborohydride (0.052 g, 0.246 mmol) were added. The mixture was stirred at rt for 45 min and the reaction was quenched with a saturated aqueous sodium bicarbonate solution. The mixture was extracted with a 3:1 mixture of chloroform/isopropanol, and the combined organic layers were dried over sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (0 → 30% methanol/DCM). LC-MS calculated for C₅₆H₆₈Cl₈N₆O₅ (M+H)+: m/z = 665.3; found 665.4.

*Step 11:* l-((8-(2-chloro-3’-(1,5-dimethyl-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridine-2-carboxamido)-2’-methylbiphenyl-3-ylamino)-1,7-naphthyridin-3-yl)methyl)azetidine-3-carboxylic acid

To a solution of methyl l-((8-(2-chloro-3’-(1,5-dimethyl-4,5,6,7-tetrahydro-1H-inddazo[4,5-c]pyridine-2-carboxamido)-2’-methyl-[1,1’-biphenyl]-3-yl)amino)-1,7-naphthyridin-3-yl)methyl)azetidine-3-carboxylate (27 mg, 0.041 mmol) in THF (203 µl) was added lithium hydroxide (3.89 mg, 0.162 mmol) in water (203 µl). The mixture was stirred at rt for 30 min. The mixture was diluted with methanol and purified by prep HPLC (pH = 2, acetonitrile/water+TFA) to provide the compound as its TFA salt. LC-MS calculated for C₃₆H₃₆Cl₈N₆O₅ (M+H)+: m/z = 651.3; found 651.3.
Example 15

(i?)-l-((5-(2-chloro-3'-(3-(((i?)^-hydroxypyrrolidin-l-yl)methyl)-l,7-naphthyridin-8-ylamino)-2'-methylbiphenyl-3-ylcarbamoyl)-l-methyl-6-oxo-l,6-dihydropyridin-3-yl)methyl)pyrrolidine-3-carboxylic acid

**Step 1: 2-chloro-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline**

In a vial was combined: 4,4,5,5,4',4',5',5'-Octamethyl-[2,2']bi[1,3,2]dioxaborolanyl] (6.15 g, 24.22 mmol), potassium acetate (2.85 g, 29.1 mmol), 3-bromo-2-chloroaniline (Enamine, cat# EN300-105778: 2.00 g, 9.69 mmol), 1,4-dioxane (48.4 ml) and [1,1'-bis(diphenylphosphino)ferrocene] dichloropalladium (II) (0.354 g, 0.484 mmol). The vial was flushed with nitrogen and was stirred at 110 °C for 2 h. The mixture was cooled, and filtered through Celite®, and concentrated under reduced pressure. The crude residue was purified by silica gel chromatography (EtOAc/hexanes) to provide the desired compound as a white solid. LC-MS calculated for C12H18BCINO2 (M+H)+: m/z = 254.1; found 254.1.

**Step 2: 8-((3-bromo-2-methylphenyl)amino)-l,7-naphthyridine-3-carbaldehyde**

A suspension of (8-((3-bromo-2-methylphenyl)amino)-l,7-naphthyridin-3-yl)methanol (Affinity Research Chemicals, #ARI-0169: 300.0 mg, 0.872 mmol) and manganese dioxide (1515 mg, 17.43 mmol) in DCM (8716 µl) was stirred at 45 °C for 1 h. The reaction was filtered through Celite® and the filtrate was concentrated to yield a crude residue, which was used directly in the next step without further purification. LC-MS calculated for CieHisBrNsO (M+H)+: m/z = 342.0; found 342.0.

**Step 3: (R)-l-((8-((3-bromo-2-methylphenyl)amino)-l,7-naphthyridin-3-yl)methyl)pyrrolidin-
A mixture of 8-((3-bromo-2-methylphenyl)amino)-1,7-naphthyridine-3-carbaldehyde (0.100 g, 0.292 mmol) and (R)-3-hydroxypyrrolidine (Combi-Blocks, #AM-2005: 0.025 g, 0.292 mmol) in 1,2-dichloroethane (1.46 ml) and N,N-diisopropylethylamine (0.051 ml, 0.292 mmol) was stirred at rt for 1 h. Sodium triacetoxyborohydride (0.093 g, 0.438 mmol) was added in portions. The reaction was stirred at rt for 2 h, then quenched with a saturated aqueous solution of sodium bicarbonate. The mixture was then extracted with a 3:1 mixture of chloroform/isopropanol. The combined organic layers were dried over sodium sulfate, and concentrated in vacuo. The crude residue was purified by silica gel chromatography (0 → 30% methanol/DCM) to give the desired product. LC-MS calculated for C_{20}H_{22}BrN_{10} (M+H)^+: m/z = 413.1; found 413.1.

*Step 4: (R)-l-(8-(3'-amino-2'-chloro-2-methylbiphenyl-3-ylamino)-l, 7-naphthyridin-3-yl)methylpyrrolidin-3-ol*

To a vial was added 2-chloro-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (Step 1 : 0.101 g, 0.399 mmol), (R)-l-l-(8-((3-bromo-2-methylphenyl)amino)-1,7-naphthyridin-3-yl)methylpyrrolidin-3-ol (0.165 g, 0.399 mmol), sodium carbonate (0.047 g, 0.439 mmol), (1,1'-bis(diphenylphosphino)ferrocene)-dichloropalladium(II) (0.029 g, 0.040 mmol), 1,4-dioxane (3.52 ml), and water (0.470 ml). The mixture was degassed, sealed, and heated to 90 °C whilst stirring for 18 h. The mixture was cooled, diluted with water and methylene chloride, and the layers were separated. The aqueous layer was further extracted with methylene chloride, and the combined organic layers were dried over MgSO4, filtered, and concentrated in vacuo. The crude residue was purified by silica gel chromatography (15% MeOH/DCM) to provide the desired product. LC-MS calculated for C_{26}H_{27}ClN_{5}O (M+H)^+: m/z = 460.2; found 460.3.

*Step 5: methyl 5-bromo-1-methyl-2-oxo-1,2-dihydropyridine-3-carboxylate*
Methyl iodide (1.713 ml, 27.5 mmol) was added to a mixture of 5-bromo-2-hydroxynicotinic acid (Combi-Blocks, cat# CA-4087: 2.0 g, 9.17 mmol), and potassium carbonate (1.811 ml, 20.18 mmol) in methanol (45.9 mL), which was stirred at 70 °C overnight. The solvent was removed, and the crude mixture was extracted with DCM/water. The organic extracts were dried over MgSO4, filtered, and concentrated under reduced pressure. The crude product was used directly in the next step without further purification.

LC-MS calculated for C8H9BrNO3 (M+H)⁺: m/z = 246.0; found 246.0.

**Step 6: l-methyl-2-oxo-5-vinyl-1,2-dihydropyridine-3-carboxylic acid**

A mixture of methyl 5-bromo-1-methyl-2-oxo-1,2-dihydropyridine-3-carboxylate (745 mg, 3.03 mmol), 4,4,5,5-tetramethyl-2-vinyl-1,3,2-dioxaborolane (565 µL, 3.33 mmol), tetrakis(triphenylphosphine)palladium(0) (175.0 mg, 0.151 mmol), 2.0 M sodium carbonate in water (4543 µL, 9.09 mmol) and 1,4-dioxane (6058 µL) was sparged with nitrogen and then heated at 100 °C for 30 min. The mixture was partitioned between EtOAc and water and the layers separated. The organic layer was washed with brine, dried over MgSO4, filtered and concentrated under reduced pressure. The crude residue was used directly in the next step without further purification. LC-MS calculated for C9H10NO3 (M+H)⁺: m/z = 180.1; found 180.1.

**Step 7: (R)-N-(2-chloro-3’-(3-(3-hydroxypyrrolidin-1-yl)methyl)-1,7-naphthyridin-8-ylamino)-2’-methylbiphenyl-3-yl)-l-methyl-2-oxo-5-vinyl-l, 2-dihydropyridine-3-carboxamide**

A mixture of 1-methyl-2-oxo-5-vinyl-1,2-dihydropyridine-3-carboxylic acid (0.0550 g, 0.307 mmol), (R)-l -(8-((3’-amino-2’-chloro-2-methyl-[l,1’-biphenyl]-3-yl)amino)-l,7-
naphthyridin-3-yl)methyl)pyrrolidin-3-ol (Step 4: 0.141 g, 0.307 mmol), N-
[(dimethylamino)-1H-1,2,3-triazolo-[4,5-b]pyridin-1-yl)methylene]-N-methylmethanaminium hexafluorophosphate N-oxide (0.140 g, 0.368 mmol), and NN-diisopropylethylamine (0.107 ml, 0.614 mmol) in 1,2-dichloroethane (4.39 ml) was stirred at rt for 2 h. The mixture was concentrated under reduced pressure. The residue was diluted with ethyl acetate, and washed with water followed by brine. The organic layer was dried over MgSO4, filtered and concentrated under reduced pressure. The crude residue was purified by silica gel chromatography (MeOH/DCM) to provide the desired compound. LC-MS calculated for C35H34CIN6O3 (M+H)+: m/z = 621.2; found 621.4.

Step 8: (R)-N-(2-chloro-3'-((3-((3-hydroxypyrrolidin-1-yl)methyl)-1,7-naphthyridin-8-ylamino)-2'-methylbiphenyl-3-yl)-5-formyl-1-methyl-2-oxo-1,2-dihydropyridine-3-carboxamide

A flask was charged with (i?)-N-(2-chloro-3'-((3-((3-hydroxypyrrolidin-1-yl)methyl)-1,7-naphthyridin-8-yl)amino)-2'-methyl-[1,1'-biphenyl]-3-yl)-1-methyl-2-oxo-5-vinyl-1,2-dihydropyridine-3-carboxamide (0.131 g, 0.211 mmol), 1,4-dioxane (40 mL) and water (40 mL). A 4% osmium tetroxide solution in water (0.094 ml, 0.015 mmol) was added to the reaction mixture. After 5 min, sodium periodate (0.361 g, 1.687 mmol) was added. The mixture was stirred overnight at rt. The mixture was diluted with water (2 mL) and 3:1 chloroform/isopropanol (5 mL), and the layers were separated. The organic extract was dried over sodium sulfate, filtered, and concentrated in vacuo. The crude aldehyde was purified by silica gel chromatography (20% MeOH/DCM). LC-MS calculated for C34H32CIN6O4 (M+H)+: m/z = 623.2; found 623.4.

Step 9: (R)-l-((5-(2-chloro-3'-((3-((3-hydroxypyrrolidin-1-yl)methyl)-1,7-naphthyridin-8-yl)amino)-2'-methyl-[1,1'-biphenyl]-3-ylcarbamoyl)-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)methyl)pyrrolidin-3-carboxylic acid

To a vial was added (i?)-N-(2-chloro-3'-((3-((3-hydroxypyrrolidin-1-yl)methyl)-1,7-naphthyridin-8-yl)amino)-2'-methyl-[1,1'-biphenyl]-3-yl)-5-formyl-1-methyl-2-oxo-1,2-dihydropyridine-3-carboxamide (0.022 g, 0.035 mmol), (i?)-pyrrolidine-3-carboxylic acid
(Combi-Blocks, cat#ST-7698: 0.012 g, 0.106 mmol), dichloromethane (0.579 ml) and triethylamine (0.016 ml, 0.115 mmol). The reaction was stirred at rt for 2 h, then sodium triacetoxyborohydride (0.037 g, 0.177 mmol) and acetic acid (6.06 µl, 0.106 mmol) were added. The reaction was stirred for 2 h, then the mixture was diluted with methanol and purified by prep HPLC (pH = 2, acetonitrile/water+TFA) to provide the desired compound as its TFA salt. LC-MS calculated for C39H41CIN7O5 (M+H)+: m/z = 722.3; found 722.2.

Example 16

(i?)-l-((8-(2,2'-dichloro-3'-(5-((3-hydroxypyrrolidin-l-yl)methyl)-l-methyl-2-oxo-l,2-
dihydropyridine-3-carboxamido)biphenyl-3-ylamino)-l,7-naphthyridin-3-
yl)methyl)azetidine-3-carboxylic acid

Step 1: methyl l-((8-(3'-amino-2,2'-dichlorobiphenyl-3-ylamino)-l,7-naphthyridin-3-
yl)methyl)azetidine-3-carboxylate

To a vial was added 2-chloro-3-(4,4,5,5-tetramethyl-l,3,2-dioxaborolan-2-yl)aniline (Example 15, Step 1: 0.137 g, 0.539 mmol), methyl l-((8-((3-bromo-2-chlorophenyl)amino)-l,7-naphthyridin-3-yl)methyl)azetidine-3-carboxylate (Example 14, Step 7: 0.166 g, 0.360 mmol), sodium carbonate (0.057 g, 0.539 mmol), (1,1'-bis(diphenylphosphino)ferrocene)-dichloropalladium(II) (0.026 g, 0.036 mmol), 1,4-dioxane (3.17 ml), and water (0.423 ml). The mixture was degassed, sealed, and heated to 90 °C whilst stirring for 1 h. The mixture was cooled, diluted with water and 3:1 chloroform/isopropanol, and the layers were separated. The aqueous layer was further extracted with 3:1 chloroform/isopropanol, and the combined organic extracts were dried over MgSO4, filtered, and concentrated in vacuo. The desired compound was purified by silica gel chromatography (20% MeOH/DCM). LC-MS calculated for C26H24Cl2N5O2 (M+H)+: m/z = 508.1; found 508.2.

Step 2: methyl l-((8-(2,2'-dichloro-3'-(l-methyl-2-oxo-5-vinyl-1,2-dihydropyridine-3-
carboxamido)biphenyl-3-ylamino)-l, 7-naphthyridin-3-yl)methyl)azetidine-3-carboxylic acid
In a vial, l-methyl-2-oxo-5-vinyl-l,2-dihydropyridine-3-carboxylic acid (Example 15, Step 6: 0.051 g, 0.285 mmol) HATU (0.130 g, 0.342 mmol) and N,N-diisopropylethylamine (0.099 ml, 0.569 mmol) were dissolved in DMF (2.85 ml). After stirring for 5 min, methyl 1-((8-(3'-amino-2',2'-dichlorobiphenyl-3-ylamino)-1,7-naphthyridin-3-yl)methyl)azetidin-3-carboxylate (0.285 mmol) was added, and the resulting mixture was stirred at 40 °C for 24 h. Excess DMF was concentrated, and the resulting oil was diluted with EtOAc and water. The layers were separated and the water layer was further extracted with ethyl acetate. The combined organic layers were washed with brine, dried over magnesium sulfate, filtered and concentrated in vacuo. After concentrating, the crude residue was triturated with DCM and filtered to provide the desired product. The filtrate was purified by silica gel chromatography (20% MeOH/DCM) to provide additional desired product. LC-MS calculated for C35H31Cl2N6O4 (M+H)+: m/z = 669.2; found 669.1.

Step 3: methyl l-((8-(2',2'-dichloro-3'- (5-formyl-l-methyl-2-oxo-l,2-dihydropyridine-3-carboxamido)biphenyl-3-ylamino)-l, 7-naphthyridin-3-yl)methyl)azetidine-3-carboxylate

This compound was prepared using similar procedures as described for Example 14 with methyl l-((8-(2',2'-dichloro-3'-((l-methyl-2-oxo-5-vinyl-l,2-dihydropyridine-3-carboxaimdo)biphenyl-3-ylamino)-1,7-naphthyridin-3-yl)methyl)azetidin-3-carboxylate replacing N-(3-bromo-2-chlorophenyl)-3-vinyl-l,7-naphthyridin-8-amine in Step 6. The crude product was purified by silica gel chromatography (20% MeOH/DCM) to provide the desired product. LC-MS calculated for C34H29Cl2N6O5 (M+H)+: m/z = 671.2; found 671.4.

Step 4: (R)-methyl l-((8-(2',2'-dichloro-3'- (5-((3-hydroxypyrrolin-l-yl)methyl)-l-methyl-2-oxo-l,2-dihydropyridine-3-carboxamido)biphenyl-3-ylamino)-1, 7-naphthyridin-3-yl)methyl)azetidine-3-carboxylate
This compound was prepared using similar procedures as described for Example 15 with methyl 1-((8-(2,2'-dichloro-3'-(5-formyl-1-methyl-2-oxo-1,2-dihydropyridine-3-carboxamido)biphenyl-3-ylamino)-1,7-naphthyridin-3-yl)methyl)azetidine-3-carboxylate replacing 8-((3-bromo-2-methylphenyl)amino)-1,7-naphthyridine-3-carbaldehyde in Step 3. The crude product was purified by silica gel chromatography (MeOH/DCM) to provide the desired product. LC-MS calculated for C_{38}H_{38}Cl_{13}N_{7}O_{5} (M+H)^+; m/z = 742.2; found 742.4.

**Step 5: (R)-l-((8-(2,2'-dichloro-3'-(5-((3-hydroxypyrrolidin-1-yl)methyl)-1-methyl-2-oxo-1,2-dihydropyridine-3-carboxamido)biphenyl-3-ylamino)-1,7-naphthyridin-3-yl)methyl)azetidine-3-carboxylic acid**

This compound was prepared using similar procedures as described for Example 14 with (R)-methyl 1-((8-(2,2'-dichloro-3'-(5-((3-hydroxypyrrolidin-1-yl)methyl)-1-methyl-2-oxo-1,2-dihydropyridine-3-carboxamido)biphenyl-3-ylamino)-1,7-naphthyridin-3-yl)methyl)azetidine-3-carboxylate replacing methyl 1-((8-(2-chloro-3'-(1,5-dimethyl-4,5,6,7-tetrahydro-IH-imidazo[4,5-c]pyridine-2-carboxamido)-2'-methyl-[l,r-biphenyl]-3-ylamino)-1,7-naphthyridin-3-yl)methyl)azetidine-3-carboxylate in Step 11. The reaction mixture was diluted with methanol and purified by prep HPLC (pH = 2, acetonitrile/water+TFA) to provide the desired compound as its TFA salt. LC-MS calculated for C_{37}H_{36}Cl_{2}N_{7}O_{5} (M+H)^+; m/z = 728.2; found 728.1.

**Example 17**

1-((8-(2,2'-dichloro-3'-(5-((2-hydroxyethylamino)methyl)-1-methyl-2-oxo-1,2-dihydropyridine-3-carboxamido)biphenyl-3-ylamino)-1,7-naphthyridin-3-yl)methyl)azetidine-3-carboxylic acid
**Step 1:** methyl l-(8-(2,2'-dichloro-3'-(5-((2-hydroxyethy lamino)methyl)-1-methyl-2-oxo-1,2-dihydropyridine-3-carboxamido)biphenyl-3-ylamino)-1,7-naphthyridin-3-yl)methyl)azetidine-3-carboxylate

A mixture of methyl l-((8-((2,2'-dichloro-3'-(5-formyl-1-methyl-2-oxo-1,2-dihydropyridine-3-carboxamido) [1J]-biphenyl)-3-yl)amino)-1,7-naphthyridin-3-yl)methyl)azetidine-3-carboxylate (Example 16, Step 3: 0.020 g, 0.030 mmol) and ethanolamine (Aldrich, cat#411000: 0.089 mmol) in methylene chloride (0.596 ml) and N,N-diisopropylethylamine (0.026 ml, 0.149 mmol) was stirred at rt for 1 h. Sodium triacetoxyborohydride (0.019 g, 0.089 mmol) was carefully added. The reaction was stirred at rt for 2 h and sodium tetrahydroborate (2.384 µl, 0.060 mmol) and methanol (6 mL) were carefully added. The mixture was stirred overnight, and the reaction was quenched with a saturated solution of sodium bicarbonate. The mixture was then extracted with a 3:1 mixture of chloroform/isopropanol. The combined organic layers were washed with brine, dried over sodium sulfate, and then concentrated in vacuo. The crude residue was purified by column chromatography (0 → 50% methanol/DCM). LC-MS calculated for C36H36Cl2N7O5 (M+H)+: m/z = 716.2; found 716.3.

**Step 2:** l-((8-(2,2'-dichloro-3'-(5-((2-hydroxyethy lamino)methyl)-1-methyl-2-oxo-1,2-dihydropyridine-3-carboxamido)biphenyl-3-ylamino)-1,7-naphthyridin-3-yl)methyl)azetidine-3-carboxylic acid

This compound was prepared using similar procedures as described for Example 14 with methyl l-((8-(2,2'-dichloro-3'-(5-((2-hydroxyethy lamino)methyl)-1-methyl-2-oxo-1,2-dihydropyridine-3-carboxamido)biphenyl-3-ylamino)-1,7-naphthyridin-3-yl)methyl)azetidine-3-carboxylate replacing methyl l-((8-(2-chloro-3'-(1,5-dimethyl-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridine-2-carboxamido)-2'-methyl-[1',1'-biphenyl]-3-yl)amino)-1,7-naphthyridin-3-yl)methyl)azetidine-3-carboxylate in Step 11. The reaction mixture was diluted with methanol and purified by prep HPLC (pH = 2, acetonitrile/water+TFA) to provide the desired compound as its TFA salt. LC-MS calculated for C35H34Cl2N7O5 (M+H)+: m/z = 702.2; found 702.2.
Example 18

**1-((8-(2,2′-dichloro-3′-(5-((2-hydroxy-2-methylpropylamino)methyl)-1-methyl-2-oxo-1,2-dihydropyridine-3-carboxamido)biphenyl-3-ylamino)-1,7-naphthyridin-3-yl)methyl)azetidine-3-carboxylic acid**

![Chemical Structure Image]

**Step 1:** Methyl 1-((8-(2,2′-dichloro-3′-(5-((2-hydroxy-2-methylpropylamino)methyl)-1-methyl-2-oxo-1,2-dihydropyridine-3-carboxamido)biphenyl-3-ylamino)-1,7-naphthyridin-3-yl)methyl)azetidine-3-carboxylate

This compound was prepared using similar procedures as described for Example 17 with l-amino-2-methyl-2-propanol (Aldrich, cat#777625) replacing ethanolamine in Step 1. The crude residue was purified by column chromatography (0→50% methanol/DCM). LC-MS calculated for C38H40Cl2N7O5 (M+H)+: m/z = 744.2; found 744.4.

**Step 2:** 1-((8-(2,2′-dichloro-3′-(5-((2-hydroxy-2-methylpropylamino)methyl)-1-methyl-2-oxo-1,2-dihydropyridine-3-carboxamido)biphenyl-3-ylamino)-1,7-naphthyridin-3-yl)methyl)azetidine-3-carboxylic acid

This compound was prepared using similar procedures as described for Example 14 with methyl 1-((8-(2,2′-dichloro-3′-(5-((2-hydroxy-2-methylpropylamino)methyl)-1-methyl-2-oxo-1,2-dihydropyridine-3-carboxando)biphenyl-3-ylamino)-1,7-naphthyridin-3-yl)methyl)azetidine-3-carboxylate replacing methyl 1-((8-(2-chloro-3′-(1,5-dimethyl-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridine-2-carboxamido)-2′-methyl-[1,1′-biphenyl]-3-yl)amino)-1,7-naphthyridin-3-yl)methyl)azetidine-3-carboxylate in Step 11. The reaction mixture was diluted with methanol and purified by prep HPLC (pH = 2, acetonitrile/water+TFA) to provide the desired compound as its TFA salt. LC-MS calculated for C37H38Cl2N7O5 (M+H)+: m/z = 730.2; found 730.2.

Example 19
2,2X(((2,2′-dimethyl-[1,1′-biphenyl]^-^-l)bis(azanediyl))bis(1,7-naphthyridine-8,3-diyl))bis(methylene))bis(azanediyl))bis(ethan-1-ol)

*Step 1:* 2-((8-(3-bromo-2-methylphenylamino)-1,7-naphthyridin-3-yl)amino)ethanol

A mixture of 8-((3-bromo-2-methylphenyl)amino)-1,7-naphthyridine-3-carbaldehyde (Example 15, Step 2: 0.100 g, 0.292 mmol) and ethanolamine (Aldrich, cat#411000: 0.292 mmol) in 1,2-dichloroethane (1.46 ml) and N,N-diisopropylethylamine (0.051 ml, 0.292 mmol) was stirred at rt for 1 h. Sodium triacetoxyborohydride (0.093 g, 0.438 mmol) was carefully added in portions. The reaction was stirred at rt for 2 h, then methanol (1 mL) and sodium borohydride (0.584 mmol) were added. The reaction was quenched with a saturated aqueous solution of sodium bicarbonate. The mixture was then extracted with a 3:1 mixture of chloroform/isopropanol. The combined organic layers were dried over sodium sulfate, then concentrated in vacuo. The crude residue was purified by silica gel chromatography (0 → 50% methanol/DCM) to give the desired product. LC-MS calculated for C18H20BrN4O (M+H)^+: m/z = 387.1; found 387.2.

*Step 2:* (8-((2-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)amino)-1,7-naphthyridin-3-yl)methanol

A mixture of 8-((3-bromo-2-methylphenyl)amino)-1,7-naphthyridin-3-yl)methanol (Affinity Research Chemicals, cat#ARI-0169: 0.300 g, 0.872 mmol), bis(pinacolato)diboron (Aldrich, #473294: 0.266 g, 1.046 mmol), dichloro[l,l’-bis(diphenylphosphino)ferrocene]palladium (II) dichloromethane adduct (0.071 g, 0.087 mmol) and potassium acetate (0.214 g, 2.179 mmol) was charged with nitrogen and stirred at 110 °C for 2 h. The crude was diluted with DCM, and then filtered through Celite®. The
filtrate was concentrated, and the resulting residue was used directly in the next step without further purification. LC-MS calculated for C22H27BN3O3 (M+H)\(^+\): m/z = 392.2; found 392.3.

Step 3: 2-((8-(3’-(3-(hydroxymethyl)-1,7-naphthyridin-8-ylamino)-2,2’-dimethylbiphenyl-3-ylamino)-l, 7-naphthyridin-3-yl)amino)ethanol

To a vial was added 2-((8-(3-(hydroxymethyl)-1,7-naphthyridin-8-ylamino)-2,2'-dimethylbiphenyl-3-yl)amino)ethanol (0.064 g, 0.165 mmol), 2-((8-(3-bromo-2-methylphenylamino)-1,7-naphthyridin-3-yl)methylamino)ethanol (Step 1: 0.058 g, 0.150 mmol), 1 M aqueous sodium carbonate (0.300 mmol), (1,1’-bis(dicyclohexylphosphino)ferrocene)-dichloropalladium(II) (10.96 mg, 0.015 mmol), and 1,4-dioxane (1.321 ml). The mixture was degassed, sealed, and heated to 90 °C whilst stirring for 4 h. The mixture was cooled, diluted with EtOAc and filtered through Celite®. The filtrate was concentrated and the crude residue was purified using silica gel chromatography (MeOH/DCM). LC-MS calculated for C34H34N7O2 (M+H)\(^+\): m/z = 572.3; found 572.4.

Step 4: 8-(3’-(3-((2-hydroxyethylamino)methyl)-1,7-naphthyridin-8-ylamino)-2,2’-dimethylbiphenyl-3-ylamino)-l, 7-naphthyridin-8-ylamino)ethanol

This compound was prepared using similar procedures as described for Example 9 with 2-((8-(3’-(3-(hydroxymethyl)-1,7-naphthyridin-8-ylamino)-2,2’-dimethylbiphenyl-3-ylamino)-1,7-naphthyridin-3-yl)amino)ethanol replacing (i?)-l-((8-((3-(3-(hydroxymethyl)-1,7-naphthyridin-8-yl)amino)-2,2’-dimethyl-[1,1’-biphenyl]-3-yl)methyl)pyrrolidin-3-ol in Step 5. LC-MS calculated for C34H32N7O2 (M+H)\(^+\): m/z = 570.3; found 570.4.
To a vial was added 8-(3’-(3-(2-hydroxyethylamino)methyl)-1,7-naphthyridin-8-ylamino)-2,2’-dimethylbiphenyl-3-ylamino)-1,7-naphthyridine-3-carbaldehyde (0.034 g, 0.065 mmol), ethanolamine (Aldrich, cat#411000: 0.024 mL, 0.194 mmol), dichloromethane (0.997 ml) and N,N-diisopropylethylamine (0.027 ml, 0.194 mmol). The reaction was stirred at rt for 2 h, then sodium triacetoxyborohydride (0.041 g, 0.194 mmol) and acetic acid (0.01 mL, 0.194 mmol) were added. After 2 h, sodium borohydride (0.130 mmol) and methanol (0.350 mL) were carefully added. The mixture was stirred overnight, then the mixture was diluted with methanol and purified by prep HPLC (pH = 2, acetonitrile/water+TFA) to provide the desired compound as its TFA salt. LC-MS calculated for C_{36}H_{56}N_{8}O_{2} (M+H)^+:

\[ m/z = 615.3 \text{; found 615.3}. \]

Example 20

(3i?i’^?i’)-1’K([2,2’-dimethyl-[1,1’-biphenyl]-3’-diyl]bis(azanediyl))bis(1,7-naphthyridine-8,3-diyl))bis(methylene))bis(pyrrolidin-3-ol)

Step 1: 8-((3-bromo-2-methylphenyl)amino)-1,7-naphthyridine-3-carbaldehyde

A suspension of (8-((3-bromo-2-methylphenyl)amino)-1,7-naphthyridin-3-yl)methanol (Affinity Research Chemicals, cat#ARI-0169: 300.0 mg, 0.872 mmol) and manganese dioxide (1515 mg, 17.43 mmol) in DCM (8716 µl) was stirred at 45 °C for 1 h. The reaction was filtered through Celite® and the filtrate was concentrated to yield a crude residue, which was used directly in the next step without further purification. LC-MS calculated for C_{36}H_{56}Br_{2}N_{6}O (M+H)^+:

\[ m/z = 342.0 \text{; found 342.0}. \]

Step 2: (R)-l-(8-((3-bromo-2-methylphenyl)amino)-1,7-naphthyridin-3-yl)methyl)pyrrolidin-3-ol
A mixture of 8-((3-bromo-2-methylphenyl)amino)-1,7-naphthyridine-3-carbaldehyde (0.100 g, 0.292 mmol) and (R)-3-hydroxypyrrolidine (Combi-Blocks, cat#AM-2005: 0.025 g, 0.292 mmol) in 1,2-dichloroethane (1.46 ml) and N,N-diisopropylethylamine (0.051 ml, 0.292 mmol) was stirred at rt for 1 h. Sodium triacetoxyborohydride (0.093 g, 0.438 mmol) was carefully added in portions. The reaction was stirred at rt for 2 h, then quenched with a saturated aqueous solution of sodium bicarbonate. The mixture was then extracted with a 3:1 mixture of chloroform/isopropanol. The combined organic layers were dried over sodium sulfate, then concentrated in vacuo. The crude residue was purified by silica gel chromatography (0 → 30% methanol/DCM) to give the desired product. LC-MS calculated for C2oH22BrN0(M+H)+: m/z = 413.1; found 413.1.

Step 3: (8-((2-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)amino)-1,7-naphthyridin-3-yl)methanol

A mixture of (8-((3-bromo-2-methylphenyl)amino)-1,7-naphthyridin-3-yl)methanol (Affinity Research Chemicals, cat#ARI-0169: 0.300 g, 0.872 mmol), bis(pinacolato)diboron (Aldrich, cat#473294: 0.266 g, 1.046 mmol), dichloro[l,l'-bis(diphenylphosphino)ferrocene]palladium (II) dichloromethane adduct (0.071 g, 0.087 mmol) and potassium acetate (0.214 g, 2.179 mmol) was charged with nitrogen and stirred at 110 °C for 2 h. The crude was diluted with DCM, and then filtered through Celite®. The filtrate was concentrated, and the resulting residue was used directly in the next step without further purification. LC-MS calculated for C22H27BN3O3 (M+H)+: m/z = 392.2; found 392.3.

Step 4: (R)-l-((8-((3'-((3-(hydroxymethyl)-1,7-naphthyridin-8-yl)amino)-2,2'-dimethyl-[1,1'-biphenyl]-3-yl)amino)-1,7-naphthyridin-3-yl)methyl)pyrrolidin-3-ol

To a vial was added (8-((2-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)amino)-1,7-naphthyridin-3-yl)methanol (0.162 g, 0.414 mmol), (R)-l-((8-((3-bromo-2-methylphenyl)amino)-1,7-naphthyridin-3-yl)methyl)pyrrolidin-3-ol (0.163 g, 0.394
mmol), 1 M aqueous sodium carbonate (0.789 mmol), [1, 1'-bis(di-
cyclohexylphosphino)ferrocene]-dichloropalladium (II) (0.029 g, 0.039 mmol), and 1,4-
dioxane (3.48 ml). The mixture was purged with nitrogen, sealed, and heated to 90 °C whilst stirring for 2 h. The mixture was cooled, diluted with EtOAc and filtered through Celite®.

The mixture was purged with nitrogen, sealed, and heated to 90 °C whilst stirring for 2 h. The mixture was cooled, diluted with EtOAc and filtered through Celite®. The filtrate was concentrated and purified using silica gel chromatography (20% MeOH/DCM) to provide the desired compound as an orange solid. LC-MS calculated for C36H34N7O2 (M+H) +: m/z = 596.3; found 596.5.

**Step 5:** \((R)-8\)-((3'-((3-hydroxypyrrolidin-1-yl)methyl)-7-naphthyridin-8-yl)amino)-2,2'-dimethyl-[1,1'-biphenyl]-3-yl)amine\)-1,7-naphthyridine-3-carbaldehyde

To a solution of \((R)-8\)-((3'-((3-(hydroxymethyl)-1,7-naphthyridin-8-yl)amino)-2,2'-dimethyl-[1,1'-biphenyl]-3-yl)amine)-1,7-naphthyridine-3-carbaldehyde (0.071 g, 0.12 mmol) in DCM (1.20 ml) was added manganese dioxide (0.208 g, 2.392 mmol). The resulting mixture was heated at 45 °C for 30 min. After cooling, the mixture was filtered through Celite® and the filtrate was concentrated. The crude orange solid was used directly in the next step. LC-MS calculated for C36H34N7O2 (M+H) +: m/z = 596.3; found 596.5.

**Step 6:** \((3R, 3R)-1',1'-((((2,2'-dimethyl-[1J 'biphenyl]-3,3'-diyl)bis(azm edyl))bis(1,7-naphthyridine-8, 3-diyl))bis(methylene))bis(pyrrolidin-3-ol)

To a vial was added \((R)-8\)-((3'-((3-(hydroxypyrrolidin-1-yl)methyl)-1,7-naphthyridin-8-yl)amino)-2,2'-dimethyl-[1,1'-biphenyl]-3-yl)amine)-1,7-naphthyridine-3-carbaldehyde (0.0085 g, 0.014 mmol), \((R)-pyrrolidin-3-ol\) (Combi-Blocks, cat#AM-2005 : 4 mg, 0.043 mmol), dichloromethane (0.357 ml) and triethylamine (5.97 µl, 0.043 mmol). The reaction was stirred at rt for 2 h, then sodium triacetoxyborohydride (0.015 g, 0.071 mmol) and acetic acid (2.45 1 µl, 0.043 mmol) were added. The reaction was stirred for 2 h, then the mixture was diluted with methanol and purified by prep HPLC (pH = 2, acetonitrile/water+TFA) to provide the desired compound as its TFA salt. LC-MS calculated for C40H43N8O2 (M+H) +: m/z = 667.3; found 667.3. ¾ NMR (600 MHz, DMSO) δ 10.68 (s, 2H), 9.09 (s, 2H), 8.53 (s, 2H), 7.96 (m, 4H), 7.41 (s, 2H), 7.24 (s, 2H), 7.10 (s, 2H), 5.62 (br...
s, 2H), 4.70 (m, 4H), 4.46 (m, 2H), 3.70-3.10 (ovrlp m, 8H), 2.31 (s, 2H), 2.07 (s, 6H), 1.93 (m, 2H).

**Example 21**

(i?)-l-((8-(3'-(3-((2-hydroxyethylamino)methyl)-1,7-naphthyridin-8-ylamino)-2,2'-dimethylbiphenyl-3-ylamino)-1,7-naphthyridin-3-yl)methyl)pyrrolidin-3-ol

This compound was prepared using similar procedures as described for Example 20 with ethanolamine (Aldrich, cat#411000) replacing (i?)-pyrrolidin-3-ol in Step 6. The reaction mixture was diluted with methanol and purified by prep HPLC (pH = 2, acetonitrile/water+TFA) to provide the desired compound as its TFA salt. LC-MS calculated for C38H41N8O2 (M+H): m/z = 641.3; found 641.3.

**Example 22**

(3i?,3'i?)-l,l'-((((2,2'-dichloro-[l,l'-biphenyl]-3,3'-diyl)bis(azanediyl))bis(l,7-naphthyridine-8,3-diyl))bis(methylene))bis(pyrrolidin-3-ol)

*Step 1: 8-chloro-3-vinyl-l, 7-naphthyridine*

A mixture of 3-bromo-8-chloro-l, 7-naphthyridine (PharmaBlock, cat#PBLJ2743 : 0.200 g, 0.821 mmol), 4,4,5,5-tetramethyl-2-vinyl-l,3,2-dioxaborolane (Aldrich, cat#663348: 153 µL, 0.904 mmol), sodium carbonate (0.174 g, 1.64 mmol) and [l,l'-bis(di-cyclohexylphosphino)ferrocene]dichloropalladium(II) (Aldrich, cat#701998: 6.2 mg, 0.0082 mmol) in tert-butyl alcohol (5.91 mL, 61.8 mmol) and water (6 mL, 300 mmol) was degassed and sealed. It was stirred at 110 °C for 2 h. The reaction mixture was cooled then extracted with ethyl acetate (3x 20 mL). The combined organic layers were washed with brine, dried over MgSO4, filtered and concentrated under reduced pressure. The crude residue was used
directly in the next step without further purification. LC-MS calculated for C10H8ClN2 (M+H)+: m/z = 191.0; found 191.0.

**Step 2: 8-chloro-1, 7-naphthyridine-3-carbaldehyde**

A flask was charged with 8-chloro-3-vinyl-1,7-naphthyridine (391. mg, 2.05 mmol), 1,4-dioxane (40. mL), a stir bar and water (40. mL). To this suspension was added a 4% w/w mixture of osmium tetroxide in water (0.84 mL, 0.132 mmol). The reaction was stirred for 5 min then sodium periodate (3.23 g, 15.11 mmol) was added and stirred for 3 h. The mixture was diluted with water (20 mL) and EtOAc (20 mL). The layers were separated and the aqueous layer was further extracted with EtOAc (2 X 20 mL). The combined organic extracts were washed with brine, dried over sodium sulfate, filtered, and concentrated in vacuo. The crude aldehyde was purified by silica gel chromatography (0 → 60% EtOAc/hexanes). LC-MS calculated for C9H6CIN2O (M+H)+: m/z = 193.0; found 192.9.

**Step 3: (R)-1-((8-chloro-1, 7-naphthyridin-3-yl)methyl)pyrrolidin-3-ol**

This compound was prepared using similar procedures as described for Example 20 with 8-chloro-1, 7-naphthyridine-3-carbaldehyde replacing 8-((3-bromo-2- methylphenyl)amino)-1,7-naphthyridine-3-carbaldehyde in Step 2. The crude amine was purified by silica gel chromatography (0 → 25% MeOH/DCM). LC-MS calculated for C13H15CIN3O (M+H)+: m/z = 264.1; found 264.1.

**Step 4: (R)-1-((8-(3-bromo-2-chlorophenylamino)-1, 7-naphthyridin-3-yl)methyl)pyrrolidin-3-ol**

In a vial, 3-bromo-2-chloroaniline (Enamine, cat#EN300-105778: 0.063 g, 0.303 mmol) and (R)-1-((8-chloro-1,7-naphthyridin-3-yl)methyl)pyrrolidin-3-ol (0.080 g, 0.303
mmol) were suspended in isopropanol (1.517 ml). Sulfuric acid (0.016 ml, 0.303 mmol) was added to the reaction mixture. The resulting mixture was heated to 100 °C for 1 h. The mixture was cooled, quenched with aqueous saturated sodium bicarbonate, and diluted with 3:1 chloroform/isopropanol. The layers were separated and the water layer was further extracted with 3:1 chloroform/isopropanol. The combined organic layers were dried over magnesium sulfate, filtered and concentrated in vacuo. The crude solid was purified by column chromatography (0→25%Methanol/DCM). LC-MS calculated for C9H9BrClN4O (M+H)+: m/z = 433.0; found 433.0.

Step 5: (R)-l-((8-(2-chloro-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenylamino)-1,7-naphthyridin-3-yl)methyl)pyrrolidin-3-ol

This compound was prepared using similar procedures as described for Example 20 with (i?)-l-((8-(3-bromo-2-chlorophenylamino)-1,7-naphthyridin-3-yl)methyl)pyrrolidin-3-ol replacing (8-(3-bromo-2-methylphenylamino)-1,7-naphthyridin-3-yl)methanol in Step 3. The crude boronic ester was used directly in the next step without further purification. LC-MS calculated for C25H31BCIN4O3 (M+H)+: m/z = 481.2; found 481.2.

Step 6: (3R,3'R)-l,l',((2,2'-dichloro-[1,1'-biphenyl]-3,3'-diyl)bis(azanediyl))bis(azanediyl))bis(l,7-naphthyridine-8,3-diyl))bis(methylene))bis(pyrrolidin-3-ol)

To a vial was added (i?)-l-((8-(3-bromo-2-chlorophenyl)amino)-1,7-naphthyridin-3-yl)methyl)pyrrolidin-3-ol (0.010 g, 0.023 mmol), (i?)-l-((8-(2-chloro-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)amino)-1,7-naphthyridin-3-yl)methyl)pyrrolidin-3-ol (0.011 g, 0.023 mmol), 1 M aqueous sodium carbonate (0.046 mmol), dioxane (0.231 ml), (1,1'-bis(di-cyclohexylphosphino)ferrocene)-dichloropalladium(II) (1.687 mg, 2.306 µmol), and a stir bar. The mixture was sparged with nitrogen and heated at 90 °C for 2 h. The mixture was diluted with methanol and purified by prep HPLC (pH = 2, acetonitrile/water+TFA) to provide the desired compound as its TFA salt. LC-MS calculated for C38H37CI2N8O2 (M+H)+: m/z = 707.2; found 707.3.
Example 23

(i?)-l-((4-(3'-(3-(((i?)-3-hydroxypyrrolidin-1-yl)methyl)-1,7-naphthyridin-8-ylamino)-2,2'-dimethylbiphenyl-3-ylamino)pyrido[3,2-d]pyrimidin-7-yl)methyl)pyrrolidin-3-ol

Step 1: (R)-l-((8-(3'-amino-2,2'-dimethylbiphenyl-3-ylamino)-1,7-naphthyridin-3-yl)methyl)pyrrolidin-3-ol

To a vial was added 2-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (Combi-Blocks, cat#PN-9127: 0.108 g, 0.465 mmol), (R)-l-((8-((3-bromo-2-methylphenyl)amino)-1,7-naphthyridin-3-yl)methyl)pyrrolidin-3-ol (Example 15, Step 3: 0.192g, 0.465 mmol), 1 M aqueous sodium carbonate (0.929 mmol), (1,1'-bis(dicyclohexylphosphino)ferrocene)-dichloropalladium(II) (0.034 g, 0.046 mmol), and 1,4-dioxane (3.10 mL). The mixture was degassed, sealed, and heated to 90 °C whilst stirring for 4 h. The mixture was cooled, diluted with EtOAc and filtered through celite. The filtrate was concentrated and the crude solid was purified by column chromatography (0→25% Methanol/DCM). LC-MS calculated for C27H30N5O (M+H)^+: m/z = 440.2; found 440.3.

Step 2: (R)-l-((8-(3'-bromopyrido[3,2-d]pyrimidin-4-ylamino)-2,2'-dimethylbiphenyl-3-ylamino)-l, 7-naphthyridin-3-yl)methyl)pyrrolidin-3-ol

To a vial was added 7-bromo-4-chloropyrido[3,2-d]pyrimidine (Synthonix, cat# B0473: 0.187g, 0.765 mmol), (i?)-l-((8-((3'-aminino-2,2'-dimethyl41 ,r-biphenyl]-3-yl)amino)-1,7-naphthyridin-3-yl)methyl)pyrrolidin-3-ol (0.336 g, 0.765 mmol), 2-propanol (3.82 ml), a stir bar and sulfuric acid (0.041 ml, 0.765 mmol). The mixture was heated to 100 °C for 2 h. After cooling to rt, the mixture was diluted with 3:1 CHCl3/isopropanol and aqueous saturated sodium bicarbonate. The layers were separated, and the aqueous phase was further
extracted. The combined organic layers were dried over MgSO4, filtered, and concentrated in vacuo. The crude solid was washed with ether to provide the desired product as a yellow solid. LC-MS calculated for C_{36}H_{32}BrN_{8}O (M+H)^+: m/z = 647.2; found 647.3.

Step 3: (R)-l-((8-(2,2'-dimethyl-3'-((7-vinylpyrido[3,2-d]pyrimidin-4-yl)amino)biphenyl-3-yl)amino)-l,7-naphthyridin-3-yl)methyl]pyrrolidin-3-ol

A mixture of (i?)-l-((8-((3'-((7-bromopyrido[3,2-d]pyrimidin-4-yl)amino)-2,2'-dimethyl-[l,1'-biphenyl]-3-yl)amino)-l,7-naphthyridin-3-yl)methyl]pyrrolidin-3-ol (0.248 g, 0.383 mmol), 4,4,5,5-tetramethyl-2-vinyl-1,3,2-dioxaborolane (0.130 ml, 0.766 mmol), sodium carbonate (0.074 ml, 0.766 mmol) and (1,1'-bis(di-cyclohexylphosphino)ferrocene)-dichloropalladium(II) (0.015 g, 0.019 mmol) in 1,4-dioxane (1.915 mL) and water (0.479 mL) was degassed and sealed. It was stirred at 90 °C for 1.5 h. The mixture was cooled to rt, and water and 3:1 chloroform/isopropanol were added. The layers were separated and the aqueous layer was further extracted with 3:1 chloroform/isopropanol. The combined organic layers were dried over Na2SO4, filtered, and concentrated in vacuo. The crude solid was then washed with ether to provide the desired compound as a yellow solid. LC-MS calculated for C_{36}H_{32}N_{8}O (M+H)^+: m/z = 595.3; found 595.3.

Step 4: (R)-4-((3-(3-hydroxypyrrolidin-1-yl)methyl)-l,7-naphthyridin-8-yl)amino)-2,2'-dimethylbiphenyl-3-yl)pyrido[3,2-d]pyrimidine-7-carbaldehyde

To a flask was added (i?)-l-((8-(2,2'-dimethyl-3'-((7-vinylpyrido[3,2-d]pyrimidin-4-yl)amino)-l,1'-biphenyl]-3-yl)amino)-l,7-naphthyridin-3-yl)methyl]pyrrolidin-3-ol (0.128 g, 0.215 mmol), THF (3.8 mL), water (1 mL), sodium periodate (0.655 g, 3.06 mmol), and 4% osmium tetroxide solution in water (0.170 ml, 0.027 mmol). The resulting mixture was stirred for 1 h at rt. The mixture was diluted with water and 3:1 CHCl3/isopropanol and the layers were separated. The aqueous layer was further extracted with CHCl3/isopropanol (3:1). The combined organic layers were washed dried over MgSO4, filtered, and concentrated in

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vacuo. The resulting solid was washed with ether to provide the desired product as a brown solid. LC-MS calculated for C35H33N8O2 (M+H)+: m/z = 597.3; found 597.5.

**Step 5**: (R)-l-((4-'(3-((fR)-3-hydroxypropyrrolidin-1-yl)methyl)-7-naphthyridin-8-ylamino)-2,2''-dimethylbiphenyl-3-ylamino)pyrido[3,2-d]pyrimidin-7-yl)methyl)pyrrolidin-3-ol

To a vial was added (i?)-4-((3'-(3-(3-hydroxypropyrrolidin-1-yl)methyl)-1,7-naphthyridin-8-yl)amino)-2,2''-dimethyl-[l ,1'-biphenyl]-3-ylamino)pyrido[3,2-d]pyrim dine-7-carbaldehyde (0.064 g, 0.107 mmol), (R)-pyrrolidin-3-ol (Combi-Blocks, cat#AM-2005: 0.037 g, 0.322 mmol), 1,2-dichloroethane (1.073 ml) and triethylamine (0.045 ml, 0.322 mmol). The reaction was stirred at rt for 2 h, then sodium triacetoxyborohydride (0.114 g, 0.536 mmol) and acetic acid (0.018 ml, 0.322 mmol) were added. The reaction was stirred for 2 h, then the mixture was diluted with methanol and purified by prep HPLC (pH = 2, acetonitrile/water+TFA) to provide the desired compound as its TFA salt. LC-MS calculated for C39H42N9O2 (M+H)+: m/z = 668.3; found 668.3.

**Example 24**

(i?)-l-((8-(3''-(7-(((2-hydroxyethylamino)methyl)pyrido[3,2-d]pyrimidin-4-ylamino)-2,2''-dimethylbiphenyl-3-ylamino)-1,7-naphthyridin-3-yl)methyl)pyrrolidin-3-ol

This compound was prepared using similar procedures as described for Example 23 with ethanolamine (Aldrich, cat#411000) replacing (R)-pyrrolidin-3-ol in Step 5. The reaction mixture was diluted with methanol and purified by prep HPLC (pH = 2, acetonitrile/water+TFA) to provide the desired compound as its TFA salt. LC-MS calculated for C37H40N9O2 (M+H)+: m/z = 642.3; found 642.3.

**Example 25**

(i?)-l-((8-(3''-(7-(((2-hydroxyethyl)(methyl)amino)methyl)pyrido[3,2-d]pyrimidin-4-ylamino)-2,2''-dimethylbiphenyl-3-ylamino)-1,7-naphthyridin-3-yl)methyl)pyrrolidin-3-ol
This compound was prepared using similar procedures as described for Example 23 with 2-(methylamino)ethanol (Aldrich, cat#471445) replacing (i?)-pyrrolidin-3-ol in Step 5. The reaction mixture was diluted with methanol and purified by prep HPLC (pH = 2, acetonitrile/water+TFA) to provide the desired compound as its TFA salt. LC-MS calculated for C38H42N9O2 (M+H)+: m/z = 656.3; found 656.4.

Example 26
(i?)-l-((8-(3'-(3-(((i?)-3-hydroxypyrrolidin-1-yl)methyl)-l,7-naphthyridin-8-ylamino)-2,2'-dimethylbiphenyl-3-ylamino)-l,7-naphthyridin-3-yl)methyl)-N,N-dimethylpyrrolidine-3-carboxamide

A mixture of (i?)-l-((8-((3'-(3-((R)-3-hydroxypyrrolidin-1-yl)methyl)-l,7-naphthyridin-8-yl)amino)-2,2'-dimethyl-[lJ'-biphenyl]-3-yl)amino)-l,7-naphthyridin-3-yl)methyl)pyrrolidine-3-carboxylic acid (Example 9, Step 6: 0.007g, 5.08 µmol), 2.0 M dimethylamine in THF (0.102 mmol), HATU (2.316 mg, 6.09 µmol), and N,N-diisopropylethylamine (8.84 µl, 0.051 mmol) in DMF (0.051 ml) was stirred at r.t. for 2 h. The reaction mixture was diluted with methanol and purified by prep HPLC (pH = 2, acetonitrile/water+TFA) to provide the desired compound as its TFA salt. LC-MS calculated for C43H48N9O2 (M+H)+: m/z = 722.4; found 722.4.

Example 27
(i?)-l-((8-(3'-(7-(((S)-2-hydroxypropylamino)methyl)pyrido[3,2-d]pyrimidin-4-ylamino)-2,2'-dimethylbiphenyl-3-ylamino)-l,7-naphthyridin-3-yl)methyl)pyrrolidin-3-ol

This compound was prepared using similar procedures as described for Example 23 with (5)-(++)l-amino-2-propanol (Aldrich, cat# 238864) replacing (i?)-pyrrolidin-3-ol in Step
5. The reaction mixture was diluted with methanol and purified by prep HPLC (pH = 2, acetonitrile/water+TFA) to provide the desired compound as its TFA salt. LC-MS calculated for C38H42N9O2 (M+H)^+: m/z = 656.3; found 656.3.

5

Example 28

(i?)-l-((8-(3'-((i?)-3-hydroxypyrrolidin-l-yl)methyl)-l-methyl-2-oxo-1,2-
dihydropyridine-3-carboxamido)-2,2'-dimethylbiphenyl-3-ylamino)-1.7-naphthyridin-3-
yl)methyl)pyrrolidine-3-carboxylic acid

\[
\text{Step 1: } N-(3\text{-bromo-2-methylphenyl})-l\text{-methyl-2-oxo-5-vinyl-l, 2-di} \\
\text{hydropyridine-3-carboxamide}
\]

A mixture of l-methyl-2-oxo-5-vinyl-l,2-dihydropyridine-3-carboxylic acid (Example 15, Step 6: 1.3 g, 7.26 mmol), 3-bromo-2-methylaniline (Aldrich, cat#530018: 0.894 ml, 7.26 mmol), HATU (3.31 g, 8.71 mmol), and N,N-diisopropylethylamine (2.53 ml, 14.51 mmol) in 1,2-dichloroethane (36.3 ml) was stirred at rt for 2 h. The mixture was concentrated under reduced pressure. The residue was diluted with ethyl acetate, and the resulting mixture was washed with water and brine. The organic layer was dried over MgSCn, filtered and concentrated under reduced pressure. The crude residue was used directly in the next step without further purification. LC-MS calculated for C16H16BrN2 (M+H)^+: m/z = 347.0; found 347.0.

\[
\text{Step 2: } N-(3\text{-bromo-2-methylphenyl})-5\text{-formyl-l-methyl-2-oxo-l, 2-di} \\
\text{hydropyridine-3-carboxamide}
\]
This compound was prepared using similar procedures as described for Example 23, Step 4 with N-(3-bromo-2-methylphenyl)-1-methyl-2-oxo-5-vinyl-1,2-dihydropyridine-3-carboxamide replacing (i?)-l-((8-((2,2′-dimethyl-3′-((7-vinylpyrido[3,2-d]pyrimidin-4-yl)amino)-1,1′-biphenyl)-3-yl)amino)-1,7-naphthyridin-3-yl)methyl)pyrrolidin-3-ol. The crude aldehyde was purified by silica gel chromatography (5% MeOH/DCM). LC-MS calculated for C_{14}H_{14}BrN_{2}O_{3} (M+H)^{+}: m/z = 349.0; found 349.1.

**Step 3:** (R)-N-(3-bromo-2-methylphenyl)-5-((3-hydroxypyrrolidin-1-yl)methyl)-1-methyl-2-oxo-1,2-dihydropyridine-3-carboxamide

![Structure](image1)

This compound was prepared using similar procedures as described for Example 20, Step 2 with N-(3-bromo-2-methylphenyl)-5-formyl-1-methyl-2-oxo-1,2-dihydropyridine-3-carboxamide replacing 8-((3-bromo-2-methylphenyl)amino)-1,7-naphthyridin-3-carbaldehyde. The crude amine was purified by silica gel chromatography (20% MeOH/DCM). LC-MS calculated for C_{19}H_{23}BrN_{3}O_{3} (M+H)^{+}: m/z = 420.1; found 420.1.

**Step 4:** (R)-N-(3′-(3-(hydroxymethyl)-1,7-naphthyridin-8-ylamino)-2,2′-dimethylbiphenyl-3-yl)-5-((3-hydroxypyrrolidin-1-yl)methyl)-1-methyl-2-oxo-1,2-dihydropyridine-3-carboxamide

![Structure](image2)

This compound was prepared using similar procedures as described for Example 20, Step 4 with (i?)-N-(3-bromo-2-methylphenyl)-5-((3-hydroxypyrrolidin-1-yl)methyl)-1-methyl-2-oxo-1,2-dihydropyridine-3-carboxamide replacing (i?)-l-((8-((3-bromo-2-methylphenyl)amino)-1,7-naphthyridin-3-yl)methyl)pyrrolidin-3-ol. The crude amine was purified by silica gel chromatography (20% MeOH/DCM). LC-MS calculated for C_{35}H_{35}N_{6}O_{4} (M+H)^{+}: m/z = 605.3; found 605.3.
Step 5: (R)-N-(3'-(3-formyl-1,7-naphthyridin-8-ylamino)-2,2'-dimethylbiphenyl-3-yl)-5-((3-hydroxypropyrridin-1-yl)methyl)-1-methyl-2-oxo-1,2-dihydropyridine-3-carboxamide

This compound was prepared using similar procedures as described for Example 20.

Step 5 with (i?)-N-(3'-(3-hydroxyethyl)-1,7-naphthyridin-8-ylamino)-2,2'-dimethylbiphenyl-3-yl)-5-((3-hydroxypropyrridin-1-yl)methyl)-1-methyl-2-oxo-1,2-dihydropyridine-3-carboxamide replacing (i?)-l-(8-((3'-(3-hydroxyethyl)-1,7-naphthyridin-8-ylamino)-2,2'-dimethyl-[1,r-biphenyl]-3-yl)amino)-1,7-naphthyridin-3-yl)methyl)pyrrolidin-3-ol. LC-MS calculated for C38H46N6O4 (M+H) +: m/z = 603.3; found 603.3.

Step 6: (R)-l-((8-(3'-(5-(((R)-2-hydroxypropylamino)methyl)pyrido[3,2-d]pyrimidin-4-ylamino)-2,2'-dimethylbiphenyl-3-ylamino)-1,7-naphthyridin-3-yl)methyl)pyrrolidine-3-carboxylic acid

To a vial was added (i?)-N-(3'-(3-formyl-1,7-naphthyridin-8-ylamino)-2,2'-dimethylbiphenyl-3-yl)-5-((3-hydroxypropyrridin-1-yl)methyl)-1-methyl-2-oxo-1,2-dihydropyridine-3-carboxamide (0.010 g, 0.017 mmol), (i?)-pyrrolidine-3-carboxylic acid (Combi-Blocks, cat#ST-7698: 6 mg, 0.050 mmol), 1,2-dichloroethane (0.4 ml) and triethylamine (6.94 µl, 0.050 mmol). The reaction was stirred at rt for 2 h, then sodium triacetoxyborohydride (0.018 g, 0.083 mmol) and acetic acid (2.85 µl, 0.050 mmol) were added. The reaction was stirred for 2 h, then the mixture was diluted with methanol and purified by prep HPLC (pH = 2, acetonitrile/water+TFA) to give the desired product as the TFA salt. LC-MS calculated for C40H44N7O5 (M+H) +: m/z = 702.3; found 702.3.

Example 29

(i?)-l-((8-(3'-(7-((i?)-2-hydroxypropylamino)methyl)pyrido[3,2-d]pyrimidin-4-ylamino)-2,2'-dimethylbiphenyl-3-ylamino)-1,7-naphthyridin-3-yl)methyl)pyrrolidin-3-ol
This compound was prepared using similar procedures as described for Example 23 with (i?)-(+)l-amino-2-propanol (Aldrich, cat# 238856) replacing (i?)-pyrrolidin-3-ol in Step 5. The reaction mixture was diluted with methanol and purified by prep HPLC (pH = 2, acetonitrile/water+TFA) to provide the desired compound as its TFA salt. LC-MS calculated for C38H42N9O2 (M+H)+: m/z = 656.3; found 656.4.

Example 30

(i?)-l-((8-(3'-(7-((2-hydroxy-2-methylpropylamino)methyl)pyrido[3,2-d]pyrimidin-4-ylamino)-2,2'-dimethylbiphenyl-3-ylamino)-1,7-naphthyridin-3-yl)methyl)pyrrolidin-3-ol

This compound was prepared using similar procedures as described for Example 23 with l-amino-2-methyl-2-propanol (Aldrich, cat# 777625) replacing (i?)-pyrrolidin-3-ol in Step 5. The reaction mixture was diluted with methanol and purified by prep HPLC (pH = 2, acetonitrile/water+TFA) to provide the desired compound as its TFA salt. LC-MS calculated for C39H44N9O2 (M+H)+: m/z = 670.3; found 670.4.

Example 31

(i?)-l-((8-(2'-chloro-3'-(1,5-dimethyl-4,5,6,7-tetrahydro-lH-imidazo[4,5-c]pyridine-2-carboxamido)-2-methylbiphenyl-3-ylamino)-1,7-naphthyridin-3-yl)methyl)pyrrolidine-3-carboxylic acid

Step 1: tert-butyl l-methyl-l,4,6, 7-tetrahydro-5H-imidazo[4,5-c]pyridine-5-carboxylate
A solution of l-methyl-4,5,6,7-tetrahydro-lH-imidazo[4,5-c]pyridine (Accela, cat#SY032476: 2.0 g, 14.58 mmol) and (Boc)_2O (3.38 mL, 14.58 mmol) in dichloromethane (60.0 mL) was stirred at room temperature for 1 h. The reaction was quenched with saturated aqueous NaHCCl solution, and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was used for next step without further purification. LC-MS calculated for C_{12}H_{20}N_{3}O_{2} (M+H)^+: m/z = 238.2; found 238.2.

**Step 2: 5-tert-butyl 2-methyl l-methyl-6,7-dihydro-lH-imidazo[4,5-c]pyridine-2,5(4H)-dicarboxylate**

\[
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\end{array}}
\]

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\text{O} \\
\text{O} \\
\end{array}}
\]

ft-Butyllithium in hexanes (2.5 M, 7.00 mL, 17.49 mmol) was added to a cold (-78 °C) solution of the crude product from Step 1 in tetrahydrofuran (60.0 mL). The reaction mixture was stirred at -78 °C for 10 min prior to the addition of methyl chloroformate (1.7 mL, 21.9 mmol). After being stirred at -78 °C for 15 min, the reaction was then quenched with saturated aqueous NaHCCl solution, and extracted with ethyl acetate, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on a silica gel column eluting with 80% ethyl acetate in hexanes to afford the desired product (). LC-MS calculated for C_{14}H_{22}N_{3}O_{4} (M+H)^+: m/z = 296.2; found 296.3.

**Step 3: tert-butoxide 2-((3-bromo-2-chlorophenyl)carbamoyl)-l-methyl-1,4,6,7-tetrahydro-5H-imidazo[4,5-c]pyridine-5-carboxylate**

\[
\text{\begin{array}{c}
\text{O} \\
\text{N} \\
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\[-\text{\begin{array}{c}
\text{N} \\
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\text{O} \\
\text{O} \\
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\]

Potassium tert-butoxide in tetrahydrofuran (1.0 M, 3.39 mL, 3.39 mmol) was added to a solution of 5-tert-butoxyl 2-methyl l-methyl-6,7-dihydro-lH-imidazo[4,5-c]pyridine-2,5(4H)-
dicarboxylate (Step 2: 500 mg, 1.69 mmol) and 3-bromo-2-chloroaniline (348 mg, 1.69 mmol) in tetrahydrofuran (12.0 mL). After being stirred at room temperature for 1 h, the reaction mixture was quenched with water, and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over Na2SO4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on a silica gel column eluting with 50% ethyl acetate in hexanes to afford the desired product. LC-MS calculated for C19H12BrClN4O (M+H)+: m/z = 469.1/471.1; found 469.1/471.1.

**Step 4: N-(3-bromo-2-chlorophenyl)-1,5-dimethyl-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridine-2-carboxamide**

A solution of tert-butyl 2-((3-bromo-2-chlorophenyl)carbamoyl)-1-methyl-1,4,6,7-tetrahydro-5H-imidazo[4,5-c]pyridine-5-carboxylate (Step 3: 300 mg, 0.64 mmol) in trifluoroacetic acid (0.2 mL) and dichloromethane (0.4 mL) was stirred at room temperature for 1 h. The solvent was evaporated, and the residue was dissolved in tetrahydrofuran (1.0 mL). 37% formaldehyde in water (0.48 mL, 6.39 mmol) and sodium triacetoxyborohydride (406 mg, 1.92 mmol) were successively added. After being stirred at room temperature for 1 h, the mixture was quenched with sat. aq. NaHCO3 solution and was extracted with ethyl acetate. The combined organic layers were washed with brine, dried over Na2SO4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on a silica gel column eluting with 10% methanol in dichloromethane to afford the desired product. LC-MS calculated for C19H17BrClN4O (M+H)+: m/z = 383.0/385.0; found 383.0/385.0.

**Step 5: N-(2-chloro-3'-(3-(hydroxymethyl)-1,7-naphthyridin-8-yl)amino)-2'-methyl-[1,1'-biphenyl]-3-yl)-1,5-dimethyl-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridine-2-carboxamide**

A mixture of N-(3-bromo-2-chlorophenyl)-1,5-dimethyl-4,5,6,7-tetrahydro-1H-
imidazo[4,5-c]pyridine-2-carboxamide (Step 4: 60 mg, 0.156 mmol), (8-((2-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)amino)-1,7-naphthyridin-3-yl)methanol (Example 9, Step 3: 73.4 mg, 0.188 mmol), sodium carbonate (66.3 mg, 0.626 mmol) and [1,1’-bis(di-cyclohexylphosphino)ferrocene]dichloropalladium(II) (11.8 mg, 0.016 mmol) in 1,4-dioxane (0.8 mL) and water (0.8 mL) was charged with nitrogen and stirred at 100 °C for 2 h. The reaction mixture was diluted with water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over Na2SO4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on a silica gel column eluting with 10% methanol in dichloromethane to afford the desired product. LC-MS calculated for C31H31CIN7O2 (M+H)+: m/z = 568.2; found 568.3.

Step 6: N-(2-chloro-3’-((3-formyl-1,7-naphthyridin-8-yl)amino)-2’-methyl-[1,1’-biphenyl]-3-yl)-l,5-dimethyl-4,5,6,7-tetrahydro-[1H-imidazo[4,5-c]pyridine-2-carboxamide

A suspension of N-(2-chloro-3’-((3-(hydroxymethyl)-1,7-naphthyridin-8-yl)amino)-2’-methyl-[1,1’-biphenyl]-3-yl)-l,5-dimethyl-4,5,6,7-tetrahydro-[1H-imidazo[4,5-c]pyridine-2-carboxamide (Step 5: 40 mg, 0.070 mmol) and manganese dioxide (92 mg, 1.056 mmol) in dichloromethane (0.5 mL) was stirred at 45 °C for 30 min. The reaction was filtered through a short pad of Celite® and then concentrated to yield a crude residue, which was used directly without further purification. LC-MS calculated for C31H29CIN7O2 (M+H)+: m/z = 566.2; found 566.2.

Step 7: (R)-l-((8-(2’-chloro-3’)-(1,5-dimethyl-4,5,6,7-tetrahydro-[1H-imidazo[4,5-c]pyridine-2-carboxamido)-2-methylbiphenyl-3-ylamino)-l, 7-naphthyridin-3-yl)methyl)pyrrolidine-3-carboxylic acid

A mixture of N-(2-chloro-3’-((3-formyl-1,7-naphthyridin-8-yl)amino)-2’-methyl-[1,1’-biphenyl]-3-yl)-l,5-dimethyl-4,5,6,7-tetrahydro-[1H-imidazo[4,5-c]pyridine-2-carboxamide (Step 6: 39.9 mg, 0.070 mmol) and (i?)-pyrrolidine-3-carboxylic acid (24.3 mg, 0.211 mmol) in dichloromethane (0.5 mL) was stirred at room temperature for 1 h. Then sodium triacetoxyborohydride (14.92 mg, 0.070 mmol) and acetic acid (4.03 µl, 0.070 mmol) was added. After being stirred at room temperature for 1 h, the reaction was diluted with MeOH
and then purified by prep-HPLC (pH = 10, acetonitrile/water+NH40H) to give the desired product. LC-MS calculated for C₃d₁₃C₅N₈O₅ (M+H)⁺: m/z = 665.3; found 665.4.

**Example 32**

(S)-N-(2-chloro-3’-(3-((3-hydroxy)pipridin-1-yl)methyl)-1,7-naphthyridin-8-ylamino)-2'-methylbiphenyl-3-yl)-1,5-dimethyl-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridine-2-carboxamide

![Chemical structure](image)

This compound was prepared using similar procedures as described for Example 31, Step 7 with (5)-pyrrolidin-3-ol (Combi-Blocks, cat#SS-7948) replacing (i?-)pyrrolidine-3-carboxylic acid. The reaction mixture was purified by prep-HPLC (pH = 10, acetonitrile/water+NH40H) to give the desired product. LC-MS calculated for C₃₅H₃₈ClN₁₈O₂ (M+H)⁺: m/z = 637.3; found 637.4.

**Example 33**

(i?-)l-((8-(2'-'chloro-3'-(1,5-dimethyl-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridine-2-carboxamido)-2-methylbiphenyl-3-ylamino)-1,7-naphthyridin-3-yl)methyl)-3-methylpyrrolidine-3-carboxylic acid

![Chemical structure](image)

This compound was prepared using similar procedures as described for Example 31, Step 7 with (i?-)3-methylpyrrolidine-3-carboxylic acid (Ark Pharm, cat#AK601708) replacing (i?-)pyrrolidine-3-carboxylic acid. The reaction mixture was purified by prep-HPLC (pH = 2, acetonitrile/water+TFA) to give the desired product. LC-MS calculated for C₃₇H₄₀C₁₈N₁₈O₃ (M+H)⁺: m/z = 679.3; found 679.2.
Example 34

(iii) - $\text{I}K(8'^{(2,2'\text{-dimethyl-3'-}(4,5,6,7\text{-tetrahydrothiazolo}[5,4-c]\text{-pyridin-2-yl})-}[1,1'\text{-biphenyl]}-3\text{-yl)amino}-1\text{'-naphthyridin-3-yl)methyl}pyrrolidine-3\text{-carboxylic acid}$

\[
\text{Chemical Structure Image}
\]

Step 1: tert-butyl 2-((3'-((3-(hydroxymethyl)-1,7-naphthyridin-8-yl)amino)-2,2'-dimethyl-[1,1'biphenyl]-3-yl)-6,7-dihydrothiazolo[5,4-c]pyridine-5(4H)-carboxylate

This compound was prepared using similar procedures as described for Example 1, Step 7 with (8-((3-bromo-2-methylphenyl)amino)-1,7-naphthyridin-3-yl)methanol (Affinity Research Chemicals, #ARI-0164) replacing 2-((8-((3-bromo-2-chlorophenyl)amino)-1,7-naphthyridin-3-yl)methyl)amino)ethan-1-ol. After 5 h, saturated aqueous NaHCO$_3$ (5 mL) solution was added to the reaction mixture followed by extraction with dichloromethane (5 mL x 3). The combined organic layers were dried over Na$_2$SO$_4$, filtered and concentrated. The crude product was used for next step without further purification. LC-MS calculated for C$_{34}$H$_{36}$N$_{5}$O$_{3}$S (M+H)$^+$: m/z = 594.2; found 594.3.

Step 2: tert-butyl 2-((3'-(formyl-1,7-naphthyridin-8-yl)amino)-2,2'-dimethyl-[1,1'biphenyl]-3-yl)-6,7-dihydrothiazolo[5,4-c]pyridine-5(4H)-carboxylate

To a solution of tert-butyl 2-((3-(hydroxymethyl)-1,7-naphthyridin-8-yl)amino)-2,2'-dimethyl-[1,1'biphenyl]-3-yl)-6,7-dihydrothiazolo[5,4-c]pyridine-5(4H)-carboxylate (130 mg, 0.22 mmol) in DCM (2 mL) was added Dess-Martin periodinane (186 mg, 0.44 mmol). After 1 h, saturated NaHCCb (5 mL) was added to the reaction mixture followed by extraction with dichloromethane (5 mL x 3). The combined organic layers were dried Na$_2$SO$_4$, filtered and concentrated. The crude product was used for next step without further purification. LC-MS calculated for C$_{34}$H$_{34}$N$_{5}$O$_{3}$S (M+H)$^+$: m/z = 592.2; found 592.3.
Step 3: (R)-l-((8-(2,2'-dimethyl-3',4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)-[1,1'-biphenyl]-3-yl)amino)-l,7-naphthyridin-3-yl)methyl)pyrrolidine-3-carboxylic acid

To a solution of tert-butyl 2-(3'-(3-formyl-7-naphthyridin-8-yl)amino)-2,2'-dimethyl-[1,1'-biphenyl]-3-yl)-6,7-dihydrothiazolo[5,4-c]pyridine-5(4H)-carboxylate (10 mg, 0.017 mmol) and DIPEA (5 uL) in DCM (0.5 nL) was added (i?)-pyrrolidine-3-carboxylic acid (5.8 mg, 0.05 mmol). After 1 h, sodium triacetoxyborohydride (6.6 mg, 0.033 mmol) was added to the reaction mixture. After 2 h, TFA (0.5 mL) was added to the reaction mixture. After another 1 h, the reaction mixture was concentrated, then dissolved in MeOH and purified by prep HPLC (pH = 2, acetonitrile/water+TFA) to provide the compound as the TFA salt. LC-MS calculated for C_{34}H_{35}N_{6}O_{2}S (M+H)^{+}: m/z = 591.2; found 591.3.

Example 35

(i?)-1K(8^(2,2',-dimethyl-3',4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yI )-[1,1'-biphenyl]-3-yl)amino)-l,7-naphthyridin-3-yl)methyl)pyrrolidin-3-ol

This compound was prepared using similar procedures as described for Example 34 with (i?)-3-hydroxypyrrolidine replacing (i?)-pyrrolidine-3-carboxylic acid in Step 3. The reaction mixture was diluted with MeOH then purified by prep-HPLC (pH = 2, acetonitrile/water+TFA) to give the desired product as the TFA salt. LC-MS calculated for C_{33}H_{35}N_{6}O_{2}S (M+H)^{+}: m/z = 563.3; found 563.3.

Example 36

(S)-l-((8-(2,2'-dimethyl-3',4,5,6,7-tetrahydrothiazolo [5,4-c]pyridin-2-yI )- [1,1'-biphenyl]-3-yl)amino )-1,7-naphthyridin-3-yl)methyl)pyrrolidin-3-ol

This compound was prepared using similar procedures as described for Example 34 with (S)-3-hydroxyprrolidine replacing (i?)-pyrrolidine-3-carboxylic acid in Step 3. The reaction mixture was diluted with MeOH then purified by prep-HPLC (pH = 2,
acetonitrile/water+TFA) to give the desired product as the TFA salt. LC-MS calculated for C33H35N6OS (M+H)+: m/z = 563.3; found 563.3.

Example 37

(i?)-2-(dimethylamino)-l-(2-(3'-((3-hydroxyprrolidin-1-yl)methyl)-1,7-naphthyridin-8-yl)amino)-2,2'-dimethyl-[1,1'-biphenyl]-3-yl)-4,6-dihydro-5H-pyrrolo[3,4-d]oxazol-5-yl)ethan-1-one

Step 1: Benzyl 6-oxa-3-azabicyclo[3.1.0]hexane-3-carboxylate

To a solution of benzyl 2,5-dihydro-lH-pyrrole-l-carboxylate (12.4 g, 61.0 mmol) in DCM (200 ml) was added m-CPBA (16.20 g, 61.0 mmol). The resulting mixture was stirred at room temperature for 3h. The reaction was quenched with saturated aqueous NaHCO₃ solution, the organic layer was separated, and the aqueous layer was extracted with DCM. The combined organic layers were dried over Na2S04, filtered and concentrated. The crude product was purified using flash chromatography (eluting with 0-50% ethyl acetate in hexanes) to give the desired product as clear oil (13 g, 97%). LC-MS calculated for C12H14NO3 (M+H)+: m/z = 220.1; found 220.1.

Step 2: Benzyl 3-amino-4-hydroxyprrolidine-l-carboxylate
To a flask was charged with benzyl 6-oxa-3-azabicyclo[3.1.0]hexane-3-carboxylate (13.0 g, 59.3 mmol) and ammonium hydroxide (115 ml, 2.96 mol). The reaction mixture was heated at 90 °C overnight. The solvent was removed. The residue was used in the next step without further purification. LC-MS calculated for C\textsubscript{12}H\textsubscript{17}N\textsubscript{2}O\textsubscript{3} (M+H): m/z = 237.1; found 237.1.

**Step 3: Benzyl 3-(3-bromo-2-methylbenzamido)-4-hydroxypyrrolidine-1-carboxylate**

A solution of 3-bromo-2-methylbenzoic acid (9.70 g, 45.1 mmol) in NN-dimethylformamide (226 ml) was added N,N,N',N'-tetramethyl-(7-azabenzotriazol-1-yl)uronium hexafluorophosphate (18.87 g, 49.6 mmol). After stirring for 5 min, benzyl 3-amino-4-hydroxypyrrolidine-1-carboxylate (10.66 g, 45.1 mmol) and NN-diisopropylethylamine (23.57 ml, 135 mmol) were added. The reaction mixture was stirred at room temperature for 2 h. The reaction was diluted with water, and the aqueous layer was extracted with DCM. The combined organic layers were dried over Na\textsubscript{2}SO\textsubscript{4}, filtered and concentrated. The residue was purified with flash chromatography (eluting with 0-60% ethyl acetate in hexanes) to give the desired product (11.5 g, 59%). LC-MS calculated for C\textsubscript{2}oH\textsubscript{22}BrN\textsubscript{2}O\textsubscript{4} (M+H): m/z = 433.1, 435.1; found 433.1, 435.1.

**Step 4: benzyl 3-(3-bromo-2-methylbenzamido)-4-oxopyrrolidine-1-carboxylate**

To a solution of benzyl 3-(3-bromo-2-methylbenzamido)-4-hydroxypyrrolidine-1-
carboxylate (16.50 g, 38.1 mmol) in DCM (200 ml) was added Dess-Martin periodinane (19.38 g, 45.7 mmol). The resulting mixture was stirred at room temperature for 2 h. The reaction mixture was diluted with Et₂O and 1 M NaOH solution. After stirring for 1 h, the organic layer was separated and dried over Na₂SO₄, filtered and concentrated. The residue was purified with flash chromatography (eluting with 0-50% ethyl acetate in hexanes) to give the desired product (9.2 g, 56%). LC-MS calculated for C₂₀H₂₀BrN₂O₄ (M+H)+: m/z = 431.1, 433.1; found 431.1, 433.1.

Step 5: benzyl 2-(3-bromo-2-methylphenyl)-4,6-dihydro-5H-pyrrolo[3,4-d]oxazole-5-carboxylate

To a solution of benzyl 3-(3-bromo-2-methylbenzamido)-4-oxopyrrolidin-1-carboxylate (9.23 g, 21.40 mmol) in 1,4-dioxane (100 ml) was added POCl₃ (1.995 ml, 21.40 mmol). The resulting mixture was stirred at 110 °C for 3 h. After cooling to room temperature, the reaction mixture was diluted with saturated NaHCO₃ solution and ethyl acetate. The aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with brine, dried over Na₂SO₄, filtered and concentrated. The precipitate was collected via filtration and washed with ethyl acetate and hexanes to give the desired product as an off white solid (4.85 g, 55%). LC-MS calculated for C₂₀H₁₈BrN₂O₃ (M+H)+: m/z = 413.0, 415.0; found 413.0, 415.0.

Step 6: 2-(3-Bromo-2-methylphenyl)-5,6-dihydro-4H-pyrrolo[3,4-d]oxazole

To solution of benzyl 2-(3-bromo-2-methylphenyl)-4,6-dihydro-5H-pyrrolo[3,4-d]oxazole-5-carboxylate (3.70 g, 8.95 mmol) in DCM (60 ml) was added 1 M BBr₃ in DCM solution (17.91 ml, 17.91 mmol) at 0 °C. After stirring at same temperature for 1 h, the reaction mixture was diluted DCM and saturated NaHCO₃ solution. The resultant precipitate was collected via filtration and dried under vacuum to give the desired product as white solid (2.0 g, 80%). LC-MS calculated for C₁₂H₁₂BrN₂O (M+H)+: m/z = 279.0, 281.0; found 279.0,
Step 7. l-(2-(3-Bromo-2-methylphenyl)-4,6-dihydro-5H-pyrrolo[3,4-d]oxazol-5-yl)-2-(dimethylamino)ethan-l-one

A solution of dimethylglycine (20.5 mg, 0.199 mmol) in N,N-dimethylformamide (1 ml) was added N,N,N’N’-tetramethyl-0-(7-azabenzotriazol-l-yl)uronium hexafluorophosphate (104 mg, 0.274 mmol). After stirring for 5 min, 2-(3-bromo-2-methylphenyl)-5,6-dihydro-4H-pyrrolo[3,4-d]oxazole (55.5 mg, 0.199 mmol) and N,N-diisopropylethylamine (104 µl, 0.596 mmol) were added. The reaction mixture was stirred at room temperature for 2 h. The reaction mixture was diluted with water, and the aqueous layer was extracted with DCM. The combined organic layers were dried over Na₂SO₄, filtered and concentrated. The residue was purified with silica gel column (eluting with 0-30% MeOH in DCM) to give the desired product (35 mg, 49%). LC-MS calculated for C_iHwBrN,C (M+H)+: m/z = 364.1, 366.1; found 364.1, 366.1.

Step 8. (R)-l-((8-((3-bromo-2-methylphenyl)amino)-l,7-naphthyridin-3-yl)methyl)pyrrolidin-3-ol

To a mixture of 8-((3-bromo-2-methylphenyl)amino)-l,7-naphthyridine-3-carbaldehyde (Example 9, Step 1: 340 mg, 0.994 mmol), (i?)-pyrrolidin-3-ol (104 mg, 1.192 mmol) in DCM (1.0 ml) was added sodium triacetoxyborohydride (316 mg, 1.490 mmol). After stirring for 2 h at room temperature, the mixture was purified with flash chromatography (0-100% ethyl acetate in hexanes, then 0-35% methanol in DCM). LC-MS calculated for C_{20}H_{22}BrN,O (M+H)+: m/z = 413.1, 415.1; found 413.1, 415.1.

Step 9. (R)-l-((8-((2-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)amino)-l,7-naphthyridin-3-yl)methyl)pyrrolidin-3-ol
A mixture of (i?)-l-((8-((3-bromo-2-methylphenyl)amino)-1,7-naphthyridin-3-yl)methyl)pyrrolidin-3-ol (281 mg, 0.680 mmol), bis(pinacolato)diboron (207 mg, 0.816 mmol), dichloro[l,l'-bis(diphenylphosphino)ferrocene]palladium (II) dichloromethane adduct (55.5 mg, 0.068 mmol), 1,4-dioxane (3.4 mL) and potassium acetate (167 mg, 1.700 mmol) was stirred at 90 °C under N₂ atmosphere for 3 h. The crude was diluted with DCM, and then filtered through a pad of Celite®. The filtrate was concentrated and purified with flash chromatography (eluting with ethyl acetate in hexane 0-100%, then methanol/DCM 0-25%) (210 mg, 67%). LC-MS calculated for C₂₆H₃₄BN₄O₃ (M+H)^+: m/z = 461.3; found 461.2.

Step 10: (R)-2-(dimethylamino)-l-(2-(3’-((3-((3-hydroxypyrrolidin-l-yl)methyl)-l,7-naphthyridin-8-yl)amino)-2,2’-dimethyl-[1,1’-biphenyl]-3-yl)-4,6-dihydro-5H-pyrrolo[3,4-d]oxazol-5-yl)ethan-1-one

A microwave vial charged with 1-(2-(3-bromo-2-methylphenyl)-4,6-dihydro-5H-pyrrolo[3,4-d]oxazol-5-yl)-2-(dimethylamino)ethan-l-one (9.49 mg, 0.026 mmol), (i?)-l-((8-((2-methyl-3-(4,4,5,5tetramethyl-l,3,2-dioxaborolan-2-yl)phenyl)amino)-1,7-naphthyridin-3-yl)methyl)pyrrolidin-3-ol (12 mg, 0.026 mmol), dicyclohexyl(2’,4’,6’-triisopropylbiphenyl-2-yl)phosphine-(2’-aminobiphenyl-2-yl)(chloro)palladium (1:1) (2.051 mg, 2.61 µmol) and tripotassium phosphate hydrate (13.21 mg, 0.057 mmol) was evacuated under high vacuum and refilled with nitrogen (repeated three times). 1,4-Dioxane (0.6mL) and water (0.2mL) was added and resulting mixture was stirred at 80 °C for 1 h. The reaction mixture was diluted with methanol and 1 N HCl solution and purified with prep-LC-MS (pH = 2, acetonitrile/water+TFA) to give the desired product as white solid. LC-MS calculated for C₃₆H₄₀N₇O₃ (M+H)^+: m/z = 618.3; found 618.3.

Example 38

(S)-2-(dimethylamino)-l-(2-(3’-((3-((3-hydroxypyrrolidin-l-yl)methyl)-l,7-naphthyridin-8-yl)amino)-2,2’-dimethyl-[l,l’-biphenyl]-3-yl)-4,6-dihydro-5H-pyrrolo[3,4-d]oxazol-5-yl)ethan-1-one
This compound was prepared using similar procedures as described for Example 37 with (S)-pyrrolidin-3-ol (Combi-Blocks, cat#SS-7948) replacing (R)-pyrrolidin-3-ol in Step 8.

LC-MS calculated for C36H40N7O3 (M+H)+: \text{m/z} = 618.3; found 618.3.

Example 39

(iR)-l-(2-(2-(3′-((3-((3-hydroxypyrrolidin-1-yl)methyl)-1,7-naphthyridin-8-yl)amino)-2,2′-dimethyl-[1,1′-biphenyl]-3-yl)-4,6-dihydro-5H-pyrrolo[3,4-d]oxazol-5-yl)-2-oxoethyl)azetidine-3-carboxylic acid

Step 1: l-(2-(3-bromo-2-methylphenyl)-4, 6-dihydro-5H-pyrrolo[3,4-d]oxazol-5-yl)-2-chloroethan-l-one

A solution of 2-(3-bromo-2-methylphenyl)-5,6-dihydro-4H-pyrrolo[3,4-d]oxazole (Example 37, Step 6: 1.04 g, 3.73 mmol) in CH2Cl2 (18 ml) was added 2-chloroacetyl chloride (0.421 g, 3.73 mmol) and N,N-diisopropylethylamine (1.947 ml, 11.18 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 2h. The reaction was diluted with water, and the aqueous layer was extracted with DCM. The combined organic layers were dried over Na2SO4, filtered and concentrated. The residue was purified with flash chromatography (eluting with 0-60% ethyl acetate in hexanes) to give the desired product as white solid (0.65 g, 49%). LC-MS calculated for C4H1BrClN3O2 (M+H)+: \text{m/z} = 355.0, 357.0; found 355.0, 357.0.
Step 2: l-(2-(2-(3-bromo-2-methylphenyl)-4,6-dihydro-5H-pyrrolo[3,4-d]oxazol-5-yl)-2-o xoethyl)azetidine-3-carboxylic acid

The mixture of l-(2-(3-bromo-2-methylphenyl)-4,6-dihydro-5H-pyrrolo[3,4-d]oxazol-5-yl)-2-chloroethan-l-one (15 mg, 0.042 mmol), azetidine-3-carboxylic acid (Aldrich, cat#391131: 4.26 mg, 0.042 mmol), TEA (0.018 ml, 0.127 mmol) and N,N-dimethylformamide (1.0 ml) was heated at 60 °C for 2 h. The reaction mixture was diluted with methanol and 1 N HCl, then purified with prep- LC-MS (pH 2) to give the desired product C (12 mg, 67%). LC-MS calculated for C_{18}H_{15}BrN_{3}O_{4} (M+H)^{+}: m/z = 420.1; found 420.1.

Step 3: (R)-l-(2-(2-(3’-(3-(((3-Hydroxypyrrolidin-1-yl)methyl)-1,7-naphthyridin-8-yl)amino)-2,2’-dimethyl-[1,1’-biphenyl]-3-yl)-4,6-dihydro-5H-pyrrolo[3,4-d]oxazol-5-yl)-2-oxoethyl)azetidine-3-carboxylic acid

This compound was prepared using similar procedures as described for Example 37, Step 10 with 1-(2-(2-(3-bromo-2-methylphenyl)-4,6-dihydro-5H-pyrrolo[3,4-d]oxazol-5-yl)-2-oxoethyl)azetidine-3-carboxylic acid replacing l-(2-(3-bromo-2-methylphenyl)-4,6-dihydro-5H-pyrrolo[3,4-d]oxazol-5-yl)-2-(dimethylamino)ethan-l-one. LC-MS calculated for C_{38}H_{40}N_{7}O_{5} (M+H)^{+}: m/z = 674.3; found 674.3.

Example 40

(\textsuperscript{\textasteriskcentered})-l-(2-(2-(3’-((3-((\textsuperscript{\textasteriskcentered})-hydroxypyrrolidin-1-yl)methyl)-1,7-naphthyridin-8-yl)amino)-2,2’-dimethyl-[1,1’-biphenyl]-3-yl)-4,6-dihydro-5H-pyrrolo[3,4-d]oxazol-5-yl)-2-oxoethyl)pyrrolidine-3-carboxylic acid
Step 1: (S)-l-(2-{2-(3-bromo-2-methylphenyl)-4,6-dihydro-5H-pyrrolo[3,4-d]oxazol-5-yl}-2-oxoethyl)pyrrolidine-3-carboxylic acid

This compound was prepared using similar procedures as described for Example 39, Step 2 with (5)-pyrrolidine-3-carboxylic acid (Combi-Blocks, #ST-1381) replacing azetidine-3-carboxylic acid. LC-MS calculated for C_{9}H_{2}iBrN_{8}O_{4} \text{(M+H)}^{+}: m/z = 434.1, 436.1; found 434.1, 436.1.

Step 2: (S)-l-{2-(2-(3''-(3'-(3-{((R)-3-hydroxypyrrolidin-1-yl)methyl}-1,7-naphthyridin-8-yl)amino)-2,2''-dimethyl-[1,1''-biphenyl]-3-yl)-4,6-dihydro-5H-pyrrolo[3,4-d]oxazol-5-yl)-2-oxoethyl}pyrrolidine-3-carboxylic acid

This compound was prepared using similar procedures as described for Example 37, Step 10 with (5)-l-{2-(2-(3-bromo-2-methylphenyl)-4,6-dihydro-5H-pyrrolo[3,4-d]oxazol-5-yl)-2-oxoethyl}pyrrolidine-3-carboxylic acid replacing 1-{2-(3-bromo-2-methylphenyl)-4,6-dihydro-5H-pyrrolo[3,4-d]oxazol-5-yl}-2-(dimethylamino)ethan-1-one. LC-MS calculated for C_{39}H_{42}N_{7}O_{5} \text{(M+H)}^{+}: m/z = 688.3; found 688.3.

Example 41
(i?)-l-{2-(2-(3''-(3-{((i?)-3-hydroxypyrrolidin-1-yl)methyl}-1,7-naphthyridin-8-yl)amino)-2,2''-dimethyl-[1,1''-biphenyl]-3-yl)-4,6-dihydro-5H-pyrrolo[3,4-d]oxazol-5-yl)-2-oxoethyl}pyrrolidine-3-carboxylic acid

Step 1: (R)-l-{2-(2-(3-bromo-2-methylphenyl)-4,6-dihydro-5H-pyrrolo[3,4-d]oxazol-5-yl)-2-oxoethyl}pyrrolidine-3-carboxylic acid
This compound was prepared using similar procedures as described for Example 39, Step 2 with (i?)-pyrrolidine-3-carboxylic acid (Combi-Blocks, cat#ST-7698) replacing azetidine-3-carboxylic acid. LC-MS calculated for C9H21BrN4O 4(M+H)+: m/z = 434.1, 436.1; found 434.1, 436.1.

\[ \text{Step 2: } (R)-1-(2-(2-(3'-(3-(((R)-3-hydroxypyrrolidin-1-yl)methyl)-1,7-naphthyridin-8-yl)amino)-2,2'-dimethyl-[1,1'-biphenyl]-3-yl)-4,6-dihydro-5H-pyrrolo[3,4-d]oxazol-5-yl)-2-oxoethyl)pyrrolidine-3-carboxylic acid} \]

This compound was prepared using similar procedures as described for Example 37, Step 10 with (i?)-l-(2-(2-(3-bromo-2-methylphenyl)-4,6-dihydro-5H-pyrrolo[3,4-d]oxazol-5-yl)-2-oxoethyl)pyrrolidine-3-carboxylic acid replacing l-(2-(3-bromo-2-methylphenyl)-4,6-dihydro-5H-pyrrolo[3,4-d]oxazol-5-yl)-2-(dimethylamino)ethan-l-one. LC-MS calculated for C39H42N7O5 (M+H)+: m/z = 688.3; found 688.3.

**Example 42**

\[ (\^)-1-(2-(2-(3'-(3-(((i?)^-hydroxypyrrolidin-1-yl)methyl)-1,7-naphthyridin-8-yl)amino)-2,2'-dimethyl-[1,1'-biphenyl]-3-yl)-4,6-dihydro-5H-pyrrolo[3,4-d]oxazol-5-yl)-2-oxoethyl)piperidine-2-carboxylic acid} \]

\[ \text{Step 1: } (S)-1-(2-(2-(3-bromo-2-methylphenyl)-4,6-dihydro-5H-pyrrolo[3,4-d]oxazol-5-yl)-2-oxoethyl)piperidine-2-carboxylic acid} \]
This compound was prepared using similar procedures as described for Example 39, Step 2 with (5)-piperidine-2-carboxylic acid (Alfa Aesar, cat#L15373) replacing azetidine-3-carboxylic acid. LC-MS calculated for C_{20}H_{23}BrN_{10}4 (M+H)^+: m/z = 448.1, 450.1; found 448.1, 450.1.

Step 2: (S)-l-(2-(2-(3'-((3-(((R)-3-hydroxypyrrolidin-l-yl)methyl)-l, 7-naphthyridin-8-yl)amino)-2',2'-dimethyl-[1,1'-biphenyl]-3-yl)-4,6-dihydro-5H-pyrrrolo[3,4-d]oxazol-5-yl)-2-oxoethyl)piperidine-2-carboxylic acid

This compound was prepared using similar procedures as described for Example 37, Step 10 with (S)-l-(2-(3-bromo-2-methylphenyl)-4,6-dihydro-5H-pyrrrolo[3,4-d]oxazol-5-yl)-2-oxoethyl)piperidine-2-carboxylic acid replacing l-(2-(3-bromo-2-methylphenyl)-4,6-dihydro-5H-pyrrrolo[3,4-d]oxazol-5-yl)-2-(dimethylamino)ethan-l-one. LC-MS calculated for C_{40}H_{44}N_{7}O_{5} (M+H)^+: m/z = 702.3; found 702.3.

Example 43

\(^{(*)}-l-(5-chloro-2-((5-cyanopyridin-3-yl)methoxy)-4-((3'-((3-(i?-3-hydroxypyrrolidin-l-yl)methyl)-l,7-naphthyridin-8-yl)amino)-2,2'-dimethyl-[l,1'-biphenyl]-3-yl)methoxy)benzyl)piperidine-2-carboxylic acid

\[\text{CN} \quad \text{N} \quad \text{O} \quad \text{Cl} \quad \text{CO}_2\text{H} \]

Step 1: 4-((3-bromo-2-methylbenzyl)oxy)-5-chloro-2-hydroxybenzaldehyde

To a mixture of (3-bromo-2-methylphenyl)methanol (Ark Pharm, cat#AKI 62869: 2.330 g, 11.59 mmol), 5-chloro-2,4-dihydroxybenzaldehyde (Ark Pharm, cat#AK199510: 2.0 g, 11.59 mmol) and triphenylphosphate (3.65 g, 13.91 mmol) in THF (10 ml) at 0 °C was added DIAD (2.93 ml, 15.07 mmol). The mixture was stirred at room temperature overnight. The mixture was concentrated and diluted with EtOAc. The solid was collected by filtration to give 4-((3-bromo-2-methylbenzyl)oxy)-5-chloro-2-hydroxybenzaldehyde (2.0 g, 5.62
A mixture of 4-((3-bromo-2-methylbenzyl)oxy)-5-chloro-2-hydroxybenzaldehyde (2.0 g, 5.62 mmol), 5-(chloromethyl)nicotinonitrile (0.927 g, 6.07 mmol) and cesium carbonate (2.75 g, 8.44 mmol) in DMF (12 ml) was stirred at 70 °C for 3 hours. The mixture was poured into water. The solid was collected by filtration and air dried to give 5-((5-((3-bromo-2-methylbenzyl)oxy)-4-chloro-2-formylphenoxy)methyl)nicotinonitrile (2.2 g, 4.66 mmol, 83 % yield). LC-MS calculated for C22Hi7BrClN20 (M+H)+: m/z = 471.0; found 471.2.

Step 3: (R)-5-((4-chloro-2-formyl-5-((3'-((3-hydroxypyrrolidin-l-yl)methyl)-1,7-naphthyridin-8-yl)amino)-2,2'-dimethyl-1,1'-biphenylJ-3-yl)methoxy)phenoxy)methyl)nicotinonitrile

A mixture of 5-((5-((3-bromo-2-methylbenzyl)oxy)-4-chloro-2-formylphenoxy)methyl)nicotinonitrile (78 mg, 0.165 mmol), (i?)-1-((8-((2-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)amino)-l,7-naphthyridin-3-yl)methyl)pyrroldin-3-ol (Example 37, Step 9: 91 mg, 0.198 mmol), potassium carbonate (45.7 mg, 0.331 mmol) and (l, l'-bis(diphenylphosphino)ferrocene)dichloropalladium(II) (12.1 mg, 0.017 mmol) in 1,4-dioxane (3 mL) and water (0.600 mL) was purged with nitrogen, and heated at 95 °C for 2 hours. The mixture was purified on prep-HPLC (pH = 2, acetonitrile/water+TFA) to give
(i?)-5-((4-chloro-2-formyl-5-((3'-(3-(3-hydroxypyrrolidin-1-yl)methyl)-1,7-naphthyridin-8-yl)amino)-2,2'-dimethyl-[1,r-biphenyl]-3-yl)methoxy)phenoxy)methyl)nicotinonitrile (60 mg, 0.083 mmol, 50.0 % yield). LC-MS calculated for C42H38ClN6O4 (M+H)^+: m/z = 725.3; found 725.2.

Step 4: (S)-l-(5-chloro-2-((5-cyanopyridin-3-yl)methoxy)-4-((3'-((3-(((RJ-3-hydroxypyrrolidin-l-yl)methyl)-l,7-naphthyridin-8-yl)amino)-2,2'-dimethyl-[1,1'-biphenyl]-3-yl)methoxy)benzyl)piperidine-2-carboxylic acid

Sodium triacetoxyborohydride (2.192 mg, 10.34 µmol) was added to a mixture of (i?)-5-((4-chloro-2-formyl-5-((3'-(3-(3-hydroxypyrrolidin-1-yl)methyl)-1,7-naphthyridin-8-yl)amino)-2,2'-dimethyl-[1,r-biphenyl]-3-yl)methoxy)phenoxy)methyl)nicotinonitrile (5mg, 6.89 µmol), (S)-piperidine-2-carboxylic acid (1.4 mg, 10.34 µmol) and triethylamine (1.92 µL, 0.014 mmol) in DCM (1.0 mL) after stirring for 2 hours at room temperature. After stirring at room temperature overnight, the mixture was purified using prep-HPLC (pH = 2, acetonitrile/water+TFA) to give the desired product as its TFA salt. LC-MS calculated for C48H49ClN7O5 (M+H)^+: m/z = 838.3; found 838.2.

Example 44

(i?)-l-(5-chloro-2-((5-cyanopyridin-3-yl)methoxy)-4-((3'-(3-(((i?)-3-hydroxypyrrolidin-1-yl)methyl)-1,7-naphthyridin-8-yl)amino)-2,2'-dimethyl-[1,l'-biphenyl]-3-yl)methoxy)benzyl)pyrrolidine-3-carboxylic acid

Sodium triacetoxyborohydride (2.192 mg, 10.34 µmol) was added to a mixture of (R)-5-((4-chloro-2-formyl-5-((3'-(3-(3-hydroxypyrrolidin-1-yl)methyl)-1,7-naphthyridin-8-yl)amino)-2,2'-dimethyl-[1,r-biphenyl]-3-yl)methoxy)phenoxy)methyl)nicotinonitrile (Example 43, Step 3: 5mg, 6.9 µmol), (i?)-pyrrolidine-3-carboxylic acid (Combi-Blocks, cat#ST-7698: 1.2 mg, 10.34 µmol) and triethylamine (1.9 µL, 0.014 mmol) in DCM (1.0 mL) after stirring for 2 h at room temperature. After stirring at room temperature for 2 h, the mixture was purified using prep-HPLC (pH = 2, acetonitrile/water+TFA) to give the desired
product as its TFA salt. LC-MS calculated for C_{47}H_{47}C_{11}N_{7}O_{5} (M+H)^+: m/z = 824.3; found 824.2.

**Example 45**

(i?)-1-((8-(2'-Chloro-2-methyl-3'-((1-methyl-4,5,6,7-tetrahydro-l H-imidazo[4,5-c]pyridine-2-carboxamido)biphenyl-3-ylamino)-l,7-naphthyridin-3-yl)methyl)-3-methylpyrroloidine-3-carboxylic acid

*Step 1:* 8-(2-methyl-3-(4,4,5,5-tetramethyl-l,3,2-dioxaborolan-2-yl)phenylamino)-l,7-naphthyridine-3-carbaldehyde

A mixture of 8-((3-bromo-2-methylphenyl)amino)-l,7-naphthyridine-3-carbaldehyde *(Example 9, Step 1: 0.684 g, 2.0 mmol), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(l,3,2-dioxaborolane) (0.660 g, 2.60 mmol), potassium acetate (0.393 g, 4.00 mmol), and PdCl$_2$ (dppf) (0.146 g, 0.200 mmol) in dioxane (10.0 mL) was vacuumed and refilled with nitrogen 3 times and then the reaction mixture was stirred at 110 °C for 7 h. The mixture was diluted with EtOAc, filtered through Celite® and concentrated under reduced pressure. The residue was purified by column chromatography eluting with CH$_2$Cl$_2$ to give the desired product. LC-MS calculated for C$_{22}$H$_{25}$BN$_3$O$_3$ (M+H)^+: m/z = 390.2; found 390.3.

*Step 2:* tert-butyl 2-(2-chloro-3'-((3-formyl-l,7-naphthyridin-8-ylamino)-2'-methylbiphenyl-3-ylcarbamoyl)-l-methyl-6, 7-dihydro-lH-imidazo[4,5-c]pyridine-5(4H)-carboxylate

A mixture of tert-butyl 2-((3-bromo-2-chlorophenyl)carbamoyl)-l-methyl-l,4,6,7-tetrahydro-5H-imidazo[4,5-c]pyridine-5-carboxylate *(Example 31, Step 3: 0.12 g, 0.255 mmol), 8-(2-methyl-3-(4,4,5,5-tetramethyl-l,3,2-dioxaborolan-2-yl)phenylamino)-l,7-
naphthyridine-3-carbaldehyde (0.10 g, 0.26 mmol), dichloro[1,1'-

bis(diphenylphosphino)ferrocene]palladium (II) dichloromethane adduct (0.019 g, 0.023 mmol) and sodium carbonate (0.049 g, 0.464 mmol) in dioxane (2.4 mL)/water (0.6 mL) was evacuated and backfilled with N₂ 3 times. The reaction mixture was stirred at 110 °C for 24 h. The mixture was diluted with ethyl acetate and washed with water, dried over Na₂SO₄, filtered and concentrated in vacuo. The product was purified by column chromatography eluting with CH₂Cl₂/EtOAc (7:3). LC-MS calculated for C₃₅H₃₅ClN₇O₄ (M+H)⁺: m/z = 652.2; found 652.2.

Step 3: (R)-l-((8-(3'-(5-(tert-butoxycarbonyl)-1-methyl-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridine-2-carboxamido)-2'-chloro-2-methylbiphenyl-3-ylamino)-l,7-naphthyridin-3-yl)methyl)-3-methylpyrrolidine-3-carboxylic acid

\[ \text{O} \]

(i?)-3-methylpyrrolidine-3-carboxylic acid (J&W PharmLab, cat#75R0495: 0.071 g, 0.552 mmol) was added to a suspension of tert-butyl 12-((2-chloro-3'-(3-formyl-1,7-naphthyridin-8-yl)amino)-2'-methyl-[1',1'-biphenyl]-3-yl)carbamoyl]-1-methyl-1,4,6,7-tetrahydro-5H-imidazo[4,5-c]pyridine-5-carboxylate (0.12 g, 0.184 mmol) in CH₂Cl₂ (1.0 mL) followed by triethylamine (0.205 mL, 1.472 mmol). The mixture was stirred at rt for 1 h. At this time sodium triacetoxyborohydride (0.117 g, 0.552 mmol) was added and then stirred at rt for 2 h. The reaction was quenched with water, extracted with CH₂Cl₂/iPrOH, and the organic phase was dried over MgSO₄, filtered, and concentrated under reduced pressure. The crude product was used directly in the next step without further purification. LC-MS calculated for C₄₁H₄₆ClN₈O₁₀ (M+H)⁺: m/z = 765.3; found 765.2.

Step 4: (R)-l-((8-(2'-chloro-2-methyl-3'-(1-methyl-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridine-2-carboxamido)biphenyl-3-ylamino)-l,7-naphthyridin-3-yl)methyl)-3-methylpyrrolidine-3-carboxylic acid

TFA (2.0 mL) was added to a mixture of (i?)-l-((8-(3'-(5-(tert-butoxycarbonyl)-1-methyl-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridine-2-carboxamido)-2'-chloro-2-methyl-[1',1'-biphenyl]-3-yl)amino)-1,7-naphthyridin-3-yl)methyl)-3-methylpyrrolidine-3-carboxylic acid (0.15 g) in CH₂Cl₂ (2.0 mL) and then stirred at rt for 30 min. The solvent was
concentrated and the mixture was diluted with acetonitrile/water and purified by prep HPLC (pH = 2, acetonitrile/water+TFA) to provide the desired compound as its TFA salt. LC-MS calculated for C_{36}H_{38}ClN_{8}O_{3} (M+H)^+: m/z = 665.3; found 665.2.

5 Example 46

(i?)-l-((8-(3'-((1,5-dimethyl-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridine-2-carboxamido)-2,2'-dimethylbiphenyl-3-ylamino)-l,7-naphthyridin-3-yl)methyl)pyrrolidine-3-carboxylic acid

Step 1: tert-butyl 2-(3-bromo-2-methylphenylcarbamoyl)-l-methyl-6,7-dihydro-1H-imidazof 4,5-c]pyridine-5(4H)-carboxylate

Potassium tert-butoxide (1.0 M THF solution, 17.61 mL, 17.61 mmol) was added to a solution of 5-/er/-butyl 2-methyl 1-methyl-6,7-dihydro-1H-imidazo[4,5-c]pyridine-2,5(4 H)-dicarboxylate (Example 14, Step 2: 2.6 g, 8.80 mmol) and 3-bromo-2-methylaniline (Aldrich, cat#530018: 1.802 g, 9.68 mmol) in THF (45 mL) at 0 °C. After being stirred at rt for 2 h, the reaction mixture was quenched with water, and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over Na2S04, filtered and concentrated under reduced pressure. The crude was stirred with 3:1 hexanes/EtOAc (40 mL) for 30 min and then filtered and dried to provide the desired product. LC-MS calculated for C_{20}H_{26}BrN_{4}O_{5} (M+H)^+: m/z = 449.1; found 449.1.

Step 2: tert-butyl 2-(3'-((3-(hydroxymethyl)-l,7-naphthyridin-8-ylamino)-2,2'-dimethylbiphenyl-3-ylcarbamoyl)-l-methyl-6,7-dihydro-1H-imidazo[4,5-c]pyridine-5(4H)-carboxylate

A mixture of tert-butyl 2-((3-bromo-2-methylphenyl)carbamoyl)-l -methyl- 1,4,6,7-tetrahydro-5 H -iridazol[4,5-c]pyridine-5-carboxylate (0.12 g, 0.267 mmol), (E)-(2-methyl-3-(4,4,5,5-tetramethyl-1 ,3,2-dioxaborolan-2-yl)phenyl)amino)-l,7-naphthyridin-3-yl)methanol (Example 9, Step 3: 0.095 g, 0.243 mmol), dichloro[l ,l'-bis(diphenylphosphino)ferrocene]palladium (II) dichloromethane adduct (0.020 g, 0.024 mmol) and sodium carbonate (0.051 g, 0.486 mmol) in dioxane (2.4 mL)/water (0.6 mL) was evacuated and backfilled with N₂. The evacuation/backfill sequence was repeated two additional times, and the reaction was stirred at 110 °C for 24 h. The mixture was diluted with ethyl acetate and washed with water, dried over Na₂SO₄, and concentrated under reduced pressure. The crude product was purified by column chromatography eluting with C₂H₅OH/EtOAc (1:1). LC-MS calculated for C₃₆H₄₀N₇O₄ (M+H)⁺: m/z = 634.3; found 634.5.

**Step 3:** N-(3′-(3-(hydroxymethyl)-l,7-naphthyridin-8-ylamino)-2,2′-dimethylbiphenyl-3-yl)-l-methyl-4,5,6,7-tetrahydro-lH-imidazo[ 4,5-c]pyridine-2-carboxamide

4 N HCl in dioxane (1.0 mL) was added to a mixture of tert-butyl 2-((3′-(3-(hydroxymethyl)-l,7-naphthyridin-8-yl)amino)-2,2′-dimethyl-[ 1,1′-biphenyl]-3-yI)carbamoyl)-l-methyl-4,6,7-tetrahydro-5 H-imidazo[4,5-c]pyridine-5-carboxylate (0.10 g, 0.158 mmol) in CH₂Cl₂ (1.0 mL), and the reaction was stirred at rt for 2 h. The solvent was removed and the crude residue was used directly in the next step without further purification. LC-MS calculated for C₃₁H₃₂N₇O₂ (M+H)⁺: m/z = 534.3; found 534.3.

**Step 4:** N-(3′-(3-(hydroxymethyl)-l,7-naphthyridin-8-ylamino)-2,2′-dimethylbiphenyl-3-yl)-1,5-dimethyl-4,5,6,7-tetrahydro-lH-imidazo[ 4,5-c]pyridine-2-carboxamide

Formaldehyde (36% H₂O solution, 6.3 µL, 0.075 mmol) was added to a mixture of N-(3′-(3-(hydroxymethyl)-l,7-naphthyridin-8-yl)amino)-2,2′-dimethyl-[ 1,1′-biphenyl]-3-yI)carbamoyl)-l-methyl-4,5,6,7-tetrahydro-1 H-mixedazol[4,5-c]pyridine-2-carboxamide (20.0 mg, 0.037 mmol) in CH₂Cl₂ (1.0 mL) followed by the addition of triethylamine (0.026 mL, 0.187 mmol). The
mixture was stirred at rt for 10 min. At this time sodium triacetoxyborohydride (23.8 mg, 0.11 mmol) was added and then the mixture was stirred at rt for 30 min. The reaction mixture was quenched with water and then extracted with CH$_2$Cl$_2$. The combined organic phase was concentrated under reduced pressure and the crude product was used directly in the next step without further purification. LC-MS calculated for C$_{32}$H$_{34}$N$_7$O$_2$ (M+H)$^+$: m/z = 548.3; found 548.4.

**Step 5:** N-(3’-(3-formyl-1,7-naphthyridin-8-ylamino)-2,2’-dimethylbiphenyl-3-yl)-l,5-dimethyl-4,5,6,7-tetrahydro-lH-imidazo[4,5-c]pyridine-2-carboxamide

Manganese dioxide (0.143 g, 1.643 mmol) was added to a solution of N-(3’-(3-(hydroxymethyl)-1,7-naphthyridin-8-ylamino)-2,2’-dimethyl-[1’,1’-biphenyl]-3-yl)-l,5-dimethyl-4,5,6j4etrahydro-l H-inddazo[4,5-c]pyridine-2-carboxamide (0.060 g, 0.110 mmol) in CH$_2$Cl$_2$ (2.0 mL) and then the mixture was stirred at 40 °C overnight. The mixture was diluted with CH$_2$Cl$_2$, filtered through Celite® and then concentrated under reduced pressure to provide the desired product which was used directly in the next step. LC-MS calculated for C$_{32}$H$_{32}$N$_7$O$_2$ (M+H)$^+$: m/z = 546.3; found 546.2.

**Step 6:** (R)-l-(8-(3’-(1,5-dimethyl-4,5,6,7-tetrahydro-lH-imidazo[4,5-c]pyridine-2-carboxamido)-2,2’-dimethylbiphenyl-3-ylamino)-l, 7-naphthyridin-3-yl)methyl)pyrrolidine-3-carboxylic acid

To a mixture of N-(3’-(3-formyl-1,7-naphthyridin-8-ylamino)-2,2’-dimethyl-[1’,1’-biphenyl]-3-yl)-l,5-dimethyl-4,5,6j4etrahydro-l H-inddazo[4,5-c]pyridine-2-carboxamide (0.010 g, 0.018 mmol) and (R)-pyrrolidine-3-carboxylic acid (Combi-Blocks, cat#ST-7698: 6.3 mg, 0.055 mmol) in CH$_2$Cl$_2$ (1.0 mL) was added triethylamine (6.3 μL, 0.11 mmol). After stirring for 10 min sodium triacetoxyborohydride (0.012 g, 0.055 mmol) was added, and the reaction was further stirred at rt for 2 h. The reaction was concentrated and the mixture was diluted with acetonitrile/water and purified by prep HPLC (pH = 2, acetonitrile/water+TFA) to provide the desired compound as its TFA salt. LC-MS calculated for C$_{37}$H$_{41}$N$_8$O$_3$ (M+H)$^+$: m/z = 645.3; found 645.4.
Example 47
ira=4-((2-(2-chloro-3'-(3-((i?)-3-hydroxypyrrolidin-1-yl)methyl)-1,7-naphthyridin-8-ylamino)-2'-methylbiphenyl-3-ylcarbamoyl)-l-methyl-6,7-dihydro-lH-imidazo[4,5-c/pyr din-5(4H)-yl)methyl)cyclohexanecarboxylic acid

\[ \text{Example 47} \]

**Step 1:**
\[
\text{tert-butyl 2-(2-chloro-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenylcarbamoyl)-l-methyl-6,7-dihydro-lH-imidazo[4,5-c]pyridine-5(4H)-carboxylate}
\]

Potassium tert-butoxide (1.0 M in THF, 2.20 mL, 2.20 mmol) was added to a solution of 5-tert-butyl 2-methyl 1-methyl-6,7-dihydro-1H-imidazo[4,5-c]pyridine-2,5(4H)-dicarboxylate \( \text{Example 14, Step 2: 0.295 g, 1.0 mmol} \) and 2-chloro-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline \( \text{Example 5, Step 1: 0.304 g, 1.200 mmol} \) in THF (4.0 mL). After being stirred at rt for 2 h, the reaction mixture was quenched with water, and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over Na2SO4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on a silica gel column eluting with ethyl acetate in hexanes (0-50%) to afford the desired product. LC-MS calculated for C25H35BCIN4O5 (M+H)+: m/z = 517.2; found 517.3.

**Step 2:**
\[
\text{tert-butyl 2-(2-chloro-3'(3-formyl-l,7-naphthyridin-8-ylamino)-2'-methylbiphenyl-3-ylcarbamoyl)-l-methyl-6,7-dihydro-lH-imidazo[4,5-c]pyridine-5(4H)-carboxylate}
\]

A mixture of tert-butyl 2-((2-chloro-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)carbamoyl)-1-methyl-1,4,6,7-tetrahydro-5 H-imidazo[4,5-c]pyridine-5-carboxylate (0.35 g, 0.677 mmol), 8-((3-bromo-2-methyl phenylamino)-l,7-naphthyridine-3-
carbaldehyde {Example 9, Step 1: 0.255 g, 0.745 mmol), dichloro[1,1'-bis(dicyclohexylphosphino)ferrocene]-palladium(II) (0.051 g, 0.068 mmol) and cesium fluoride (0.514 g, 3.39 mmol) in t-BuOH (3.00 mL)/water (1.2 mL) was evacuated and backfilled with N2 3 times. The reaction was stirred at 105 °C for 2 h. The mixture was cooled to rt, diluted with ethyl acetate, and washed with water. The organic layers were washed with brine, dried over MgSO4, filtered, and concentrated under reduced pressure. The product was purified by column chromatography eluting with CH2Cl2/MeOH (7:3). LC-MS calculated for C35H35CIN7O4 (M+H)+: m/z = 652.2; found 652.4.

Step 3: (R)-tert-butyl 2-(2-chloro-3'-(3-((3-hydroxypyrrolidin-1-yl)methyl)-1,1'-naphthyridin-8-ylamino)-2'-methylbiphenyl-3-ylcarbamoyl)-1-methyl-6,7-dihydro-1H-imidazo[4,5-c]pyridine-5(4H)-carboxylate

(iR)-pyrrolidin-3-ol (Combi-Blocks, cat#AM-2005: 0.072 g, 0.828 mmol) was added to a solution of tert-butyl 2-((2-chloro-3'-(3-formyl-1,7-naphthyridin-8-yl)amino)-2'-methyl-[1,1'-biphenyl]-3-yl)carbamoyl)-1-methyl-1,4,6,7-tetrahydro-5H-imidazo[4,5-c]pyridine-5-carboxylate (0.180 g, 0.276 mmol) in CH2Cl2 (1.0 mL). Triethylamine (0.308 mL, 2.208 mmol) was then added and the mixture was stirred at rt for 1 h. At this time sodium triacetoxyborohydride (0.175 g, 0.828 mmol) was added and then stirred at rt for 2 h. The reaction was quenched with water, extracted with CH2Cl2, and the organic phase was dried over MgSO4, filtered, and concentrated under reduced pressure. The product was purified by column chromatography eluting with CH2Cl2/MeOH (9:1). LC-MS calculated for C39H44CIN8O4 (M+H)+: m/z = 723.3; found 723.5.

Step 4: (R)-N-(2-chloro-3'-(3-((3-hydroxypyrrolidin-1-yl)methyl)-1,1'-naphthyridin-8-ylamino)-2'-methylbiphenyl-3-yl)-1-methyl-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridine-2-carboxamide

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4 N HCl in dioxane (2.0 mL) was added to a mixture of tert-butyl ((R)-2-(2-chloro-3'-(3-((3-hydroxy)pyrrolidin-1-yl)methyl)-1,7-naphthyridin-8-ylamino)-2'-methyl-[1,1'-biphenyl]-3-yl)carbamoyl)-1-methyl-1,4,6,7-tetrahydro-5H-imidazo[4,5-c]pyridine-5-carboxylate (0.18 g, 0.249 mmol) in CH2Cl2 (1.0 mL)/MeOH (1.0 mL) and the reaction was stirred at rt for 2 h. The solvent was removed and the crude HCl salt was used directly in the next step. LC-MS calculated for C34H36CIN8O2 (M+H)+: m/z = 623.3; found 623.3.

Step 5: trans-4-((2-(2-chloro-3'-(3-((R)-3-hydroxy)pyrrolidin-1-yl)methyl)-1,7-naphthyridin-8-ylamino)-2'-methylbiphenyl-3-yl)carbamoyl)-1-methyl-6,7-dihydro-1H-imidazo[4,5-c]pyridin-5(4H)-yl)methyl)cyclohexanecarboxylic acid

To a mixture of ((R)-N-(2-chloro-3'-(3-((3-hydroxy)pyrrolidin-1-yl)methyl)-1,7-naphthyridin-8-yl)amino)-2'-methyl-[1,1'-biphenyl]-3-yl)-1-methyl-4,5,6,7-tetrahydro-5H-imidazo[4,5-c]pyridine-2-carboxamide (Example 47, Step 4: 85.0 mg, 0.136 mmol) in DMF, triethylamine (0.01 mL, 0.201 mmol) and methyl trans-A-formylcyclohexane-1-carboxylate (Ark Pharm, cat#AK-50935: 0.014 g, 0.080 mmol) in CH2Cl2 (1.0 mL) was added triethylamine (0.01 mL, 0.201 mmol) and the resulting mixture was stirred for 10 min. Sodium triacetoxylborohydride (0.026 g, 0.120 mmol) was added and the reaction was stirred at rt for 2 h. The solvent was removed and the crude residue was redissoved in methanol/THF/water (0.5/0.5/0.2 mL) and LiOH monohydrate (20 mg) was added. The mixture was then stirred at rt for 3 h. The mixture was diluted with acetonitrile/water, acidified to pH = 2, and purified by prep HPLC (pH = 2, acetonitrile/water+TFA) to provide the desired compound as its TFA salt. LC-MS calculated for C42H48CIN8O4 (M+H)+: m/z = 763.3; found 763.3.

Example 48

 cis-4-((2-(2-chloro-3'-(3-((R)-3-hydroxy)pyrrolidin-1-yl)methyl)-1,7-naphthyridin-8-ylamino)-2'-methylbiphenyl-3-yl)carbamoyl)-1-methyl-6,7-dihydro-1H-imidazo[4,5-c]pyridin-5(4H)-yl)methyl)cyclohexanecarboxylic acid

To a mixture of ((R)-N-(2-chloro-3'-(3-((3-hydroxy)pyrrolidin-1-yl)methyl)-1,7-naphthyridin-8-yl)amino)-2'-methyl-[1,1'-biphenyl]-3-yl)-1-methyl-4,5,6,7-tetrahydro-5H-imidazo[4,5-c]pyridine-2-carboxamide (Example 47, Step 4: 85.0 mg, 0.136 mmol) in DMF
(2.0 mL) was added methyl cis-4-(((methylsulfonyl)oxy)methyl)cyclohexane-1-carboxylate (Aldlab Chemicals, cat#JPM2-1 1253: 102 mg, 0.409 mmol), potassium carbonate (56.6 mg, 0.409 mmol), potassium iodide (22.64 mg, 0.136 mmol) and benzyltriethylammonium chloride (31.1 mg, 0.136 mmol). The mixture was then stirred at 75 °C overnight. The solvent was removed and the crude residue was redissolved in methanol/THF/water (0.5/0.5/0.2 mL). LiOH hydrate (20 mg) was added and the mixture was stirred at rt for 5 h. The mixture was diluted with acetonitrile/water, acidified to pH = 2 and purified by prep HPLC (pH = 2, acetonitrile/water+TFA) to provide the desired compound as its TFA salt.

**LC-MS** calculated for C42H48CIN8O4 (M+H)+: m/z = 763.3; found 763.4.

**Example 49**

cis-4-((2-(2-chloro-2'-methyl-3'-(3-(pyrrolidin-1-ylmethyl)-1,7-naphthyridin-8-ylamino)biphenyl-3-ylcarbamoyl)-1-methyl-6,7-dihydro-1H-imidazo[4,5-c]pyridine-5(4H)-yl)methyl)cyclohexanecarboxylic acid

![Chemical Structure]

**Step 1:** N-(3-bromo-2-methylphenyl)-3-(pyrrolidin-1-ylmethyl)-1,7-naphthyridin-8-amine

A mixture of 8-((3-bromo-2-methylphenyl)amino)-1,7-naphthyridine-3-carbaldehyde (Example 9, Step 1: 0.342 g, 1.0 mmol) and pyrrolidine (0.107 g, 1.500 mmol) in CH2Cl2 (8.0 mL) was stirred at rt for 10 min. Sodium triacetoxyborohydride (0.424 g, 2.000 mmol) was then added and the mixture was stirred at rt for 2 h. The mixture was diluted with CH2Cl2, washed with 1 N NaOH, water, brine, and the organic phase was separated and dried over Na2SO4, filtered and concentrated under reduced pressure. The product was purified by column chromatography eluting with C8/H2N4 (9:1). LC-MS calculated for C22H22BrN4 (M+H)+: m/z = 397.1; found 397.2.

**Step 2:** tert-butyl 2-(2-chloro-2'-methyl-3'-(3-(pyrrolidin-1-ylmethyl)-1,7-naphthyridin-8-ylamino)biphenyl-3-ylcarbamoyl)-1-methyl-6,7-dihydro-1H-imidazo[4,5-c]pyridine-5(4H)-carboxylate
A mixture of tert-butyl 2-((2-chloro-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)carbamoyl)-1-methyl-1,4,6,7-tetrahydro-5H-imidazo[4,5-c]pyridine-5-carboxylate (Example 47, Step 1: 1.0 g, 1.935 mmol), N-(3-bromo-2-methylphenyl)-3-(pyrrolidin-1-ylmethyl)-1,7-naphthyridin-8-amine (0.846 g, 2.128 mmol), dichloro[l,l’-bis(dicyclohexylphosphino)ferrocene]palladium(II) (0.146 g, 0.193 mmol) and cesium fluoride (1.470 g, 9.67 mmol) in t-BuOH (3.00 mL)/water (1.2 mL) was evacuated and backfilled with N2 3 times. The reaction mixture was stirred at 105 °C for 2 h. The mixture was diluted with ethyl acetate and washed with water, dried over Na2SO4, filtered, and concentrated under reduced pressure. The product was purified by column chromatography eluting with CH2Cl2/MeOH (9:1). LC-MS calculated for C39H44CIN8O3 (M+H)+: m/z = 707.3; found 707.5.

Step 3: N-(2-chloro-2’-methyl-3’-(3-(pyrrolidin-1-ylmethyl)-1,7-naphthyridin-8-ylamino)biphenyl-3-yl)-1-methyl-4,5,6,7-tetrahydro-lH-imidazo[4,5-c]pyridine-2-carboxamide

This compound was prepared using a similar procedure as described for Example 47, Step 4 with tert-butyl 2-(2-chloro-2’-methyl-3’-(3-(pyrrolidin-1-ylmethyl)-1,7-naphthyridin-8-ylamino)biphenyl-3-ylcarbamoyl)-1-methyl-6,7-dihydro-1H-indazole[4,5-c]pyridine-5(4H)-carboxylate replacing tert-butyl (i?)-2-((2-chloro-3’-((3-((3-hydroxy-pyrrolidin-1-yl)methyl)-1,7-naphthyridin-8-yl)amino)-2’-methyl-[l’-biphenyl]-3-yl)carbamoyl)-1-methyl-1,4,6,7-tetrahydro-5H-imidazo[4,5-c]pyridine-5-carboxylate. LC-MS calculated for C34H36CIN8O (M+H)+: m/z = 607.3; found 607.4.

Step 4: cis-4-((2-chloro-2’-methyl-3’-(3-(pyrrolidin-1-ylmethyl)-l, 7-naphthyridin-8-ylamino)biphenyl-3-ylcarbamoyl)-1-methyl-6, 7-dihydro-IH-imidazo[4,5-c]pyridin-5(4H)-yl)methyl)cyclohexanecarboxylic acid
This compound was prepared using a similar procedure as described for Example 48 with \( \text{N}-(2\text{-chloro-2'-methyl-3'}-(3\text{-pyrrolidin-1-ylmethyl})-7\text{-naphthyridin-8-ylamino)}\text{-biphenyl-3-yl)}\text{-methyl-4,5,6,7tetrahydro-1H-imidazo[4,5-c]pyridine-2-carboxamide replacing (i?)\text{-N}(2\text{-chloro-3'}-(3\text{-((3-hydroxypyrrolidin-1-yl)methyl)-1,7-naphthyridin-8-ylamino)}\text{-2'-methyl-}[l,r\text{-biphenyl}]-3\text{-yl)}\text{-methyl-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridine-2-carboxamide.} \) LC-MS calculated for C42H48CIN8O3 (M+H)\(^+\): m/z = 747.4; found 747.5.

**Example 50**

\( \text{m} \equiv \text{s-4-(2-(2-chloro-3'-(3-(((S)-1-hydroxypropan-2-ylamino)methyl)-1,7-naphthyridin-8-ylamino)-2'-methylbiphenyl-3-ylcarbamoyl)-1-methyl-6,7-dihydro-1H-imidazo[4,5-c/pyridin-5(4H)-yl)methyl)cyclohexanecarboxylic acid} \)

**Step 1:** tert-butyl 2-(2-chloro-3'-(3-(hydroxymethyl)-1,7-naphthyridin-8-ylamino)-2'-methylbiphenyl-3-ylcarbamoyl)-1-methyl-6,7-dihydro-1H-imidazo[4,5-c/pyridin-5(4H)-yl)methyl)cyclohexanecarboxylic acid

A mixture of tert-butyl 2-(2-chloro-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)carbamoyl)-1-methyl-1,4,6,7-tetrahydro-5 \( \text{H-imidazo[4,5-c]pyridine-5-carboxylate} \) (Example 47, Step 1: 1.0 g, 1.935 mmol), (8-(3-bromo-2-methylphenyl)amino)-1,7-naphthyridin-3-yl)methanol (Affinity Research Chemicals, #ARI-0169: 0.733 g, 2.128 mmol), dichloro[I, 1'-bis(dicyclohexylphosphino)ferrocene]palladium(II) (0.146 g, 0.193 mmol) and cesium fluoride (1.470 g, 9.67 mmol) in \( \text{/BuOH} \) (3.00 mL) /water (1.2 mL) was evacuated and backfilled with N23 times. The reaction was stirred at 105 °C for 2 h. The mixture was diluted with ethyl acetate and washed with water, brine, dried over Na2SO4, and concentrated under reduced pressure. The product was purified by column chromatography.
eluting with CH$_2$Cl$_2$/EtOAc (1:1). LC-MS calculated for C$_{35}$H$_{37}$ClN$_7$O$_4$ (M+H$^+$): m/z = 654.2; found 654.2.

**Step 2:** N-(2-chloro-3′-(3-(hydroxymethyl)-1,7-naphthyridin-8-ylamino)-2′-methylbiphenyl-3-yl)-l-methyl-4, 5, 6, 7-tetrahydro-lH-imidazo[4,5-c]pyridine-2-carboxamide

This compound was prepared using a similar procedure as described for Example 47.

**Step 4** with tert-butyl 2-(2-chloro-3′-(3-(hydroxymethyl)-1,7-naphthyridin-8-ylamino)-2′-methylbiphenyl-3-ylcarbamoyl)-l-methyl-6,7-dihydro-l H-imidazo[4,5-c]pyridine-5(4 H)-carboxylate replacing tert-butyl (i?)-2-((2-chloro-3′-((3-hydroxypropyridin-l-yl)methyl)-1,7-naphthyridin-8-yl)amino)-2′-methyl-l ,r-biphenyl]-3-yl)carbamoyl]-l-methyl-l,4,6,7-tetrahydro-5 H-imidazo[4,5-c]pyridine-5-carboxylate. LC-MS calculated for C$_{30}$H$_{29}$ClN$_7$O$_2$ (M+H$^+$): m/z = 554.2; found 554.2.

**Step 3:** trans-methyl 4-((2-(2-chloro-3′-(3-(hydroxymethyl)-1,7-naphthyridin-8-ylamino)-2′-methylbiphenyl-3-ylcarbamoyl)-l-methyl-6,7-dihydro-lH-imidazo[4,5-c]pyridin-5(4H)-yl)methyl)cyclohexanecarboxylate

To a mixture of N-(2-chloro-3′-((3-(hydroxymethyl)-1,7-naphthyridin-8-yl)amino)-2′-methyl-l ,r-biphenyl]-3-yl)-l-methyl-4,5,6,7-tetrahydro-lH-imidazo[4,5-c]pyridine-2-carboxamide (0.075 g, 0.135 mmol) and methyl fraes-4-formylocyclohexane-1-carboxylate (Ark Pharm, cat#AK-50935: 0.046 g, 0.271 mmol) in CH$_2$Cl$_2$ (1.0 mL) was added triethylamine (0.039 mL, 0.677 mmol), and the resulting mixture was stirred at 40 °C for 30 min. Sodium triacetoxyborohydride (0.086 g, 0.406 mmol) was added and stirred at rt for 4 h. The mixture was diluted with CH$_2$Cl$_2$ and washed with 1 N NaOH, water, and brine. The organic phase was concentrated under reduced pressure and the crude product was purified by column chromatography eluting with CH$_2$Cl$_2$/MeOH (9:1). LC-MS calculated for C$_{39}$H$_{43}$ClN$_7$O$_4$ (M+H$^+$): m/z = 708.3; found 708.4.
Step 4: trans-methyl 4-((2-(2-chloro-3′-((3-formyl-1,7-naphthyridin-8-ylamino)-2′-methylbiphenyl-3-yl)carbamoyl)-1-methyl-6,7-dihydro-[1H-imidazo[4,5-c]pyridin-5(4H)-yl)methyl)cyclohexanecarboxylate

Manganese dioxide (0.313 g, 3.60 mmol) was added to a solution of methyl trans-4-((2-((2-chloro-3′-((3-(hydroxymethyl)-1,7-naphthyridin-8-yl)amino)-2′-methyl-1,1'-biphenyl)-3-yl)carbamoyl)-1-methyl-1,4,6,7-tetrahydro-[1H-imidazo[4,5-c]pyridin-5-yl)methyl)cyclohexane-1-carboxylate (0.17 g, 0.240 mmol) in CH2Cl2 (5.0 mL) and the mixture was stirred at 45 °C for 5 h. The mixture was diluted with CH2Cl2, filtered through Celite® and then concentrated under reduced pressure. The crude product which was purified by column chromatography eluting with CH2Cl2/MeOH (9:1). LC-MS calculated for C39H41CIN7O4 (M+H)+: m/z = 706.3; found 706.4.

Step 5: trans-4-((2-(2-chloro-3′-((3-(((S)-1-hydroxypropan-2-yl)amino)methyl)-1,7-naphthyridin-8-ylamino)-2′-methylbiphenyl-3-yl)carbamoyl)-1-methyl-6,7-dihydro-[1H-imidazo[4,5-c]pyridin-5(4H)-yl)methyl)cyclohexanecarboxylic acid

A mixture of methyl trans-4-((2-((2-chloro-3′-((3-formyl-1,7-naphthyridin-8-ylamino)-2′-methylbiphenyl-3-yl)carbamoyl)-1-methyl-1,4,6,7-tetrahydro-[1H-imidazo[4,5-c]pyridin-5(4H)-yl)methyl)cyclohexane-1-carboxylate (0.010 g, 0.014 mmol) and (5)-2-aminopropan-1-ol (Aldrich, cat#A76206: 5.32 mg, 0.071 mmol) in CH2Cl2 (1.0 mL) was stirred for 30 min at rt. Sodium triacetoxyborohydride (9.0 mg, 0.042 mmol) was added and the mixture was stirred at rt overnight. The solvent was removed and the crude material was redissolved in methanol/THF/water (0.5/0.5/0.2 mL). LiOH monohydrate (40 mg) was added and the mixture was stirred at rt for 5 h. The mixture was diluted with acetonitrile/water, acidified to pH = 2 and purified by prep HPLC (pH = 2, acetonitrile/water+TFA) to provide the desired compound as its TFA salt. LC-MS calculated for C41H48CIN8O4 (M+H)+: m/z = 751.3; found 751.4.

Example 51
This compound was prepared using a similar procedure as described for Example 50 with (S)-2-aminopropan-1-ol (Ark Pharm, cat#AK-88109) replacing (S)-2-aminopropan-1-ol in Step 5. LC-MS calculated for C43H50CIN8O4 (M+H)+: m/z = 777.4; found 777.4.

Example 52

trans 4-(2-(2-(2-chloro-3'-(3-(((R)-3-hydroxypyrrolidin-1-yl)methyl)-1,7-naphthyridin-8-ylamino)-2'-methylbiphenyl-3-ylcarbamoyl)-1-methyl-6,7-dihydro-1H-imidazo[4,5-c]pyridin-5(4H)-yl)ethyl)cyclohexanecarboxylic acid

This compound was prepared using a similar procedure as described for Example 47 with methyl 4-(2-oxoethyl)cyclohexane-1-carboxylate (Enamine, cat#EN300-198655) replacing methyl fra-s-4-formylicyclohexane-1-carboxylate in Step 5 as a mixture of diastereomers. The diastereomers were separated using prep HPLC (pH = 2, acetonitrile/water+TFA), with the trans isomer eluting first in the column, peak 1; retention time on analytical LCMS (pH=2, acetonitrile/water+TFA) t_r = 0.80 min; LC-MS calculated for C43H50CIN8O4 (M+H)+: m/z = 777.4; found 777.4.

Example 53

cis 4-(2-(2-(2-chloro-3'-(3-(((R)-3-hydroxypyrrolidin-1-yl)methyl)-1,7-naphthyridin-8-ylamino)-2'-methylbiphenyl-3-ylcarbamoyl)-1-methyl-6,7-dihydro-1H-imidazo[4,5-c]pyridin-5(4H)-yl)ethyl)cyclohexanecarboxylic acid
This compound was prepared using a similar procedure as described for Example 52. The diastereomers were separated using prep HPLC (pH = 2, acetonitrile/water+TFA), with the minor cis isomer eluting later in the column. **peak 2**: retention time on analytical LCMS (pH=2, acetonitrile/water+TFA) \( t_r = 0.82 \text{ min} \); LC-MS calculated for C43H50CIN8O4 (M+H)^+: m/z = 777.4; found 777.4.

**Example 54**

3-(2-(2-chloro-3'-(3-(((S)-3-hydroxypyrrolidin-1-yl)methyl)-1,7-naphthyridin-8-ylamino)-2'-methylbiphenyl-3-ylcarbamoyl)-1-methyl-6,7-dihydro-1H-imidazo[4,5-c]pyridin-5(4H)-yl)butanoic acid

This compound was prepared using a similar procedure as described for Example 47 with methyl 3-oxobutanoate (Aldrich, cat#537365) replacing methyl trans-A-formylcyclohexane-1-carboxylate in Step 5. LC-MS calculated for C38H42CIN8O4 (M+H)^+: m/z = 709.3; found 709.2.

**Example 55**

cis 4-(2-(2-chloro-3'-(3-(((S)-3-hydroxypyrrolidin-1-yl)methyl)-1,7-naphthyridin-8-ylamino)-2'-methylbiphenyl-3-ylcarbamoyl)-1-methyl-6,7-dihydro-1H-imidazo[4,5-c]pyridin-5(4H)-yl)methyl)cyclohexanecarboxylic acid
Step 1: \(N\)-(2-chloro-3'-(3-formyl-1,7-naphthyridin-8-ylamino)-2'-methylbiphenyl-3-yl)-l-methyl-4, 5, 6, 7-tetrahydro-IH-imidazo[ 4,5-c]pyridine-2-carboxamide

TFA (2.0 mL, 26.0 mmol) was added to a solution of tert-butyl 2-(2-chloro-3'-(3-formyl-1,7-naphthyridin-8-yl)amino)-2'-methyl-[ 1,1'-biphenyl]-3-yl)carbamoyl]-l-methyl-1,4,6,7-tetrahydro-5 H-imidazo[4,5-c]pyridine-5-carboxylate (Example 45, Step 2 : 0.20 g, 0.307 mmol) in CH2Cl2 (1.0 mL) at rt and the the reaction was stirred for 30 min. The solvent was removed under vacuum and the crude TFA salt was used directly in the next step without further purification. LC-MS calculated for C30H27CIN7O2 (M+H)^+ : m/z = 552.2; found 552.1.

Step 2: cis-methyl 4-((2-(2-chloro-3'-(3-formyl-1,7-naphthyridin-8-ylamino)-2'-methylbiphenyl-3-yl)carbamoyl)-l-methyl-6, 7-dihydro-IH-imidazo[ 4,5-c]pyridin-5(4H)-yl)methyl)cyclohexanecarboxylate

To a mixture of N-(2-chloro-3'-(3-formyl-1,7-naphthyridin-8-yl)amino)-2'-methyl-[ 1,1'-biphenyl]-3-yl)-l-methyl-4, 5, 6, 7-tetrahydro-IH-imidazo[4,5-c]pyridine-2-carboxamide (150.0 mg, 0.272 mmol) in DMF (2.0 mL) was added methyl cis-4-(((methylsulfonyl)oxy)methyl)cyclohexane-1-carboxylate (Aldlab Chemicals, cat#JPM2-11253: 136 mg, 0.543 mmol), potassium carbonate (113 mg, 0.815 mmol), potassium iodide (45.1 mg, 0.272 mmol), and benzyltriethylammonium chloride (61.9 mg, 0.272 mmol). The resulting mixture was then stirred at 75 °C overnight. The mixture was diluted with CH2Cl2 and then washed with water and brine. The organic phase was dried over MgSO4, filtered, and concentrated under reduced pressure. The product was purified by column chromatography eluting with CH2Cl2/MeOH (9:1). LC-MS calculated for C39H41CIN7O4 (M+H)^+ : m/z = 706.3; found 706.4.

Step 3: cis-4-((2-(2-chloro-3'-(3-((S)-3-hydroxypyrrolidin-1-yl)methyl)-1,7-naphthyridin-8-ylamino)-2'-methylbiphenyl-3-yl)carbamoyl)-l-methyl-6, 7-dihydro-IH-imidazo[ 4,5-c]pyridin-5(4H)-yl)methyl)cyclohexanecarboxylic acid
A mixture of methyl cis-4-((2-(2-chloro-3’-((3-formyl-1,7-naphthyridin-8-yl)amino)-2’-methyl-[1,1’-biphenyl]-3-yl) carbamoyl)-1-methyl-1,4,6,7-tetrahydro-5H-imidazo[4,5-c]pyridin-5-yl)methyl)cyclohexane-1-carboxylate (0.010 g, 0.014 mmol) and (S)-pyrrolidin-3-ol (Combi-Blocks, cat#SS-7948, 1.234 mg, 0.014 mmol) in CH2Cl2 (1.0 mL) was stirred for 30 min and then sodium triacetoxyborohydride (9.00 mg, 0.042 mmol) was added and stirred at rt overnight. The solvent was removed and the crude was redissolved in methanol/THF/water (0.5/0.5/0.2 mL). LiOH monohydrate (40 mg) was added and the mixture was stirred at rt for 5 h. The mixture was diluted with acetonitrile/water, acidified to pH = 2 and purified by prep HPLC (pH = 2, acetonitrile/water+TFA) to provide the desired compound as its TFA salt. LC-MS calculated for C42H48CIN8O4 (M+H)+: m/z = 763.3; found 763.5.

Example 56

cis 4-((2-(2-chloro-3’-((i?)-3-hydroxy-3-methylpyrrolidin-1-yl)methyl)-1,7-naphthyridin-8-ylamino)-2’-methylbiphenyl-3-ylcarbamoyl)-1-methyl-6,7-dihydro-1H-imidazo[4,5-c]pyridin-5(4H)-yl)methyl)cyclohexanecarboxylic acid

This compound was prepared using a similar procedure as described for Example 55 with (i?)-3-methylpyrrolidin-3-ol (Ark Pharm, cat#AK100499) replacing (S)-pyrrolidin-3-ol in Step 3. LC-MS calculated for C43H50CIN8O4 (M+H)+: m/z = 777.3; found 777.3.

Example 57

(i?)-4-((2-(2-chloro-3’-((3-hydroxy-3-methylpyrrolidin-1-yl)methyl)-1,7-naphthyridin-8-ylamino)-2’-methylbiphenyl-3-ylcarbamoyl)-1-methyl-6,7-dihydro-1H-imidazo[4,5-c]pyridin-5(4H)-yl)cyclohexanecarboxylic acid
Step 1: tert-butyl 4-(2-(2-chloro-3’-(3-(hydroxymethyl)-1,7-naphthyridin-8-ylamino)-2’-methylbiphenyl-3-ylcarbamoyl)-1-methyl-6,7-dihydro-1H-imidazo[4,5-c]pyridin-5(4H)-yl)cyclohexanecarboxylate

To a mixture of N-(2-chloro-3’-(3-(hydroxymethyl)-1,7-naphthyridin-8-yl)amino)-2’-methyl[1’,r-biphenyl]-3-yl)-1-methyl-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridine-2-carboxamide (Example 50, Step 2: 0.275 g, 0.496 mmol) and tert-butyl 4-oxocyclohexane-1-carboxylate (Ark Pharm, cat#AK-40114: 0.197 g, 0.993 mmol) in CH2Cl2 (1.0 mL) was added triethylamine (0.142 mL, 2.482 mmol). The resulting mixture was stirred at 40 °C for 30 min and then sodium triacetoxyborohydride (0.316 g, 1.489 mmol) was added and stirred at rt overnight. The mixture was diluted with CH2Cl2 and washed with 1 N NaOH, water, and brine. The solvent was removed and the product was purified by column chromatography eluting with CH2Cl2/MeOH (9:1). LC-MS calculated for C41H47CIN7O4 (M+H)+: m/z = 736.3; found 736.3.

Step 2: tert-butyl 4-(2-(2-chloro-2’-methyl-3’-(3-((methylsulfonyloxy)methyl)-l,7-naphthyridin-8-ylamino)biphenyl-3-ylcarbamoyl)-l-methyl-6,7-dihydro-1H-imidazo[4,5-c]pyridin-5(4H)-yl)cyclohexanecarboxylate
Methanesulfonyl chloride (0.023 g, 0.204 mmol) was added to a solution of tert-butyl 4-(2-((2-chloro-3-((3-hydroxymethyl)-1H-naphthyridin-8-yl)amino)-2'-methyl-[1,1']-biphenyl]-3-yl)carbamoyl)-l-methyl-1,4,6,7-tetrahydro-5H-imidazo[4,5-c]pyridin-5-yl)cyclohexane-1-carboxylate (0.10 g, 0.136 mmol) and triethylamine (0.057 mL, 0.407 mmol) in CH2Cl2 (2.0 mL) at 0 °C and then the reaction was stirred at this temperature for 30 min. The mixture was quenched by adding aqueous saturated NaHCO3, and the aqueous phase was extracted with methylene chloride. The combined organic layers were dried over Na2SO4, filtered, and concentrated under reduced pressure, and the crude product was used directly in the next step. LC-MS calculated for C42H49CIN7O6S (M+H)⁺: m/z = 814.3; found 814.3.

Step 3: (R)-4-(2-(2-chloro-3-((3-hydroxy-3-methylpyrrolidin-1-yl)methyl)-1,7-naphthyridin-8-ylamino)-2'-methylbiphenyl-3-ylcarbamoyl)-l-methyl-6,7-dihydro-1H-imidazof[4,5-c]pyridin-5(4H)-yl)cyclohexanecarboxylic acid

(iR)-3-methylpyrrolidin-3-ol (Ark Pharm, cat#AK100499: 2.484 mg, 0.025 mmol) was added to a solution of tert-butyl 4-(2-(2-chloro-2'-methyl-3'-((3-(((methylsulfonyl)oxy)methyl)-1H-naphthyridin-8-yl)amino)-[1,1']-biphenyl]-3-yl)carbamoyl)-l-methyl-1,4,6,7-tetrahydro-5H-imidazo[4,5-c]pyridin-5-yl)cyclohexane-1-carboxylate (0.020 g, 0.025 mmol) and triethylamine (0.021 mL, 0.147 mmol) in CH2Cl2 (0.8 mL) at rt. The reaction was stirred at 30 °C for 1 h. The solvent was removed and the residue was treated with 4 N HCl in dioxane (1.0 mL) for 2 h. The mixture was diluted with acetonitrile/water, acidified to pH = 2 and purified by prep HPLC (pH = 2, acetonitrile/water+TFA) to provide the desired compound as its TFA salt. LC-MS calculated for C42H49CIN7O6S (M+H)⁺: m/z = 814.3; found 814.3.
Example 58

(S)-4-(2-(2-chloro-3’-(3-((3-hydroxy-3-methylpyrrolidin-1-yl)methyl)-1H-7-naphthyridin-8-ylamino)-2’-methylbiphenyl-3-ylcarbamoyl)-1-methyl-6,7-dihydro-1H-imidazo[4,5-c]pyridin-5(4H)-yl)cyclohexanecarboxylic acid

This compound was prepared using a similar procedure as described for Example 57 with (S)-3-methylpyrrolidin-3-ol (J&W Pharma, cat#75R0496) replacing (R)-3-methylpyrrolidin-3-ol in Step 3. LC-MS calculated for C₄₂H₄₈CIN₈O₄ (M+H)+: m/z = 763.3; found 763.3.

Example 59

trans 4-(2-(2-(2-chloro-3’-(3-(((I)-l-hydroxypropan-2-ylamino)methyl)-1H-7-naphthyridin-8-ylamino)-2’-methylbiphenyl-3-ylcarbamoyl)-1-methyl-6,7-dihydro-1H-imidazo[4,5-c]pyridin-5(4H)-yl)ethyl)cyclohexanecarboxylic acid

Step 1: trans methyl 4-(2-(2-(2-chloro-3’-(3-((hydroxymethyl)-1H-7-naphthyridin-8-ylamino)-2’-methylbiphenyl-3-ylcarbamoyl)-1-methyl-6,7-dihydro-1H-imidazo[4,5-c]pyridin-5(4H)-yl)ethyl)cyclohexanecarboxylate
To a mixture of N-(2-chloro-3’-((3-(hydroxymethyl)-1,7-naphthyridin-8-yl)amino)-2'-methyl-[1,1’-biphenyl]-3-yl)-1-methyl-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridine-2-carboxamide (Example 50, Step 2: 0.075 g, 0.135 mmol) and methyl trans-4-(2-oxoethyl)cyclohexane-1-carboxylate (Enamine, cat#EN300-1 98655: 0.050 g, 0.271 mmol) in CH$_2$Cl$_2$ (1.0 mL) was added triethylamine (0.039 mL, 0.677 mmol) and the resulting mixture was stirred at 40 °C for 30 min. Sodium triacetoxyborohydride (0.086 g, 0.406 mmol) was added and stirred at rt for 4 h. The mixture was diluted with CH$_2$Cl$_2$ and washed with 1 N NaOH, water, and brine. The solvent was removed and the product was purified by column chromatography eluting with CH$_2$Cl$_2$/MeOH (9:1). LC-MS calculated for C$_{40}$H$_{45}$CIN$_7$O$_4$ (M+H)$^+$: m/z = 722.3; found 722.4.

Step 2: trans methyl 4-(2-((2-chloro-2'-methyl-3'-(3-((methylsulfonyloxy)methyl)-1,7-naphthyridin-8-ylamino)biphenyl-3-ylcarbamoyl)-1-methyl-1,4,6,7-tetrahydro-5H-imidazo[4,5-c]pyridin-5(4H)-yl)ethyl)cyclohexanecarboxylate

Methanesulfonyl chloride (0.024 g, 0.208 mmol) was added to a solution of trans methyl 4-(2-((2-chloro-3’-((3-(hydroxymethyl)-1,7-naphthyridin-8-yl)amino)-2’-methyl-[1,1’-biphenyl]-3-yl)carbamoyl)-1-methyl-1,4,6,7-tetrahydro-5H-imidazo[4,5-c]pyridin-5-yl)ethyl)cyclohexane-1-carboxylate (0.10 g, 0.138 mmol) and triethylamine (0.058 mL, 0.415 mmol) in CH$_2$Cl$_2$ (2.0 mL) at 0 °C and then the reaction was stirred at this temperature for 30 min. The mixture was quenched by adding aqueous saturated NaHCO$_3$, and the reaction was extracted with methylene chloride. The combined organic layers were dried over Na$_2$SO$_4$, filtered, and concentrated under reduced pressure. The crude product was used directly in the next step. LC-MS calculated for C$_{41}$H$_{47}$CIN$_7$O$_6$S (M+H)$^+$: m/z = 800.3; found 800.3.

Step 3: trans-4-(2-((2-chloro-3’-((R)-1-hydroxypropan-2-ylamino)methyl)-1,7-naphthyridin-8-ylamino)-2’-methylbiphenyl-3-ylcarbamoyl)-1-methyl-1,4,6,7-tetrahydro-5H-imidazo[4,5-c]pyridin-5(4H)-yl)ethyl)cyclohexanecarboxylic acid

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(5)-2-aminopropan-1-ol (Aldrich, cat#297682: 1.9 mg, 0.025 mmol) was added to a solution of trans methyl 4-(2-(2-chloro-2'-methyl-3'-((3-(((methylsulfonyl)oxy)methyl)-1,7-naphthyridin-8-yl)amino)-l,r-biphenyl)-3-yl)carbamoyl)-l-methyl-l,4,6,7-tetrahydro-5H-imidazo[4,5-c]pyridin-5-yl)ethyl)cyclohexane-1-carboxylate (20 mg, 0.025 mmol) and triethylamine (0.021 mL, 0.147 mmol) in CH2Cl2 (0.8 mL) at rt. The reaction was stirred at 30 °C for 1 h. The solvent was removed and the residue was dissolved in MeOH/THF/water (0.4/0.4/0.2 mL). LiOH monohydrate (40 mg) was added and stirred at rt for 4 h. The mixture was diluted with acetonitrile/water, acidified to pH = 2 and purified by prep HPLC (pH = 2, acetonitrile/water+TFA) to provide the desired compound as its TFA salt. LC-MS calculated for C42H50CIN8O4 (M+H) +: m/z = 765.4; found 765.5.

Example 60

trans 4-(2-(2-chloro-3'-((S)-3-hydroxy-3-methylpyrrolidin-1-yl)methyl)-l,7-naphthyridin-8-ylamino)-2'-methylbiphenyl-3-ylcarbamoyl)-l-methyl-6,7-dihydro-1H-imidazo[4,5-c]pyridin-5(4H)-yl)ethyl)cyclohexanecarboxylic acid

This compound was prepared using a similar procedure as described for Example 59 with (5)-2-aminopropan-1-ol (Aldrich, cat#A76206) replacing (5)-2-aminopropan-1-ol in Step 3. LC-MS calculated for C42H50CIN8O4 (M+H) +: m/z = 765.4; found 765.5.

Example 61

ira<s-4-(2-(2-chloro-3'-((i?)-3-hydroxy-3-methylpyrrolidin-1-yl)methyl)-l,7-naphthyridin-8-ylamino)-2'-methylbiphenyl-3-ylcarbamoyl)-l-methyl-6,7-dihydro-1H-imidazo[4,5-c]pyridin-5(4H)-yl)ethyl)cyclohexanecarboxylic acid
This compound was prepared using a similar procedure as described for Example 59 with (i?)-3-methylpyrrolidin-3-ol (Ark Pharm, cat#AK100499) replacing (i?)-2-aminopropan-1-ol in Step 3. LC-MS calculated for C44H52CIN8O4 (M+H)⁺: m/z = 791.4; found 791.4.

Example 62
(i?)-4-(2-(3'-(3-hydroxypyrrolin-l-yl)methyl)-7-naphthyridin-8-ylamino)-2,2'-dimethylbiphenyl-3-ylcarbamoyl)-l-methyl-6,7-dihydro-lH-imidazo[4,5-c]pyridin-5(4H)-yl-1-methylcyclohexanecarboxylic acid

Step 1: (R)-tert-butyl 2-(3'-((3-hydroxypyrrolidin-l-yl)methyl)-l, 7-naphthyridin-8-ylamino)-2,2'-dimethylbiphenyl-3-ylcarbamoyl)-l-methyl-6,7-dihydro-lH-imidazo[4,5-c]pyridine-5(4H)-carboxylate

A mixture of tert-butyl 1-methyl-2-((2-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)carbamoyl)-1,4,6,7-tetrahydro-5H-imidazo[4,5-c]pyridine-5-carboxylate (Example 14, Step 3: 0.25 g, 0.504 mmol), (i?)-1-((8-((3-bromo-2-methylphenyl)amino)-1,7-naphthyridin-3-yl)methyl)pyrrolidin-3-ol (Example 9, Step 2: 0.229 g, 0.554 mmol), dichloro[l. 1'-bis(dicyclohexylphosphino)ferrocene]palladium(II) (0.038 g, 0.050 mmol), and cesium fluoride (0.383 g, 2.52 mmol) in i-BuOH (8.00 mL)/water (3.0 mL) was evacuated and backfilled with N₂. The evacuation/backfill sequence was repeated two more times, and then the reaction was stirred at 105 °C for 2 h. The mixture was diluted
with ethyl acetate and washed with water and brine. The organic phase was dried over MgSO4, filtered, and concentrated. The product was purified by column chromatography eluting with CH2Cl2/MeOH (9:1). LC-MS calculated for C40H47N8O4 (M+H) +: m/z = 703.4; found 703.6.

5 Step 2: (R)-N-(3’-(3-(3-hydroxy pyrrolidin-1-yl)methyl)-1,7-naphthyridin-8-ylamino)-2,2’-dimethylbiphenyl-3-yl)-l-methyl-4,5,6,7-tetrahydro-lH-imidazo[4,5-c]pyridine-2-carboxamide

This compound was prepared using a similar procedure as described for Example 47.

Step 4 with (R)-tert-butyl 2-(3’-(3-(3-hydroxy pyrrolidin-1-yl)methyl)-1,7-naphthyridin-8-ylamino)-2,2’-dimethylbiphenyl-3-ylcarbamoyl)-l-methyl-6,7-dihydro-l H-imidazo[4,5-c]pyridine-5(4H)-carboxylate replacing tert-butyl (i?)-2-((2-chloro-3’-((3-(3-hydroxy pyrrolidin-1-yl)methyl)-1,7-naphthyridin-8-ylamino)-2’-methyl-1,1’-biphenyl)-3-yl)carbamoyl)-l-methyl-1,4,6,7-tetrahydro-5 H-imidazo[4,5-c]pyridine-5-carboxylate. LC-MS calculated for C35H39N8O2 (M+H) +: m/z = 603.3; found 603.3.

Step 3: (R)-4-(2’-(3-(3-hydroxy pyrrolidin-1-yl)methyl)-7-naphthyridin-8-ylamino)-2,2’-dimethylbiphenyl-3-ylcarbamoyl)-l-methyl-6J-dihydro-lH-imidazo[4,5-4]pyridin-5(4H)-yl)-1-methylcyclohexane carboxylic acid

To a mixture of (i)?)-N-(3’-(3-(3-hydroxy pyrrolidin-1-yl)methyl)-1,7-naphthyridin-8-yl)andno)-2,2’-dimethyl-[l r-biphenyl]-3-yl)-l-methyl-4,5,6,7-tetrahydro-lH-imidazo[4,5-c]pyridine-2-carboxamide (0.025 g, 0.041 mmol) and 1-methyl-4-oxocyclohexane-l-carboxylic acid (Aurum Pharmatech, cat#U31985: 6.48 mg, 0.041 mmol) in CH2Cl2 (1.0 mL) was added triethylamine (0.012 mL, 0.207 mmol), and the reaction was stirred for 30 min at 40 °C. Sodium triacetoxyborohydride (0.026 g, 0.124 mmol) was added and stirred at 40 °C for 4 h. The mixture was diluted with acetonitrile/water, acidified to pH = 2 and purified by prep HPLC (pH = 2, acetonitrile/water+TFA) to provide the two desired compounds as TFA salts.

Peak 1: retention time on analytical LCMS (pH=2, acetonitrile/water+TFA) \( t_r = 0.686 \) min; LC-MS calculated for C43H51N8O4 (M+H) +: m/z = 743.4; found 743.4.
Peak 2: retention time on analytical LCMS (pH=2, acetonitrile/water+TFA) $t_r = 0.700$ min; LC-MS calculated for C43H51N8O4 (M+H)$^+$: m/z = 743.4; found 743.4.

Example 63

\[ \text{ira=}-4-(2-(3'-(3-((\text{H})-3-hydroxypyrrolidin-l-yl)methyl)-1,7-naphthyridin-8-ylamino)-2,2'-dimethylbiphenyl-3-ylcarbamoyl)-1-methyl-6,7-dihydro-l \text{-imidazo}[4,5-c/pyridin}-5(4H)-yl)ethyl)cyclohexanecarboxylic \text{ acid} \]

To a mixture of (i?)-N-(3'-(3-(hydroxypyrrolidin-l-yl)methyl)-1,7-naphthyridin-8-yl)amino)-2,2'-dimethyl[41J-biphenyl]-3-yl)-1-methyl-4,5,6j tetrahydro-l \text{-imidazo}[4,5-c]pyridine-2-carboxamide (Example 62, Step 2: 0.025 g, 0.041 mmol) and methyl trans 4-(2-oxoethyl)cyclohexane-l-carboxylate (Enamine, cat#:EN300-198655: 0.015 g, 0.083 mmol) in CH2Cl2 (1.0 mL) was added triethylamine (0.012 mL, 0.207 mmol). The resulting mixture was stirred for 10 min and then sodium triacetoxyborohydride (0.026 g, 0.124 mmol) was added and stirred at rt overnight. The solvent was removed and the crude was redissolved in methanol/THF/water (0.5/0.5/0.2 mL). LiOH monohydrate (20 mg) was added and the mixture was stirred at rt for 3 h. The mixture was diluted with acetonitrile/water, acidified to pH = 2, and purified by prep HPLC (pH = 2, acetonitrile/water+TFA) to provide the desired compound as its TFA salt. LC-MS calculated for C44H55N8O4 (M+H)$^+$: m/z = 757.4; found 757.6.

Example 64

(i?)-4-(2-(3'-(3-(hydroxypyrrolidin-l-yl)methyl)-1,7-naphthyridin-8-ylamino)-2,2'-dimethylbiphenyl-3-ylcarbamoyl)-1-methyl-6,7-dihydro-l \text{-imidazo}[4,5-c]pyridin-5(4H)-yl)cyclohexanecarboxylic \text{ acid}
To a mixture of (i)-N-(3′-((3-hydroxypyrrolidin-1-yl)methyl)-1,7-naphthyridin-8-yl)amino)-2,2′-dimethyl-[1J′-biphenyl]-3-yl)-1-methyl-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridine-2-carboxamide (Example 62, Step 2: 0.275 g, 0.456 mmol) and tert-butyl 4-oxocyclohexane-1-carboxylate (Ark Pharm, cat#AK-401 14: 0.181 g, 0.912 mmol) in CH2Cl2 (1.0 mL) was added triethylamine (0.131 mL, 2.281 mmol). The mixture was stirred at 40 °C for 30 min and then sodium triacetoxyborohydride (0.290 g, 1.369 mmol) was added and stirred at rt overnight to provide (R)-tert-buty1 4-((2-(3′-((3-hydroxypyrrolidin-1-yl)methyl)-1,7-naphthyridin-8-ylamino)-2,2′-dimethylbiphenyl-3-ylcarbamoyl)-1-methyl-6,7-dihydro-1H-imidazo[4,5-c]pyridin-5(4H)-yl)ethyl)cyclohexanecarboxylate as a mixture of cis & trans isomers which were separated by prep-HPLC (pH = 10, acetonitrile/water+NFUOH):

**Peak 1**: retention time on analytical LCMS (pH=10, acetonitrile/water+NLUOH), \( t_r = 1.78 \) min; LC-MS calculated for \( C_{14}H_{35}N_8O_4 \) (M+H)+: \( m/z = 785.4 \); found 785.4. **Peak 2**: retention time on analytical LCMS (pH=10, acetonitrile/water +NH4OH), \( t_r = 1.82 \) min; LC-MS calculated for \( C_{46}H_{57}N_8O_4 \) (M+H)+: \( m/z = 785.4 \); found 785.4.

The fractions of each peak were combined, concentrated under reduced pressure, and the resulting residues were then treated with 4 N HCl (in dioxane) for 4 h. The respective mixtures were diluted with acetonitrile/water, acidified to pH = 2 and purified by prep HPLC (pH = 2, acetonitrile/water+TFA) to provide each isomer as its TFA salt.

**Peak 1**: retention time on analytical LCMS (pH=2, acetonitrile/water+TFA), \( t_r = 0.656 \) min; LC-MS calculated for \( C_{42}H_{49}N_8O_4 \) (M+H)+: \( m/z = 729.4 \); found 729.4.

**Peak 2**: retention time on analytical LCMS (pH=2, acetonitrile/water+TFA), \( t_r = 0.663 \) min; LC-MS calculated for \( C_{42}H_{49}N_8O_4 \) (M+H)+: \( m/z = 729.4 \); found 729.4.

Example 65

rare-4-(2-(2,2′-dichloro-3′-((i?-)^-hydroxypyrrolidin-1-yl)methyl)-1,7-naphthyridin-8-ylamino)biphenyl-3-ylcarbamoyl)-1-methyl-6,7-dihydro-1H-imidazo [4,5-c] pyridin-5(4H)-yl)ethyl)cyclohexanecarboxylic acid
**Step 1:** (R)-tert-butyl 2-((2,2′-dichloro-3′-(3-((3-hydroxypyrrolidin-1-yl)methyl)-1,7-naphthyridin-8-ylamino)biphenyl-3-ylcarbamoyl)-1-methyl-6,7-dihydro-1H-imidazo[4,5-c]pyridine-5(4H)-carboxylate

A mixture of tert-butyl 2-((2-chloro-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)carbamoyl)-1-methyl-1,4,6,7-tetrahydro-5H-imidazo[4,5-c]pyridine-5-carboxylate (Example 47, Step 1: 0.050 g, 0.097 mmol), (i)-l-((8-((3-bromo-2-chlorophenyl)amino)-1,7-naphthyridin-3-yl)methyl)pyrrolidin-3-ol (Example 22, Step 4: 0.046 g, 0.106 mmol), dichloro[1,r-bis(dicyclohexylphosphino)ferrocene]palladium(II) (7.31 mg, 9.67 μmol) and cesium fluoride (0.073 g, 0.484 mmol) in 1-BuOH (8.00 mL)/water (3.0 mL) was evacuated and flushed with N2 3 times. The reaction was stirred at 105 °C for 2 h. The mixture was diluted with ethyl acetate and washed with water and brine. The organic layer was separated, dried over Na2SO4, filtered, and concentrated under reduced pressure. The product was purified by column chromatography eluting with CH2Cl2/MeOH (9:1). LC-MS calculated for C38H41Cl2N8O4 (M+H) +: m/z = 743.3; found 743.3.

**Step 2:** (R)-N-(2,2′-dichloro-3′-(3-((3-hydroxypyrrolidin-1-yl)methyl)-1,7-naphthyridin-8-ylamino)biphenyl-3-yl)-1-methyl-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridine-2-carboxamide

This compound was prepared using a similar procedure as described for Example 47, Step 4 with (R)-tert-butyl 2-((2,2′-dichloro-3′-(3-((3-hydroxypyrrolidin-1-yl)methyl)-1,7-naphthyridin-8-ylamino)biphenyl-3-ylcarbamoyl)-1-methyl-6,7-dihydro-1H-imidazo[4,5-c]pyridine-5(4H)-carboxylate.
c]pyridine-5(4 H)-carboxylate replacing tert-butyl ((R)-2-((2-chloro-3'-((3-((3-hydroxypyrrolidin-l -yl)methyl)-1,7-naphthyridin-8-yl)amino)-2'-methyl-[1,1'-biphenyl]-3-yl)carbamoyl)-l-methyl-4,6j4etrahydro-5 H-imidazo[4,5-c]pyridine-5-carboxylate. LC-MS calculated for C33H33Cl2N8O2 (M+H)+: m/z = 643.2; found 643.2.

Step 3: Trans 4-(2-(2,(2',2''-dichloro-3'-(3-(((R)-3-hydroxypyrrolidin-l-yl)methyl)-1,7-naphthyridin-8-ylamino)biphenyl-3-ylcarbamoyl)-l-methyl-6,7-dihydro-lH-imidazo[4,5-c]pyridin-5(4H)-yl)ethyl)cyclohexanecarboxylic acid

This compound was prepared using a similar procedure as described for Example 63 with ((R))-N-(2,2'-dichloro-3'-(3-((3-hydroxyppyrrolidin-l-yl)methyl)-l,7-naphthyridin-8-yl)amino)-[l,1'-biphenyl]-3-yl-l-methyl-4,5,6j4etrahydro-l H-imidazo[4,5-c]pyridine-2-carboxamide replacing ((R))-N-(3'-(3-hydroxyppyrrolidin-l -yl)methyl)-1,7-naphthyridin-8-ylamino)-2,2''-dimethyl-[l,1'-biphenyl]-3-yl-l-methyl-4,5,6j4etrahydro-l H-imidazo[4,5-c]pyridine-2-carboxamide. LC-MS calculated for C42H47Cl2N8O4 (M+H)+: m/z = 797.3; found 797.2.

Example 66

trans 4-(2-(2',chboro-3'-(3-(((R)-3-hydroxyppyrrolidin-l-yl)methyl)-l,7-naphthyridin-8-ylamino)-2-methylbiphenyl-3-ylcarbamoyl)-l-methyl-6,7-dihydro-lH-imidazo[4,5-c]pyridin-5(4H)-yl)ethyl)cyclohexanecarboxylic acid

Step 1: (R)-tert-butyl 2-(2',chboro-3'-(3-((3-hydroxyppyrrolidin-l-yl)methyl)-l,7-naphthyridin-8-ylamino)-2-methylbiphenyl-3-ylcarbamoyl)-l-methyl-6,7-dihydro-lH-imidazo[4,5-c]pyridine-5(4H)-carboxylate
This compound was prepared using a similar procedure as described for Example 65 with tert-butyl 1-methyl-2-(2-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenylcarbamoyl)-6-fluro-4H-imidazo[4,5-c]pyridine-5(4H)-carboxylate (Example 14, Step 3) replacing tert-butyl 2-(2-chloro-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenylcarbamoyl)-1-methyl-4,6,7,4 tetrahydro-5H-imidazo[4,5-c]pyridine-5-carboxylate in Step 1. LC-MS calculated for C39H44CIN8O4 (M+H)+: m/z = 723.3; found 723.3.

Step 2: (R)-N-(2'-chloro-3'-3-(3-hydroxypyrrolidin-1-yl)methyl)-7-naphthyridin-8-ylamino)-2-methylbiphenyl-3-yl)-l-methyl-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridine-2-carboxamide

This compound was prepared using a similar procedure as described for Example 47 with (R)-tert-butyl 2-((2'-chloro-3'-3-((R)-3-hydroxypyrrolidin-1-yl)methyl)-7-naphthyridin-8-ylamino)-2-methylbiphenyl-3-yl)carbamoyl)-1-methyl-6,7-dihydro-1H-imidazo[4,5-c]pyridine-5-carboxylate replacing tert-butyl (i?-)2-((2-chloro-3'-3-((3-hydroxypyrrolidin-1-yl)methyl)-7-naphthyridin-8-yl)amino)-2'-methyl-[1,1'-biphenyl]-3-yl)carbamoyl)-1-methyl-4,6,7-tetrahydro-5H-imidazo[4,5-c]pyridine-5-carboxylate in Step 4. LC-MS calculated for C34H36CIN8O2 (M+H)+: m/z = 623.3; found 623.3.

Step 3: trans 4-(2-(2'-chloro-3'-3-((R)-3-hydroxypyrrolidin-1-yl)methyl)-7-naphthyridin-8-ylamino)-2-methylbiphenyl-3-yl)carbamoyl)-1-methyl-6,7-dihydro-1H-imidazo[4,5-c]pyridin-5(4H)-yl)ethyl)cyclohexanecarboxylic acid

This compound was prepared using a similar procedure as described for Example 63 with (R)-N-(2'-chloro-3'-3-((3-hydroxypyrrolidin-1-yl)methyl)-7-naphthyridin-8-ylamino)-2-methylbiphenyl-3-yl)-1-methyl-6,7-dihydro-1H-imidazo[4,5-c]pyridine-2-carboxamide replacing (i?-)N-(3'-3-((3-hydroxypyrrolidin-1-yl)methyl)-7-naphthyridin-8-yl)amino)-2',2'-dimethyl-[1',r-biphenyl]-3-yl)-1-methyl-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridine-2-carboxamide. LC-MS calculated for C43H50CIN8O4 (M+H)+: m/z = 777.4; found 777.4.
Example 67

(i?)-l-((4-(2’-chloro-3’-(1,5-dimethyl-4,5,6,7-tetrahydro-lH-imidazo[4,5-c]pyridine-2-carboxamido)-2-methylbiphenyl-3-ylamino)pyrido[3,2-i]pyrimidin-7-yl)methyl)-3-methylpyrrolidine-3-carboxylic acid

Step 1: tert-butyl 2-(3’-amino-2-chloro-2’-methylbiphenyl-3-ylcarbamoyl)-1-methyl-6,7-dihydro-1H-imidazo[4,5-c]pyridine-5(4H)-carboxylate

A mixture of tert-butyl 2-((3-bromo-2-chlorophenyl)carbamoyl)-1-methyl-4,6,7-tetrahydro-5H-imidazo[4,5-c]pyridine-5-carboxylate (Example 31, Step 3: 0.470 g, 1.0 mmol), 2-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (Combi-Blocks, cat#PN-9127: 0.233 g, 1.000 mmol), dichloro[l,l’-bis(diphenylphosphino)ferrocene]palladium (II) dichloromethane adduct (0.082 g, 0.100 mmol) and sodium carbonate (0.212 g, 2.000 mmol) in dioxane (6 mL)/water (2 mL) was evacuated under vacuum and flushed with N2 3 times. The reaction was stirred at 110 °C overnight. The mixture was diluted with ethyl acetate and washed with saturated NaHCO3, water, and brine. The organic phase was separated and dried over Na2SO4, filtered, and concentrated under reduced pressure. The product was purified by silica gel chromatography using CH2Cl2/EtOAc (1:1). LC-MS calculated for C26H31ClN5O3 (M+H)+: m/z = 496.2; found 496.1.

Step 2: tert-butyl 2-(3’-(7-bromopyrido[3,2-d]pyrimidin-4-ylamino)-2-chloro-2’-methylbiphenyl-3-ylcarbamoyl)-1-methyl-6, 7-dihydro-1H-imidazo[4,5-c]pyridine-5(4H)-carboxylate
7-Bromo-4-chloropyrido[3,2-cf]pyrimidine (Synthonix, cat#B0473: 0.217 g, 0.887 mmol) was added to a mixture of tert-butyl 2-((3′-amino-2-chloro-2′-methyl-[1′,1′-biphenyl]-3-yl)carbamoyl)-1-methyl-1,4,6,7-tetrahydro-5 H-imidazo[4,5-c]pyridine-5-carboxylate (0.40 g, 0.806 mmol) and triethylamine (0.225 mL, 1.613 mmol) in 2-propanol (5.0 mL) at rt. The reaction was stirred at 100 °C for 2 h. Diethyl ether (5.0 mL) was added to the reaction mixture and the resulting precipitate was filtered and dried to provide the crude product which was used directly in the next step without further purification. LC-MS calculated for C33H33BrClN8O (M+H)+: m/z = 703.2; found 703.3.

Step 3: tert-butyl 2-(2-chloro-2′-methyl-3′-(7-vinylpyrido[3,2-d]pyrimidin-4-ylamino)biphenyl-3-ylcarbamoyl)-l-methyl-6,7-dihydro-lH-imidazo[4,5-c]pyridine-5(4H)-carboxylate

A mixture of tert-butyl 2-((3′-((7-bromopyrido[3,2-d]pyrimidin-4-yl)amino)-2-chloro-2′-methyl-[1′,1′-biphenyl]-3-yl)carbamoyl)-1-methyl-1,4,6,7-tetrahydro-5 H-imidazo[4,5-c]pyridine-5-carboxylate (0.35 g, 0.497 mmol), 4,4,5,5-tetramethyl-2-vinyl-1,3,2-dioxaborolane (Aldrich, cat#663348: 0.115 g, 0.746 mmol), dichloro[1′,1′-bis(diphenylphosphino)ferrocene]-palladium (II) dichloromethane adduct (0.041 g, 0.050 mmol) and sodium carbonate (0.105 g, 0.994 mmol) in dioxane (6 mL)/water (2 mL) was evacuated under vacuum and flushed with N2 3 times. The reaction was stirred at 110 °C for 2 h. The mixture was diluted with ethyl acetate and washed with saturated NaHCO3, water, and brine. The organic phase was separated, dried over Na2SO4, and concentrated under reduced pressure. The product was purified by column chromatography using CH3Cl/EtOAc (7:3). LC-MS calculated for C35H36ClN8O3 (M+H)+: m/z = 651.3; found 651.2.

A vial was charged with tert-butyl 2-((2-chloro-2'-methyl-3'-((7-vinylpyrido[3,2-d]pyrimidin-4-yl)amino)-[1,1'-biphenyl]-3-yl)carbamoyl)-1-methyl-1,4,6,7-tetrahydro-5 H-imidazo[4,5-c]pyridine-5-carboxylate (10.0 mg, 0.015 mmol), a stir bar, THF (2.0 mL) and water (0.8 mL). To this suspension was added a 4% w/w mixture of osmium tetroxide in water (12.0 µL, 1.529 µmol). The reaction was stirred for 5 min then sodium periodate (16.42 mg, 0.077 mmol) was added. After stirring at rt for 1 h, the reaction was quenched with a saturated aqueous solution of sodium thiosulfate. The mixture was then extracted with ethyl acetate (2 X 10 mL), and the combined organic layers were washed with brine, dried over Na2S04, filtered, and concentrated in vacuo. The crude residue was used directly in the next step. LC-MS calculated for C34H34CIN8O4 (M+H) + : m/z = 653.2; found 653.2.

**Step 5: (R)-3-tetrahydro-5 H-imidazo[4,5-c]pyridine-5-carboxylic acid (J&W PharmLab, cat#75R0495 : 0.01 5 g, 0.115 mmol) was added to a suspension of tert-butyl 2-((2-chloro-3'-((7-formylpyrido[3,2-d]pyrimidin-4-yl)amino)-2'-methyl-[1,1'-biphenyl]-3-yl)carbamoyl)-1-methyl-1,4,6,7-tetrahydro-5 H-imidazo[4,5-c]pyridine-5-carboxylate (0.025 g, 0.038 mmol) in CH2Cl2 (1.0 mL). Triethylamine (0.043 mL, 0.306 mmol) was added and the mixture was stirred at rt for 1 h. At this time sodium triacetoxyborohydride (0.024 g, 0.115 mmol) was added and then stirred at rt for 2 h. The reaction was quenched with water, extracted with CH2Cl2/PrOH, and the layers were separated. The organic phase was dried over Na2S04, filtered, and concentrated under reduced pressure. The resulting crude residue was redissolved in CH2Cl2 (0.2 mL) and then TFA (0.5 mL) was added and the reaction was stirred at rt for 30 min. The solvent was removed and the crude product was used directly in the next step. LC-MS calculated for C35H37CIN9O3 (M+H) + : m/z = 666.3; found 666.5.
Step 6: (R)-l-((4-(2’-chloro-3’-(1,5-dimethyl-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridine-2-carboxamido)-2-methylbiphenyl-3-ylamino)pyrido[3,2-d]pyrimidin-7-yl)methyl)-3-methylpyrrolidine-3-carboxylic acid

Formaldehyde (4.5 mg, 0.15 mmol) was added to a mixture of (i?-)l-((4-(2’-chloro-2-methyl-3’-(1-methyl-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridine-2-carboxamido)biphenyl-3-ylamino)pyrido[3,2-d]pyrimidin-7-yl)methyl)-3-methylpyrrolidine-3-carboxylic acid (20 mg, 0.03 mmol) in CH2Cl2 (1.0 mL) followed by the addition of triethylamine (0.021 mL, 0.15 mmol). The mixture was stirred at rt for 10 min. At this time sodium triacetoxyborohydride (19 mg, 0.09 mmol) was added and then stirred at rt for 30 min. The mixture was diluted with acetonitrile/water, acidified to pH = 2 and purified by prep HPLC (pH = 2, acetonitrile/water+TFA) to provide the desired compound as its TFA salt. LC-MS calculated for C36H39CIN9O3 (M+H)+: m/z = 680.3; found 680.4.

Example 68

(i?)-4-(2-(2-chloro-3’-(7-((3-hydroxypyrrolidin-1-yl)methyl)pyrido[3,2-d]pyrimidin-4-ylamino)-2’-methylbiphenyl-3-ylcarbamoyl)-1-methyl-6,7-dihydro-1H-imidazo[4,5-c]pyridin-5(4H)-yl)-l-methylcyclohexanecarboxylic acid

Step 1: (R)-tert-butyl 2-(2-chloro-3’-(7-((3-hydroxypyrrolidin-1-yl)methyl)pyrido[3,2-d]pyrimidin-4-ylamino)-2’-methylbiphenyl-3-ylcarbamoyl)-1-methyl-6,7-dihydro-1H-imidazo[4,5-c]pyridine-5(4H)-carboxylate

A mixture of tert-butyl 2-(2-chloro-3’-(7-formylpyrido[3,2-c]pyrimidin-4-yl)amino)-2’-methyl-1,1’-biphenyl-3-yl)carbamoyl)-1-methyl-1,4,6,7-tetrahydro-5H-imidazo[4,5-c]pyridine-5-carboxylate (Example 67, Step 4: 0.10 g, 0.153 mmol) and (R)-pyrrolidin-3-ol (Combi-Blocks, cat#AM-2005: 0.027 g, 0.306 mmol) in CH2Cl2 (8.0 mL)
was stirred at rt for 10 min. Sodium triacetoxyborohydride (0.097 g, 0.459 mmol) was then added and the mixture was stirred at rt for 2 h. The mixture was diluted with CH2Cl2, washed with 1 N NaOH, water, and brine. The organic phase was dried over Na2S04, filtered and concentrated. The product was purified by silica gel chromatography eluting with CH2Cl2/MeOH (9: 1). LC-MS calculated for C38H43CIN9O4 (M+H)+: m/z = 724.3; found 724.5.

Step 2: (R)-N-(2-chloro-3’-(7-((3-hydroxypyrrolidin-1-yl)methyl)pyrido[3,2-d]pyrimidin-4-ylamino)-2’-methylbiphenyl-3-yl)-l-methyl-4, 5, 6, 7-tetrahydro-lH-imidazo[4,5-c]pyridine-2-carboxamide

This compound was prepared using a similar procedure as described for Example 47 with (R)-tert-butyl\((2-chloro-3’-(7-((3-hydroxypyrrolidin-1-yl)methyl)pyrido[3,2-d]pyrimidin-4-ylamino)-2’-methylbiphenyl-3-yl)carbamoyl)-l-methyl-6,7-dihydro-lH-imidazo[4,5-c]pyridine-5(4H)-carboxylate replacing tert-butyl (i?-)2-(2-chloro-3’-((3-(3-hydroxypyrrolidin-1-yl)methyl)-1,7-naphthyridin-8-yl)amino)-2’-methyl-[1,1’-biphenyl]-3-yl)carbamoyl)-l-methyl-1,4,6,7-tetrahydro-5 H-imidazo[4,5-c]pyridine-5-carboxylate in Step 4. LC-MS calculated for C33H35CIN9O2 (M+H)+: m/z = 624.3; found 624.2.

Step 3: (R)-4-((2-chloro-3’-(7-((3-hydroxypyrrolidin-1-yl)methyl)pyrido[3,2-d]pyrimidin-4-ylamino)-2’-methylbiphenyl-3-yl)carbamoyl)-l-methyl-6,7-dihydro-lH-imidazo[4,5-c]pyridin-5(4H)-yl)-l-methylcyclohexanecarboxylic acid

This compound was prepared using a similar procedure as described for Example 62 with (i?-)N(2-chloro-3’-(7-((3-hydroxypyrrolidin-1-yl)methyl)pyrido[3,2-ii]pyrimidin-4-ylatinono)-2’-methylbiphenyl-3-yl)-l-methyl-4,5,6,7-tetrahydro-l H-indazol[4,5-c]pyridine-2-carboxamide replacing (i?-)N(3’-((3-(3-hydroxypyrrolidin-1-yl)methyl)-l,7-naphthyridin-8-yl)amino)-2,2’-dimethyl-[1,r-biphenyl]-3-yl)-l-methyl-4,5,6,7-tetrahydro-l H-imidazo[4,5-c]pyridine-2-carboxamide in Step 3.

Peak 1: retention time on analytical LCMS (pH=2, acetonitrile/water+TFA) \(t_r = 0.796\) min; LC-MS calculated for C41H47CIN9O4 (M+H)+: m/z = 764.3; found 764.4.

Peak 2: retention time on analytical LCMS (pH=2, acetonitrile/water+TFA) \(t_r = 0.805\) min; LC-MS calculated for C41H47CIN9O4 (M+H)+: m/z = 764.3; found 764.4.
Example 69

Trans 4-((2-(2-chloro-3’-((i?)-3-hydroxypyrrolidin-1-yl)methyl)pyrido[3,2-
rf]pyrimidin-4-ylamino)-2’-methylbiphenyl-3-ylcarbamoyl)-1-methyl-6,7-dihydro-l H-
imidazo[4,5-c]pyridin-5(4H)-yl)methyl)cyclohexanecarboxylic acid

This compound was prepared using a similar procedure as described for Example 47 with (i?)-N-(2-chloro-3’-((3-hydroxy)pyrrolidin-1-yl)methyl)pyrido[3,2-d]pyrimidin-4-
ylamino)-2’-methylbiphenyl-3-yl)-l-methyl-4,5,6,7-tetrahydro-l H-imidazo[4,5-c]pyridine-2-
carboxamide (Example 68, Step 2) replacing (i?)-N-(2-chloro-3’-((3-hydroxy)pyrrolidin-1-
yl)methyl)-1,7-naphthyridin-8-ylamino)-2’-methyl-[l,r-biphenyl]-3-yl)-l-methyl-4,5,6,7-
tetrahydro-l H-imidazo[4,5-c]pyridine-2-carboxamide in Step 5. LC-MS calculated for
C41H47CIN9O4 (M+H)+: m/z = 764.3; found 764.5.

Example 70

(i?)-l-((5-(3’-((i?)-3-hydroxypyrrolidin-1-yl)methyl)-1,7-naphthyridin-8-ylamino)-
2,2’-dimethylbiphenyl-3-ylamino)pyrido[4,3-Z]pyrazin-2-yl)methyl)pyrrolidine-3-
carboxylic acid

Step 1: 5-(3-chloro-2-methylphenylamino)pyrido[4,3-b]pyrazin-2(1H)-one

In a vial was combined 3-chloro-2-methylaniline (Aldrich, cat# 101621: 351 mg,
2.478 mmol), 5-chloropyrido[3,4-Z]pyrazin-2(1 H)-one (Ark Pharm, cat#AK329687: 500mg,
2.75 mmol), isopropanol (5.0 mL), and sulfuric acid (0.147 mL, 2.75 mmol). The vial was
sealed, then the reaction was heated to 100 °C for 1 hour. The mixture was cooled to rt,
quenched with sat. NaHCO₃, diluted with ethyl acetate and the layers were separated. The aqueous layer was further extracted with ethyl acetate, and the combined organic layers were washed with brine, dried over MgSO₄, and filtered. The filtrate was concentrated in vacuo and the crude residue was purified by silica gel chromatography (50% EtOAc/hexanes) to provide the desired compound as a yellow oil. LC-MS calculated for C₁₄H₁₂CIN₄O (M+H): m/z = 287.1; found 287.1.

**Step 2: 2-bromo-N-(3-chloro-2-methylphenyl)pyrido[4,3-b]pyrazin-5-amine**

![Chemical Structure]

In a vial, a mixture of 5-(3-chloro-2-methylphenylamino)pyrido[4,3-b]pyrazin-2(1H)-one (200 mg, 0.698 mmol), phosphorus (V) oxybromide (1000 mg, 3.49 mmol), and MeCN (6.0 mL) was stirred at 80 °C for 4 hours. The mixture was cooled to rt, quenched with sat. NaHCO₃, diluted with ethyl acetate and the layers were separated. The aqueous layer was further extracted with ethyl acetate, and the combined organic layers were washed with brine, dried over MgSO₄, and filtered. The filtrate was concentrated in vacuo and the crude residue was purified by silica gel chromatography (20% EtOAc/hexanes) to provide the desired compound as a brown oil. LC-MS calculated for C₁₄H₁₀ClBrN₄ (M+H): m/z = 349.0; found 349.0.

**Step 3: N-(3-chloro-2-methylphenyl)-2-vinylpyrido[4,3-b]pyrazin-5-amine**

![Chemical Structure]

In a vial, a mixture of 2-bromo-N-(3-chloro-2-methylphenyl)pyrido[4,3-b]pyrazin-5-amine (30 mg, 0.086 mmol), 4,4,5,5-tetramethyl-2-vinyl-1,3,2-dioxaborolane (Aldrich, cat#663348: 29.1 µL, 0.172 mmol), sodium carbonate (27.3 mg, 0.257 mmol), palladiumtetrakis (9.92 mg, 8.58 µmol) and 1,4-dioxane (2.0 mL) was stirred at 90 °C for 2 hours. The mixture was cooled to rt, diluted with ethyl acetate and washed with water and brine, dried over MgSCN, and filtered. The filtrate was concentrated in vacuo and the crude
residue was purified by silica gel chromatography (20% EtOAc/hexanes) to provide the desired compound as a brown oil. LC-MS calculated for C16H14CIN4 (M+H)^+: m/z = 297.1; found 297.1.

Step 4: 5-(3-chloro-2-methylphenylamino)pyrido[4,3-b]pyrazine-2-carbaldehyde

A 10 mL vial was charged with N-(3-chloro-2-methylphenyl)-2-vinylpyrido[4,3-Z]pyrazin-5-amine (25.6 mg, 0.086 mmol), 1,4-dioxane (2 mL) and water (2 mL). A 4% osmium tetroxide solution in water (38.2 µL, 6.01 µmol) was added to the reaction mixture. After 5 min, sodium periodate (147 mg, 0.686 mmol) was added. The reaction was stirred at rt for 2 hours before being quenched with sat. NaHCCb. The resulting mixture was extracted with DCM, and the combined organic layers were washed with water and brine, dried over MgSO4, and filtered. The filtrate was concentrated in vacuo and the crude residue was used directly in next step without further purification. LC-MS calculated for C15H12CIN4O (M+H)^+: m/z = 299.1; found 299.1.

Step 5: (R)-l-(5-(3-chloro-2-methylphenylamino)pyrido[4,3-b]pyrazin-2-yl)methyl]pyrrolidine-3-carboxylic acid

A 10 mL vial was charged with 5-(3-chloro-2-methylphenylamino)pyrido[4,3-Z]pyrazine-2-carbaldehyde (10.0 mg, 0.033 mmol), (i?)-pyrrolidine-3-carboxylic acid (Combi-Blocks, cat#ST-7698: 5.8 mg, 0.050 mmol) and DCM (1 mL). Triethylamine (9.3 µL, 0.067 mmol) and sodium triacetoxyborohydride (14.2 mg, 0.067 mmol) were added subsequently. The resulting reaction mixture was stirred at rt overnight before being quenched with sat. NaHCCb. The resulting mixture was extracted with a 3:1 DCM/IPA mixture, and the combined organic layers were washed with water and brine, dried over MgSO4, and filtered. The filtrate was concentrated in vacuo and the crude residue was used
directly in next step without further purification. LC-MS calculated for C20H21CIN5O2 (M+H)⁺: m/z = 398.1; found 398.1.

**Step 6:** (R)-l-((5-(3’-((fR)-3-hydroxyprrolidin-l-yl)methyl)-l, 7-naphthyridin-8-ylamino)-2,2’-dimethylbiphenyl-3-ylamino)pyrido[4,3-b]pyrazin-2-yl)methyl]pyrrolidine-3-carboxylic acid

A mixture of (i)-1-((5-(3-chloro-2-methylphenylamino)pyridin-2-yl)methyl]pyrrolidine-3-carboxylic acid (10.0 mg, 0.025 mmol), (i?)-l-((8-((2-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)amino)-l,7-naphthyridin-3-yl)methyl]pyrrolidin-3-ol {Example 37, step 9: 23.14 mg, 0.050 mmol), XPhos Pd G2 (2.0 mg, 2.51 μmol), and sodium carbonate (5.3 mg, 0.050 mmol) in 1,4-dioxane (1 mL) and water (0.2 mL) was degassed and sealed. It was stirred at 90 °C overnight. The reaction mixture was cooled then diluted with methanol, then purified with prep-LC-MS (pH = 2, acetonitrile/water+TFA) to give the desired product as its TFA salt. LC-MS calculated for C40H42N9O3 (M+H)⁺: m/z = 696.3; found 696.3.

**Example 71**

(3i?)-l-((8-(2,2’-dimethyl-3’-(3-(pyrrolidin-2-yl)-l,7-naphthyridin-8-ylamino)biphenyl-3-ylamino)-l,7-naphthyridin-3-yl)methyl]pyrrolidine-3-carboxylic acid

**Step 1:** tert-butyl 4-(8-chloro-1,7-naphthyridin-3-yl)-4-oxobutylcarbamate

To a solution of 3-bromo-8-chloro-l,7-naphthyridine (PharmaBlock, cat#PBLJ2743 : 100.2 mg, 0.411 mmol) in THF (10 mL) was added w-butyllithium (1.6 M, 0.26 mL, 0.411 mmol) dropwise at -78 °C. After stirring at this temperature for 1 hour, tert-butyl 2-oxopyrrolidine-1-carboxylate (0.14 mL, 0.821 mmol) was added. The reaction was further stirred at -78 °C for 2 hours. After completion, the reaction mixture was quenched by adding sat. NH4Cl, which was then extracted with EtOAc. The combined organic layers were washed...
with water and brine, dried over MgSO₄, and filtered. The filtrate was concentrated in vacuo
and the crude residue was purified by silica gel chromatography (80% EtOAc/hexanes) to
provide the desired compound as a brown oil. LC-MS calculated for C₁₇H₂₁CIN₃O₃ (M+H)⁺:
m/z = 350.1; found 350.1.

Step 2: tert-butyl 2-(8-(3-bromo-2-methylphenylamino)-1,7-naphthyridin-3-yl)pyrrolidine-1-carboxylate

In a vial combined 3-bromo-2-methylaniline (Aldrich, cat#530018: 51.1 mg, 0.274 mmol), tert-butyl (4-(8-chloro-1,7-naphthyridin-3-yl)-4-oxobutyl)carbamate (80.0 mg, 0.229 mmol), isopropanol (2.0 mL), and sulfuric acid (13.4 µL, 0.252 mmol). The vial was
sealed, then the reaction was heated to 100 °C for 1 hour. The mixture was cooled to rt,
quenched with solid NaHCO₃, diluted with ethyl acetate and filtered. The filtrate was
concentrated in vacuo and the crude residue was dissolved in DCM (2.0 mL). Triethylamine
(63.8 µL, 0.457 mmol) and sodium triacetoxyborohydride (72.7 mg, 0.343 mmol) were added
to the above solution. The reaction was stirred at rt overnight before being quenched with sat.
NaHCO₃. The resulting mixture was extracted with 3:1 DCM/IPA mixture, and the combined
organic layers were washed with water and brine, dried over MgSO₄, and filtered. The filtrate
was concentrated in vacuo and the crude residue was dissolved in dry DCM (4.0 mL)
followed by addition of triethylamine (0.064 mL, 0.458 mmol) and Boc-anhydride (0.10 g,
0.458 mmol). The reaction mixture was stirred at rt for 2 hours before being quenched with sat.
NaHCO₃. The resulting mixture was extracted with DCM, and the combined organic
layers were washed with water and brine, dried over MgSCn, and filtered. The filtrate was
concentrated in vacuo and the residue was purified by silica gel chromatography (50% EtOAc/hexanes) to provide the desired compound as a yellow oil. LC-MS calculated for
C₂₄H₂₈BrN₁₀ 2(M+H)⁺: m/z = 483.1; found 483.1.

Step 3: tert-butyl 2-(8-(3’-(3-(hydroxymethyl)-1,7-naphthyridin-8-ylamino)-2,2’-dimethylbiphenyl-3-ylamino)-1,7-naphthyridin-3-yl)pyrrolidine-1-carboxylate
A mixture of tert-butyl 2-(8-(3-bromo-2-methylphenylamino)-1,7-naphthyridin-3-yl)pyrrolidine-1-carboxylate (200 mg, 0.414 mmol), (8-(2-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenylamino)-1,7-naphthyridin-3-yl)methanol (Example 20, step 3) 23.1 mg, 0.050 mmol), tetrakis(triphenylphosphine)palladium(0) (47.8 mg, 0.041 mmol), and sodium carbonate (88 mg, 0.827 mmol) in 1,4-dioxane (10 mL) and water (2 mL) was degassed and sealed. It was stirred at 100 °C overnight. The reaction mixture was cooled and then diluted with EtOAc. The organic layer was washed with water and brine, dried over MgSO4, and filtered. The filtrate was concentrated in vacuo and the crude residue was purified by silica gel chromatography (90% EtOAc/hexanes) to provide the desired compound as a brown oil. LC-MS calculated for C40H42N7O3 (M+H)+: m/z = 668.3; found 668.3.

**Step 4: tert-butyl 2-(8-(3'-(3-formyl-1,7-naphthyridin-8-ylamino)-2,2'-dimethylbiphenyl-3-ylamino)-1,7-naphthyridin-3-yl)pyrrolidine-1-carboxylate**

To a stirred solution of tert-butyl 2-(8-(3'-(3-(hydroxymethyl)-1,7-naphthyridin-8-ylamino)-2,2'-dimethylbiphenyl-3-ylamino)-1,7-naphthyridin-3-yl)pyrrolidine-1-carboxylate (276 mg, 0.414 mmol) in DCM (10.0 mL) was added manganese dioxide (719 mg, 8.27 mmol). The resulted mixture was stirred at 45 °C for 2 hours, then filtered. The filtrate was concentrated under reduced pressure. The residue was used in the next step directly without further purification. LC-MS calculated for C40H42N7O3 (M+H)+: m/z = 666.3; found 666.3.

**Step 5: (3R)-1-(8-(2,2'-dimethyl-3'-(3-(pyrrolidin-2-yl)-1,7-naphthyridin-8-ylamino)biphenyl-3-ylamino)-1,7-naphthyridin-3-yl)methylpyrrolidine-3-carboxylic acid**

To a solution of tert-butyl 2-(8-(3'-(3-formyl-1,7-naphthyridin-8-ylamino)-2,2'-dimethylbiphenyl-3-ylamino)-1,7-naphthyridin-3-yl)pyrrolidine-1-carboxylate (20 mg, 0.030 mmol) in DCM (1 mL) was added (i?)-pyrrolidine-3-carboxylic acid (Combi-Blocks,
cat#ST-7698: 3.5 mg, 0.030 mmol) and triethylamine (8.4 µl, 0.060 mmol). The mixture was stirred at rt for 60 min, then sodium triacetoxyborohydride (9.6 mg, 0.045 mmol) was added. The resulting mixture was stirred at rt overnight before 1 mL of TFA was added. The reaction mixture was further stirred for 1 h. The reaction mixture was concentrated then purified with prep- LC-MS (pH 2, acetonitrile/water+TFA) to give the desired product as its TFA salt. LC-MS calculated for C40H41N8O2 (M+H)^+: m/z = 665.3; found 665.3.

Example 72

(iR)-l-((8-(2,2'-dichloro-3',3'-((2-hydroxyethylamino)methyl)imidazo[1,2-fl]pyrazin-8-ylamino)biphenyl-3-ylamino)-1,7-naphthyridin-3-yl)methyl)pyrrolidin-3-ol

Step 1: (R)-l-((8-(3'-amino-2,2'-dichlorobiphenyl-3-ylamino)1,7-naphthyridin-3-yl)methyl)pyrrolidin-3-ol

In a vial was combined 2-chloro-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (Example 5, step 1: 0.474 g, 1.870 mmol), (iR)-l-((8-(3'-bromo-2-chlorophenyl)amino)-1,7-naphthyridin-3-yl)methyl)pyrrolidin-3-ol (Example 22, step 4: 0.676 g, 1.559 mmol), sodium carbonate (0.330 g, 3.12 mmol), (l,l'-bis(di-cyclohexylphosphino)ferrocene)-dichloropalladium(II) (Aldrich, cat#ST-7698: 0.023 g, 0.031 mmol), 1,4-dioxane (2.92 mL) and water (0.974 mL). The mixture was degassed, sealed, and heated to 90 °C whilst stirring for 2 h. The mixture was cooled, diluted with EtOAc and filtered through celite. The filtrate was concentrated and purified using flash chromatography (0 → 15% MeOH/DCM). LC-MS calculated for C25H24Cl2N5O (M+H)^+: m/z = 480.1; found 480.2.

Step 2: (R)-l-((8-(3'-bromoimidazo[1,2-alpyrazin-8-ylamino)-2,2'-dichlorobiphenyl-3-ylamino)-1,7-naphthyridin-3-yl)methyl)pyrrolidin-3-ol
In a vial was combined (iR)-l-((8-((3'-amino-2,2'-dichloro-[1 1'-biphenyl]-3-yl)amino)-1,7-naphthyridin-3-yl)methyl)pyrrolidin-3-ol (497 mg, 1.035 mmol) and 3-bromo-8-chloroimidazo[1,2-a]pyrazine (Combi-Blocks, cat# QA-2223: 361 mg, 1.552 mmol). The reactants were diluted with 2-propanol (5173 µL). To this was then added sulfuric acid (83 µL, 1.552 mmol) drop-wise. The reaction mixture was heated to 100 °C overnight. The solvent was removed under reduced pressure. The crude residue was taken back up in a 3:1 chloroform/IPA mixture and was neutralized with a saturated solution of sodium bicarbonate. The aqueous layer was extracted once more with 3:1 chloroform/IPA. The combined organic layers were washed with brine, dried over magnesium sulfate and filtered. The filtrate was concentrated and purified using flash chromatography (0 → 40% MeOH/DCM). LC-MS calculated for C33H29Cl2N8O (M+H)+: m/z = 675.1; found 675.1.

Step 3: (R)-l-((8-(2,2'-dichloro-3'-((3-vinylimidazo[1,2-a]pyrazin-8-yl)amino)biphenyl-3-ylamino)-, 7-naphthyridin-3-yl)methyl)pyrrolidin-3-ol

A mixture of (iR)-l-((8-((3'-((3-bromimidazo[1,2-a]pyrazin-8-yl)amino)biphenyl-3-ylamino)-2,2'-dichloro-[1,1'-biphenyl]-3-yl)amino)-1,7-naphthyridin-3-yl)methyl)pyrrolidin-3-ol (458 mg, 0.677 mmol), 4,4,5,5-tetramethyl-2-vinyl-1,3,2-dioxaborolane (Sigma-Aldrich, cat#633348: 126 µL, 0.745 mmol), sodium carbonate (2.03 mmol) and [1,1'-bis(di-cyclohexylphosphino)ferrocene]dichloropalladium(II) (Aldrich, cat#701 998: 25.7 mg, 0.034 mmol) in 1,4-dioxane (3224 µL) and water (1290 µL) was degassed and sealed. It was stirred at 90 °C for 1.5 h. The crude reaction mixture was diluted with water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over magnesium sulfate and filtered. The filtrate was concentrated under reduced pressure and used without further purification. LC-MS calculated for C33H29Cl2N8O (M+H)+: m/z = 623.2; found 623.4.

Step 4: (R)-8-(2,2'-dichloro-3'-(3-(3-hydroxypyrrolidin-1-yl)methyl)-1, 7-naphthyridin-8-ylamino)biphenyl-3-ylamino)imidazo[1,2-a]pyrazine-3-carbaldehyde
In a vial was combined \((i?)-l-(8-(2,2',dichloro-3'-(3-vinylimidazo[1,2-a]pyrazin-8-yl)amino)-1,l'-biphenyl]-3-yl)amino)-l,7-naphthyridin-3-yl)methyl]pyrrolidin-3-ol \((200 \text{ mg, } 0.321 \text{ mmol})\) and THF \((2053 \mu \text{l})\). The material was sonicated until it was fully in solution. To this, in order, was then added water \((513 \mu \text{l})\), 2,6-lutidine \((191 \mu \text{l}, 1.636 \text{ mmol})\), sodium periodate \(343 \text{ mg, } 1.604 \text{ mmol}\) and potassium osmate dihydrate \((17.73 \text{ mg, } 0.048 \text{ mmol})\). The reaction was allowed to stir at room temperature for 30 min. The reaction was diluted with water and was extracted with ethyl acetate. The combined organic layers were washed with brine, dried over magnesium sulfate, and was filtered. The filtrate was concentrated and purified using flash chromatography \((0 \rightarrow 40\% \text{ MeOH/DCM})\). LC-MS calculated for C32H27Cl2N8O2 \((M+H)^{+}\): 
\[m/z = 625.2; \text{ found 625.2.}\]

**Step 5: (R)-l-(8-(2,2'-dichloro-3'-(3-(hydroxyethylamino)methyl)imidazo[1,2-a]pyrazin-8-ylamino)biphenyl-3-ylamino)-l,7-naphthyridin-3-yl)methyl]pyrrolidin-3-ol**

In a vial \((i?)-8-(2,2'-dichloro-3'-(3-(3-hydroxy[pyrrolidin-1-ylmethyl]-l,7-naphthyridin-8-ylamino)biphenyl-3-yl)amino)imidazo[1,2-a]pyrazine-3-carbaldehyde \((10 \text{ mg, } 0.016 \text{ mmol})\) was combined with ethanolamine \((9.67 \mu \text{l}, 0.160 \text{ mmol})\) and was diluted with methanol \((160 \mu \text{l})\). To this was then added acetic acid \((13.73 \mu \text{l}, 0.240 \text{ mmol})\) followed by sodium cyanoborohydride \((2.009 \text{ mg, } 0.032 \text{ mmol})\) as a solution in methanol \((160 \mu \text{l})\). The reaction was allowed to stir at room temperature for 15 minutes after which time the reaction mixture was further diluted to a final volume of 5 mL with methanol and purified by prep HPLC \((\text{pH }= 2, \text{ acetonitrile/water+TFA})\) to provide the desired compound as the TFA salt. LC-MS calculated for C34H34Cl2N9O2 \((M+H)^{+}\): 
\[m/z = 670.2; \text{ found 670.5.}\]

**Example 73**

\((i?)-l-(8-(2,2'-dimethyl^a'-(3-(pyrrolidin-l-ylmethyl)-l,7-naphthyridin-8-y)lamino)-[l,l'-biphenyl]-3-yl)amino)-l,7-naphthyridin-3-yl)methyl]pyrrolidin-3-ol

This compound was prepared using similar procedures as described for Example 20 with pyrrolidine \((\text{Aldrich, cat#394238})\) replacing \((i?)-pyrrolidin-3-ol\) in Step 6. The reaction mixture was diluted with methanol and purified by prep HPLC \((\text{pH }= 2, \text{ acetonitrile/water+TFA})\) to provide the desired compound as its TFA salt. LC-MS calculated for C40H43N8O \((M+H)^{+}\): 
\[m/z = 651.4; \text{ found 651.3.}\]
Example 74

(S)-1-((8'-(2'-chloro-3'-((3-((i?)-3-hydroxypyrrolidin-1-yl)methyl)-1,7-naphthyridin-8-yl)amino)-2-methyl-[1,1'-biphenyl]-3-yl)amino)-1,7-naphthyridin-3-yl)(methyl)pyrrolidin-3-ol

Step 1: (R)-1-((8-((2-chloro-3'-((3-(hydroxymethyl)-1,7-naphthyridin-8-yl)amino)-2'-methyl-[1,1'-biphenyl]-3-yl)amino)-1,7-naphthyridin-3-yl)methyl)pyrrolidin-3-ol

To a vial was added (8-((2-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)amino)-1,7-naphthyridin-3-yl)methanol (Example 9, Step 3: 0.166 g, 0.424 mmol), (i?)-1-((8-((3-bromo-2-chlorophenyl)amino)-1,7-naphthyridin-3-yl)methyl)pyrrolidin-3-ol (Example 22, Step 4: 0.184 g, 0.424 mmol), 1 M aqueous sodium carbonate (0.848 mmol), tetrakis (0.049 g, 0.042 mmol), and 1,4-dioxane (3.74 mL). The mixture was degassed, sealed, and heated to 110°C whilst stirring for 4 h. The mixture was cooled, diluted with EtOAc and filtered through celite. The filtrate was concentrated and purified by silica gel chromatography (15% MeOH/DCM) to provide the desired product as a yellow solid. LC-MS calculated for C35H33CIN7O2 (M+H)+: m/z = 618.2; found 618.3.

Step 2: (R)-8-((2'-chloro-3'-((3-(hydroxypyrrolidin-1-yl)methyl)-1,7-naphthyridin-8-yl)amino)-2-methyl-[1,1'-biphenyl]-3-yl)amino)-1,7-naphthyridine-3-carbaldehyde

This compound was prepared using similar procedures as described for Example 9 with (i?)-1-((8-((2-chloro-3'-((3-(hydroxymethyl)-1,7-naphthyridin-8-yl)amino)-2'-methyl-[1,1'-biphenyl]-3-yl)amino)-1,7-naphthyridin-3-yl)methyl)pyrrolidin-3-ol replacing (i?)-1-((8-((3'-((3-(hydroxymethyl)-1,7-naphthyridin-8-yl)amino)-2,2'-dimethyl-[1,1'-biphenyl]-3-yl)amino)-1,7-naphthyridin-3-yl)methyl)pyrrolidin-3-ol in Step 5. LC-MS calculated for C35H31CIN7O2 (M+H)+: m/z = 616.2; found 616.3.
Step 3: (S)-l-((8-((2'-chloro-3'-((3-((R)-3-hydroxypropylidin-1-yl)methyl)-1,7-naphthyridin-8-yl)amino)-2-methyl-[1,1'-biphenyl]-3-yl)amino)-1,7-naphthyridin-3-yl)methyl)pyrrolidin-3-ol

To a vial was added (i?)-8-((2'-chloro-3'-((3-((3-hydroxypropylidin-1-yl)methyl)-1,7-naphthyridin-8-yl)amino)-2-methyl-[1,1'-biphenyl]-3-yl)amino)-1,7-naphthyridin e-3-carbaldehyde (0.015 g, 0.024 mmol), (5)-pyrrolidin-3-ol (Combi-Blocks, cat#SS-7948: 6.4 mg, 0.073 mmol), a stir bar, and 1,2-dichloroethane (0.122 mL). The mixture was stirred for 5 min, then sodium triacetoxyborohydride (0.015 g, 0.073 mmol) and acetic acid (0.011 mL, 0.195 mmol) were added. The mixture was stirred for 1 h, then was diluted with methanol and purified by prep HPLC (pH = 2, acetonitrile/water+TFA) to provide the desired compound as its TFA salt. LC-MS calculated for C39H40CIN8O2 (M+H)+: m/z = 687.3; found 687.4.

**Example 75**

(i?)-l-((8-((2'-chloro-3'-((3-((3-hydroxypropylidin-1-yl)methyl)-1,7-naphthyridin-8-yl)amino)-2-methyl-[1,1'-biphenyl]-3-yl)amino)-1,7-naphthyridin-3-yl)methyl)azetidine-3-carboxylic acid

This compound was prepared using similar procedures as described for Example 74 with azetidine-3-carboxylic acid (Aldrich, cat#391131) replacing (5)-pyrrolidin-3-ol in Step 3. The reaction mixture was diluted with methanol and purified by prep HPLC (pH = 2, acetonitrile/water+TFA) to provide the desired compound as its TFA salt. LC-MS calculated for C39H38CIN8O3 (M+H)+: m/z = 701.3; found 7013.

**Example 76**

(i?)-l-((8-((2,2'-dichloro-3'-((3-(((R)-3-hydroxypropylidin-1-yl)methyl)-1,7-naphthyridin-8-yl)amino)-[1,1'-biphenyl]-3-yl)amino)-1,7-naphthyridin-3-yl)methyl)-3-methylpyrrolidin-3-ol
**Step 1**: (8-((3-bromo-2-chlorophenyl)amino)-1,7-naphthyridin-3-yl)methanol

A flask was charged with 8-((3-bromo-2-chlorophenyl)amino)-1,7-naphthyridine-3-carbaldehyde (Example 14, Step 6: 0.586 g, 1.625 mmol), methanol (6.7 mL), and a stir bar. The mixture was cooled to 0 °C, and sodium borohydride (0.255 g, 6.74 mmol) was added portionwise over 1 h. After the final addition, the mixture was warmed to rt and stirred for 1 h. Another portion of sodium borohydride (0.050 g, 1.349 mmol) was added and stirred for 30 min. Saturated aqueous sodium bicarbonate was added (5 mL), and the mixture was further extracted with DCM (2 X 10 mL). The combined organic extracts were dried over MgSO₄, filtered, and concentrated in vacuo. The crude product was purified by silica gel chromatography (0 → 46% EtOAc/hexanes). LC-MS calculated for C₃₅H₂₂BrClN₀ (M+H)^+: m/z = 364.0; found 364.0.

**Step 2**: (8-((2-chloro-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)amino)-1,7-naphthyridin-3-yl)methanol

This compound was prepared using similar procedures as described for Example 9 with (8-((3-bromo-2-chlorophenyl)amino)-1,7-naphthyridin-3-yl)methanol replacing (8-((3-bromo-2-methylphenyl)amino)-1,7-naphthyridin-3-yl)methanol in Step 3. LC-MS calculated for C₂₁H₂₄BCIN₃O₃ (M+H)^+: m/z = 412.2; found 412.2.

**Step 3**: (R)-1-((8-((2,2'-dichloro-3'-((3-(hydroxymethyl)-1,7-naphthyridin-8-yl)amino)-[1,1'-biphenyl]-3-yl)amino)-1,7-naphthyridin-3-yl)methyl)pyrrolidin-3-ol


This compound was prepared using similar procedures as described for Example 74 with (8-((2-chloro-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)amino)-1,7-naphthyridin-3-yl)methanol replacing (8-((2-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)amino)-1,7-naphthyridin-3-yl)methanol in Step 1. LC-MS calculated for C34H30Cl2N7O2 (M+H)^+; m/z = 638.2; found 638.2.

**Step 4:** (R)-8-((2,2'-dichloro-3'-(3-((3-hydroxy)pyrrolidin-1-yl)methyl)-1,7-naphthyridin-3-yl)amino)-[1,1'-biphenyl]-3-yl)amino)-1,7-naphthyridine-3-carbaldehyde

This compound was prepared using similar procedures as described for Example 9 with (i?)-l-((8-(2,2'-dichloro-3'-(3hydroxymethyl)-1J-naphthyridin-8-yl)amino)-[1,1'-biphenyl]-3-yl)amino)-1,7-naphthyridin-3-yl)methyl)pyrrolidin-3-ol replacing (i?)-l-((8-((3-(hydroxymethyl)-1,7-naphthyridin-8-yl)amino)-2,2'-dimethyl-[1,1'-biphenyl]-3-yl)amino)-1,7-naphthyridin-3-yl)methyl)pyrrolidin-3-ol in Step 5. LC-MS calculated for C34H28Cl2N7O2 (M+H)^+; m/z = 636.2; found 636.2.

**Step 5:** (R)-l-((8-((2,2'-dichloro-3'-(3-((R)-3-hydroxypyrrolidin-1-yl)methyl)-1,7-naphthyridin-8-yl)amino)-[1,1'-biphenyl]-3-yl)amino)-1,7-naphthyridine-3-carbaldehyde

To a vial was added (i?)-8-((2,2'-dichloro-3'-(3-((3-hydroxy)pyrrolidin-1-yl)methyl)1J-naphthyridin-8-yl)amino)-[1,1'-biphenyl]-3-yl)amino)-1,7-naphthyridine-3-carbaldehyde (0.0150 g, 0.024 mmol), (i?)-3-methylpyrrolidin-3-ol (Ark Pharm, cat#AK100499: 7.15 mg, 0.071 mmol), a stir bar, and 1,2-dichloroethane (0.236 mL). The mixture was stirred for 5 min, then sodium triacetoxyborohydride (0.015 g, 0.071 mmol) and acetic acid (4.05 µL, 0.071 mmol) were added. The reaction was stirred for 1 h, and the mixture was diluted with methanol and purified by prep HPLC (pH = 2, acetonitrile/water+TFA) to provide the desired compound as its TFA salt. LC-MS calculated for C39H39Cl2N8O2 (M+H)^+; m/z = 721.3; found 721.3.

**Example 77**

(i?)-lK(8^8(2,2'-dichloro-3'K(3K((2-hydroxyethyl)amino)methyl)-1,7-naphthyridin-8-yl)amino)-[1,1'-biphenyl]-3-yl)amino)-1,7-naphthyridin-3-yl)methyl)pyrrolidin-3-ol
This compound was prepared using similar procedures as described for *Example 76* with ethanolamine (Aldrich, cat#411000) replacing (i?)-3-methylpyrrolidin-3-ol in *Step 5*. LC-MS calculated for C_{36}H_{15}Cl_{3}N_{8}O_{2} (M+H)^{+}; m/z = 681.2; found 681.2.

**Example 78**

(i?)-l^{8K(2,2'-dichloro-3',5'-K(3^((i?)0-hydroxypyrrolidin-1-yl)methyl)-l,7-naphthyridin-8-yl)amino}[l,l'-biphenyl]-3-yl)amino)-l,7-naphthyridin-3-yl)methyl)pyrrolidine-3-carboxylic acid

This compound was prepared using similar procedures as described for *Example 76* with (i?)-pyrrolidine-3-carboxylic acid (Combi-Blocks, cat#ST-7698) replacing (i?)-3-methylpyrrolidin-3-ol in *Step 5*. LC-MS calculated for C_{39}H_{37}Cl_{2}N_{8}O_{3} (M+H)^{+}; m/z = 735.2; found 735.2.

**Example 79**

(i?)-l-((8-((2-chloro-3'-((3-(((i?)3-hydroxypyrrolidin-1-yl)methyl)-l,7-naphthyridin-8-yl)amino)-2'-methyl-[l,l'-biphenyl]-3-yl)amino)-l,7-naphthyridin-3-yl)methyl)pyrrolidine-3-carboxylic acid

*Step 1:* (R)-l-((8-(2'-chloro-2-methyl-3'-((3-vinyl-l,7-naphthyridin-8-yl)amino)-[l,l'-biphenyl]-3-yl)amino)-l,7-naphthyridin-3-yl)methyl)pyrrolidin-3-ol

To a vial was added N-(3-bromo-2-chlorophenyl)-3-vinyl-1,7-naphthyridin-8-amine *(Example 14, Step 5: 0.141 g, 0.391 mmol)*, (i?)-l-((8-((2-methyl-3-(4,4,5,5-tetramethyl-...
Step 1: (R)-8-((2-chloro-3'-((3-((3-hydroxypyrrolidin-1-yl)methyl)-1,7-naphthyridin-8-yl)amino)-2'-methyl-1,1'-biphenyl)-3-yl)amino)-l,7-naphthyridine-3-carbaldehyde

To a vial was added (i?)-l-((8-((2'-chloro-2-methyl-3'-((3-vinyl-1,7-naphthyridin-8-yl)amino)-1,1'-biphenyl)-3-yl)amino)-1,7-naphthyridin-3-yl)methyl)pyrrolidin-3-ol (0.108 g, 0.176 mmol), tetrahydrofuran (1.125 mL), water (0.281 mL), 2,6-lutidine (0.107 mL, 0.914 mmol), sodium periodate (0.188 g, 0.879 mmol), then potassium osmate dihydrate (9.72 mg, 0.026 mmol). The mixture was stirred for 30 min at rt. The mixture was diluted with 3:1 CHCl/IPA (5 mL) and water (2 mL), and the layers were separated. The aqueous layer was further extracted with 3:1 CHCl/IPA, dried over MgSCn, filtered and concentrated under reduced pressure. The solid was slurried with 5:1 Et20/DCM, and filtered to provide the desired product as a beige solid. LC-MS calculated for C35H31CIN7O2 (M+H) +: m/z = 616.2; found 616.2.

Step 3: (R)-1-((8-((2-chloro-3'-((3-((3-hydroxypyrrolidin-1-yl)methyl)-1,7-naphthyridin-8-yl)amino)-2'-methyl-1,1'-biphenyl)-3-yl)amino)-1,7-naphthyridin-3-yl)methyl)pyrrolidine-3-carboxylic acid

To a vial was added (i?)-8-((2-chloro-3'-((3-(3-hydroxypyrrolidin-1-yl)methyl)-1,7-naphthyridin-8-yl)amino)-2'-methyl-[1,1'-biphenyl]-3-yl)amino)-1,7-naphthyridine-3-carbaldehyde (0.0350 g, 0.057 mmol), (i?)-pyrrolidine-3-carboxylic acid (Combi-Blocks, cat#ST-7698: 0.020 g, 0.170 mmol), a stir bar, and 1,2-dichloroethane (0.568 mL). The mixture was stirred for 5 min, then sodium triacetoxyborohydride (0.036 g, 0.170 mmol) and acetic acid (0.020 mL, 0.341 mmol) were added. The reaction was stirred for 1 h, and the mixture was diluted with methanol and purified by prep HPLC (pH = 2.
acetonitrile/water+TFA) to provide the desired compound as its TFA salt. LC-MS calculated for C40H40CIN8O3 (M+H)+: m/z = 715.3; found 715.3.

Example 80

(i?)-l-((8-((2-chloro-3'-((3-((3-hydroxy)pyrrolidin-1-yl)methyl)-1,7-naphthyridin-8-y1)amino)-2'-methyl-[1,1'-biphenyl]-3-yl)amino)-1,7-naphthyridin-3-yl)(methyl)azetidine-3-carboxylic acid

This compound was prepared using similar procedures as described for Example 79 with azetidine-3-carboxylic acid (Aldrich, cat#391 131) replacing (i?)-pyrrolidine-3-carboxylic acid in Step 3. LC-MS calculated for C39H38ClN8O3 (M+H)+: m/z = 701.3; found 701.3.

Example 81

(i?)^-(((8-((2-chloro-3'-((3-((3-hydroxy)pyrrolidin-1-yl)methyl)-1,7-naphthyridin-8-y1)amino)-2'-methyl-[1,1'-biphenyl]-3-yl)amino)-1,7-naphthyridin-3-yl)(methyl)amino)propanoic acid

This compound was prepared using similar procedures as described for Example 79 with β-alanine (Aldrich, cat#146064) replacing (i?)-pyrrolidine-3-carboxylic acid in Step 3. LC-MS calculated for C38H38ClN8O3 (M+H)+: m/z = 689.3; found 689.3.

Example 82

(i?)-l-((8K(2,2'-dichloro-3'-(3-((S)0-hydroxy)pyrrolidin-1-yl)methyl)-1,7-naphthyridin-8-y1)amino)-[1,1'-biphenyl]-3-yl)amino)-1,7-naphthyridin-3-yl)methyl)pyrrolidine-3-carboxylic acid
Step 1: \((S)\)-l-((8-((3-bromo-2-chlorophenyl)amino)-1,7-naphthyridin-3-yl)methyl)pyrrolidin-3-ol

To a vial was added 8-((3-bromo-2-chlorophenyl)amino)-1,7-naphthyridine-3-carbaldehyde \{Example 14, Step 6: 0.200 g, 0.552 mmol\}, \((S)\)-3-hydroxypyrrolidine (Combi-Blocks, cat#SS-7948: 0.144 g, 1.655 mmol), DCE (2.76 mL), and a stir bar. The mixture was stirred at rt for 15 min, then sodium cyanoborohydride (0.104 g, 1.655 mmol) and acetic acid (0.120 mL, 2.096 mmol) were added. The mixture was stirred at rt for 1 h, then the reaction was quenched with aqueous saturated sodium bicarbonate (5 mL). 3:1 CHCh/IPA was added (5 mL), and the layers were separated. The aqueous layer was further extracted with 3:1 CHCh/IPA (2 X 5 mL), and the combined organic layers were dried over MgSCn, filtered, and concentrated under reduced pressure. The resulting brown residue was purified by silica gel chromatography (0 → 15% MeOH/DCM) to provide the desired product as a brown solid. LC-MS calculated for C_{9}H_{19}BrClN_{0} (M+H)^+; m/z = 433.0; found 433.2.

Step 2: \((S)\)-l-((8-((2,2'-dichloro-3'-((3-(hydroxymethyl)-1,7-naphthyridin-8-yl)amino)-[1,1'-biphenyl]-3-yl)amino)-1,7-naphthyridin-3-yl)methyl)pyrrolidin-3-ol

To a vial was added (8-((2-chloro-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)amino)-1,7-naphthyridin-3-yl)methanol \{Example 76, Step 2: 0.163 g, 0.396 mmol\}, \((\epsilon\)-l-((8-((3-bromo-2-chlorophenyl)amino)-1,7-naphthyridin-3-yl)methyl)pyrrolidin-3-ol (0.172 g, 0.396 mmol), 1 M aqueous sodium carbonate (0.792 mmol), tetrakis (0.046 g, 0.040 mmol), and 1,4-dioxane (2.97 mL). The mixture was degassed, sealed, and heated to 110 °C whilst stirring for 4 h. The mixture was cooled, diluted with EtOAc and filtered through celite. The filtrate was concentrated and purified by silica gel chromatography (15% MeOH/DCM) to provide the desired product as a yellow solid. LC-MS calculated for C_{34}H_{30}Cl_{2}N_{7}O_{2} (M+H)^+: m/z = 638.2; found 638.2.

Step 3: \((S)\)-8-((2,2'-dichloro-3'-(3-(3-hydroxypyrrolidin-1-yl)methyl)-1,7-naphthyridin-8-yl)amino)-[1,1'-biphenyl]-3-yl(amo)-l,7-naphthyridine-3-carbaldehyde
This compound was prepared using similar procedures as described for Example 9 with \((S)\)-\(8-((2,2',dichloro-3'-(3-(hydroxymethyl)-l,7-naphthyridin-8-yl)amino)-[1',1'-biphenyl]-3-yl)amino)-l,7-naphthyridin-3-yl)methyl)pyrrolidin-3-ol replacing \((R)-l-((8-((3'-(3-(hydroxymethyl)-l,7-naphthyridin-8-yl)amino)-2,2'-dimethyl-[1',1'-biphenyl]3-yl)amino)-l,7-naphthyridin-3-yl)methyl)pyrrolidin-3-ol in Step 5. LC-MS calculated for C34H28Cl2N7O2 (M+H)+: m/z = 636.2; found 636.2.

Step 4: \((R)-l-((8-((2,2',dichloro-3'-(3-(((S)-3-hydroxypyrrolidin-1-yl)methyl)-l,7-naphthyridin-8-yl)amino)-[1,1'-biphenyl]-3-yl)amino)-l,7-naphthyridin-3-yl)methyl)pyrrolidine-3-carboxylic acid

To a vial was added \((5)-8-((2,2',dichloro-3'-(3-((3-hydroxy)pyrrolidin-1-yl)methyl)-1,7-naphthyridin-8-yl)amino)-[1,1'-biphenyl]-3-yl)amino)-l,7-naphthyridine-3-carbaldehyde (0.009 g, 0.014 mmol), \((i?)\)-pyrrolidine-3-carboxylic acid (Combi-Blocks, cat#ST-7698: 4.88 mg, 0.042 mmol), a stir bar, N,N-dimethylformamide (0.141 mL), and DIPEA (7.41 µL, 0.042 mmol). The mixture was stirred for 5 min, then sodium cyanoborohydride (2.67 mg, 0.042 mmol) and was added. The reaction was stirred for 1 h, then the mixture was diluted with methanol and purified by prep HPLC (pH = 2, acetonitrile/water+TFA) to provide the desired compound as its TFA salt. LC-MS calculated for C39H37Cl2N8O3 (M+H)+: m/z = 735.2; found 735.2.

Example 83

\((S)-l-((8-((2,2',dichloro-3'-(3-(((S)-3-hydroxy)pyrrolidin-1-yl)methyl)-1,7-naphthyridin-8-yl)amino)-[1,1'-biphenyl]-3-yl)amino)-l,7-naphthyridin-3-yl)methyl)pyrrolidine-3-carboxylic acid

This compound was prepared using similar procedures as described for Example 82 with \((5)\)-pyrrolidine-3-carboxylic acid (Combi-Blocks, cat#ST-1381) replacing \((R)-\)
pyrrolidine-3-carboxylic acid in Step 4. LC-MS calculated for C_{39}H_{37}Cl_{2}N_{8}O_{3} (M+H)^{+}: m/z = 735.2; found 735.2.

Example 84

(i?)-l-(8-((3’-(5-(dimethylglycyl)-5,6-dihydro-4 H-pyrrolo[3,4-i]/oxazol-2-yl)-2,2’-dimethyl-[1,1’-biphenyl]-3-yl)amino)-l ,7-naphthyridin-3-yl)methyl)pyrrolidine-3-carboxylic acid

\[
\text{Step 1: } 2-(\text{dimethylamino})-l-(2-(3’-(3-(hydroxymethyl)-l,7-naphthyridin-8-yl)amino)-2,2’-dimethyl-[1,1’-biphenyl]-3-yl)-4, 6-dihydro-5H-pyrrolo[3,4-d]oxazol-5-yl)ethan-l-one
\]

A mixture of l-(2-(3-bromo-2-methylphenyl)-4,6-dihydro-5H-pyrrolo[3,4-cf]oxazol-5-yl)-2-(dimethylamino)ethan-l-one (Example 37, Step 7: 112 mg, 0.307 mmol), (8-((2-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)amino)-l,7-naphthyridin-3-yl)methanol (Example 9, Step 3: 120 mg, 0.307 mmol), dicyclohexyl(2’,4’,6’-triisopropylbiphenyl-2-yl)phosphine-(2’-aminobiphenyl-2-yl)(chloro)palladium (1:1) (24.13 mg, 0.031 mmol) and tripotassium phosphate (155 mg, 0.675 mmol) in 1,4-dioxane (3mL)/water (1mL) was stirred at 80 °C for 1 h. The residue was dissolved in methanol and 1 N HCl and purified with prep-LCMS (pH 2, acetonitrile/water+TFA) to give the desired compound as light yellow solid. LC-MS calculated for C_{32}H_{33}N_{6}O_{3} (M+H)^{+}: m/z = 549.3; found 549.3.

Step 2: 8-((3’-(5-(dimethylglycyl)-5,6-dihydro-4H-pyrrolo[3,4-d]oxazol-2-yl)-2,2’-dimethyl-[1,1’-biphenyl]-3-yl)amino)-l ,7-naphthyridine-3-carbaldehyde
This compound was prepared using similar procedures as described for Example 34, with 2-(dimethylamino)-1-(2-(3'-(3-(hydroxymethyl)-1,7-naphthyridin-8-yl)amino)-2,2'-dimethyl-[1,1'-biphenyl]-3-yl)-4,6-dihydro-5H-pyrrolo[3,4-cf]oxazol-5-yl)ethan-1-one replacing tert-butyl 2-(3'-(3-(hydroxymethyl)-1,7-naphthyridin-8-yl)amino)-2,2'-dimethyl-[1,1'-biphenyl]-3-yl)-6,7-dihydrothiazolo[5,4-c]pyridine-5(4H)-carboxylate in Step 2. LC-MS calculated for C32H31N6O3 (M+H)+: m/z = 547.2; found 547.3.

Step 3. (R)-l-[(8-((3'(5-(dimethylglycyl)-5,6-dihydro-4H-pyrrolo[3,4-d]oxazol-2-yl)-2,2'-dimethyl-[1,1'-biphenyl]-3-yl)amino)-l,7-naphthyridin-3-yl)methyl]pyrrolidine-3-carboxylic acid
This compound was prepared using similar procedures as described for Example 31 with 8-(((3'(5-(dimethylglycyl)-5,6-dihydro-4H-pyrrolo[3,4-cf]oxazol-2-yl)-2,2'-dimethyl-[1,1'-biphenyl]-3-yl)amino)-l,7-naphthyridine-3-carbaldehyde replacing N-(2-chloro-3'-(3'-formyl-1,7-naphthyridin-8-yl)amino)-2'-methyl-[1,1'-biphenyl]-3-yl)-1,5-dimethyl-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridine-2-carboxamide in Step 7. LC-MS calculated for C37H40N7O4 (M+H)+: m/z = 646.3; found 646.3.

Example 85
(R)-1K(8-((3'K5-(dimethylglycyl)-5,6-dihydro-4H-pyrrolo[3,4-i]thiazol-2-yl)-2,2'-dimethyl-[1,1'-biphenyl]-3-yl)amino)-1,7-naphthyridin-3-yl)methyl]pyrrolidine-3-carboxylic acid

Step 1: tert-butyl 2-bromo-4H-pyrrolo[3,4-d]thiazole-5(6H)-carboxylate
To a stirred solution of 2-bromo-5,6-dihydro-4\textit{H}-pyrrolo[3,4-cf]thiazole, HBr salt (AurumPharm, cat\# MR22320: 220.0 mg, 0.769 mmol) and \textit{N\textsubscript{2}}\textit{N}-diisopropylethylamine (0.269 mL, 1.539 mmol) in DCM (5.0 mL), Boc-anhydride (201 mg, 0.923 mmol) was added at room temperature. After 1 hour, the reaction mixture was diluted with EtOAc (100 mL), and washed with water (3 x 15 mL). The organic layer was dried over Na\textsubscript{2}SO\textsubscript{4}, filtered and the filtrate was concentrated to afford crude \textit{tert-butyl} 2-bromo-4,6-dihydro-5\textit{H}-pyrrolo[3,4-cf]thiazole-5(6\textit{H})-carboxylate (220 mg, 0.724 mmol, 93.6 \% yield), which was used directly in the next step without further purification. LC-MS calculated for C\textsubscript{10}H\textsubscript{14}BrN\textsubscript{2}O\textsubscript{2}S (M+H): m/z = 305.0/307.0; found 305.0/307.0.

\textbf{Step 2: \textit{tert-butyl} 2-(3-chloro-2-methylphenyl)-4,6-dihydro-5\textit{H}-pyrrolo[3,4-d]thiazole-5-carboxylate}

\begin{center}
\includegraphics[width=0.5\textwidth]{structure.png}
\end{center}

(3-Chloro-2-methylphenyl)boronic acid (344 mg, 2.02 mmol) (Combi-blocks, cat\#BB-2035), \textit{tert-butyl} 2-bromo-4,6-dihydro-5\textit{H}-pyrrolo[3,4-cf]thiazole-5-carboxylate (616 mg, 2.02 mmol), sodium carbonate (428 mg, 4.04 mmol) in 1,4-dioxane (8 mL) and water (2 mL) was added palladiumtetrakis (233 mg, 0.202 mmol). The resulting mixture was purged with N\textsubscript{2}, then heated at 100°C. After 3 h, the reaction was concentrated, and diluted with DCM. The crude product was added to a silica gel column and was eluted with ethyl acetate/hexane from 0\% to 40\% to give \textit{tert-butyl} 2-(3-chloro-2-methylphenyl)-4,6-dihydro-5\textit{H}-pyrrolo[3,4-cf]thiazole-5-carboxylate (541 mg, 76 \% yield). LC-MS calculated for C\textsubscript{17}H\textsubscript{20}CIN\textsubscript{2}O\textsubscript{2}S (M+H\textsuperscript{+}): m/z = 351.1; found 351.0.

\textbf{Step 3: \textit{tert-butyl} 2-(2-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-4,6-dihydro-5\textit{H}-pyrrolo[3,4-d]thiazole-5-carboxylate}

\begin{center}
\includegraphics[width=0.5\textwidth]{structure.png}
\end{center}

A mixture of \textit{tert-butyl} 2-(3-chloro-2-methylphenyl)-4,6-dihydro-5\textit{H}-pyrrolo[3,4-cf]thiazole-5-carboxylate (261 mg, 0.715 mmol), 4,4,5,5,4',4',5',5'-octamethyl-[2,2']bi[1,3,2]dioxaborolanyl (Aldrich, cat\#473294: 545 mg, 2.14 mmol), palladium acetate
(6.42 mg, 0.0286 mmol), K3PO4 (455 mg, 2.14 mmol) and 2-(dicyclohexylphosphino)-2',6'-
dimethoxy-l,l'-biphenyl (Strem Chemicals, cat#15-1143: 29.4 mg, 0.0715 mmol) in 1,4-
dioxane was degassed and stirred at rt for 16 h. The mixture was diluted with DCM, and
washed with water. The organic layer was concentrated in vacuo and purified by silica-gel
chromatography (5% EtOAc/DCM). LC-MS calculated for C23H32BN2O4S (M+H)^+: m/z =
443.2; found 443.3.

**Step 4: tert-butyl 2-((3'-((3-formyl-l,7-naphthyridin-8-yl)amino)-2,2'-dimethyl-[l,l'-
biphenyl]-3-yl)-4,6-dihydro-5H-pyrrolo[3,4-d]thiazole-5-carboxylate**

To a vial was added tert-butyl 2-(2-methyl-3-(4,4,5,5-tetramethyl-l,3,2-dioxaborolan-
2-yl)phenyl)-4,6-dihydro-5H-pyrrolo[3,4-d]thiazole-5-carboxylate (0.013 g, 0.029 mmol), 8-
((3-bromo-2-methylphenyl)amino)-l,7-naphthyridine-3-carbaldehyde, [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (1.436 mg, 1.962 μmol), 1,4-dioxane (0.346 mL), and water (0.046 mL). The mixture was degassed, sealed, and heated to 90 °C
whilst stirring for 4 h. After cooling, the mixture was diluted with DCM and water. The
layers were separated and the aqueous layer was further extracted. The combined organic
layers were dried over magnesium sulfate, filtered, concentrated in vacuo, and purified by
silica gel chromatography (MeOH/DCM). LC-MS calculated for C33H32N5O3S (M+H)^+: m/z =
578.2; found 578.4.

**Step 5: (R)-l-((8-((3'-(5-(tert-butoxycarbonyl)-5,6-dihydro-4H-pyrrolo[3,4-d]thiazol-2-yl)-
2,2'-dimethyl-[l,l'-biphenyl]-3-yl)amino)-l,7-naphthyridin-3-yl)methyl)pyrrolidine-3-
carboxylic acid**

To a vial was added tert-butyl 2-(3'-((3-formyl-l,7-naphthyridin-8-yl)amino)-2,2'-
dimethyl-[l,l'-biphenyl]-3-yl)-4,6-dihydro-5H-pyrrolo[3,4-cf]thiazole-5-carboxylate (9 mg,
0.02 mmol), (i?)-pyrrolidine-3-carboxylic acid (Combi-Blocks, cat#ST-7698: 0.017 g, 0.152 mmol), dichloromethane (0.829 mL) and triethylamine (0.016 mL, 0.115 mmol). The reaction was stirred at rt for 2 h, then sodium triacetoxyborohydride (0.054 g, 0.253 mmol) and acetic acid (8.7 µL, 0.15 mmol) were added. The reaction was stirred at rt for 2 h, then quenched with a saturated aqueous solution of sodium bicarbonate. The mixture was then extracted with a 3:1 mixture of chloroform/isopropanol. The combined organic layers were dried over sodium sulfate, then concentrated in vacuo to provide the desired compound. LC-MS calculated for C_{38}H_{41}N_{6}O_{7}S (M+H)^+: m/z = 677.3; found 677.2.

Step 6: (R)-l-((8-((3’-(5,6-dihydro-4H-pyrrolo[3,4-d]thiazol-2-yl)-2,2’-dimethyl-[1,1’-biphenyl]-3-yl)amino)-1,7-naphthyridin-3-yl)methyl)pyrrolidine-3-carboxylic acid

To a solution of (i?)-l-((8-((3’-(5-(terti-butoxycarbonyl)-5,6-dihydro-4H-pyrrolo[3,4-t]thiazol-2-yl)-2,2’-dimethyl-[1,1’-biphenyl]-3-yl)amino)-1,7-naphthyridin-3-yl)methyl)pyrrolidine-3-carboxylic acid (7 mg, 0.02 mmol) in DCM (0.5 mL) was added TFA (0.2 mL). After 2 h, the reaction mixture was concentrated, and then the crude product was used directly in the next step. LC-MS calculated for C_{33}H_{33}N_{6}O_{2}S (M+H)^+: m/z = 577.2; found 577.3.

Step 7: (R)-l-((8-((3’-(5-(dimethylglycyl)-5,6-dihydro-4H-pyrrolo[3,4-d]thiazol-2-yl)-2,2’-dimethyl-[1,1’-biphenyl]-3-yl)amino)-1,7-naphthyridin-3-yl)methyl)pyrrolidine-3-carboxylic acid

In a 1 dram vial (i?)-l-((8-((3’-(5,6-dihydro-4H-pyrrolo[3,4-cf]thiazol-2-yl)-2,2’-dimethyl-[1,1’-biphenyl]-3-yl)amino)-1,7-naphthyridin-3-yl)methyl)pyrrolidine-3-carboxylic acid (6 mg, 0.02 mmol) and N,N-Dimethylglycine (6 mg, 0.06 mmol) were dissolved in DMF (0.2 mL). DIPEA (14 µL, 0.08 mmol) and HATU (18 mg, 0.05 mmol) were added to the reaction mixture in one portion. After 5 h, the reaction mixture was diluted with MeOH then purified by prep-HPLC (pH = 10, acetonitrile/water+NFUOH) to give the desired product. LC-MS calculated for C_{37}H_{40}N_{7}O_{3}S (M+H)^+: m/z = 662.3; found 662.2. ¾ NMR (600 MHz, DMSO-d_{6}) δ 9.30 (s, 1H), 8.85 (d, J = 2.0 Hz, 1H), 8.43 (d, J = 8.1 Hz, 1H), 8.17 (d, J = 1.7 Hz, 1H).
Hz, 1H), 8.05 (d, J = 5.8 Hz, 1H), 7.66 (d, J = 7.8 Hz, 1H), 7.42 (td, J = 7.6, 2.4 Hz, 1H), 7.32 (t, J = 7.8 Hz, 1H), 7.28 (d, J = 7.7 Hz, 1H), 7.17 (d, J = 5.8 Hz, 1H), 6.89 (d, J = 7.5 Hz, 1H), 5.06 - 4.96 (m, 1H), 4.88 (t, J = 2.8 Hz, 1H), 4.77 - 4.68 (m, 1H), 4.63 - 4.54 (m, 1H), 3.81 (q, J = 13.8 Hz, 2H), 3.16 (d, J = 1.9 Hz, 2H), 2.97 - 2.85 (m, 1H), 2.75 (t, J = 8.7 Hz, 1H), 2.66 (dd, J = 9.1, 6.5 Hz, 1H), 2.61 - 2.52 (m, 2H), 2.25 (s, 6H), 2.21 (s, 3H), 2.08 (s, 3H), 1.96 (q, J = 7.2 Hz, 2H).

Example 86

2-((i?)-3-hydroxyprrolidin-1-yl)-l-(2-((3'-((3-(((i?)-3-hydroxyprrolidin-1-yl)methyl)-
1,7-naphthyridin-8-yl)amino)-2,2'-dimethyl-[l,l'-biphenyl]-3-yl)-4,6-dihydro-5 H-
pyrrolo[3,4-d]thiazol-5-yl)ethan-1-one

Step 1: tert-butyl (R)-2-((3'-(3-((3-hydroxyprrolidin-1-yl)methyl)-1,7-naphthyridin-8-
yl)amino)-2,2'-dimethyl-[l,l'-biphenyl]-3-yl)-4,6-dihydro-5H-pyrrolo[3,4-d]thiazo-
le-5-carboxylate

This compound was prepared using a similar procedure as described for Example 85.

Step 2 with (i?)-l-((8-((3-bromo-2-methylphenyl)amino)-1,7-naphthyridin-3-
yl)methyl)pyrrolidin-3-ol  (Example 20, Step 2) replacing 8-((3-bromo-2-
methylphenyl)amino)-1,7-naphthyridine-3-carbaldehyde. The crude compound was diluted
with DCM and water. The layers were separated and the aqueous layer was further extracted.
The combined organic layers were dried over magnesium sulfate, filtered, and concentrated
in vacuo. LC-MS calculated for C_{35}H_{44}N_{6}O_{3}S (M+H)^+; m/z = 649.3; found 649.2.

Step 2: (R)-l-((8-((3'-(5, 6-dihydro-4H-pyrrolo[3,4-d]thiazol-2-yl)-2,2'-dimethyl-[l, 1-
biphenyl]-3-yl)amino)-l, 7-naphthyridin-3-yl)methyl)pyrrolidin-3-ol
To a solution of tert-butyl (i?)-2-(3’-((3-hydroxypyrrolidin-1-yl)methyl)-1,7-naphthyridin-8-yl)anuno)-2,2’-dimethyl-[1,1’-biphenyl]-3-yl)-4,6-dihydro-5H-pyrrolo[3,4-d]thiazole-5-carboxylate (147 mg, 0.226 mmol) in DCM (3 mL) was added TFA (1 mL). After 2 h, the reaction mixture was concentrated, and then the crude product was used directly in the next step. LC-MS calculated for C32H33N6O6S (M+H)+: m/z = 549.2; found 549.3.

Step 3: (R)-2-chloro-1-(2-(3’-((3-hydroxypyrrolidin-1-yl)methyl)-1,7-naphthyridin-8-yl)amino)-2,2’-dimethyl-[1,1’-biphenyl]-3-yl)-4,6-dihydro-5H-pyrrolo[3,4-d]thiazol-5-yl)ethan-1-one

To a solution of the above crude product and DIPEA (118 µL, 0.678 mmol) in DCM (3 mL) was added chloroacetyl chloride (20 µL, 0.25 mmol) at -78°C. After 15 min, the reaction mixture was warmed to room temperature slowly. After 30 min, the reaction mixture was concentrated and diluted with MeOH then purified by prep-HPLC (pH = 2, acetonitrile/water+TFA) to give the desired product as the TFA salt. LC-MS calculated for C34H34ClIN6O2S (M+H)+: m/z = 625.2; found 625.2.

Step 4: 2-((R)-3-hydroxypyrrolidin-1-yl)-1-(2-(3’-((3-((R)-3-hydroxypyrrolidin-1-yl)methyl)-1,7-naphthyridin-8-yl)amino)-2,2’-dimethyl-[1,1’-biphenyl]-3-yl)-4,6-dihydro-5H-pyrrolo[3,4-d]thiazol-5-yl)ethan-1-one

In a 1 dram vial (i?)-2-chloro-1-(2-(3’-((3-hydroxypyrrolidin-1-yl)methyl)-1,7-naphthyridin-8-yl)amino)-2,2’-dimethyl-[1,1’-biphenyl]-3-yl)-4,6-dihydro-5H-pyrrolo[3,4-d]thiazol-5-yl)ethan-1-one (5 mg, 8.00 µmol) was dissolved in acetonitrile (400 µL) to give a yellow solution. (i?)-pyrrolidin-3-ol (Combi-Blocks, cat#AM-2005; 5 mg) and DIPEA (1.5 µL, 8.0 µmol) were added to the reaction mixture. The reaction mixture was heated to 60 °C. After 12h, the reaction mixture was diluted with MeOH then purified by prep-HPLC (pH = 2,
acetonitrile/water+TFA) to give the desired product as the TFA salt. LC-MS calculated for C38H42N7O3S (M+H)^+; m/z = 676.3; found 676.3.

Example 87

(iR)-H(8-((3"K5-(dimethylglycyl)\textsuperscript{-dihydro-4H-pyrrolo[3,4-d]thiazol-2-yl)-2,2'\textendash;dimethyl-[1,1'-biphenyl]-3-yl)amino)-1,7-naphthyridin-3-yl)methyl)-3-methylpyrrolidine-3-carboxylic acid

This compound was prepared using a similar procedure as described for Example 85, Step 5 with (iR)-3-methylpyrrolidine-3-carboxylic acid (J&W PharmLab, cat#75R0495) replacing (iR)-pyrrolidine-3-carboxylic acid. LC-MS calculated for C38H42N7O3S (M+H)^+; m/z = 676.3; found 676.3.

Example 88

l-((8-((3\'-5-(dimethylglycyl)-5,6-dihydro\textsuperscript{-4H-pyrrolo[3,4-d]thiazol-2-yl)-2,2'\textendash;dimethyl-[1,1'-biphenyl]-3-yl)amino)-1,7-naphthyridin-3-yl)methyl)azetidine-3-carboxylic acid

This compound was prepared using a similar procedure as described for Example 85, Step 5 with azetidine-3-carboxylic acid (Aldrich, cat#391 13 1) replacing (iR)-pyrrolidine-3-carboxylic acid. LC-MS calculated for C36H38N7O3S (M+H)^+; m/z = 648.3; found 648.3.

Example 89

(iR)-l-((8-((2-chloro-3\'-5-(dimethylglycyl)-5,6-dihydro\textsuperscript{-4H -pyrrolo[3,4-i]thiazol-2-yl)-2'\textendash;methyl-[1,1'-biphenyl]-3-yl)amino)-1,7-naphthyridin-3-yl)methyl)pyrrolidine-3-carboxylic acid
This compound was prepared using a similar procedure as described for Example 85, Step 4 with 8-((3-bromo-2-chlorophenyl)amino)-1,7-naphthyridine-3-carbaldehyde (Example 14, Step 6) replacing 8-((3-bromo-2-methylphenyl)amino)-1,7-naphthyridine-3-carbaldehyde. The crude compound was diluted with DCM and water. The layers were separated and the aqueous layer was further extracted. The combined organic layers were dried over magnesium sulfate, filtered, and concentrated in vacuo. LC-MS calculated for C32H29CIN5O3S (M+H)⁺: m/z = 598.2; found 598.3.

Step 2: (R)-l-((8-((2-chloro-3′-((5-(dimethylglycyl)-5,6-dihydro-4H-pyrrolo[3,4-d]thiazol-2-yl)-2′-methyl-[1,1′-biphenyl]-3-yl)amino)-1,7-naphthyridin-3-yl)methyl)pyrrolidine-3-carboxylic acid

This compound was prepared using a similar procedure as described for Example 85, Steps 5-7 with tert-butyl 2-(2′-chboro-3′-((3-formyl-1,7-naphthyridin-8-yl)amino)-2-methyl-[1′-biphenyl]-3-yl)-4,6-dihydro-5 H-pyrrolo[3,4-cf]thiazole-5-carboxylate replacing tert-butyl 2-(3′-((3-formyl-1,7-naphthyridin-8-yl)amino)-2,2′-dimethyl-[1′,1″-biphenyl]-3-yl)-4,6-dihydro-5 H-pyrrolo[3,4-cf]thiazole-5-carboxylate. LC-MS calculated for C36H37CIN7O3S (M+H)⁺: m/z = 682.2; found 682.3.

Example 90

(i?)-l-((8-((2-chloro-3′-5-(N-methylglycyl)-5,6-dihydro-4H-pyrrolo[3,4-i/thiazol-2-yl)-2′-methyl-[1,1′-biphenyl]-3-yl)amino)-1′,7-naphthyridin-3-yl)methyl)pyrrolidine-3-carboxylic acid
This compound was prepared using a similar procedure as described for Example 85 with 8-((3-bromo-2-chlorophenyl)amino)-1,7-naphthyridine-3-carbaldehyde (Example 14, Step 6) replacing 8-((3-bromo-2-methylphenyl)amino)-1,7-naphthyridine-3-carbaldehyde in Step 4 and N-ethyl-N-methylglycine replacing N,N-dimethylglycine in Step 7. LC-MS calculated for C37H39CIN7O3S (M+H)+: m/z = 696.2; found 696.3.

Example 91

(iR)-2-((8-((2-chloro-3′-(5-(dimethylglycyl)-5,6-dihydro-4H-pyrrolo[3,4-i][thiazol-2-yl)-2′-methyl-[1,l′-biphenyl]-3-yl)amino)-1,7-naphthyridin-3-yl)methyl)pyrrolidin-3-yl)acetic acid

This compound was prepared using a similar procedure as described for Example 85 with 8-((3-bromo-2-chlorophenyl)amino)-1,7-naphthyridine-3-carbaldehyde (Example 14, Step 6) replacing 8-((3-bromo-2-methylphenyl)amino)-1,7-naphthyridine-3-carbaldehyde in Step 4 and (iR)-2-(pyrrolidin-3-yl)acetic acid (Combi-Blocks, cat#QE61 16) replacing (R)-pyrrolidine-3-carboxylic acid in Step 5. LC-MS calculated for C37H39CIN7O3S (M+H)+: m/z = 696.2; found 696.3.

Example 92

2-((8-((2-chloro-3′-(5-(dimethylglycyl)-5,6-dihydro-4H-pyrrolo[3,4-i][thiazol-2-yl)-2′-methyl-[1,l′-biphenyl]-3-yl)amino)-1,7-naphthyridin-3-yl)methyl)-2-azabicyclo[2.2.1]heptane-5-carboxylic acid
This compound was prepared using a similar procedure as described for Example 85 with 8-((3-bromo-2-chlorophenyl)amino)-1,7-naphthyridine-3-carbaldehyde [Example 14, Step 6] replacing 8-((3-bromo-2-methylphenyl)amino)-1,7-naphthyridine-3-carbaldehyde in Step 4 and 2-azabicyclo[2.2.1]heptane-5-carboxylic acid (Aurora Fine Chemicals, cat#A30.309.242) replacing (i?)-pyrrolidine-3-carboxylic acid in Step 5. LC-MS calculated for C₃₈H₃₉CIN₇O₃S (M+H)⁺: m/z = 708.2; found 708.3.

**Example 93**

(i?)-2^¹K(8K2-chloro-3'K5^²Kethyl(methyl)amino)acetyl)-5,6-dihydro-4H-pyrrolo[3,4-i/thiazol-2-yl)-2'-methylbiphenyl-3-y1amino)-1,7-naphthyridin-3-yl)methyl)pyrrolidin-3-yl)acetic acid

This compound was prepared using a similar procedure as described for Example 85 with 8-((3-bromo-2-chlorophenyl)amino)-1,7-naphthyridine-3-carbaldehyde [Example 14, Step 6] replacing 8-((3-bromo-2-methylphenyl)amino)-1,7-naphthyridine-3-carbaldehyde in Step 4, (i?)-2-(pyrrolidin-3-yl)acetic acid (Combi-Blocks, cat#QE6116) replacing (R)-pyrrolidine-3-carboxylic acid in Step 5 and N-ethyl-N-methylglycine replacing NN-dimethylglycine in Step 7. LC-MS calculated for C₃₈H₄₁CIN₇O₃S (M+H)⁺: m/z = 710.3; found 710.3.

**Example 94**

2-((8-(2-chloro-3'-((2-(ethyl(methyl)amino)acetyl)-5,6-dihydro-4H-pyrrolo[3,4-d]thiazol-2-yl)-2'-methylbiphenyl-3-y1amino)-1,7-naphthyridin-3-yl)methyl)-2-azabicyclo[2.2.1]heptane-5-carboxylic acid
This compound was prepared using a similar procedure as described for Example 85 with 8-((3-bromo-2-chlorophenyl)amino)-1,7-naphthyridine-3-carbaldehyde (Example 14, Step 6) replacing 8-((3-bromo-2-methylphenyl)amino)-1,7-naphthyridine-3-carbaldehyde in Step 4, 2-azabicyclo[2.2.1]heptane-5-carboxylic acid (Aurora Fine Chemicals, cat#A30.309.242) replacing (i?)-pyrrolidine-3-carboxylic acid in Step 5 and N-ethyl-N-methylglycine replacing N,N-dimethylglycine in Step 7. LC-MS calculated for C39H41CIN7O3S (M+H)+: m/z = 722.3; found 722.3.

Example 95

(i?)-l^(8^(2-chloro-3'K5-(2-((i?)-3-hydroxypyrrolidin-1-yl)acetyl)-5,6-dihydro-4 H-pyrrolo[3,4-i][thiazol-2-yl]-2'-methyl-[l,l'-biphenyl]-3-yl)amino)-l ,7-naphthyridin-3-yl)methyl)pyrrolidine-3-carboxylic acid

Step 1: (R)-l-((8-((2-chloro-3'-(5-(2-chloroacetyl)-5, 6-dihydro-4H-pyrrolo[3,4-d]thiazol-2-yl)2'-methyl-[l,l'-biphenyl]-3-yl)amino)-l, 7-naphthyridin-3-yl)methyl)pyrrolidine-3-carboxylic acid

This compound was prepared using a similar procedure as described for Example 90 with chloracetyl acid replacing N-ethyl-N-methylglycine. The reaction mixture was diluted with MeOH then purified by prep-HPLC (pH = 2, acetonitrile/water+TFA) to give the desired product as the TFA salt. LC-MS calculated for C34H31Cl2N6O3S (M+H)+: m/z = 673.2; found 673.3.
Step 2: (R)-l-((8-((2-chloro-3'-((5-((R)-3-hydroxypyrrolidin-1-yl)acetyl)-5,6-dihydro-4H-
pyrrolo[3,4-d]thiazol-2-yl)-2'-methyl-[1,1'-biphenyl]-3-yl)amino)-l,7-naphthyridin-3-
yl)methyl)pyrrolidine-3-carboxylic acid

In a 1 dram vial (i?)-l-((8-((2-chloro-3'-((5-(2-chloroacetyl)-5,6-dihydro-4H-
pyrrolo[3,4-d]thiazol-2-yl)-2'-methyl-[1,1'-biphenyl]-3-yl)amino)-l,7-naphthyridin-3-
yl)methyl)pyrrolidine-3-carboxylic acid (5 mg, 8.00 µmol) was dissolved in acetonitrile (400 µL) to give a yellow solution. (i?)-pyrrolidin-3-ol (Combi-Blocks, cat#AM-2005 : 5 mg) and DIPEA (1.5 µL, 8.0 µmol) were added to the reaction mixture. The reaction mixture was heated to 60 °C. After 12h, the reaction mixture was diluted with MeOH then purified by prep-HPLC (pH = 2, acetonitrile/water+TFA) to give the desired product as the TFA salt. LC-MS calculated for C38H39CIN7O4S (M+H)+: m/z = 724.3; found 724.2.

Example 96

(i?)-l-((8-((2-chloro-3'-((5-((2-hydroxyethyl)-Y-methylglycyl)-5,6-dihydro-4H-
pyrrolo[3,4-d]thiazol-2-yl)-2'-methyl-[1,1'-biphenyl]-3-yl)amino)-l,7-naphthyridin-3-
yl)methyl)pyrrolidine-3-carboxylic acid

This compound was prepared using a similar procedure as described for Example 95 with N-(2-hydroxyethyl)-N-methyamine replacing (i?)-pyrrolidin-3-ol in Step 2. LC-MS calculated for C37H39CIN7O4S (M+H)+: m/z = 712.3; found 712.3.

Example 97

(i?)-l-((8-((2-chloro-3'K5-((2K(^)-(3-hydroxyopyrrolidin-1-yl)acetyl)-5,6-dihydro-4H-
pyrrolo[3,4-d]thiazol-2-yl)-2'-methyl-[1,1'-biphenyl]-3-yl)amino)-l,7-naphthyridin-3-
yl)methyl)pyrrolidine-3-carboxylic acid
This compound was prepared using a similar procedure as described for Example 95 with (5)-pyrrolidin-3-ol (Combi-Blocks, cat#SS-7948) replacing (i?)-pyrrolidin-3-ol in Step 2. LC-MS calculated for C38H39CIN7O4S (M+H)+: m/z = 724.3; found 724.3.

Example 98

(i?)-l-((8-((2-chloro-3'-((5-(2-(3-hydroxyazidin-1-yl)acetyl)-5,6-dihydro-4H-pyrrolo[3,4-i/thiazol-2-yl)-2'-methyl-[l,l'-biphenyl]-3-yl)amino)-1,7-naphthyridin-3-yl)methyl)pyrrolidine-3-carboxylic acid

This compound was prepared using a similar procedure as described for Example 95 with 3-hydroxyazetidine hydrochloride (Ark Pharm, cat#AK-25536) replacing (i?)-pyrrolidin-3-ol in Step 2. LC-MS calculated for C37H37CIN7O4S (M+H)+: m/z = 710.3; found 710.3.

Example 99

Cis-4-((2-(3'-((R)-3-hydroxyazpidin-1-yl)methyl)-1,7-naphthyridin-8-ylamino)-2,2'-dimethylbiphenyl-3-ylcarbamoyl)- l-methyl-6,7-dihydro-IH-imidazo[4,5-c]pyridine-5(4H)-yl)methyl)cyclohexanecarboxylic acid

This compound was prepared using a similar procedure as described for Example 48 with (R)-N-((3-((3-hydroxyazpidin-1-yl)methyl)-1,7-naphthyridin-8-ylamino)-2,2'-dimethylbiphenyl-3-yl)-l-methyl-4,5,6,7tetrahydro-IH-imidazo[4,5-c]pyridine-2-carboxamide (Example 62, Step 2) replacing (i?)-N-(2-chloro-3'-(3-((3-hydroxyazpidin-1-yl)methyl))amino)-2,2'-dimethylbiphenyl-3-yl)-l-methyl-4,5,6,7tetrahydro-IH-imidazo[4,5-c]pyridine-2-carboxamide (Example 62, Step 2), replacing (i?)-N-(2-chloro-3'-(3-((3-hydroxyazpidin-1-yl)methyl))amino)-2,2'-dimethylbiphenyl-3-yl)-l-methyl-4,5,6,7tetrahydro-IH-imidazo[4,5-c]pyridine-2-carboxamide (Example 62, Step 2).
...l) (methyl)-1,7-naphthyridin-8-yl) anrino)-2'-mem^ 1- [1, 1'- biphenyl]-3-yl)-1-methyl-4, 5, 6, 7-
tetrahydro-1 H -imidazo[4, 5-c] pyridine-2-carboxamide. The reaction mixture was purified by
prep HPLC (pH = 2, acetonitrile/water+TFA) to give the desired compound as its TFA salt.
LC-MS calculated for C43H58N8O4 (M+H)^+; m/z = 743.4; found 743.4.

Example A. PD-1/PD-L1 Homogeneous Time-Resolved Fluorescence (HTRF) binding assay

The assays were conducted in a standard black 384-well polystyrene plate with a final
volume of 20 µL. Inhibitors were first serially diluted in DMSO and then added to the plate
wells before the addition of other reaction components. The final concentration of DMSO in
the assay was 1%. The assays were carried out at 25°C in the PBS buffer (pH 7.4) with
0.05% Tween-20 and 0.1% BSA. Recombinant human PD-L1 protein (19-238) with a His-
tag at the C-terminus was purchased from AcroBiosystems (PD1-H5229). Recombinant
human PD-1 protein (25-167) with Fc tag at the C-terminus was also purchased from
AcroBiosystems (PD1-H5257). PD-L1 and PD-1 proteins were diluted in the assay buffer
and 0 µL, was added to the plate well. Plates were centrifuged and proteins were
preincubated with inhibitors for 40 minutes. The incubation was followed by the addition of
0 µL of HTRF detection buffer supplemented with Europium cryptate-labeled anti-human
IgG (PerkinElmer-AD0212) specific for Fc and anti-His antibody conjugated to SureLight®-
Allophycocyanin (APC, PerkinElmer-AD0059H). After centrifugation, the plate was
incubated at 25°C for 60 min. before reading on a PHERAstar FS plate reader
(665nm/620nm ratio). Final concentrations in the assay were - 3 nM PD1, 10 nM PD-L1, 1
nM europium anti-human IgG and 20 nM anti-His-Allophycocyanin. IC50 determination was
performed by fitting the curve of percent control activity versus the log of the inhibitor
concentration using the GraphPad Prism 5.0 software.

Compounds of the present disclosure, as exemplified in the Examples, showed IC50
values in the following ranges: + = IC50 ≤ 10 nM; ++ = 10 nM < IC50 ≤ 100 nM; +++ = 100
nM < IC50 ≤ 1000 nM.

Data obtained for the Example compounds using the PD-1/PD-L1 homogenous time-
resolved fluorescence (HTRF) binding assay described in Example A is provided in Table 1.

<table>
<thead>
<tr>
<th>Example</th>
<th>PD-1/PD-L1 HTRF IC50 (nM)</th>
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<tr>
<td>1</td>
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Table 1
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<th>Example</th>
<th>PD-1/PD-L1 HTRF IC₅₀ (nM)</th>
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Various modifications of the invention, in addition to those described herein, will be apparent to those skilled in the art from the foregoing description. Such modifications are also intended to fall within the scope of the appended claims. Each reference, including without limitation all patent, patent applications, and publications, cited in the present application is incorporated herein by reference in its entirety.
What is claimed is:

1. A compound of Formula (I):

![Chemical Structure Diagram]

or a pharmaceutically acceptable salt or a stereoisomer thereof, wherein:

- Ring A is 5- to 14-membered heteroaryl, 4- to 14-membered heterocycloalkyl, C_{6-10} aryl or C_{3-4} cycloalkyl, wherein the 5- to 14-membered heteroaryl and 4- to 14-membered heterocycloalkyl each has 1-4 heteroatoms as ring members selected from B, P, N, O and S, wherein the P, N or S atom as ring members is optionally oxidized and one or more carbon atoms as ring members are each optionally replaced by a carbonyl group; and wherein ring A is optionally substituted with 1, 2, 3, 4 or 5 R^6 substituents;

- L is a bond, -C(0)NR_{13}^-, -NR_{13}^1(C=)-, -C(=S)NR_{13}^-, -NR_{13}^1(N=C=S)-, -C(=NR_{13}^1)NR_{13}^-, -NR_{13}^1C(=NR_{13}^1)-, -C(=NOR_{13}^1)NR_{13}^-, -NR_{13}^1C(=N(NO)NR_{13}^-), -C(=NCN)NR_{13}^-, -NR_{13}^1C(=CN)-, O, -(CR_{14}^1R_{15}^1)_q-, -(CR_{10}R_{15}^1)_q-O-, -(CR_{10}^1R_{15}^-)_q-, -NR_{13}^1-, -(CR_{10}^1R_{15}^-)_q-NR_{13}^1-, -NR_{13}^1-(CR_{14}^1R_{15}^-)_q-, -CH=CH-, —C≡C—, —SO_{2}NR_{13}^1-,-NR_{13}^1SO_{2}^-,-NR_{13}^1SO_{2}NR_{13}^1-, -NR_{13}^1C(0)0-, -OC(0)NR_{13}^1 or -NR_{13}^1C(0)NR_{13}^1-;

- X is N or CR_{17}^1;

- R^3 is methyl, halo, CN or C_{4-8}haloalkyl;

- R^4 is C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkoxy, CN, halo, OH, -COOH, NH_{2}, -NH_{2}C_{1-4} alkyl or -(N(Ci_{1-4} alkyl))_{2};

- R^5 is C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkoxy, CN, halo, OH, -COOH, NH_{2}, -NH_{2}C_{1-4} alkyl or -(N(Ci_{1-4} alkyl))_{2};

- R^6, R^7, R^17 and R^{18} are each independently selected fromH, halo, C_{1-6} alkyl, C_{1-6} alkenyl, C_{2-4} alkynyl, C_{6-14} haloalkyl, C_{6-14} haloalkoxy, C_{4-10} aryl, C_{3-10} cycloalkyl, 5-14 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkyl-, C_{3-10} cycloalkyl-C_{1-4} alkyl-, (5-14 membered heteroaryl)-C_{1-4} alkyl-,-(4-10 membered heterocycloalkyl)-C_{1-4} alkyl-, CN, N_{0-2}, OR^6, SR^6, NRHOR^6, C(0)R^6, C(0)NR^6R^6, C(0)OR^6, C(0)NR^6S(0)R^6, OC(0)R^6, OC(0)NR^6R^6, NHR^6, NR^6R^6, NR^6C(0)R^6, NR^6C(0)OR^6, NR^6C(0)NR^6R^6, C(=NR^6)R^6, C(=NOR^6)R^6, NR^6S(0)R^6, NR^6S(0)NR^6R^6, S(0)R^6, S(0)NR^6R^6, S(0)NR^6R^6, S(0)NR^6C(0)R^6, -P(0)OR^6, -P(0)(OR^6)^2, -B(0)H^2, -B(0)OR^6 and S(0)NR^6R^6, wherein the C_{1-6} alkyl, C_{1-6} alkenyl, C_{1-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-14...
membered heteroaryl, 4-10 membered heterocycloalkyl, C\textsubscript{6-10} aryl-C\textsubscript{1} alkyl-, C\textsubscript{3-10} cycloalkyl-C\textsubscript{1} alkyl-, (5-14 membered heteroaryl)-C\textsubscript{1} alkyl- and (4-10 membered heterocycloalkyl)-C\textsubscript{1} alkyl- of R\textsubscript{5}, R\textsubscript{7}, R\textsubscript{17} and R\textsubscript{18} are each optionally substituted with 1, 2, 3, 4 or 5 independently selected R\textsubscript{8} substituents;

or two R\textsubscript{8} substituents attached to the same ring carbon atom taken together with the ring carbon atom to which they are attached form spiro C\textsubscript{3-6} cycloalkyl or spiro 4- to 7-membered heterocycloalkyl, each of which is optionally substituted with 1, 2, or 3 independently selected R\textsubscript{9} substituents;

each R\textsubscript{13} is independently H, C\textsubscript{1-6} haloalkyl or C\textsubscript{1-6} alkyl optionally substituted with a substituent selected from C\textsubscript{1-4} alkyl, C\textsubscript{1-4} haloalkyl, C\textsubscript{1-4} haloalkoxy, CN, halo, OH, -COOH, NH\textsubscript{2}, -NHC\textsubscript{1} alkyl and -N(C\textsubscript{1} alkyl)\textsubscript{2};

R\textsubscript{14} and R\textsubscript{15} are each independently selected from H, halo, CN, OH, -COOH, C\textsubscript{1-4} alkyl, C\textsubscript{1-4} alkoxy, -NHC\textsubscript{1} alkyl, -N(C\textsubscript{1} alkyl)\textsubscript{2}, C\textsubscript{1-4} haloalkyl, C\textsubscript{1-4} haloalkoxy, C\textsubscript{3-6} cycloalkyl, phenyl, 5-6 membered heteroaryl and 4-6 membered heterocycloalkyl, wherein the C\textsubscript{1-4} alkyl, C\textsubscript{1-4} alkoxy, C\textsubscript{1-4} haloalkyl, C\textsubscript{1-4} haloalkoxy, C\textsubscript{3-6} cycloalkyl, phenyl, 5-6 membered heteroaryl and 4-6 membered heterocycloalkyl of R\textsubscript{14} or R\textsubscript{15} are each optionally substituted with 1, 2, or 3 independently selected R\textsubscript{9} substituents;

or R\textsubscript{14} and R\textsubscript{15} taken together with the carbon atom to which they are attached form 3-, 4-, 5- or 6-membered cycloalkyl or 3-, 4-, 5- or 6-membered heterocycloalkyl, each of which is optionally substituted with 1 or 2 independently selected R\textsubscript{9} substituents;

each R\textsubscript{8} is independently selected from H, CN, C\textsubscript{1-6} alkyl, C\textsubscript{1-4} haloalkyl, C\textsubscript{2-6} alkenyl, C\textsubscript{2-6} alkynyl, C\textsubscript{6-10} aryl, C\textsubscript{3-10} cycloalkyl, 5-14 membered heteroaryl, 4-14 membered heterocycloalkyl, C\textsubscript{6-10} aryl-C\textsubscript{1} alkyl-, C\textsubscript{3-10} cycloalkyl-C\textsubscript{1} alkyl-, (5-14 membered heteroaryl)-C\textsubscript{1} alkyl- and (4-14 membered heterocycloalkyl)-C\textsubscript{1} alkyl-, wherein the C\textsubscript{1-4} alkyl, C\textsubscript{2-6} alkenyl, C\textsubscript{6-10} aryl, C\textsubscript{3-10} cycloalkyl, 5-14 membered heteroaryl, 4-14 membered heterocycloalkyl, C\textsubscript{6-10} aryl-C\textsubscript{1} alkyl-, C\textsubscript{3-10} cycloalkyl-C\textsubscript{1} alkyl-, (5-14 membered heteroaryl)-C\textsubscript{1} alkyl- and (4-14 membered heterocycloalkyl)-C\textsubscript{1} alkyl- of R\textsubscript{8} are each optionally substituted with 1, 2, 3, 4, or 5 independently selected R\textsubscript{9} substituents;

each R\textsubscript{d} is independently selected from C\textsubscript{1-6} alkyl, C\textsubscript{1-6} haloalkyl, halo, C\textsubscript{6-10} aryl, 5-14 membered heteroaryl, C\textsubscript{3-10} cycloalkyl, 4-14 membered heterocycloalkyl, C\textsubscript{6-10} aryl-C\textsubscript{1} alkyl-, C\textsubscript{3-10} cycloalkyl-C\textsubscript{1} alkyl-, (5-14 membered heteroaryl)-C\textsubscript{1} alkyl- and (4-14 membered heterocycloalkyl)-C\textsubscript{1} alkyl-.
NR^2C(=NCN)NR^2, S(0)NR^2, S(0)NR, S(0) \_2NR^2C(0)NR^2, NR^2S(0) \_2R^2,
NR^2S(0) \_2NR, -P(0)R^2, -P(0)(OR) \_2(OR) \_2, -B(OH) \_2, -B(OR) \_2, and S(0) \_2NR^2R^2,
wherein the Ci-6 alkyl, Ci-6haloalkyl, C_{6-10} aryl, 5-14 membered heteroaryl, c_{3-10} cycloalkyl, 4-14
membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkyl-, c_{3-10}cycloalkyl-Ci-4 alkyl-, (5-14 membered
heteroaryl)-Ci-4 alkyl-, and (4-14 membered heterocycloalkyl)-Ci-4 alkyl- of R^d are each
optionally substituted with 1, 2, or 3 independently selected R^f substituents;

each R^g is independently selected from H, Ci-6 alkyl, Ci-6haloalkyl, C_{2-6} alkenyl, C_{2-6}
alkynyl, C_{6-10} aryl, c_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl,
C_{6-10} aryl-Ci-4 alkyl-, c_{3-10} cycloalkyl-Ci-4 alkyl-, (5-10 membered heteroaryl)-Ci-4 alkyl-, and (4-
10 membered heterocycloalkyl)-Ci-4 alkyl-, wherein the Ci-6 alkyl, Ci-6haloalkyl, C_{2-6} alkenyl,
c_{2-6} alkynyl, C_{6-10} aryl, c_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered
heterocycloalkyl, C_{6-10} aryl-Ci-4 alkyl-, c_{3-10} cycloalkyl-Ci-4 alkyl-, (5-10 membered heteroaryl)-
c_{14} alkyl- and (4-10 membered heterocycloalkyl)-Ci-4 alkyl- of R^g are each optionally
substituted with 1, 2 or 3 independently selected R^f substituents;

each R^b substituent is independently selected from halo, Ci-6 alkyl, C_{2-6} alkenyl, C_{2-6}
alkynyl, Ci-6 haloalkyl, Ci-6haloalkoxy, C_{6-10} aryl, c_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-
10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkyl-, c_{3-10}cycloalkyl-Ci-4 alkyl-, (5-10
membered heteroaryl)-Ci-4 alkyl-, (4-10 membered heterocycloalkyl)-Ci-4 alkyl-, CN, OH, NH_{2},
N=O, NHOR, OR, SR, C(0)R, C(0)NR, C(0)OR, C(0)NR^2, O(0)R, OC(0)R,
OC(0)NR, C(=NR)^2NR^2R^2, NR=NR=NR^2R^2, NHR, NR^2R, NR^2C(0)R, NR^2C(=NR)^2R^2,
NR^2C(0)OR, NR^2C(0)NR, NR^2S(0)R, NR^2S(0)R, NR^2S(0)_2R^2, NR^2S(0)_2R^2, S(0)R, S(0)NR, S(0)
NR, S(0)_2R^2, S(0)_2NR^2S(0), (5-10 membered heteroaryl)-Ci-4 alkyl- and (4-10 membered
heterocycloalkyl)-Ci-4 alkyl- of R^b are each further optionally substituted with 1, 2, or 3
independently selected R^d substituents;

each R^e is independently selected from H, Ci-6 alkyl, C_{1-4} haloalkyl, C_{2-6} alkenyl, C_{2-6}
alkynyl, C_{6-10} aryl, c_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl,
C_{6-10} aryl-Ci-4 alkyl-, c_{3-10} cycloalkyl-Ci-4 alkyl-, (5-10 membered heteroaryl)-Ci-4 alkyl-, and (4-
10 membered heterocycloalkyl)-Ci-4 alkyl-, wherein the Ci-6 alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-}
10 aryl, c_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-
c_{1-4} alkyl-, c_{3-10} cycloalkyl-Ci-4 alkyl-, (5-10 membered heteroaryl)-Ci-4 alkyl- and (4-10
membered heterocycloalkyl)-Ci-4 alkyl- of R^f are each optionally substituted with 1, 2, 3, 4, or 5 independently selected R^f substituents;

each R^f is independently selected from Ci-4 alkyl, Ci-4 haloalkyl, C-2-6 alkenyl, C-2-6 alkynyl, C-6-10 aryl, C-3-10 cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C-6-10 aryl-Ci-4 alkyl-, C-3-10 cycloalkyl-Ci-4 alkyl-, (5-10 membered heteroaryl)-Ci-4 alkyl-, (4-10 membered heterocycloalkyl)-Ci-4 alkyl-, halo, CN, NHOR, OR, SR, C(0)R^g, C(0)NR^gR^g, R^gS(0)I(OR)^g, OC(0)I(OR)^g, OC(0)NR^gR^g, NHR^g, NR^gR^g, NR^gR^gC(0)I(OR)^g, NR^gR^g(S(0)I(OR)^g), NR^gS(0)I(OR)^g, NR^gRS(0)I(OR)^g, -P(0)I(OR)^gR^g, -P(0)I(OR)^g(R^g), -B(OH)I(OR)^g, -B(OR)^gI(OR)^g, S(0)I(OR)^g and where C^M alkyl, Ci-4 haloalkyl, C-2-6 alkenyl, C-2-6 alkynyl, C-6-10 aryl, C-3-10 cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C-6-10 aryl-Ci-4 alkyl-, C-3-10 cycloalkyl-Ci-4 alkyl-, (5-10 membered heterocycloalkyl)-Ci-4 alkyl-, and (4-10 membered heterocycloalkyl)-Ci-4 alkyl- of R^f are each optionally substituted with 1, 2, 3, 4, or 5 independently selected R^f substituents;

each R^g is independently selected from C-1-4 alkyl, Ci-4 haloalkyl, C-2-6 alkenyl, C-2-6 alkynyl, C-6-10 aryl, C-3-10 cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C-6-10 aryl-Ci-4 alkyl-, C-3-10 cycloalkyl-Ci-4 alkyl-, (5-10 membered heteroaryl)-Ci-4 alkyl-, (4-10 membered heterocycloalkyl)-Ci-4 alkyl-, halo, CN, NHOR, OR, SR, C(0)R^g, C(0)NR^gR^g, R^gS(0)I(OR)^g, OC(0)I(OR)^g, OC(0)NR^gR^g, NHR^g, NR^gR^g, NR^gR^gC(0)I(OR)^g, NR^gR^g(S(0)I(OR)^g), NR^gS(0)I(OR)^g, NR^gRS(0)I(OR)^g, -P(0)I(OR)^gR^g, -P(0)I(OR)^g(R^g), -B(OH)I(OR)^g, -B(OR)^gI(OR)^g, S(0)I(OR)^g and where C^M alkyl, Ci-4 haloalkyl, C-2-6 alkenyl, C-2-6 alkynyl, C-6-10 aryl, C-3-10 cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C-6-10 aryl-Ci-4 alkyl-, C-3-10 cycloalkyl-Ci-4 alkyl-, (5-10 membered heteroaryl)-Ci-4 alkyl-, and (4-10 membered heterocycloalkyl)-Ci-4 alkyl- of R^g are each optionally substituted with 1, 2, 3, 4, or 3 independently selected R^g substituents;

eas each R^g is independently selected from H, C-1-6 alkyl, Ci-4 haloalkyl, C-2-6 alkenyl, C-2-6 alkynyl, C-6-10 aryl, C-3-10 cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C-6-10 aryl-Ci-4 alkyl-, C-3-10 cycloalkyl-Ci-4 alkyl-, (5-10 membered heteroaryl)-Ci-4 alkyl-, and (4-10 membered heterocycloalkyl)-Ci-4 alkyl-, wherein the C-1-6 alkyl, C-2-6 alkenyl, C-2-6 alkynyl, C-6-10 aryl, C-3-10 cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C-6-10 aryl-Ci-4 alkyl-, C-3-10 cycloalkyl-Ci-4 alkyl-, (5-10 membered heteroaryl)-Ci-4 alkyl- and (4-10 membered heterocycloalkyl)-Ci-4 alkyl- of R^g are each optionally substituted with 1, 2, or 3 independently selected R^g substituents;
each R³ is independently selected from Ci-6 alkyl, Ci-6 alkenyl, C2-6 alkynyl, C6-10 aryl, C3-10 cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C6-10 aryl-Ci-4 alkyl-, C3-10 cycloalkyl-Ci-4 alkyl-, (5-10 membered heteroaryl)-Ci-4 alkyl-, (4-10 membered heterocycloalkyl)-Ci-4 alkyl-, halo, CN, NHOR, OR, SR, C(0)R, C(0)NR, C(0)OR, C(0)NR'S(S)R, OC(0)R, OC(0)NR, NHR, NR'R, NR'C(0)R, NR'C(=NR')R, NR'C(=NOH)NR'R, NR'C(=NCN)NR'R, S(0)R, S(0)NR'R, S(0)R, S(0)2NR'C(0)R, NR'S(0)R, NR'S(0)2R, NR'S(0)2NR'R, -P(0)(OR)2, -P(0)(OR)'(OR)2, -B(OH)2, -B(OR)2 and S(0)2NR'R, whereas the Ci-6 alkyl, Ci-6 alkenyl, C2-6 alkynyl, C6-10 aryl, C3-10 cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C6-10 aryl-Ci-4 alkyl-, C3-10 cycloalkyl-Ci-4 alkyl-, (5-10 membered heteroaryl)-Ci-4 alkyl- and (4-10 membered heterocycloalkyl)-Ci-4 alkyl- of R³ is optionally substituted with 1, 2 or 3 independently selected R³ substituents;

or any two R³ substituents together with the boron, phosphorus or nitrogen atom to which they are attached form a 4-, 5-, 6-, 7-, 8-, 9- or 10-membered heterocycloalkyl group optionally substituted with 1, 2 or 3 independently selected R³ substituents;

each R³ is independently selected from Ci-6 alkyl, C3-10 cycloalkyl, 4-7 membered heterocycloalkyl, C6-10 aryl, C5-6 membered heteroaryl, C6-10 aryl-Ci-4 alkyl-, C3-10 cycloalkyl-Ci-4 alkyl-, (5-6 membered heteroaryl)-Ci-4 alkyl-, (4-7 membered heterocycloalkyl)-Ci-4 alkyl-, Ci-6 haloalkoxy, Ci-6 alkenyl, C2-6 alkynyl, halo, CN, OR, SR, NHOR, C(0)R, C(0)NR, C(0)OR, C(0)NR'S(S)R, OC(0)R, OC(0)NR, NHR, NR'R, NR'C(0)R, NR'C(=NR')R, NR'C(=NOH)NR'R, NR'C(=NCN)NR'R, S(0)R, S(0)NR'R, S(0)2R, S(0)2NR'C(0)R, NR'S(0)R, NR'S(0)2R, NR'S(0)2NR'R, -P(0)(OR)2, -P(0)(OR)'(OR)2, -B(OH)2, -B(OR)2 and S(0)2NR'R, wherein the Ci-6 alkyl, C2-6 alkenyl, C2-6 alkynyl, C6-10 aryl, C3-10 cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C6-10 aryl-Ci-4 alkyl-, C3-10 cycloalkyl-Ci-4 alkyl-, (5-10 membered heteroaryl)-Ci-4 alkyl- and (4-10 membered heterocycloalkyl)-Ci-4 alkyl- of R³ are each further optionally substituted by 1, 2, or 3 independently selected R³ substituents;

each R³ is independently selected from C3-6 cycloalkyl, C6-10 aryl, 5 or 6-membered heteroaryl, 4-7 membered heterocycloalkyl, C2-4 alkenyl, C2-4 alkynyl, halo, C1-4 alkyl, C1-4 haloalkyl, C1-4 haloalkoxy, CN, NHOR, OR, SR, C(0)R, C(0)NR, C(0)OR, C(0)NR'S(S)R, OC(0)R, OC(0)NR, NHR, NR'R, NR'C(0)R, NR'C(=NR')R, NR'C(=NOH)NR'R, NR'C(=NCN)NR'R, S(0)R, S(0)NR'R, S(0)2R, S(0)2NR'C(0)R, NR'S(0)R, NR'S(0)2R, NR'S(0)2NR'R, -P(0)(OR)2, -P(0)(OR)'(OR)2, -B(OH)2, -B(OR)2 and S(0)2NR'R, wherein the C1-4 alkyl, C3-6 cycloalkyl, C6-10 aryl, 5 or 6-
membered heteroaryl, 4-7 membered heterocycloalkyl, C2-4 alkenyl, C2-4 alkynyl, Ci-4 haloalkyl
and Ci-4 haloalkoxy of R i are each optionally substituted with 1, 2 or 3 independently selected R 9
substituents;

or two R b groups attached to the same carbon atom of the 4- to 10-membered
heterocycloalkyl taken together with the carbon atom to which they are attached form a C3-6
cycloalkyl or 4- to 6-membered heterocycloalkyl having 1-2 heteroatoms as ring members
selected from O, N or S;

or any two R e substituents together with the boron, phosphorus or nitrogen atom to which
they are attached form a 4-, 5-, 6-, 7-, 8-, 9- or 10-membered heterocycloalkyl group optionally
substituted with 1, 2, or 3 independently selected R b substituents;

or any two R e substituents together with the boron, phosphorus or nitrogen atom to which
they are attached form a 4-, 5-, 6-, 7-, 8-, 9- or 10-membered heterocycloalkyl group optionally
substituted with 1, 2, or 3 independently selected R b substituents;

or any two R e substituents together with the boron, phosphorus or nitrogen atom to which
they are attached form a 4-, 5-, 6-, 7-, 8-, 9- or 10-membered heterocycloalkyl group optionally
substituted with 1, 2, or 3 independently selected R b substituents;

or any two R e substituents together with the boron, phosphorus or nitrogen atom to which
they are attached form a 4-, 5-, 6-, 7-, 8-, 9- or 10-membered heterocycloalkyl group optionally
substituted with 1, 2, or 3 independently selected R b substituents, or 1, 2, or 3 independently
selected R e substituents;

or any two R e substituents together with the boron, phosphorus or nitrogen atom to which
they are attached form a 4-, 5-, 6-, 7-, 8-, 9- or 10-membered heterocycloalkyl group optionally
substituted with 1, 2, or 3 independently selected R b substituents, or 1, 2, or 3 independently
selected R e substituents;

or any two R e substituents together with the boron, phosphorus or nitrogen atom to which
they are attached form a 4-, 5-, 6-, 7-, 8-, 9- or 10-membered heterocycloalkyl group optionally
substituted with 1, 2, or 3 independently selected R b substituents, or 1, 2, or 3 independently
selected R e substituents;

or any two R e substituents together with the boron, phosphorus or nitrogen atom to which
they are attached form a 4-, 5-, 6-, 7-, 8-, 9- or 10-membered heterocycloalkyl group optionally
substituted with 1, 2, or 3 independently selected R b substituents;
6-membered heteroaryl, 4-7 membered heterocycloalkyl, C2-4 alkenyl, and C2-4 alkynyl of R₁, Rₖ, R° or Rₗ are each optionally substituted with 1, 2 or 3 R⁸ substituents;

each Rₙ is independently selected from halo, OH, CN, -COOH, NH₂, -NH-C₄ alkyl, -N(C₆ heterocycloalkyl)₂, C₆ alkyl, C₆ alkoxy, C₆ haloalkyl, C₆ haloalkoxy, phenyl, 5-6 membered heteroaryl, 4-6 membered heterocycloalkyl and C₃-6 cycloalkyl, wherein the C₆ alkyl, phenyl, C₃-6 cycloalkyl, 4-6 membered heterocycloalkyl, and 5-6 membered heteroaryl of R⁸ are each optionally substituted with 1, 2, or 3 substituents selected from halo, OH, CN, -COOH, NH₂, C₄ alkyl, C₄ alkoxy, C₄ haloalkyl, C₄ haloalkoxy, phenyl, C₃-10 cycloalkyl, 5-6 membered heteroaryl and 4-6 membered heterocycloalkyl;

the subscript m is an integer of 0, 1, 2 or 3;

the subscript n is an integer of 0, 1, 2 or 3;

each subscript q is independently an integer of 1, 2, 3 or 4; and

the subscript s is an integer of 1, 2, or 3.

2. The compound of claim 1, having Formula (I):

![Chemical Structure](image)

(I)
or a pharmaceutically acceptable salt or a stereoisomer thereof, wherein:

ring A is 5- to 14-membered heteroaryl, 4- to 14-membered heterocycloalkyl, C₆₋₁₀ aryl or C₃-14 cycloalkyl, wherein the 5- to 14-membered heteroaryl and 4- to 14-membered heterocycloalkyl each has 1-4 heteroatoms as ring members selected from B, P, N, O and S, wherein the P, N or S atom as ring members is optionally oxidized and one or more carbon atoms as ring members are each optionally replaced by a carbonyl group; and wherein ring A is optionally substituted with 1, 2, 3, 4 or 5 R⁶ substituents;

L is a bond, -C(0)NR₁₃—, -NR₁₃-C(0)-, O, -(CR₁₄R₁₅)₉₋₁₀, -(CR₁₄R₁₅)₀₋₁₀, -O(CR₁₄R₁₅)₀₋₁₀, -NR₁₃₋₁₀, -(CR₁₄R₁₅)₉₋₁₀, -NR₁₃₋₁₀-CR₁₄R₁₅₋₁₀, -(CR₁₄R₁₅)₀₋₁₀, -CH=CH₂, -C=CH₂, -SO₂R₄₋₁₀, -NR₁₃S₀₂₋₁₀, -NR₁₃-C(0)-, -OC(0)NR₁₃₋₁₀ or -NR₁₃-C(0)NR₁₃₋₁₀;

X is N or CR₁₇;

R₃ is methyl, halo, CN or C₄ haloalkyl;

R₄ is C₄ alkyl, C₄ alkoxy, C₄ haloalkyl, C₄ haloalkoxy, CN, halo, OH, -COOH, NH₂, -NHC₄ alkyl or N(C₆ heterocycloalkyl)₂.
R^5 is Cl-4 alkyl, Cl-4 alkoxy, C_M haloalkyl, C_M haloalkoxy, CN, halo, OH, -COOH, NH_2, -NHCi-4 alkyl or -N(Ci-4 alkyl);  

R^6, R^7, R^17 and R^18 are each independently selected from H, halo, Cl-6 alkyl, C_2-6 alkenyl, C_2-6 alkynyl, Cl-6 haloalkyl, Cl-6 haloalkoxy, C_6-10 aryl, C_3-10 cycloalkyl, 5-14 membered heteroaryl, 4-10 membered heterocycloalkyl, C_6-10 aryl-Cl-4 alkyl-, C_3-10 cycloalkyl-Cl-4 alkyl-, (5-14 membered heteroaryl)-Cl-4 alkyl-, (4-10 membered heterocycloalkyl)-Cl-4 alkyl-, CN, N(O)R, OR, SR, NHOR, C(0)R, C(0)NR, C(0)OR, OC(0)R, OC(0)NR, OOCR, NHR, NR^2, NR^2C(0)R, NR^2C(0)OR, NR^2C(0)NR, NR^2C(0)NR^2, C(=NR^2)R, C(=NR^2)NR^2, NR^2C(=NR^2)NR^2, NR^2S(0)R, NR^2S(0)R, NR^2S(0)R, S(0)R, S(0)NR, S(0)NR, S(0)NR^2, S(0)NR^2, S(0)NR, S(0)NR, S(0)NR, S(0)NR, S(0)NR, S(0)R, ... -P(0)(OR)^2(OR)^2, -B(OH)_, -B(OR)^2, S(0)NR^2, wherein the Cl-e alkyl, C_2-6 alkynyl, C_6-10 aryl, C_3-10 cycloalkyl, 5-14 membered heteroaryl, 4-10 membered heterocycloalkyl, C_6-10 aryl-Cl-4 alkyl-, C_3-10 cycloalkyl-Cl-4 alkyl-, (5-14 membered heteroaryl)-Cl-4 alkyl- and (4-10 membered heterocycloalkyl)-Cl-4 alkyl- of R^6, R^7, R^17 and R^18 are each optionally substituted with 1, 2, 3, 4 or 5 independently selected R^8 substituents;  

or two R^8 substituents attached to the same ring carbon atom taken together with the ring carbon atom to which they are attached form spiro C_3-6 cycloalkyl or spiro 4- to 7-membered heterocycloalkyl, each of which is optionally substituted with 1, 2, or 3 independently selected R^f substituents;  

each R^13 is independently selected from H, Cl-6 haloalkyl or Cl-6 alkyl optionally substituted with a substituent selected from C_M alkyl, Cl-4 alkoxy, C_l-4 haloalkyl, C_l-4 haloalkoxy, CN, halo, OH, -COOH, NH_2, -NHCi-4 alkyl and -N(Cl-M alkyl);  

R^14 and R^15 are each independently selected from H, halo, CN, OH, -COOH, C_M alkyl, C_M alkoxy, -NHCi-4 alkyl, -N(Ci-l-4 alkyl), C_l-4 haloalkyl, C_M haloalkoxy, C_3-6 cycloalkyl, phenyl, 5-6 membered heteroaryl and 4-6 membered heterocycloalkyl, wherein the C_M alkyl, Cl-4 alkoxy, C_M haloalkyl, C_M haloalkoxy, C_3-6 cycloalkyl, phenyl, 5-6 membered heteroaryl and 4-6 membered heterocycloalkyl of R^14 or R^15 are each optionally substituted with 1, 2, or 3 independently selected R^8 substituents;  

or R^14 and R^15 taken together with the carbon atom to which they are attached form 3-, 4-, 5- or 6-membered cycloalkyl or 3-, 4-, 5- or 6-membered heterocycloalkyl, each of which is optionally substituted with 1 or 2 independently selected R^8 substituents;  

each R^a is independently selected from H, CN, Cl-6 alkyl, C_l-4 haloalkyl, C_l-4 alkenyl, C_l-4 alkynyl, C_6-10 aryl, C_3-10 cycloalkyl, 5-14 membered heteroaryl, 4-14 membered heterocycloalkyl, C_6-10 aryl-Cl-4 alkyl-, C_3-10 cycloalkyl-Cl-4 alkyl-, (5-14 membered heteroaryl)-Cl-4 alkyl- and (4-14 membered heterocycloalkyl)-Cl-4 alkyl-, wherein the Cl-l-6 alkyl, C_l-4 alkenyl, C_l-4 alkynyl, C_6-10 aryl-Cl-4 alkyl-
aryl, C₃-10 cycloalkyl, 5-14 membered heteroaryl, 4-14 membered heterocycloalkyl, C₆-ιο aryl-
c₄-ιο alkyl-, C₃-ιο cycloalkyl-Cι-4 alkyl-, (5-14 membered heteroaryl)-Ci-4 alkyl- and (4-14
membered heterocycloalkyl)-Ci-4 alkyl- of Rₐ are each optionally substituted with 1, 2, 3, 4, or 5
independently selected Rᵢ substituents;

each Rᵢ is independently selected from Ci-6 alkyl, Ci-6haloalkyl, halo, C₆-io aryl, 5-14
membered heteroaryl, C₃-ιο cycloalkyl, 4-14 membered heterocycloalkyl, C₆-ιο aryl-Cι-4 alkyl-
c₃-ιο cycloalkyl-Ci-4 alkyl-, (5-14 membered heteroaryl)-Ci-4 alkyl-, (4-14 membered
heterocycloalkyl)-Ci-4 alkyl-, CN, NH₂, NHOR ɵ, OR ɵ, SR ɵ, C(0)R ɵ, C(0)NR ɵ, C(0)OR ɵ,
OC(0)R ɵ, OC(0)NR ɵ, NHR ɵ, N₃R ɵ, NR₂R ɵ, NR₃C(0)R ɵ, NR₂C(0)NR ɵ, NR₂C(0)OR ɵ,
C(NR ɵ)NR ɵR ɵ, NR₃C(NR ɵ)NR ɵR ɵ, NR₃C(=NOH)NR ɵR ɵ, NR₃C(=NCH)NR ɵR ɵ, S(0)R ɵ,
S(0)NR ɵR ɵ, S(0)₂R ɵ, NR₂S(0)₂R ɵ, NR₂S(0)₂NR₂R ɵ, P(0)R ɵR ɵ, -P(0)(OR ɵ)(OR ɵ), -B(OH) ɵ₂,
B(OR ɵ)₂ and S(0)₂NR₂R ɵ, wherein the Ci-e alkyl, Ci-e haloalkyl, Ci-e aryl, 5-14 membered
heteroaryl, C₃-ιο cycloalkyl, 4-14 membered heterocycloalkyl, C₆-ιο aryl-Cι-4 alkyl-, C₃-ιο
cycloalkyl-Ci-4 alkyl-, (5-14 membered heteroaryl)-Ci-4 alkyl-, and (4-14 membered
heterocycloalkyl)-Ci-4 alkyl- of Rᵢ are each optionally substituted with 1, 2, or 3 independently
selected Rᵢ substituents;

each Rᵢ is independently selected from H, Ci-6 alkyl, Ci-6haloalkyl, C₂₆ alkenyl, C₂₆
alkynyl, C₆-ιο aryl, C₃-ιο cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl,
c₆-ιο aryl-Cι-4 alkyl-, C₃-ιο cycloalkyl-Ci-4 alkyl-, (5-10 membered heteroaryl)-Ci-4 alkyl-, and (4-
10 membered heterocycloalkyl)-Ci-4 alkyl-, wherein the Ci-6 alkyl, Ci-6haloalkyl, C₂₆ alkenyl,
c₂₆ alkenyl, C₆-ιο aryl, C₃-ιο cycloalkyl, 5-10 membered heteroaryl, 4-10 membered
heterocycloalkyl, C₆-ιο aryl-Cι-4 alkyl-, C₃-ιο cycloalkyl-Ci-4 alkyl-, (5-10 membered heteroaryl)-
c₄-ιο alkyl- and (4-10 membered heterocycloalkyl)-Ci-4 alkyl- of Rᵢ are each optionally
substituted with 1, 2 or 3 independently selected Rᵢ substituents;

each Rᵢ substituent is independently selected from halo, Ci-6 alkyl, C₂₆ alkenyl, C₂₆
alkynl, Ci-6 haloalkyl, Ci-6haloalkoxy, C₆-ιο aryl, C₃-ιο cycloalkyl, 5-10 membered heteroaryl, 4-
10 membered heterocycloalkyl, C₆-ιο aryl-Cι-4 alkyl-, C₃-ιο cycloalkyl-Ci-4 alkyl-, (5-10
membered heteroaryl)-Ci-4 alkyl-, (4-10 membered heterocycloalkyl)-Ci-4 alkyl-, CN, OH, NH₂,
N₀₂, NHOR ɵ, OR ɵ, SR ɵ, C(0)R ɵ, C(0)NR ɵ, C(0)OR ɵ, OC(0)R ɵ, OC(0)NR ɵR ɵ,
C(NR ɵ)NR ɵR ɵ, NR₃C(NR ɵ)NR ɵR ɵ, NR₂R ɵ, NR₃C(0)R ɵ, NR₂C(0)OR ɵ, NR₂C(0)NR ɵR ɵ,
NR₂S(0)R ɵ, NR₂S(0)₂R ɵ, S(0)₂R ɵ, S(0)NR ɵR ɵ, S(0)₂R ɵ, -P(0)R ɵR ɵ, -P(0)(OR ɵ)(OR ɵ),
-B(OH) ɵ₂, -B(OR ɵ)₂ and S(0)₂NR₂R ɵ, wherein the Ci-e alkyl, Ci-e haloalkyl, Ci-e
haloalkoxy, C₂₆ alkenyl, C₂₆ alkenyl, C₆-ιο aryl, C₃-ιο cycloalkyl, 5-10 membered heteroaryl, 4-
10 membered heterocycloalkyl, C₆-ιο aryl-Cι-4 alkyl-, C₃-ιο cycloalkyl-Ci-4 alkyl-, (5-10
membered heteroaryl)-C1-4 alkyl-and (4-10 membered heterocycloalkyl)-C1-4 alkyl- of R are each further optionally substituted with 1, 2, or 3 independently selected R substituents;

each R is independently selected from H, C6 alkyl, C4 haloalkyl, C2-6 alkenyl, C2-6 alkynyl, C6+1 aryl, C3-10 cycloalkyl, 5-10 membered heterocycloalkyl, C6+1 aryl-C1-4 alkyl-, C3-10 cycloalkyl-C1-4 alkyl-, (5-10 membered heterocycloalkyl)-C1-4 alkyl-, and (4-10 membered heterocycloalkyl)-C1-4 alkyl-, wherein the C6 alkyl, C2-6alkenyl, C2-6 alkynyl, C6+1 aryl, C3-10 cycloalkyl, 5-10 membered heterocycloalkyl, C6+1 aryl-C1-4 alkyl-, C3-10 cycloalkyl-C1-4 alkyl-, (5-10 membered heterocycloalkyl)-C1-4 alkyl- and (4-10 membered heterocycloalkyl)-C1-4 alkyl- of R are each optionally substituted with 1, 2, 3, 4, or 5 independently selected R substitutions;

each R is independently selected from C1-4 alkyl, C4 haloalkyl, C2-6 alkenyl, C2-6 alkynyl, C6+1 aryl, C3-10 cycloalkyl, 5-10 membered heterocycloalkyl, 4-10 membered heterocycloalkyl, C6+1 aryl-C1-4 alkyl-, C3-10 cycloalkyl-C1-4 alkyl-, (5-10 membered heterocycloalkyl)-C1-4 alkyl-, (4-10 membered heterocycloalkyl)-C1-4 alkyl-, halogen, CN, NHOR, OR, SR, C(0)R, C(0)NR, C(0)OR, C(0)N=C(=NR)NR, O=C(0)R, O=C(0)NR, NH, NHOR, R= C(0)NR, NR= C(0)NR, NR= C(0)OR, NR= C(0)N=C(=NR)NR, NR= C(0)OR, NR= C(0)O=C(0)R, NR= C(0)O=C(0)NR, NR= C(0)O=C(0)OR, NR= C(0)O=C(0)N=C(=NR)NR, NR= C(0)OR, NR= C(0)O=C(0)N=C(=NR)NR, NR= C(0)OR, -B(OH) 2, B(OH) 2, and S(0) 2NR or R= C(0)OR, O=C(0)NR, R=-P(0)OR=, -P(0)OR=, wherein the C1-4 alkyl, C4 haloalkyl, C2-6 alkenyl, C2-6 alkynyl, C6+1 aryl, C3-10 cycloalkyl, 5-10 membered heterocycloalkyl, C6+1 aryl-C1-4 alkyl-, C3-10 cycloalkyl-C1-4 alkyl-, (5-10 membered heterocycloalkyl)-C1-4 alkyl- and (4-10 membered heterocycloalkyl)-C1-4 alkyl- of R are each optionally substituted with 1, 2, 3, 4, or 5 independently selected R substitutions;

each R is independently selected from C1-4 alkyl, C4 haloalkyl, C2-6 alkenyl, C2-6 alkynyl, C6+1 aryl, C3-10 cycloalkyl, 5-10 membered heterocycloalkyl, 4-10 membered heterocycloalkyl, C6+1 aryl-C1-4 alkyl-, C3-10 cycloalkyl-C1-4 alkyl-, (5-10 membered heterocycloalkyl)-C1-4 alkyl-, (4-10 membered heterocycloalkyl)-C1-4 alkyl-, halogen, CN, NHOR, OR, SR, C(0)R, C(0)NR, C(0)OR, C(0)N=C(=NR)NR, O=C(0)R, O=C(0)NR, NH, NHOR, R= C(0)NR, NR= C(0)NR, NR= C(0)OR, NR= C(0)N=C(=NR)NR, NR= C(0)OR, NR= C(0)O=C(0)R, NR= C(0)O=C(0)NR, NR= C(0)O=C(0)OR, NR= C(0)O=C(0)N=C(=NR)NR, NR= C(0)OR, NR= C(0)O=C(0)N=C(=NR)NR, NR= C(0)OR, NR= C(0)O=C(0)N=C(=NR)NR, NR= C(0)OR, NR= C(0)O=C(0)N=C(=NR)NR, NR= C(0)OR, NR= C(0)O=C(0)N=C(=NR)NR, NR= C(0)OR, NR= C(0)O=C(0)N=C(=NR)NR, NR= C(0)OR, S(0) 2NR or R= C(0)OR, O=C(0)NR, R=-P(0)OR=, -P(0)OR=, wherein the C1-4 alkyl, C4 haloalkyl, C2-6 alkenyl, C2-6 alkynyl, C6+1 aryl, C3-10 cycloalkyl, 5-10 membered heterocycloalkyl, C6+1 aryl-C1-4 alkyl-, C3-10 cycloalkyl-C1-4 alkyl-, (5-10 membered heterocycloalkyl)-C1-4 alkyl- and (4-10 membered heterocycloalkyl)-C1-4 alkyl- of R are each optionally substituted with 1, 2, 3, 4, or 5 independently selected R substituents;
each R is independently selected from H, Ci-6 alkyl, Ci-haloalkyl, C2-6 alkenyl, C6-10 aryl, C3-10 cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C6-10 aryl-Ci-4 alkyl-, C3-10 cycloalkyl-Ci-4 alkyl-, (5-10 membered heteroaryl)-Ci-4 alkyl-, and (4-10 membered heterocycloalkyl)-Ci-4 alkyl-, wherein the Ci-6 alkyl, C2-6 alkenyl, C6-10 aryl, C3-10 cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C6-10 aryl-Ci-4 alkyl-, C3-10 cycloalkyl-Ci-4 alkyl-, (5-10 membered heteroaryl)-Ci-4 alkyl- and (4-10 membered heterocycloalkyl)-Ci-4 alkyl- of R are each optionally substituted with 1, 2, or 3 independently selected R substituents;

each R is independently selected from Ci-6 alkyl, Ci-haloalkyl, C2-6 alkenyl, C6-10 aryl, C3-10 cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C6-10 aryl-Ci-4 alkyl-, C3-10 cycloalkyl-Ci-4 alkyl-, (5-10 membered heteroaryl)-Ci-4 alkyl-, (4-10 membered heterocycloalkyl)-Ci-4 alkyl-, halo, CN, NHOR, OR, SR, C(0)R, C(0)NR, R, C(OR)R, OR, S(0)R, S(0)R, S(0)2R, R, R, R, R, wherein the Ci-alkyl, Ci-haloalkyl, C2-6 alkynyl, C2-6 alkenyl, Ce-10 aryl, C3-10 cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C6-10 aryl-Ci-4 alkyl-, C3-10 cycloalkyl-Ci-4 alkyl-, (5-10 membered heteroaryl)-Ci-4 alkyl- and (4-10 membered heterocycloalkyl)-Ci-4 alkyl- of R is optionally substituted with 1, 2 or 3 independently selected R substituents;

or any two R substituents together with the boron, phosphorus or nitrogen atom to which they are attached form a 4-, 5-, 6-, 7-, 8-, 9- or 10-membered heterocycloalkyl group optionally substituted with 1, 2 or 3 independently selected R substituents;

each R is independently selected from Ci-6 alkyl, C3-10 cycloalkyl, 4-7 membered heterocycloalkyl, C6-10 aryl, 5-6 membered heteroaryl, C6-10 aryl-C1-4 alkyl-, C3-10 cycloalkyl-C1-4 alkyl-, (5-6 membered heteroaryl)-C1-4 alkyl-, (4-7 membered heterocycloalkyl)-C1-4 alkyl-, Ci-6 haloalkyl, Ci-haloalkoxy, C2-6 alkynyl, C2-6 alkenyl, halo, CN, OR, SR, NHOR, C(O)R, C(O)N R[R], 0(0)O, O C(O)R, O C(O)N R[R], NHR, N R[R], N R C(O)R, N R C(O)N R[R], N R C(O)OR, C(=NR) R[R], N R C N R N R[R], S(0)O, S(0) N R[R], S(0) 2 R, NR O R, NR S(0) N R[R], -P(O) R[R], -P(0)(0)O(0), -B (OH) 2, -B (0) 2 and S(0) N R[R], wherein the Ci-6 alkyl, C2-6 alkenyl, C3-10 cycloalkyl, 4-7 membered heterocycloalkyl, C6-10 aryl, 5-6 membered heteroaryl, C6-10 aryl-C1-4 alkyl-, C3-10 cycloalkyl-C1-4 alkyl-, (5-6 membered heteroaryl)-C1-4 alkyl-, (4-7 membered heterocycloalkyl)-C1-4 alkyl- of R are each further optionally substituted by 1, 2 or 3 independently selected Rs substituents;
each \( R^i \) is independently selected from \( C_{3-6} \) cycloalkyl, \( C_{6-10} \) aryl, 5 or 6-membered heteroaryl, 4-7 membered heterocycloalkyl, \( C_2-4 \) alkenyl, \( C_2-4 \) alkynyl, halo, \( C_1-4 \) alkyl, \( C_1-4 \) haloalkyl, \( C_1-4 \) haloalkoxy, CN, NHOR \( k \), OR \( k \), SR \( k \), C(0)R \( k \), C(0)NR \( k \)R \( k \), C(0)OR \( k \), OC(0)R \( k \), OC(0)NR \( k \)R \( k \), NHR \( k \), NR \( k \)R \( k \), NRC(0)R \( k \), NR \( k \)C(0)NR \( k \)R \( k \), NR \( k \)C(0)OR \( k \), C(=NR \( k \))NR \( k \)R \( k \), NR \( k \)C(=NR \( k \))NR \( k \)R \( k \), S(0)R \( k \), S(0)NR \( k \)R \( k \), S(0)OC(0)R \( k \), NR \( k \)S(0) \( 2 \)R \( k \), NR \( k \)S(0) \( 2 \)NR \( k \)R \( k \), -P(0)(OR \( k \))(OR \( k \)), -B(OH) \( 2 \), -B(OR \( k \)) \( 2 \) and S(0) \( n \)NR \( k \)R \( k \), wherein the \( C_1 M \) alkyl, \( C_3-6 \) cycloalkyl, \( C_6-10 \) aryl, 5- or 6-membered heteroaryl, 4-7 membered heterocycloalkyl, \( C_2-4 \) alkenyl, \( C_2-4 \) alkynyl, \( C_1-4 \) haloalkyl and \( C_1-4 \) haloalkoxy of \( R^i \) are each optionally substituted with 1, 2 or 3 independently selected \( \text{R}^g \) substituents;

or two \( R^h \) groups attached to the same carbon atom of the 4- to 10-membered heterocycloalkyl taken together with the carbon atom to which they are attached form a \( C_{3-6} \) cycloalkyl or 4- to 6-membered heterocycloalkyl having 1-2 heteroatoms as ring members selected from O, N or S;

or any two \( \text{R}^e \) substituents together with the boron, phosphorus or nitrogen atom to which they are attached form a 4-, 5-, 6-, 7-, 8-, 9- or 10-membered heterocycloalkyl group optionally substituted with 1, 2, or 3 independently selected \( \text{R}^h \) substituents;

or any two \( \text{R}^e \) substituents together with the boron, phosphorus or nitrogen atom to which they are attached form a 4-, 5-, 6-, 7-, 8-, 9- or 10-membered heterocycloalkyl group optionally substituted with 1, 2, or 3 independently selected \( \text{R}^h \) substituents;

or any two \( \text{R}^g \) substituents together with the boron, phosphorus or nitrogen atom to which they are attached form a 4-, 5-, 6-, 7-, 8-, 9- or 10-membered heterocycloalkyl group optionally substituted with 1, 2, or 3 independently selected \( \text{R}^h \) substituents;

or any two \( \text{R}^i \) substituents together with the boron, phosphorus or nitrogen atom to which they are attached form a 4-, 5-, 6-, 7-, 8-, 9- or 10-membered heterocycloalkyl group optionally substituted with 1, 2, or 3 independently selected \( \text{R}^h \) substituents, or 1, 2, or 3 independently selected \( \text{R}^h \) substituents;

or any two \( \text{R}^k \) substituents together with the boron, phosphorus or nitrogen atom to which they are attached form a 4-, 5-, 6-, 7-, 8-, 9- or 10-membered heterocycloalkyl group optionally substituted with 1, 2, or 3 independently selected \( \text{R}^h \) substituents, or 1, 2, or 3 independently selected \( \text{R}^h \) substituents;
or any two R⁵ substituents together with the boron, phosphorus or nitrogen atom to which they are attached form a 4-, 5-, 6-, 7-, 8-, 9- or 10-membered heterocycloalkyl group optionally substituted with 1, 2, or 3 independently selected R⁶ substituents;

each R⁺, R⁻, R⁰ or R⁵ is independently selected from H, Ci-4 alkyl, C₃-6 cycloalkyl, C₆-10 aryl, 5 or 6-membered heteroaryl, 4-7 membered heterocycloalkyl, Ci-6 haloalkyl, Ci-6 haloalkoxy, C₂-4 alkenyl, and C₂-4 alkynyl, wherein the Ci-4 alkyl, C₃-6 cycloalkyl, C₆-10 aryl, 5 or 6-membered heteroaryl, 4-7 membered heterocycloalkyl, C₂-4 alkenyl, and C₂-4 alkynyl of R⁺, R⁻, R⁰ or R⁵ are each optionally substituted with 1, 2 or 3 R⁶ substituents;

each R₃ is independently selected from halo, OH, CN, -COOH, NH₂, -NH-Ci-e alkyl, -N(Ci-6 alkyl)₂, Ci-6 alkyl, Ci-6 alkoxy, C₃-6 alkythio, Ci-6 haloalkyl, Ci-6 haloalkoxy, phenyl, 5-6 membered heteroaryl, 4-6 membered heterocycloalkyl and C₃-6 cycloalkyl, wherein the Ci-6 alkyl, phenyl, C₃-6 cycloalkyl, 4-6 membered heterocycloalkyl, and 5-6 membered heteroaryl of R₃ are each optionally substituted with 1, 2, or 3 substituents selected from halo, OH, CN, -COOH, NH₂, Ci-4 alkyl, Ci-4 alkoxy, Ci-4 haloalkyl, Ci-4 haloalkoxy, phenyl, C₃-10 cycloalkyl, 5-6 membered heteroaryl and 4-6 membered heterocycloalkyl;
The subscript m is an integer of 0, 1, 2 or 3;
the subscript n is an integer of 0, 1, 2 or 3;
each subscript q is independently an integer of 1, 2, 3 or 4; and
the subscript s is an integer of 1, 2, or 3.

3. The compound of claim 1 or 2, having Formula (I):

or a pharmaceutically acceptable salt or a stereoisomer thereof, wherein:

ring A is 5- to 14-membered heteroaryl, 4- to 14-membered heterocycloalkyl, C₆-10 aryl or C₃-14 cycloalkyl, wherein the 5- to 14-membered heteroaryl and 4- to 14-membered heterocycloalkyl each has 1-4 heteroatoms as ring members selected from N, O and S, wherein the N or S atom as ring members is optionally oxidized and one or more carbon atoms as ring members are each optionally replaced by a carbonyl group; and wherein ring A is optionally substituted with 1, 2, 3, 4 or 5 R⁶ substituents;
L is a bond, -C(0)NR 13-,-NR 13C(0)-, O, -(CR 14R 15)Q,-(CR 14R 15)Q-O-, -0(CR 14R 15)Q-, -
NR 13S0, -NR 13C(0)0-, -O(C(0)NR 13 or -NR 13C(0)NR 13-;
X is N or CR 17;
R 3 is methyl, halo, CN or C4-haloalkyl;
R 4 is C4 alkyl, C4 haloalkyl, C4 haloalkoxy, CN, halo, OH, -COOH, NH 2,-
-NHC 6 alkyl or N(C4 alkyl) 2;
R 5 is C4 alkyl, C4 haloalkoxycM C4 haloalkyl, C4 haloalkoxy, CN, halo, OH, -COOH, NH 2,-
-NHC 6 alkyl or N(C4 alkyl) 2;
R 6, R 7, R 17 and R 18 are each independently selected fromH, halo, C6 alkyl, C2-6 alkenyl,
C2-6 alkynyl, C6 haloalkyl, C6 haloalkoxy, C4-6 aryl, C3-10 cycloalkyl, 5-14 membered
heteroaryl, 4-10 membered heterocycloalkyl, C6-10 aryl-C4 alkyl-, C3-10 cycloalkyl-C4 alkyl-, (5-14 membered heteroaryl)-C4 alkyl-, (4-10 membered heterocycloalkyl)-C4 alkyl-, CN, NO 2,
OR, SR, NHOR, C(0)R, C(0)NR aR a, C(0)OR a, OC(0)R a, OC(0)NR aR a, NHR a, NR aR a,
NR aC(0)R a, NR aC(0)OR a, NR aC(0)NR aR a, C(NR aR a)R a, C(NR aR a)NR aR a,
NR aC(NR aR a)NR aR a, NR aS(0)R a, NR aS(0) 2R a, NR aS(0) 2NR aR a, S(0)R a, S(0)NR aR a,
S(0) 2R a, and S(0) 2NR aR a,
wherein the C6 alkyl, C2-6 alkenyl, C2-6 alkynyl, C6-10 aryl, C3-10 cycloalkyl, 5-14 membered
heteroaryl, 4-10 membered heterocycloalkyl, C6-10 aryl-C4 alkyl-, C3-10 cycloalkyl-C4 alkyl-, (5-14 membered heteroaryl)-C4 alkyl- and (4-10 membered heterocycloalkyl)-C4 alkyl- of R 6,
R 7, R 17 and R 18 are each optionally substituted with 1, 2, 3, 4 or 5 independently selected R 6
substituents;
or two R 6 substituents attached to the same ring carbon atom taken together with the ring
carbon atom to which they are attached form spiro C4-6 cycloalkyl or spiro 4- to 7-membered
heterocycloalkyl, each of which is optionally substituted with 1, 2, or 3 independently selected R 6
substituents;
each R 13 is independently H, C6 haloalkyl or C6 alkyl optionally substituted with a
substituent selected from C4 alkyl, C4 haloalkoxy, C4 haloalkyl, C4 haloalkoxy, CN, halo, OH, -
-COOH, NH 2, -NHC 6 alkyl and -N(C4 alkyl) 2;
R 14 and R 15 are each independently selected from H, halo, CN, OH, -COOH, C4 alkyl,
C4 haloalkoxycNHC 4 alkyl, -N(C4 alkyl) 2, C4 haloalkyl, C4 haloalkoxy, C4 cycloalkyl,
phenyl, 5-6 membered heteroaryl and 4-6 membered heterocycloalkyl, wherein the C4 alkyl, C4
haloalkoxy, C4 haloalkyl, C4 haloalkoxy, C4 cycloalkyl, phenyl, 5-6 membered heteroaryl and 4-6
membered heterocycloalkyl of R 14 or R 15 are each optionally substituted with 1, 2, or 3
independently selected R 6 substituents;
or R\textsuperscript{14} and R\textsuperscript{15} taken together with the carbon atom to which they are attached form 3-, 4-, 5- or 6-membered cycloalkyl or 3-, 4-, 5- or 6-membered heterocycloalkyl, each of which is optionally substituted with 1 or 2 independently selected R\textsuperscript{8} substituents;

each R\textsuperscript{9} is independently selected from H, CN, Ci-6 alkyl, Ci-4haloalkyl, C2-6 alkenyl, C6-10 aryl, C3-10 cycloalkyl, 5-14 membered heteroaryl, 4-14 membered heterocycloalkyl, C6-10 aryl-Ci-4 alkyl-, C3-10 cycloalkyl-Ci-4 alkyl-, (5-14 membered heteroaryl)-Ci-4 alkyl-, and (4-14 membered heterocycloalkyl)-Ci-4 alkyl-, wherein the Ci-6 alkyl, C2-6 alkenyl, C6-10 aryl, C3-10 cycloalkyl, 5-14 membered heteroaryl, 4-14 membered heterocycloalkyl, C6-10 aryl-Ci-4 alkyl-, C3-10 cycloalkyl-Ci-4 alkyl-, (5-14 membered heteroaryl)-Ci-4 alkyl- and (4-14 membered heterocycloalkyl)-Ci-4 alkyl- of R\textsuperscript{9} are each optionally substituted with 1, 2, 3, 4, or 5 independently selected R\textsuperscript{10} substituents;

each R\textsuperscript{10} is independently selected from Ci-6 alkyl, Ci-6haloalkyl, halo, C6-10 aryl, 5-14 membered heteroaryl, C3-10 cycloalkyl, 4-14 membered heterocycloalkyl, C6-10 aryl-Ci-4 alkyl-, C3-10 cycloalkyl-Ci-4 alkyl-, (5-14 membered heteroaryl)-Ci-4 alkyl-, (4-14 membered heterocycloalkyl)-Ci-4 alkyl-, CN, NH2, NHOR \textgreek{e}, OR \textgreek{e}, SR \textgreek{e}, C(0)R \textgreek{e}, C(0)NR \textgreek{e}, C(0)OR \textgreek{e}, OC(0)R \textgreek{e}, OC(0)NR \textgreek{e}, NHRC(0) \textgreek{e}, NRC(0)R \textgreek{e}, NRC(0)NR \textgreek{e}, NRC(0)OR \textgreek{e}, C(=NR \textgreek{e})NR \textgreek{e}, C(=NR \textgreek{e})C(=NOH)NR \textgreek{e}, C(=NR \textgreek{e})C(=NCN)NR \textgreek{e}, S(0) \textgreek{e}, S(0)R \textgreek{e}, R(0)2S(0) \textgreek{e}, NRC(0)R \textgreek{e}, and S(0)2NR \textgreek{e}, and S(0)2NR \textgreek{e}, wherein the Ci-e alkyl, Ci-6haloalkyl, C6-10 aryl, 5-14 membered heteroaryl, C3-10 cycloalkyl, 4-14 membered heterocycloalkyl, C6-10 aryl-Ci-4 alkyl-, C3-10 cycloalkyl-Ci-4 alkyl-, (5-14 membered heteroaryl)-Ci-4 alkyl-, and (4-14 membered heterocycloalkyl)-Ci-4 alkyl- of R\textsuperscript{10} are each optionally substituted with 1, 2, or 3 independently selected R\textsuperscript{11} substituents;

each R\textsuperscript{11} is independently selected from H, Ci-6 alkyl, Ci-6haloalkyl, C2-6 alkenyl, C2-6 alkynyl, C6-10 aryl, C3-10 cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C6-10 aryl-Ci-4 alkyl-, C3-10 cycloalkyl-Ci-4 alkyl-, (5-10 membered heteroaryl)-Ci-4 alkyl-, and (4-10 membered heterocycloalkyl)-Ci-4 alkyl- of R\textsuperscript{11} are each optionally substituted with 1, 2 or 3 independently selected R\textsuperscript{12} substituents;
NO₂, NHOR, OR, SR, C(0)R, C(0)OR, OC(0)R, OC(0)NR, C(=NR)NR, C(NR)O, N(R)S(O)₂, and S(O)₂NR₄⁺, wherein the C₅₋₆ alkyl, C₅₋₆ haloalkyl, C₅₋₆ haloalkoxy, C₂₋₆ alkenyl, C₆₋₁₀ aryl, C₃₋₁₀ cycloalkyl, 5-10 membered heterocycloalkyl, 4-10 membered heterocycloalkyl, C₆₋₁₀ aryl-C₄ alky1-, C₃₋₁₀ cycloalkyl-C₄ alky1-, (5-10 membered heteroaryl)-C₄ alky1- and (4-10 membered heterocycloalkyl)-C₄ alky1- of R₈ are each further optionally substituted with 1, 2, or 3 independently selected R₄ substituents;

each R₅ is independently selected from H, C₁₋₄ alkyl, C₁₋₄ haloalkyl, C₂₋₆ alkenyl, C₆₋₁₀ aryl, C₃₋₁₀ cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C₆₋₁₀ aryl-C₄ alky1-, C₃₋₁₀ cycloalkyl-C₄ alky1-, (5-10 membered heteroaryl)-C₄ alky1- and (4-10 membered heterocycloalkyl)-C₄ alky1- of R₈ are each further optionally substituted with 1, 2, 3, 4, or 5 independently selected R₄ substi tuents;

each R₆ is independently selected from C₁₋₄ alkyl, C₁₋₄ haloalkyl, C₂₋₆ alkenyl, C₆₋₁₀ aryl, C₃₋₁₀ cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C₆₋₁₀ aryl-C₄ alky1-, C₃₋₁₀ cycloalkyl-C₄ alky1-, (5-10 membered heteroaryl)-C₄ alky1- and (4-10 membered heterocycloalkyl)-C₄ alky1- of R₈ are each further optionally substituted with 1, 2, 3, 4, or 5 independently selected R₄ substituents;

each R₇ is independently selected from C₅₋₆ alkyl, C₅₋₆ haloalkyl, C₂₋₆ alkenyl, C₆₋₁₀ aryl, C₃₋₁₀ cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C₆₋₁₀ aryl-C₄ alky1-, C₃₋₁₀ cycloalkyl-C₄ alky1-, (5-10 membered heteroaryl)-C₄ alky1- and (4-10 membered heterocycloalkyl)-C₄ alky1- of R₈ are each further optionally substituted with 1, 2, 3, 4, or 5 independently selected R₄ substituents;

each R₈ is independently selected from C₅₋₆ alkyl, C₅₋₆ haloalkyl, C₂₋₆ alkenyl, C₆₋₁₀ aryl, C₃₋₁₀ cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C₆₋₁₀ aryl-C₄ alky1-, C₃₋₁₀ cycloalkyl-C₄ alky1-, (5-10 membered heteroaryl)-C₄ alky1- and (4-10 membered heterocycloalkyl)-C₄ alky1- of R₈ are each further optionally substituted with 1, 2, 3, 4, or 5 independently selected R₄ substituents;
alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{4} alkyl-, C_{3-10} cycloalkyl-C_{4} alkyl-, (5-10 membered heteroaryl)-C_{4} alkyl-, and (4-10 membered heterocycloalkyl)-C_{4} alkyl- of R^{8} are each optionally substituted with 1, 2 or 3 independently selected R^{9} substituents; each R^{8} is independently selected from H, Ci-6 alkyl, Ci-haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{4} alkyl-, C_{3-10} cycloalkyl-C_{4} alkyl-, (5-10 membered heteroaryl)-C_{4} alkyl-, and (4-10 membered heterocycloalkyl)-C_{4} alkyl-, wherein the Ci-6 alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{4} alkyl-, C_{3-10} cycloalkyl-C_{4} alkyl-, (5-10 membered heteroaryl)-C_{4} alkyl- and (4-10 membered heterocycloalkyl)-C_{4} alkyl- of R^{8} are each optionally substituted with 1, 2, or 3 independently selected R^{9} substituents; each R^{9} is independently selected from Ci-6 alkyl, Ci-haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{4} alkyl-, C_{3-10} cycloalkyl-C_{4} alkyl-, (5-10 membered heteroaryl)-C_{4} alkyl-, (4-10 membered heterocycloalkyl)-C_{4} alkyl- and (4-10 membered heterocycloalkyl)-C_{4} alkyl- of R^{9} is optionally substituted with 1, 2 or 3 independently selected R^{10} substituents; or any two R^{3} substituents together with the nitrogen atom to which they are attached form a 4-, 5-, 6-, 7-, 8-, 9- or 10-membered heterocycloalkyl group optionally substituted with 1, 2 or 3 independently selected R^{8} substituents; each R^{b} is independently selected from Ci-6 alkyl, C_{3-10} cycloalkyl, 4-7 membered heterocycloalkyl, C_{6-10} aryl, 5-6 membered heteroaryl, C_{6-10} aryl-C_{4} alkyl-, C_{3-10} cycloalkyl-C_{4} alkyl-, (5-6 membered heteroaryl)-C_{4} alkyl-, (5-10 membered heterocycloalkyl)-C_{4} alkyl-, (4-7 membered heterocycloalkyl)-C_{4} alkyl-, (5-6 membered heteroaryl)-C_{4} alkyl-, (5-10 membered heterocycloalkyl)-C_{4} alkyl- and (4-10 membered heterocycloalkyl)-C_{4} alkyl- of R^{b} is optionally substituted with 1, 2 or 3 independently selected R^{8} substituents; each R^{g} is independently selected from Ci-6 alkyl, C_{3-10} cycloalkyl, 4-7 membered heterocycloalkyl, C_{6-10} aryl, 5-6 membered heteroaryl, C_{6-10} aryl-C_{4} alkyl-, C_{3-10} cycloalkyl-C_{4} alkyl-, (5-6 membered heteroaryl)-C_{4} alkyl-, (4-7 membered heterocycloalkyl)-C_{4} alkyl-, Ci-haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, halo, CN, OR^{1}, SR^{1}, NHOR^{1}, C(O)R^{1}, C(O)NR^{1}R^{2}, OC(O)A^{n}, O(C(O)N)R^{1}R^{2}, NHR^{i}, NR^{i}R^{j}, NRC(=O)NR^{1}R^{2}, NRC(O)NR^{1}R^{2}, NRC(=O)NR^{1}R^{2}, S(O)A^{n}, S(0)NR^{1}R^{2}, S(0)NR^{1}R^{2}, NRS(0)_{2}NR^{1}R^{2}, S(O)NR^{1}R^{2}, S(0)NR^{1}R^{2}, NRS(0)_{2}NR^{1}R^{2}, S(O)NR^{1}R^{2}, S(0)NR^{1}R^{2}, NRS(0)_{2}NR^{1}R^{2}, wherein the Ci-e alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 4-7 membered heterocycloalkyl, C_{6-10} aryl-C_{4} alkyl-
alkyl-, C_{3-10} cycloalkyl-C_i-4 alkyl-, (5-6 membered heteroary 1)-C_{1-4} alkyl-, (4-7 membered heterocycloalkyl)-C_{1-4} alkyl- of R^h are each further optionally substituted by 1, 2, or 3 independently selected R\textsuperscript{i} substituents;

each R\textsuperscript{i} is independently selected from C_{3-6} cycloalkyl, C_{6-10} aryl, 5 or 6-membered heteroaryl, 4-7 membered heterocycloalkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, halo, C_{1-4} alkyl, C_{1-4} halalkyl, Cl_{4} halalkoxy, CN, NH\textsubscript{OR}^k, OR^k, SR^k, C(\textsubscript{0})R^k, C(\textsubscript{0})OR^k, OC(\textsubscript{0})R^k, OC(\textsubscript{0})NR^kR^k, C(\textsubscript{0})OR^k, OC(\textsubscript{0})R^k, OC(\textsubscript{0})NR^kR^k, NHR^k, NR^kR^k, NR^kC(\textsubscript{0})R^k, NR^kC(\textsubscript{0})NR^kR^k, NR^kC(\textsubscript{0})OR^k, C(=NR^k)NR^kR^k, NR^kC(=NR^k)NR^kR^k, S(\textsubscript{0})R^k, S(\textsubscript{0})NR^kR^k, S(\textsubscript{0})_2R^k, NR^kS(\textsubscript{0})_2R^k, NR^kS(\textsubscript{0})_2NR^kR^k, and S(\textsubscript{0})_2NR^kR^k; wherein the C_{1-4} alkyl, C_{3-6} cycloalkyl, C_{6-10} aryl, 5 or 6-membered heteroaryl, 4-7 membered heterocycloalkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{1-4} halalkyl and Cl_{4} halalkoxy of R\textsuperscript{i} are each optionally substituted with 1, 2 or 3 independently selected R\textsuperscript{g} substituents;

or two R\textsuperscript{g} groups attached to the same carbon atom of the 4- to 10-membered heterocycloalkyl taken together with the carbon atom to which they are attached form a C_{3-6} cycloalkyl or 4- to 6-membered heterocycloalkyl having 1-2 heteroatoms as ring members selected from O, N or S;

or any two R\textsuperscript{f} substituents together with the nitrogen atom to which they are attached form a 4-, 5-, 6-, 7-, 8-, 9- or 10-membered heterocycloalkyl group optionally substituted with 1, 2, or 3 independently selected R\textsuperscript{h} substituents;

or any two R\textsuperscript{f} substituents together with the nitrogen atom to which they are attached form a 4-, 5-, 6-, 7-, 8-, 9- or 10-membered heterocycloalkyl group optionally substituted with 1, 2, or 3 independently selected R\textsuperscript{h} substituents;

or any two R\textsuperscript{g} substituents together with the nitrogen atom to which they are attached form a 4-, 5-, 6-, 7-, 8-, 9- or 10-membered heterocycloalkyl group optionally substituted with 1, 2, or 3 independently selected R\textsuperscript{h} substituents;

or any two R\textsuperscript{1} substituents together with the nitrogen atom to which they are attached form a 4-, 5-, 6-, 7-, 8-, 9- or 10-membered heterocycloalkyl group optionally substituted with 1, 2, or 3 independently selected R\textsuperscript{h} substituents;

or any two R\textsuperscript{1} substituents together with the nitrogen atom to which they are attached form a 4-, 5-, 6-, 7-, 8-, 9- or 10-membered heterocycloalkyl group optionally substituted with 1, 2, or 3 independently selected R\textsuperscript{h} substituents;

or any two R\textsuperscript{g} substituents together with the nitrogen atom to which they are attached form a 4-, 5-, 6-, 7-, 8-, 9- or 10-membered heterocycloalkyl group optionally substituted with 1, 2, or 3 independently selected R\textsuperscript{h} substituents;

or any two R\textsuperscript{g} substituents together with the nitrogen atom to which they are attached form a 4-, 5-, 6-, 7-, 8-, 9- or 10-membered heterocycloalkyl group optionally substituted with 1, 2, or 3 independently selected R\textsuperscript{h} substituents;
or any two R substituted together with the nitrogen atom to which they are attached form a 4-, 5-, 6-, 7-, 8-, 9- or 10-membered heterocycloalkyl group optionally substituted with 1, 2, or 3 independently selected R substituents;

each R, R, R or R is independently selected from H, Ci-4 alkyl, C,-6 cycloalkyl, C,-6 aryl, 5 or 6-membered heteroaryl, 4-7 membered heterocycloalkyl, Ci-6 haloalkyl, Ci-6 haloalkoxy, C,-4 alkenyl, and C,-4 alkynyl, wherein the Ci-4 alkyl, C,-6 cycloalkyl, C,-6 aryl, 5 or 6-membered heteroaryl, 4-7 membered heterocycloalkyl, C,-4 alkenyl, and C,-4 alkynyl of R, R, R, R, R are each optionally substituted with 1, 2 or 3 R substituted;

each R is independently selected from halo, OH, CN, -COOH, NH, -NH-Ci-alkyl, -N(Ci-6 alkyl)2, Ci-6 alkyl, Ci-6 alkoxy, Ci-6 alkylthio, Ci-6 haloalkyl, Ci-6 haloalkoxy, phenyl, 5-6 membered heteroaryl, 4-6 membered heterocycloalkyl and C,-6 cycloalkyl, wherein the Ci-6 alkyl, phenyl, C,-6 cycloalkyl, 4-6 membered heterocycloalkyl, and 5-6 membered heteroaryl of R are each optionally substituted with 1, 2, or 3 substituents selected from halo, OH, CN, -COOH, NH, Ci-4 alkyl, Ci-4 alkoxy, Ci-4 haloalkyl, Ci-4 haloalkoxy, phenyl, C,-10 cycloalkyl, 5-6 membered heteroaryl and 4-6 membered heterocycloalkyl;

the subscript m is an integer of 0, 1, 2 or 3;
the subscript n is an integer of 0, 1, 2 or 3;
each subscript q is independently an integer of 1, 2, 3 or 4; and
the subscript s is an integer of 1, 2, or 3.

4. The compound of any one of claims 1-3, having Formula (I):

(I)

or a pharmaceutically acceptable salt or a stereoisomer thereof, wherein:

ring A is 5- to 14-membered heteroaryl, 4- to 14-membered heterocycloalkyl, C,-6 aryl or C,-10 cycloalkyl, wherein the 5- to 10-membered heteroaryl and 4- to 11-membered heterocycloalkyl each has 1-4 heteroatoms as ring members selected from N, O and S, wherein the N or S atom as ring members is optionally oxidized and one or more carbon atoms as ring members are each optionally replaced by a carbonyl group; and wherein ring A is optionally substituted with 1, 2, 3, 4 or 5 independently selected R substituted;
L is a bond, -C(0)NR^13-, -NR^13C(0)-, O, -(CR^14R^15)_q-, -(CR^14R^15)_q-0-, -0(CR^14R^15)_q-, -NR^13-, -(CR^14R^15)_q-NR^13-, -NR^13-(CR^14R^15)_q-, -CH=CH_-,-C=C-,-SO_2NR^13-, -NR^13SO_2-, -NR^13SO_2NR^13-, -NR^13C(0)(0)- or -NR^13C(0)NR^13-;

X is N or CR^17;

R^3 is methyl, halo, CN or Cl-4-haloalkyl;

R^4 is Cl-4 alkyl, Cl-4 alkoxy, C_M haloalkyl, C_M haloalkoxy, CN, halo, OH, -COOH, NH_2, -NHCl-4 alkyl or N(Cl-4 alkyl)_2;

R^5 is C_M alkyl, Cl-4 alkoxy, C_M haloalkyl, C_M haloalkoxy, CN, halo, OH, -COOH, NH_2, -NHCl-4 alkyl or N(Cl-4 alkyl)_2;

R^6, R^7, R^17 and R^18 are each independently selected from H, halo, Cl-6 alkyl, C_2-6 alkenyl, C_7-6 alkynyl, Cl-6 haloalkyl, Cl-6 haloalkoxy, C_4-10 aryl, C_5-10 cycloalkyl, 5-14 membered heteroaryl, 4-10 membered heterocycloalkyl, C_6-10 aryl-C_4 alkyl-, C_3-10 cycloalkyl-C_4 alkyl-, (5-14 membered heteroaryl)-C_4 alkyl-, (4-10 membered heterocycloalkyl)-C_4 alkyl-, CN, N(O)_2, OR^a, SR^a, NHor^a, C(O)R^a, C(O)NR^aR^a, C(O)OR^a, OC(O)NR^aR^a, NHR^a, NR^aR^a, NR^aC(O)R^a, NR^aC(O)OR^a, NR^aC(O)NR^aR^a, C(=NR^a)R^a, C(=NR^a)NR^aR^a, NR^aC(=NR^a)NR^aR^a, NR^aS(O)R^a, NR^aS(O)NR^aR^a, S(O)NR^aR^a, and S(O)NR^aR^a, wherein the Cl-6 alkyl, C_2-6 alkenyl, C_7-6 alkynyl, C_6-10 aryl, C_3-10 cycloalkyl, 5-14 membered heteroaryl, 4-10 membered heterocycloalkyl, C_6-10 aryl-C_4 alkyl-, C_3-10 cycloalkyl-C_4 alkyl-, (5-14 membered heteroaryl)-C_4 alkyl- and (4-10 membered heterocycloalkyl)-C_4 alkyl- of R^6, R^7, R^17 and R^18 are each optionally substituted with 1, 2, 3, 4 or 5 independently selected R^b substituents;

each R^13 is independently H, Cl-6 haloalkyl or Cl-6 alkyl optionally substituted with a substituent selected from C_M alkyl, Cl-4 alkoxy, C_1-4 haloalkyl, C_1-4 haloalkoxy, CN, halo, OH, -COOH, NH_2, -NHCl-4 alkyl and -N(C_M alkyl)_2;

R^14 and R^15 are each independently selected from H, halo, CN, OH, -COOH, C_M alkyl, C_M alkoxy, -NHCl-4 alkyl, -N(Cl-4 alkyl)_2, C_1-4 haloalkyl, C_M haloalkoxy, C_3-6 cycloalkyl, phenyl, 5-6 membered heteroaryl and 4-6 membered heterocycloalkyl, wherein the C_M alkyl, Cl-4 alkoxy, C_M haloalkyl, C_M haloalkoxy, C_3-6 cycloalkyl, phenyl, 5-6 membered heteroaryl and 4-6 membered heterocycloalkyl of R^14 or R^15 are each optionally substituted with 1, 2, or 3 independently selected independently selected R^4 substituents;

or R^14 and R^15 taken together with the carbon atom to which they are attached form 3-, 4-, 5- or 6-membered cycloalkyl or 3-, 4-, 5- or 6-membered heterocycloalkyl, each of which is optionally substituted with 1 or 2 independently selected R^8 substituents;
each R is independently selected from H, CN, C6-alkyl, C6-haloalkyl, C2-6 alkenyl, C2-6 alkynyl, C6-aryl, C3-10 cycloalkyl, 5-14 membered heteroaryl, 4-14 membered heterocycloalkyl, C6-10 aryl-C4 alkyl-, C3-10 cycloalkyl-C4 alkyl-, (5-14 membered heteroaryl)-C4 alkyl-, and (4-14 membered heterocycloalkyl)-C4 alkyl-, wherein the C6-alkyl, C2-6 alkenyl, C2-6 alkynyl, C6-10 aryl, C3-10 cycloalkyl, 5-14 membered heteroaryl, 4-14 membered heterocycloalkyl, C6-10 aryl-C4 alkyl-, C3-10 cycloalkyl-C4 alkyl-, (5-14 membered heteroaryl)-C4 alkyl- and (4-14 membered heterocycloalkyl)-C4 alkyl- of R are each optionally substituted with 1, 2, 3, 4, or 5 independently selected R substituents;

each R is independently selected from C6-alkyl, C6-haloalkyl, halo, C6-10 aryl, 5-14 membered heteroaryl, C3-10 cycloalkyl, 4-14 membered heterocycloalkyl, C6-10 aryl-C4 alkyl-, C3-10 cycloalkyl-C4 alkyl-, (5-14 membered heteroaryl)-C4 alkyl-, (4-14 membered heterocycloalkyl)-C4 alkyl-, CN, NH2, NHOR, OR, SR, C(0)R, C(0)NR R, C(0)OR, OC(0)R, OC(0)NR R, NHR, NR R, NR C(0) NR R, NR C(0) OR R, C(=NR)NR R, N R C(=NR) NR R, N R C(=NOH) NR R, N R C(=NCN) NR R, S(0)R, wherein the C6-alkyl, C6-haloalkyl, C6-10 aryl, 5-14 membered heteroaryl, C3-10 cycloalkyl, 4-14 membered heterocycloalkyl, C6-10 aryl-C4 alkyl-, C3-10 cycloalkyl-C4 alkyl-, (5-14 membered heteroaryl)-C4 alkyl- and (4-14 membered heterocycloalkyl)-C4 alkyl- of R are each optionally substituted with 1, 2, or 3 independently selected R substituents;

each R is independently selected from H, C6-alkyl, C6-haloalkyl, C2-6 alkenyl, C2-6 alkynyl, C6-10 aryl, C3-10 cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C6-10 aryl-C4 alkyl-, C3-10 cycloalkyl-C4 alkyl-, (5-10 membered heteroaryl)-C4 alkyl-, and (4-10 membered heterocycloalkyl)-C4 alkyl-, wherein the C6-alkyl, C2-6 alkenyl, C2-6 alkynyl, C6-10 aryl, C3-10 cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C6-10 aryl-C4 alkyl-, C3-10 cycloalkyl-C4 alkyl-, (5-10 membered heteroaryl)-C4 alkyl- and (4-10 membered heterocycloalkyl)-C4 alkyl- of R are each optionally substituted with 1, 2, or 3 independently selected R substituents;

each R is independently selected from C6-alkyl, C6-haloalkyl, C2-6 alkenyl, C2-6 alkynyl, C6-10 aryl, C3-10 cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C6-10 aryl-C4 alkyl-, C3-10 cycloalkyl-C4 alkyl-, (5-10 membered heteroaryl)-C4 alkyl-, (4-10 membered heterocycloalkyl)-C4 alkyl-, CN, OH, NH2, NO2, NHOR, OR, SR, C(0)R, C(0)NR R, C(0)OR, OC(0)R, OC(0)NR R, NHR, NR R, NR C(0) NR R, NR C(0) OR R, C(=NR)NR R, N R C(=NR) NR R, N R C(=NOH) NR R, N R C(=NCN) NR R, S(0)R, wherein the C6-alkyl, C6-haloalkyl, C6-10 aryl, 5-14 membered heteroaryl, C3-10 cycloalkyl, 4-14 membered heterocycloalkyl, C6-10 aryl-C4 alkyl-, C3-10 cycloalkyl-C4 alkyl-, (5-14 membered heteroaryl)-C4 alkyl- and (4-14 membered heterocycloalkyl)-C4 alkyl- of R are each optionally substituted with 1, 2, or 3 independently selected R substituents;

each R is independently selected from C6-alkyl, C6-haloalkyl, C2-6 alkenyl, C2-6 alkynyl, C6-10 aryl, C3-10 cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C6-10 aryl-C4 alkyl-, C3-10 cycloalkyl-C4 alkyl-, (5-10 membered heteroaryl)-C4 alkyl-, (4-10 membered heterocycloalkyl)-C4 alkyl-, CN, OH, NH2, NO2, NHOR, OR, SR, C(0)R, C(0)NR R, C(0)OR, OC(0)R, OC(0)NR R, NHR, NR R, NR C(0) NR R, NR C(0) OR R, C(=NR)NR R, N R C(=NR) NR R, N R C(=NOH) NR R, N R C(=NCN) NR R, S(0)R, wherein the C6-alkyl, C6-haloalkyl, C6-10 aryl, 5-14 membered heteroaryl, C3-10 cycloalkyl, 4-14 membered heterocycloalkyl, C6-10 aryl-C4 alkyl-, C3-10 cycloalkyl-C4 alkyl-, (5-10 membered heteroaryl)-C4 alkyl- and (4-10 membered heterocycloalkyl)-C4 alkyl- of R are each optionally substituted with 1, 2, or 3 independently selected R substituents;
wherein the Ci-6 alkyl, Ci-6 haloalkyl, Ci-6 haloalkoxy, C2-6 alkenyl, C2-6 alkynyl, C6-10 aryl, C3-10
cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C6-10 aryl-Ci-4 alkyl-,
c3-10 cycloalkyl-Ci-4 alkyl-, (5-10 membered heteroaryl)-Ci-4 alkyl- and (4-10 membered
heterocycloalkyl)-Ci-4 alkyl- of R^8 are each further optionally substituted with 1, 2, or 3
independently selected R^d substituents;

each R^c is independently selected from H, Ci-6 alkyl, C1-4 haloalkyl, C2-6 alkenyl, C2-6
alkynyl, C6-10 aryl, C3-10 cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl,
C6-10 aryl-Ci-4 alkyl-, C3-10 cycloalkyl-Ci-4 alkyl-, (5-10 membered heteroaryl)-Ci-4 alkyl-,
and (4-10 membered heterocycloalkyl)-Ci-4 alkyl-, wherein the Ci-6 alkyl, C2-6 alkenyl, C2-6
alkynyl, C6-10 aryl, C3-10 cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl,
C6-10 aryl-Ci-4 alkyl-, C3-10 cycloalkyl-Ci-4 alkyl-, (5-10 membered heteroaryl)-Ci-4 alkyl-
and (4-10 membered heterocycloalkyl)-Ci-4 alkyl- of R^c are each optionally substituted with 1, 2, 3, 4, or 5
independently selected R^d substituents;

or any two R^2 substituents together with the nitrogen atom to which they are attached
form a 4-, 6-, 7-, 8-, 9- or 10-membered heterocycloalkyl group optionally substituted with 1,
2 or 3 independently selected R^h substituents;

or any two R^c substituents together with the nitrogen atom to which they are attached
form a 4-, 6-, 7-, 8-, 9- or 10-membered heterocycloalkyl group optionally substituted with 1,
2 or 3 independently selected R^h substituents;

or any two R^c substituents together with the nitrogen atom to which they are attached
form a 4-, 6-, 7-, 8-, 9- or 10-membered heterocycloalkyl group optionally substituted with 1,
2 or 3 independently selected R^h substituents;

each R^h is independently selected from Ci-6 alkyl, C3-10 cycloalkyl, 4-7 membered
heterocycloalkyl, C6-10 aryl, 5-6 membered heteroaryl, C6-10 aryl-Ci-4 alkyl-, C3-10
cycloalkyl-Ci-4 alkyl-, (5-6 membered heteroaryl)-Ci-4 alkyl-, (4-7 membered heterocycloalkyl)-Ci-4
alkyl-, Ci-6 haloalkyl, Ci-6 haloalkoxy, C2-6 alkenyl, C2-6 alkynyl, halo, CN, OR^1, SR^1, NHOR^1,
C(O)R^1, C(O)NR^1R^1, O(C(O))^n, O(C(O)NR^1R^1), NHR^1, NR^1R^1, NR^1C(O)R^1,
NR^1C(O)NR^1R^1, C(=NR^1)NR^1R^1, NR^1C(=NR^1)NR^1R^1, S(O)^n, S(O)NR^1R^1,
S(O)S(O)NR^1R^1, S(O)NR^1R^1NR^1R^1, and wherein the Ci-6 alkyl, C2-6 alkenyl, C2-6
alkynyl, C3-10
cycloalkyl, 4-7 membered heterocycloalkyl, C6-10 aryl, 5-6 membered heteroaryl, C6-10 aryl-Ci-4
alkyl-, C3-10 cycloalkyl-Ci-4 alkyl-, (5-6 membered heteroaryl)-Ci-4 alkyl-, (4-7 membered
heterocycloalkyl)-Ci-4 alkyl- of R^h are each further optionally substituted by 1, 2, or 3
independently selected R^i substituents;
each R is independently selected from C3-6 cycloalkyl, C6-10 aryl, 5 or 6-membered heteroaryl, 4-7 membered heterocycloalkyl, C2-4 alkenyl, C2-4 alkynyl, halo, C1-4 alkyl, C1-4 haloalkyl, Ci-4 haloalkoxy, CN, NHOR, OR, SR, C(0)R, C(0)NR, C(0)OR, OC(0)OR, OC(0)NR, NHR, NRk, NRkC(0)R, NRkC(0)NR, NRkC(0)OR, C(=NR)NRkR, NRkC(=NR)NRkR, S(0)R, S(0)kR, S(0)k2R, NRkS(0)k2R, NRkS(0)k2NRkR, and S(0)2NRkR, wherein the C1-4 alkyl, C3-6 cycloalkyl, C6-10 aryl, 5- or 6-membered heteroaryl, 4-6 membered heterocycloalkyl, C2-4 alkenyl, C2-4 alkynyl, C1-4 haloalkyl, and C1-4 haloalkoxy of Rj are each optionally substituted with 1, 2 or 3 independently selected R substituents;
each of R and R is independently selected from H, C1-4 alkyl, C3-6 cycloalkyl, C6-10 aryl, 5 or 6-membered heteroaryl, 4-7 membered heterocycloalkyl, C1-6 haloalkyl, Ci-6 haloalkoxy, C2-4 alkenyl, and C2-4 alkynyl, wherein the C1-4 alkyl, C3-6 cycloalkyl, C6-10 aryl, 5 or 6-membered heteroaryl, 4-7 membered heterocycloalkyl, C2-4 alkenyl, and C2-4 alkynyl of R or R are each optionally substituted with 1, 2 or 3 independently selected R substituents;
each R is independently selected from halo, OH, CN, -COOH, NH2, -NH-Ci-e alkyl, -N(Ci-6 alkyl)2, Ci-6 alkyl, Ci-6 alkoxy, C1-6 alkylthio, Ci-6 haloalkyl, Ci-6 haloalkoxy, phenyl, 5-6 membered heteroaryl, 4-6 membered heterocycloalkyl and C3-6 cycloalkyl, wherein the Ci-6 alkyl, phenyl, C3-6 cycloalkyl, 4-6 membered heterocycloalkyl, and 5-6 membered heteroaryl of R are each optionally substituted with 1, 2, or 3 substituents selected from halo, OH, CN, -COOH, NH2, Ci-4 alkyl, Ci-4 alkoxy, Ci-4 haloalkyl, Ci-4 haloalkoxy, phenyl, C3-10 cycloalkyl, 5-6 membered heteroaryl and 4-6 membered heterocycloalkyl;
the subscript m is an integer of 0, 1, 2 or 3;
the subscript n is an integer of 0, 1, 2 or 3;
each subscript q is independently an integer of 1, 2, 3 or 4; and
the subscript s is an integer of 1, 2, or 3.

5. The compound of any one of claims 1-4, having Formula (I):

![Chemical Structure](image)

or a pharmaceutically acceptable salt or a stereoisomer thereof, wherein:
ring A is 5- to 10-membered heteroaryl, 4- to 11-membered heterocycloalkyl, C6-10 aryl or C3-10 cycloalkyl, wherein the 5- to 10-membered heteroaryl and 4- to 11-membered
heterocycloalkyl each has 1-4 heteroatoms as ring members selected from N, O and S, wherein
the N or S atom as ring members is optionally oxidized and one or more carbon atoms as ring
members are each optionally replaced by a carbonyl group; and wherein ring A is optionally
substituted with 1, 2, 3, 4 or 5 R^6 substituents;

NR^[13]C(0)O- or NR^[13]C(0)NR^[13]-;

X is N or CR^[17];

R^3 is methyl, halo, CN or Ci-4haloalkyl;

R^4 is Ci-4 alkyl, Ci-4 alkoxy, c m haloalkyl, c m haloalkoxy, CN, halo, OH, -COOH, NH_2,
-NHCl-4 alkyl or N(Ci-4 alkyl)_2;

R^5 is c m alkyl, Ci-4 alkoxy, c m haloalkyl, c m haloalkoxy, CN, halo, OH, -COOH, NH_2,
-NHCl-4 alkyl or N(Ci-4 alkyl)_2;

R^6, R^7, R^17 and R^18 are each independently selected from H, halo, Ci-6 alkyl, C_2-6 alkenyl,
C_2-6 alkynyl, Ci-6 haloalkyl, Ci-6 haloalkoxy, c_6-10 aryl, c_3-10 cycloalkyl, 5-14 membered
heteroaryl, 4-10 membered heterocycloalkyl, C_6-10 aryl-Ci-4 alkyl-, c_3-10 cycloalkyl-Ci-4 alkyl-,
(5-14 membered heteroaryl)-Ci-4 alkyl-, (4-10 membered heterocycloalkyl)-Ci-4 alkyl-,
CN, NO_2, OR^a, SR^a, NHOR^a, C(0)R^a, C(0)NR^4R^a, C(0)OR^a, OC(0)R^a, OC(0)NR^4R^a, NH^aR^a,
NR^4R^a, NR^4C(0)R^a, NR^4C(0)OR^a, NR^4C(0)NR^4R^a, C(=NR^a)R^a, C(=NR^a)NR^4R^a, NR^4C(=NR^a)NR^4R^a,
NR^4S(0)R^a, NR^4S(0)_2R^a, NR^4S(0)_2NR^4R^a, S(0)R^a, S(0)NR^4R^a, S(0)_2R^a, and S(0)_2NR^4R^a,
wherein the Ci-6 alkyl, C_2-6 alkenyl, C_2-6 alkynyl, C_6-10 aryl, c_3-10 cycloalkyl, 5-14 membered
heteroaryl, 4-10 membered heterocycloalkyl, C_6-10 aryl-Ci-4 alkyl-, c_3-10 cycloalkyl-Ci-4 alkyl-,
(5-14 membered heteroaryl)-Ci-4 alkyl- and (4-10 membered heterocycloalkyl)-Ci-4 alkyl- of R^6,
R^7, R^17 and R^18 are each optionally substituted with 1, 2, 3, 4 or 5 R^b substituents;

or two R^b substituents attached to the same ring carbon atom taken together with the ring
carbon atom to which they are attached form spiro c_3-6 cycloalkyl or spiro 4- to 7-membered
heterocycloalkyl, each of which is optionally substituted with 1, 2, or 3 independently selected R^f
substituents;

each R^[13] is independently H, Ci-6 haloalkyl or Ci-6 alkyl optionally substituted with a
substituent selected from c m alkyl, Ci-4alkoxy, c m haloalkyl, c_1-4 haloalkoxy, CN, halo, OH,
-COOH, NH_2, -NHCl-4 alkyl and -N(c_3-6 alkyl)_2;

R^[14] and R^[15] are each independently selected from H, halo, CN, OH, -COOH, c m alkyl,
c m alkoxy, -NHCl-4 alkyl, -N(Ci-4 alkyl)_2, Ci-4 haloalkyl, c m haloalkoxy, c_3-6 cycloalkyl,
phenyl, 5-6 membered heteroaryl and 4-6 membered heterocycloalkyl, wherein the c_1-4 alkyl, Ci-
alkoxy, Ci-4haloalkyl, Ci-4haloalkoxy, C3-6 cycloalkyl, phenyl, 5-6 membered heteroaryl and 4-6 membered heterocycloalkyl of R₁⁴ or R₁⁵ are each optionally substituted with 1, 2, or 3 independently selected R⁹ substituents;

or R₁⁴ and R₁⁵ taken together with the carbon atom to which they are attached form 3-, 4-, 5- or 6-membered cycloalkyl or 3-, 4-, 5- or 6-membered heterocycloalkyl, each of which is optionally substituted with 1 or 2 R⁹ substituents;

each R⁸ is independently selected from H, CN, Ci-6 alkyl, Ci-4haloalkyl, C2-6 alkenyl, C2-6 alkynyl, C6-10 aryl, C3-10 cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C6-10 aryl-Ci-4 alkyl-, C3-10 cycloalkyl-Ci-4 alkyl-, (5-10 membered heteroaryl)-Ci-4 alkyl-, and (4-10 membered heterocycloalkyl)-Ci-4 alkyl-, wherein the Ci-6 alkyl, C2-6 alkenyl, C2-6 alkynyl, C6-10 aryl, C3-10 cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C6-10 aryl-Ci-4 alkyl-, C3-10 cycloalkyl-Ci-4 alkyl-, (5-10 membered heteroaryl)-Ci-4 alkyl- and (4-10 membered heterocycloalkyl)-Ci-4 alkyl- of R⁸ are each optionally substituted with 1, 2, 3, 4, or 5 R⁹ substituents;

each R⁹ is independently selected from Ci-6 alkyl, Ci-6haloalkyl, halo, C6-10 aryl, 5-10 membered heteroaryl, C3-10 cycloalkyl, 4-10 membered heterocycloalkyl, C6-10 aryl-Ci-4 alkyl-, C3-10 cycloalkyl-Ci-4 alkyl-, (5-10 membered heteroaryl)-Ci-4 alkyl-, (4-10 membered heterocycloalkyl)-Ci-4 alkyl-, CN, NH₂, NHOR ᵇ, OR ᵇ, SR ᵇ, C(0)OR ᵇ, C(0)NR ᵇR ᵇ, C(0)S(R ᵇ), C(0)OR ᵇ, C(0)S(R ᵇ), C(0)NR ᵇR ᵇ, C(0)S(R ᵇ). In these formulas, R is C(=NOH)NR ᵇ, C(=NR ᵇ)N(C(=NOH))NR ᵇ, C(=NR ᵇ)N(C(=NCN))NR ᵇ, S(0)OR ᵇ, S(0)N(R ᵇ)R ᵇ, N(R ᵇ)S(0)R ᵇ, N(R ᵇ)S(0)R ᵇ, N(R ᵇ)S(0)N(R ᵇ)R ᵇ, S(0)N(R ᵇ)R ᵇ, S(0)OR ᵇ, wherein the Ci-e alkyl, Ci-6haloalkyl, C6-10 aryl, 5-10 membered heteroaryl, C3-10 cycloalkyl, 4-10 membered heterocycloalkyl, C6-10 aryl-Ci-4 alkyl-, C3-10 cycloalkyl-Ci-4 alkyl-, (5-10 membered heteroaryl)-Ci-4 alkyl-, and (4-10 membered heterocycloalkyl)-Ci-4 alkyl- of R⁹ are each optionally substituted with 1, 2, or 3 independently selected R⁹ substituents;

each R⁹ is independently selected from H, Ci-6 alkyl, Ci-6haloalkyl, C2-6 alkenyl, C2-6 alkynyl, C6-10 aryl, C3-10 cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C6-10 aryl-Ci-4 alkyl-, C3-10 cycloalkyl-Ci-4 alkyl-, (5-10 membered heteroaryl)-Ci-4 alkyl-, and (4-10 membered heterocycloalkyl)-Ci-4 alkyl-, wherein the Ci-6 alkyl, Ci-6haloalkyl, C2-6 alkenyl, C2-6 alkynyl, C6-10 aryl, C3-10 cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C6-10 aryl-Ci-4 alkyl-, C3-10 cycloalkyl-Ci-4 alkyl-, (5-10 membered heteroaryl)-Ci-4 alkyl- and (4-10 membered heterocycloalkyl)-Ci-4 alkyl- of R⁹ are each optionally substituted with 1, 2 or 3 independently selected R⁹ substituents;
each R^b substituent is independently selected from halo, C\textsubscript{1-6} alkyl, C\textsubscript{2-6} alkenyl, C\textsubscript{2-6} alkynyl, C\textsubscript{1-6} haloalkyl, C\textsubscript{1-6} haloalkoxy, C\textsubscript{6-10} aryl, C\textsubscript{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C\textsubscript{6-10} aryl-C\textsubscript{14} alkyl-, C\textsubscript{3-10} cycloalkyl-C\textsubscript{14} alkyl-, (5-10 membered heteroaryl)-C\textsubscript{14} alkyl-, (4-10 membered heterocycloalkyl)-C\textsubscript{14} alkyl-, CN, OH, NH\textsubscript{2}, NO\textsubscript{2}, NH\textsubscript{2}OR\textsubscript{s}, OR\textsubscript{\textring{R}}, SR\textsubscript{\textring{R}}, C(0)R\textsubscript{\textring{R}}, C(0)NR\textsubscript{\textring{R}}, C(0)OR\textsubscript{\textring{R}}, OC(0)R\textsubscript{\textring{R}}, OC(0)NR\textsubscript{\textring{R}}, C(=NR\textsubscript{\textring{R}})NR\textsubscript{\textring{R}}, NR\textsubscript{\textring{R}}C(=NR\textsubscript{\textring{R}})NR\textsubscript{\textring{R}}, NR\textsubscript{\textring{R}}R\textsubscript{\textring{R}}, NR\textsubscript{\textring{R}}C(0)R\textsubscript{\textring{R}}, NR\textsubscript{\textring{R}}C(0)OR\textsubscript{\textring{R}}, NR\textsubscript{\textring{R}}C(0)NR\textsubscript{\textring{R}}, NR\textsubscript{\textring{R}}S(0)R\textsubscript{\textring{R}}, NR\textsubscript{\textring{R}}S(0)\textsubscript{\textring{R}}R\textsubscript{\textring{R}}, NR\textsubscript{\textring{R}}S(0)\textsubscript{\textring{R}}R\textsubscript{\textring{R}}, S(0)R\textsubscript{\textring{R}}, S(0)\textsubscript{\textring{R}}R\textsubscript{\textring{R}} and S(0)\textsubscript{\textring{R}}R\textsubscript{\textring{R}});

wherein the C\textsubscript{1-6} alkyl, C\textsubscript{1-6} haloalkyl, C\textsubscript{1-6} haloalkoxy, C\textsubscript{2-6} alkenyl, C\textsubscript{2-6} alkynyl, C\textsubscript{6-10} aryl, C\textsubscript{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C\textsubscript{6-10} aryl-C\textsubscript{14} alkyl-, C\textsubscript{3-10} cycloalkyl-C\textsubscript{14} alkyl-, (5-10 membered heteroaryl)-C\textsubscript{14} alkyl- and (4-10 membered heterocycloalkyl)-C\textsubscript{14} alkyl- of R^b are each further optionally substituted with 1, 2, or 3 independently selected R^d substituents;

each R^c is independently selected from H, C\textsubscript{1-6} alkyl, C\textsubscript{14} haloalkyl, C\textsubscript{2-6} alkenyl, C\textsubscript{2-6} alkynyl, C\textsubscript{6-10} aryl, C\textsubscript{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C\textsubscript{6-10} aryl-C\textsubscript{14} alkyl-, C\textsubscript{3-10} cycloalkyl-C\textsubscript{14} alkyl-, (5-10 membered heteroaryl)-C\textsubscript{14} alkyl-, and (4-10 membered heterocycloalkyl)-C\textsubscript{14} alkyl- wherein the C\textsubscript{1-6} alkyl, C\textsubscript{2-6} alkenyl, C\textsubscript{2-6} alkynyl, C\textsubscript{6-10} aryl, C\textsubscript{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C\textsubscript{6-10} aryl-C\textsubscript{14} alkyl-, C\textsubscript{3-10} cycloalkyl-C\textsubscript{14} alkyl-, (5-10 membered heteroaryl)-C\textsubscript{14} alkyl- and (4-10 membered heterocycloalkyl)-C\textsubscript{14} alkyl- of R^c are each optionally substituted with 1, 2, 3, 4, or 5 R^f substituents;

each R^f is independently selected from C\textsubscript{14} alkyl, C\textsubscript{14} haloalkyl, C\textsubscript{2-6} alkenyl, C\textsubscript{2-6} alkynyl, C\textsubscript{6-10} aryl, C\textsubscript{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C\textsubscript{6-10} aryl-C\textsubscript{14} alkyl-, C\textsubscript{3-10} cycloalkyl-C\textsubscript{14} alkyl-, (5-10 membered heteroaryl)-C\textsubscript{14} alkyl-, and (4-10 membered heterocycloalkyl)-C\textsubscript{14} alkyl- wherein the C\textsubscript{14} alkyl, C\textsubscript{2-6} alkenyl, C\textsubscript{2-6} alkynyl, C\textsubscript{6-10} aryl, C\textsubscript{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C\textsubscript{6-10} aryl-C\textsubscript{14} alkyl-, C\textsubscript{3-10} cycloalkyl-C\textsubscript{14} alkyl-, (5-10 membered heteroaryl)-C\textsubscript{14} alkyl- and (4-10 membered heterocycloalkyl)-C\textsubscript{14} alkyl- of R^f are each optionally substituted with 1, 2, 3, 4, or 5 R^g substituents;

each R^g is independently selected from C\textsubscript{14} alkyl, C\textsubscript{14} haloalkyl, C\textsubscript{2-6} alkenyl, C\textsubscript{2-6} alkynyl, C\textsubscript{6-10} aryl, C\textsubscript{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C\textsubscript{6-10} aryl-C\textsubscript{14} alkyl-, C\textsubscript{3-10} cycloalkyl-C\textsubscript{14} alkyl-, (5-10 membered heteroaryl)-C\textsubscript{14} alkyl- and (4-10 membered heterocycloalkyl)-C\textsubscript{14} alkyl- of R^g are each optionally substituted with 1, 2, 3, 4, or 5 R^h substituents;

each R^h is independently selected from C\textsubscript{14} alkyl, C\textsubscript{14} haloalkyl, C\textsubscript{2-6} alkenyl, C\textsubscript{2-6} alkynyl, C\textsubscript{6-10} aryl, C\textsubscript{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C\textsubscript{6-10} aryl-C\textsubscript{14} alkyl-, C\textsubscript{3-10} cycloalkyl-C\textsubscript{14} alkyl-, (5-10 membered heteroaryl)-C\textsubscript{14} alkyl- and (4-10 membered heterocycloalkyl)-C\textsubscript{14} alkyl- of R^h are each optionally substituted with 1, 2, 3, 4, or 5 R^i substituents;
membered heterocycloalkyl)-Ci-alkyl, halo, CN, NHOR°, OR°, SR°, C(=O)R°, C(=O)NR°R°, C(=O)OR°, OC(=O)R°, OC(=O)NR°R°, NR°R°, NR°C(=O)NR°R°, NR°C(=O)OR°, C(=NR°)NR°R°, NR°C(=NR°)NR°R° 0, S(=O)R°, S(=O)NR°R°, S(=O)2R°, NR°S(=O)2R°, NR°NR°R°, NR°S(=O)R°, and S(=O)2NR°R°, wherein the CM alkyl, Ci-haloalkyl, C2-6 alkenyl, C2-6 alkynyl, C6-10 aryl, C3-10 cycloalkyl, 4-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C6-10 aryl-Ci-4 alkyl-, C3-10 cycloalkyl-Ci-4 alkyl-, (5-10 membered heteroaryl)-Ci-4 alkyl-, and (4-10 membered heterocycloalkyl)-Ci-4 alkyl- of R® are each optionally substituted with 1, 2 or 3 independently selected R® substituents:

each R® is independently selected fromH, Ci-6 alkyl, Ci-haloalkyl, C2-6 alkenyl, C2-6 alkynyl, C6-10 aryl, C3-10 cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C6-10 aryl-Ci-4 alkyl-, C3-10 cycloalkyl-Ci-4 alkyl-, (5-10 membered heteroaryl)-Ci-4 alkyl-, and (4-10 membered heterocycloalkyl)-Ci-4 alkyl-, wherein the Ci-6 alkyl, C2-6 alkenyl, C2-6 alkynyl, C6-10 aryl, C3-10 cycloalkyl, 4-10 membered heterocycloalkyl, C6-10 aryl-Ci-4 alkyl-, C3-10 cycloalkyl-Ci-4 alkyl-, (5-10 membered heteroaryl)-Ci-4 alkyl- and (4-10 membered heterocycloalkyl)-Ci-4 alkyl- of R® are each optionally substituted with 1, 2 or 3 R® substituents:

each R® is independently selected from Ci-6 alkyl, Ci-haloalkyl, C2-6 alkenyl, C2-6 alkynyl, C6-10 aryl, C3-10 cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C6-10 aryl-Ci-4 alkyl-, C3-10 cycloalkyl-Ci-4 alkyl-, (5-10 membered heteroaryl)-Ci-4 alkyl-, (4-10 membered heterocycloalkyl)-Ci-4 alkyl-, halo, CN, NHOR°, OR°, SR°, C(=O)R°, C(=O)NR°R°, C(=O)OR°, OC(=O)R°, OC(=O)NR°R°, NR°R°, NR°C(=O)NR°R°, NR°C(=O)OR°, C(=NR°)NR°R°, NR°C(=NR°)NR°R° 0, S(=O)R°, S(=O)NR°R°, S(=O)2R°, NR°S(=O)2R°, NR°NR°R°, NR°S(=O)R°, and S(=O)2NR°R°, wherein the Ci-e alkyl, Ci-e haloalkyl, C2-6 alkenyl, C2-6 alkynyl, C6-10 aryl, C3-10 cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C6-10 aryl-Ci-4 alkyl-, C3-iocycloalkyl-Ci-4 alkyl-, (5-10 membered heteroaryl)-Ci-4 alkyl- and (4-10 membered heterocycloalkyl)-Ci-4 alkyl- of R® is optionally substituted with 1, 2 or 3 R® substituents:

or any two R® substituents together with the nitrogen atom to which they are attached form a 4-, 5-, 6-, 7-, 8-, 9- or 10-membered heterocycloalkyl group optionally substituted with 1, 2 or 3 R® substituents:

each R® is independently selected from Ci-6 alkyl, C3-10 cycloalkyl, 4-7 membered heterocycloalkyl, C6-10 aryl, 5-6 membered heteroaryl, C6-10 aryl-Ci-4 alkyl-, C3-10 cycloalkyl-Ci-4 alkyl-, (5-6 membered heteroaryl)-Ci-4 alkyl-, (4-7 membered heterocycloalkyl)-Ci-4 alkyl-, Ci-6 haloalkyl, Ci-ehaloalkoxy, C2-6 alkenyl, C2-6 alkynyl, halo, CN, OR°, SR°, NHOR°, C(=O)R°,
C(0)NR'R', C(0)OR, O C(0)R, O C(0)NR'R', O C(0)NR'R', NHR', NRR', NRC(0)R', NRC(0)NR'R', NR'C(0)R', NR'C(0)NR'R',
NR'C(0)OR', C(=NR')NR'R', NR'C(=NR')NR'R', S(0)R', S(0)NR'R', S(0)R', S(0)2R', NR'S(0)2R',
NRSCO^NRR, and S(O)2NR'R', wherein the C1-6 alkyl, C2-6 alkenyl, C2-6 alkynyl, C3-10
cycloalkyl, 4-7 membered heterocycloalkyl, C6-10 aryl, 5-6 membered heteroaryl, C6-10 aryl-C4
alkyl-, C3-10 cycloalkyl-C4 alkyl-, (5-6 membered heteroaryl)-C1-4 alkyl-, (4-7 membered
erhocycloalkyl)-C4 alkyl- of R^h are each further optionally substituted by 1, 2, or 3 R^i
substituents;

each R^j is independently selected from C3-6 cycloalkyl, C6-10 aryl, 5 or 6-membered
erhoaryl, 4-7 membered heterocycloalkyl, C2-4 alkene, C2-4 alkynyl, halo, C1-4 alkyl, C1-4
haloalkyl, CN, NHOR', OR', SR', C(0)R', C(0)NR'R', C(0)OR', O C(0)R', O C(0)NR'R',
NHR', NRR', NR'C(0)R', NR'C(0)NR'R', NR'C(0)OR', C(=NR')NR'R', NR'C(=NR')NR'R',
NR'C(0)OR', C(=NR')NR'R', NRR', NRC(0)R', NRC(0)NR'R', NRC(0)OR', C(=NR')
NR'R', NR'C(=NR')NR'R', S(0)NR'R', S(0)2NR'R', S(0)2R', S(0)2R', NR'S(0)2R',
NR'S(0)2R', and S(0)2NR'R', wherein the C1-4 alkyl, C3-6 cycloalkyl, C6-10 aryl, 5 or 6-membered heteroaryl, 4-6
membered heterocycloalkyl, C2-4 alkenyl, C2-4 alkynyl, C1-4 haloalkyl, and C4 haloalkoxy of R^j
are each optionally substituted with 1, 2 or 3 independently selected R^q substituents;
or two R^h groups attached to the same carbon atom of the 4- to 10-membered
erhocycloalkyl taken together with the carbon atom to which they are attached form a C3-6
cycloalkyl or 4- to 6-membered heterocycloalkyl having 1-2 heteroatoms as ring members
selected from O, N or S;
or any two R^e substituents together with the nitrogen atom to which they are attached
form a 4-, 5-, 6-, or 7-membered heterocycloalkyl group optionally substituted with 1, 2, or 3
independently selected R^h substituents;
or any two R^e substituents together with the nitrogen atom to which they are attached
form a 4-, 5-, 6-, or 7-membered heterocycloalkyl group optionally substituted with 1, 2, or 3
independently selected R^h substituents;
or any two R^e substituents together with the nitrogen atom to which they are attached
form a 4-, 5-, 6-, or 7-membered heterocycloalkyl group optionally substituted with 1, 2, or 3
independently selected R^h substituents;
or any two R^i substituents together with the nitrogen atom to which they are attached
form a 4-, 5-, 6-, or 7-membered heterocycloalkyl group optionally substituted with 1, 2, or 3
independently selected R^h substituents;
or any two R^i substituents together with the nitrogen atom to which they are attached
form a 4-, 5-, 6-, or 7-membered heterocycloalkyl group optionally substituted with 1, 2, or 3
independently selected R^h substituents;
or any two R\textsuperscript{a} substituents together with the nitrogen atom to which they are attached form a 4-, 5-, 6-, or 7-membered heterocycloalkyl group optionally substituted with 1, 2, or 3 independently selected R\textsuperscript{b} substituents;

or any two R\textsuperscript{f} substituents together with the nitrogen atom to which they are attached form a 4-, 5-, 6-, or 7-membered heterocycloalkyl group optionally substituted with 1, 2, or 3 independently selected R\textsuperscript{b} substituents;

each R\textsuperscript{1}, R\textsuperscript{k}, R\textsuperscript{o} or R\textsuperscript{f} is independently selected from H, C\textsubscript{1-4} alkyl, C\textsubscript{3-6} cycloalkyl, C\textsubscript{6-10} aryl, 5 or 6-membered heteroaryl, 4-7 membered heterocycloalkyl, C\textsubscript{1-6} haloalkyl, C\textsubscript{6} haloalkoxy, C\textsubscript{2-4} alkenyl, and C\textsubscript{2-4} alkynyl, wherein the C\textsubscript{1-4} alkyl, C\textsubscript{3-6} cycloalkyl, C\textsubscript{6-10} aryl, 5 or 6-membered heteroaryl, 4-7 membered heterocycloalkyl, C\textsubscript{2-4} alkenyl, and C\textsubscript{2-4} alkynyl of R\textsuperscript{1}, R\textsuperscript{k}, R\textsuperscript{o} or R\textsuperscript{f} are each optionally substituted with 1, 2 or 3 R\textsuperscript{g} substituents;

each R\textsuperscript{g} is independently selected from halo, OH, CN, -COOH, NH\textsubscript{2}, -NH-C\textsubscript{1-6} alkyl, -N(C\textsubscript{1-6} alkyl)\textsubscript{2}, C\textsubscript{1-6} alkyl, C\textsubscript{1-6} alkoxy, C\textsubscript{1-6} alkythio, C\textsubscript{1-6} haloalkyl, C\textsubscript{1-6} haloalkoxy, phenyl, 5-6 membered heteroaryl, 4-6 membered heterocycloalkyl and C\textsubscript{3-6} cycloalkyl, wherein the C\textsubscript{1-6} alkyl, phenyl, C\textsubscript{3-6} cycloalkyl, 4-6 membered heterocycloalkyl, and 5-6 membered heteroaryl of R\textsuperscript{g} are each optionally substituted with 1, 2, or 3 substituents selected from halo, OH, CN, -COOH, NH\textsubscript{2}, C\textsubscript{1-4} alkyl, C\textsubscript{1-4} alkoxy, C\textsubscript{1-4} haloalkyl, C\textsubscript{1-4} haloalkoxy, phenyl, C\textsubscript{3-10} cycloalkyl, 5-6 membered heteroaryl and 4-6 membered heterocycloalkyl;

the subscript m is an integer of 0, 1, 2 or 3;

the subscript n is an integer of 0, 1, 2 or 3;

each subscript q is independently an integer of 1, 2, 3 or 4; and

the subscript s is an integer of 1, 2, or 3.

6. The compound of any one of claims 1-5, or a pharmaceutically acceptable salt or a stereoisomer thereof, wherein:

any two R\textsuperscript{1} substituents together with the nitrogen atom to which they are attached form a 4-, 5-, 6-, 7-, 8-, or 10-membered heterocycloalkyl group optionally substituted with 1, 2, or 3 independently selected R\textsuperscript{g} substituents;

or any two R\textsuperscript{k} substituents together with the nitrogen atom to which they are attached form a 4-, 5-, 6-, 7-, 8-, or 10-membered heterocycloalkyl group optionally substituted with 1, 2, or 3 independently selected R\textsuperscript{g} substituents.

7. The compound of any one of claims 1-6, having Formula (la):
or a pharmaceutically acceptable salt or a stereoisomer thereof, wherein:

R\textsuperscript{1} is H, C\textsubscript{1-4} alkyl, C\textsubscript{1-}4 alkoxy, C\textsubscript{M} haloalkyl, C\textsubscript{M} haloalkoxy, CN, halo, OH, -COOH, NH\textsubscript{2}, -NHC\textsubscript{1-4} alkyl or -N(Ci \textsubscript{4} alkyl)\textsubscript{2}, wherein the C\textsubscript{1-4} alkyl and C\textsubscript{1-4} alkoxy are each optionally substituted with 1 or 2 substituents independently selected from CN, halo and - C(0)NH\textsubscript{2};

one of R\textsuperscript{1} and R\textsuperscript{2} is -(CR \textsuperscript{8}R\textsuperscript{9})\textsubscript{p}-NR\textsuperscript{10}R\textsuperscript{11} and the other is H, C\textsubscript{M} alkyl, C\textsubscript{M} alkoxy, C\textsubscript{M} haloalkyl, C\textsubscript{M} haloalkoxy, CN, halo, OH, -COOH, NH\textsubscript{2}, -NHC\textsubscript{1-4} alkyl or-N(Ci \textsubscript{4} alkyl)\textsubscript{2}, wherein the C\textsubscript{1-4} alkyl and C\textsubscript{1-4} alkoxy of R\textsuperscript{1} or R\textsuperscript{2} is optionally substituted with 1 or 2 substituents independently selected from C\textsubscript{M} alkoxy, C\textsubscript{M} haloalkyl, C\textsubscript{M} haloalkoxy, CN, halo, OH, -COOH, C(0)NH\textsubscript{2}, NH\textsubscript{2}, -NHC\textsubscript{1-4} alkyl and -N(CM\textsubscript{1-4} alkyl)\textsubscript{2};

R\textsuperscript{7} is H, C\textsubscript{M} alkyl, C\textsubscript{M} alkoxy, C\textsubscript{M} haloalkyl, C\textsubscript{M} haloalkoxy, CN, halo, OH, -COOH, NH\textsubscript{2}, -NHC\textsubscript{1-4} alkyl or-N(Ci \textsubscript{4} alkyl)\textsubscript{2}, wherein the C\textsubscript{1-4} alkyl and C\textsubscript{1-4} alkoxy are each optionally substituted with 1 or 2 substituents independently selected from CN, halo or -C(0)NH\textsubscript{2};

R\textsuperscript{8} and R\textsuperscript{9} are each independently selected from H, halo, CN, OH, -COOH, C\textsubscript{M} alkyl, C\textsubscript{4} alkoxy, -NHC\textsubscript{1-4} alkyl, -N(C\textsubscript{1-4} alkyl)\textsubscript{2}, C\textsubscript{M} haloalkyl, C\textsubscript{M} haloalkoxy, C\textsubscript{3-6} cycloalkyl, phenyl, 5-6 membered heteroaryl and 4-6 membered heterocycloalkyl, wherein the C\textsubscript{M} alkyl, C\textsubscript{1-4} alkoxy, C\textsubscript{1-4} haloalkyl, C\textsubscript{1-4} haloalkoxy, C\textsubscript{3-6} cycloalkyl, phenyl, 5-6 membered heteroaryl and 4-6 membered heterocycloalkyl of R\textsuperscript{8} or R\textsuperscript{9} are each optionally substituted with 1, 2 or 3 independently selected R\textsuperscript{8} substituents;

or R\textsuperscript{8} and R\textsuperscript{9} taken together with the carbon atom to which they are attached form 3-, 4-, 5- or 6-membered cycloalkyl or 4-, 5-, 6- or 7-membered heterocycloalkyl, each of which is optionally substituted with 1 or 2 R\textsuperscript{8} substituents;

or R\textsuperscript{8} and R\textsuperscript{10} taken together with the atoms to which they are attached form 4-, 5-, 6- or 7-membered heterocycloalkyl, having zero to one additional heteroatoms as ring members selected from O, N or S, wherein the 4-, 5-, 6- or 7-membered heterocycloalkyl formed by R\textsuperscript{8} and R\textsuperscript{10} are each optionally substituted with 1 or 2 R\textsuperscript{8} substituents;

R\textsuperscript{10} and R\textsuperscript{11} are each independently selected from H, C\textsubscript{6} alkyl, C\textsubscript{6} haloalkyl, C\textsubscript{3-6} cycloalkyl, C\textsubscript{6-10} aryl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C\textsubscript{6-10} aryl-Ci \textsubscript{4} alkyl-\textsubscript{1}, C\textsubscript{3-6} cycloalkyl-Ci \textsubscript{4} alkyl-, (5-10 membered heteroaryl)-Ci \textsubscript{4} alkyl-, (4-10 membered heteroaryl)-Ci \textsubscript{4} alkyl-
heterocycloalkyl)-Ci-4 alkyl-, -C(0)R®, -C(0)OR®, -C(0)NR₃®, -SO₂R and -SO₂NR₃®, wherein the Ci-6 alkyl, Ci-6haloalkyl, C₃-6 cycloalkyl, C₆-10 aryl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C₆-10 aryl-C₁-4 alkyl-, C₃-6 cycloalkyl-C₁-4 alkyl-, (5-10 membered heteroaryl)-Ci-4 alkyl-, and (4-10 membered heterocycloalkyl)-Ci-4 alkyl- of R¹0 or R¹¹ are each optionally substituted with 1, 2, or 3 independently selected R¹ substituents;

or R¹⁰ and R¹¹ taken together with the nitrogen atom to which they are attached form 4-, 5-, 6-, 7-, 8-, 9-, 10-, or 11-membered heterocycloalkyl, wherein the 4-11membered heterocycloalkyl is each optionally substituted with 1, 2 or 3 R¹ substituents;

R¹² is H, Ci-4 alkyl, Ci-4 alkoxy, CM haloalkyl, CM haloalkoxy, CN, halo, OH, -COOH, NH₂, -NHCl-4 alkyl or-N(Ci-4 alkyl)₂; and

the subscript p is an integer of 1, 2, 3 or 4.

8. The compound of any one of claims 1-7, or a pharmaceutically acceptable salt or a stereoisomer thereof, wherein (1) when L is - C(0)NH-, ring A is not 4,5,6,7-tetrahydro-lH-imidazo[4,5-c]pyridin-2-yl; (2) when L is a bond, ring A is not [1,2,4]triazolo[1,5-a]pyridin-2-yl; (3) when L is a bond, ring A is not 2-benzoxazolyl; or (4) when L is - C(0)NH-, ring A is not 2-pyridyl.

9. The compound of any one of claims 7-8, having Formula (II):

![Formula II](image)

or a pharmaceutically acceptable salt or a stereoisomer thereof.

10. The compound of any one of claim 7-9, having Formula (IIa):

![Formula IIa](image)

or a pharmaceutically acceptable salt or a stereoisomer thereof.
11. The compound of any one of claims 7-10, having Formula (lib):

![Chemical Structure](image)

or a pharmaceutically acceptable salt or a stereoisomer thereof.

12. The compound of any one of claims 7-8, having Formula (III):

![Chemical Structure](image)

or a pharmaceutically acceptable salt or a stereoisomer thereof.

13. The compound of any one of claims 7, 8 and 12, having Formula (Illa):

![Chemical Structure](image)

or a pharmaceutically acceptable salt or a stereoisomer thereof.

14. The compound of any one of claims 7-8, 12, and 13, having Formula (Illb):

![Chemical Structure](image)

or a pharmaceutically acceptable salt or a stereoisomer thereof.

15. The compound of any one of claims 7-11, having Formula (lie):
or a pharmaceutically acceptable salt or a stereoisomer thereof, wherein:

- \(X^1, X^2, X^3, X^4, X^5\) and \(X^6\) are each independently \(\text{N} \) or \(\text{CH}\), with the proviso that \(X^1, X^5\) and \(X^6\) are not simultaneously \(\text{N}\);
- \(R_{13}\) is \(\text{H}\) or \(\text{Ci-4} \) alkyl; and
- the subscript \(r\) is an integer of 1, 2 or 3.

16. The compound of any one of claims 7-11 and 15, having Formula (IIc-1):

or a pharmaceutically acceptable salt or a stereoisomer thereof.

17. The compound of any one of claims 7-16, or a pharmaceutically acceptable salt or a stereoisomer thereof, wherein \(R_{13}\) is \(\text{H}\).

18. The compound of any one of claims 7-10, having Formula (IIa-1):

or a pharmaceutically acceptable salt or a stereoisomer thereof, wherein:

- ring \(A\) is 5- to 10-membered heteroaryl, 4- to 11-membered heterocycloalkyl or \(\text{C}_{6-10}\) aryl, wherein the 5- to 10-membered heteroaryl and 4- to 11-membered heterocycloalkyl each has 1-4 heteroatoms as ring members selected from \(\text{N}, \text{O}\) and \(\text{S}\), wherein the \(\text{N}\) or \(\text{S}\) atom as ring members is optionally oxidized and one or more carbon atoms as ring members are each optionally replaced by a carbonyl group; and wherein ring \(A\) is optionally substituted with 1, 2 or 3 \(R^6\) substituents; \(L\) is a bond, -\(\text{C}(0)\)NH-, -NH- or -OCH2-, wherein the carbonyl group in the -\(\text{C}(0)\)NH- linkage or the oxygen atom in the -OCH2- linkage is attached to ring \(A\); and...
X is CH or N.

19. The compound of any one of claims 7-10 and 18, having Formula (IIa-2):

![Chemical Structure](image)

(IIa-2)
or a pharmaceutically acceptable salt or a stereoisomer thereof.

20. The compound of any one of claims 7-10, having Formula (IId):

![Chemical Structure](image)

(IIId)
or a pharmaceutically acceptable salt or a stereoisomer thereof, wherein:

- $R_{13}$ is H or Ci-4 alkyl;
- $R_{19}$ is H, Ci-6 alkyl, Ci-4 haloalkyl, C2-6 alkenyl, C2-6 alkynyl, C6-10 aryl, C3-10 cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C6-10 aryl-Ci-4 alkyl-, C3-10 cycloalkyl-Ci-4 alkyl-, (5-10 membered heteroaryl)-Ci-4 alkyl-, or (4-10 membered heterocycloalkyl)-Ci-4 alkyl-, wherein the Ci-6 alkyl, C2-6 alkenyl, C2-6 alkynyl, C6-10 aryl, C3-10 cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C6-10 aryl-Ci-4 alkyl-, C3-10 cycloalkyl-Ci-4 alkyl-, (5-10 membered heteroaryl)-Ci-4 alkyl- and (4-10 membered heterocycloalkyl)-Ci-4 alkyl- of $R_{18}$ are each optionally substituted with 1, 2, or 3 $R_{b}$ substituents; and
- the subscript $t$ is an integer of 0, 1 or 2.

21. The compound of any one of claims 7-10 and 20, having Formula (IId-1):

![Chemical Structure](image)

(IId-1)
or a pharmaceutically acceptable salt or a stereoisomer thereof.

22. The compound of any one of claims 7-10, having Formula (Ile):

![Chemical Structure](image)

or a pharmaceutically acceptable salt or a stereoisomer thereof.

23. The compound of any one of claims 7-10, having Formula (Ilf):

![Chemical Structure](image)

or a pharmaceutically acceptable salt or a stereoisomer thereof.

24. The compound of any one of claims 1-14 and 17-19, or a pharmaceutically acceptable salt or a stereoisomer thereof, wherein ring A is selected from:

![Chemical Structures](image)
25. The compound of any one of claims 1-14 and 17-19, or a pharmaceutically acceptable salt or a stereoisomer thereof, wherein ring A is selected from:

![Chemical structures](image1)

The compound of any one of claims 1-26, or a pharmaceutically acceptable salt or a stereoisomer thereof, wherein ring A is selected from:

![Chemical structures](image2)

The compound of any one of claims 1-26, or a pharmaceutically acceptable salt or a stereoisomer thereof, wherein ring A is selected from:

![Chemical structures](image3)

carboxypyrrolidin-1-yl)ethanoyl, (S)-2-(3-carboxypyrrolidin-1-yl)ethanoyl, (R)-2-(3-carboxypyrrolidin-1-yl)ethanoyl, (5-cyanopyridin-3-yl)methoxy, halo or CN.

28. The compound of any one of claims 1-26, or a pharmaceutically acceptable salt or a stereoisomer thereof, wherein R₆ is (4-carboxycyclohexyl)methyl, trans-(4-carboxycyclohexyl)methyl, cis-(4-carboxycyclohexyl)methyl, 1-carboxy-2-propyl, (R)-1-carboxy-2-propyl, (S)-1-carboxy-2-propyl, (4-carboxy-4-methylcyclohexyl)methyl, 2-pyrrolidinyl, 2-(3-hydroxypyrrolidin-1-yl)acetyl, 2-((R)-3-hydroxypyrrolidin-1-yl)acetyl, 2-((S)-3-hydroxyazetidin-1-yl)acetyl, 2-(2-hydroxyethyl)(methyl)amino)acetyl, (4-carboxycyclohexyl)ethyl, 4-carboxycyclohexyl, 4-carboxy-4-methylcyclohexyl, dimethylglycyl, or N-ethyl-N-methylglycyl.

29. The compound of any one of claims 1-14, 18, 19, and 24-28, or a pharmaceutically acceptable salt or a stereoisomer thereof, wherein L is a bond, -NH-, -CH=CH- or -C(0)NH-, wherein the carbonyl group in the -C(0)NH- linkage is attached to ring A.

30. The compound of any one of claims 1-14, 18, 19, and 24-28, or a pharmaceutically acceptable salt or a stereoisomer thereof, wherein L is -C(0)NH-.

31. The compound of any one of claims 1-14, 18, 19, and 24-28, or a pharmaceutically acceptable salt or a stereoisomer thereof, wherein L is -NH-.

32. The compound of any one of claims 1-14, 18, 19, and 24-28, or a pharmaceutically acceptable salt or a stereoisomer thereof, wherein L is a bond, -NH- or -C(0)NH-.

33. The compound of any one of claims 1-10, 12, 13, and 24-32, or a pharmaceutically acceptable salt or a stereoisomer thereof, wherein the subscript m is 0.

34. The compound of any one of claims 1-10, 12, 13, 17, and 24-33, or a pharmaceutically acceptable salt or a stereoisomer thereof, wherein the subscript n is 1 and R⁵ is halo or Ci₄ alkyl.

35. The compound of any one of claims 1-34, or a pharmaceutically acceptable salt or a stereoisomer thereof, wherein R³ is methyl, CN or Cl.
36. The compound of any one of claims 7-10, 12, 13, and 17-35, or a pharmaceutically acceptable salt or a stereoisomer thereof, wherein \( R^{12} \) is H, halo, CN, \( \text{Ci}_4 \) alkyl or \( \text{Ci}_4 \) alkoxy.

37. The compound of any one of claims 7-10, 12, 13, and 17-36, or a pharmaceutically acceptable salt or a stereoisomer thereof, wherein \( R^7 \) is H, halo, CN, \( \text{Ci}_4 \) alkyl, \( \text{Ci}_4 \) alkoxy or \( \text{Ci}_4 \) haloalkoxy, wherein the \( \text{Ci}_4 \) alkyl and \( \text{Ci}_4 \) alkoxy of \( R^7 \) are each optionally substituted with CN.

38. The compound of any one of claims 7-10 and 17-37, or a pharmaceutically acceptable salt or a stereoisomer thereof, wherein \( R^2 \) is H.

39. The compound of any one of claims 7-10 and 17-37, or a pharmaceutically acceptable salt or a stereoisomer thereof, wherein \( R^2, R^7 \) and \( R^{12} \) are each H.

40. The compound of any one of claims 1-33 and 36-39, or a pharmaceutically acceptable salt or a stereoisomer thereof, wherein \( R^3 \) and \( R^5 \) are each independently halo, methyl or CN.

41. The compound of any one of claims 7, 12, 13, 17, and 24-40, or a pharmaceutically acceptable salt or a stereoisomer thereof, wherein \( R^1 \) is H.

42. The compound of any one of claims 7-14, 17, 18, and 24-41, or a pharmaceutically acceptable salt or a stereoisomer thereof, wherein the subscript p is 1.

43. The compound of any one of claims 7-14, 17, 18, and 24-41, or a pharmaceutically acceptable salt or a stereoisomer thereof, wherein \( R^8 \) and \( R^9 \) are each H.

44. The compound of any one of claims 7-43, or a pharmaceutically acceptable salt or a stereoisomer thereof, wherein \( R^{10} \) is H.

45. The compound of any one of claims 7-44, or a pharmaceutically acceptable salt or a stereoisomer thereof, wherein \( R^{11} \) is 2-hydroxyethyl, \([\text{I-(hydroxymethyl)cylopropyl}]\text{methyl}\) \([\text{I-(hydroxymethyl)cylobutyl}]\text{methyl}\) or 2-(dimethylamino)-2-oxo-ethyl.

46. The compound of any one of claims 7-44, or a pharmaceutically acceptable salt or a stereoisomer thereof, wherein \( R^{11} \) is 1-hydroxy-2-propyl, 2-carboxyethyl, or 2-hydroxycyclopentyl.
47. The compound of any one of claims 7-43, or a pharmaceutically acceptable salt or a stereoisomer thereof, wherein -NR \(^{10}\)R \(^{11}\) is (2-hydroxyethyl)amino, 3-hydroxyprrolidin-1-yl, (R)-3-hydroxyprrolidin-1-yl, (S)-3-hydroxyprrolidin-1-yl, 3-carboxyprrolidin-1-yl, (R)-3-carboxyprrolidin-1-yl, (S)-3-carboxyprrolidin-1-yl, 3-carboxyazetidin-1-yl, (S)-3-carboxyazetidin-1-yl, 2-carboxy-l-piperidinyl, (R)-2-carboxy-l-piperidinyl, (S)-2-carboxy-l-piperidinyl, 2-oxooxazolidin-3-yl, [1-(hydroxymethyl)cyclopropyl]methylamino, [1-(hydroxymethyl)cyclobutyl]methylamino, [2-(dimethylamino)-2-oxo-ethyl]amino, 3-(dimethylaminocarbonyl)pyrrolidin-1-yl, (R)-3-(dimethylaminocarbonyl)pyrrolidin-1-yl, (S)-3-(dimethylaminocarbonyl)pyrrolidin-1-yl, 2-hydroxypropylamino, 2-hydroxy-2-methylpropylamino, or 3-methyl-3-carboxyprrolidin-1-yl.

48. The compound of any one of claims 7-43, or a pharmaceutically acceptable salt or a stereoisomer thereof, wherein -NR \(^{10}\)R \(^{11}\) is (2-hydroxyethyl)amino, 3-hydroxyprrolidin-1-yl, 3-carboxyprrolidin-1-yl, 3-carboxyazetidin-1-yl, 2-carboxy-l-piperidinyl, 2-oxooxazolidin-3-yl, [1-(hydroxymethyl)cyclopropyl]methylamino, [1-(hydroxymethyl)cyclobutyl]methylamino, [2-(dimethylamino)-2-oxo-ethyl]amino, 3-(dimethylaminocarbonyl)pyrrolidin-1-yl, (R)-3-(dimethylaminocarbonyl)pyrrolidin-1-yl, (S)-3-(dimethylaminocarbonyl)pyrrolidin-1-yl, 2-hydroxypropylamino, 2-hydroxy-2-methylpropylamino, or 3-methyl-3-carboxyprrolidin-1-yl.

49. The compound of any one of claims 7-43, or a pharmaceutically acceptable salt or a stereoisomer thereof, wherein -NR \(^{10}\)R \(^{11}\) is 1-pyrrolidinyl, (3-carboxy-3-methyl)pyrrolidin-1-yl, (R)-(3-carboxy-3-methyl)pyrrolidin-1-yl, (S)-(3-carboxy-3-methyl)pyrrolidin-1-yl, (1-hydroxy-2-propyl)amino, (R)-(1-hydroxy-2-propyl)amino, (S)-(1-hydroxy-2-propyl)amino, (3-hydroxy-3-methyl)pyrrolidin-1-yl, (R)-(3-hydroxy-3-methyl)pyrrolidin-1-yl, (S)-(3-hydroxy-3-methyl)pyrrolidin-1-yl, (2-hydroxycyclopentyl)amino, ((IR,2S)-2-hydroxycyclopentyl)amino, ((IR,2R)-2-hydroxycyclopentyl)amino, ((IS,2S)-2-hydroxycyclopentyl)amino, ((IS,2R)-2-hydroxycyclopentyl)amino, 2-carboxyethylamino, 3-(carboxymethyl)pyrrolidin-1-yl, or 5-carboxy-2-azabicyclo[2.2.1]heptan-2-yl.

50. The compound of any one of claims 1-14, 17-19, and 27-49, or a pharmaceutically acceptable salt or a stereoisomer thereof, wherein ring A is 2-pyridyl, optionally substituted with 1, 2, 3, or 4 independently selected R\(^{6}\) substituents.

51. The compound of any one of claims 1-10, 12, 13, and 17-50, or a pharmaceutically acceptable salt or a stereoisomer thereof, wherein X is N or CH.
52. The compound of claim 1 selected from:

2-(((8-((2-chloro-2'-methyl-3'(4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)-[1,1'-biphenyl]-3-yl)amino)-1',7-naphthyridin-3-yl)methyl)amino)ethan-1-ol;

1-(((6-(2-fluoro-3'-(3-((2-hydroxyethylamino)methyl)-1,7-naphthyridin-8-ylamino)-2'-methylbiphenyl-3-ylcarbamoyl)pyridin-3-yl)methylamino)cyclobutane-carboxylic acid;

(S)-1-(((6-(2-fluoro-3'-(3-((2-hydroxyethylamino)methyl)-1,7-naphthyridin-8-ylamino)-2'-methylbiphenyl-3-yl)carbamoyl)pyridin-3-yl)methyl)piperidine-2-carboxylic acid;

N-(2-fluoro-3'-(3-(((2-hydroxyethylamino)methyl)-1,7-naphthyridin-8-yl)amino)-2'-methyl-[1,1'-biphenyl]-3-yl)-5-(((2-hydroxyethylamino)methyl)picolinamide;

N-(2-chloro-3'-(3-((2-hydroxyethylamino)methyl)-1,7-naphthyridin-8-yl)amino)-2'-methyl-[1,1'-biphenyl]-3-yl)-5-(((2-hydroxyethylamino)methyl)picolinamide;

N-(2-chloro-3'-(3-(((R)-3-hydroxy-3-pyrrolidinyl)methyl)-1,7-naphthyridin-8-yl)amino)-2'-methyl-[1,1'-biphenyl]-3-yl)-5-(((R)-3-hydroxy-3-pyrrolidinyl)methyl)pyrrolidine-3-carboxylic acid;

and

(R)-1-((8-((2'-chloro-3'-(5-(((R)-3-hydroxy-3-pyrrolidinyl)methyl)picolinamido)-2'-methyl-[1,1'-biphenyl]-3-yl)amino)-1,7-naphthyridin-3-yl)methyl)pyrrolidine-3-carboxylic acid;

or a pharmaceutically acceptable salt or a stereoisomer thereof.

53. The compound of claim 1 selected from:

(i?)-1-((8-(3'-(3-(((i?)-3-hydroxy-3-pyrrolidinyl)methyl)-1,7-naphthyridin-8-yl)amino)-2,2'-dimethyl-[1,1'-biphenyl]-3-yl)methyl)pyrrolidine-3-carboxylic acid;

(5)-1-((8-(3'-(3-(((i?)-3-hydroxy-3-pyrrolidinyl)methyl)-1,7-naphthyridin-8-yl)amino)-2,2'-dimethyl-[1,1'-biphenyl]-3-yl)methyl)pyrrolidine-3-carboxylic acid;

(i?)-1-((8-(3'-(3-((2-hydroxyethylamino)methyl)-1,7-naphthyridin-8-yl)amino)-2,2'-dimethyl-[1,1'-biphenyl]-3-yl)methyl)pyrrolidine-3-carboxylic acid;

2,2'-dimethyl-[1,1'-biphenyl]-3-yl)methyl)pyrrolidine-3-carboxylic acid;
(i?-l-((8-((3’-((3-((5)-3-hydroxypyrrolidin-l-yl)methyl)-l,7-naphthyridin-8-yl)amino)-2,2’-dimethyl-[l ,l’-biphenyl]-3-yl)amino)-l ,7-naphthyridin-3-yl)methyl)pyrrolidine-3-carboxylic acid; and
(5-1-((8-((3’-((5)-3-hydroxypyrrolidin-1 -yl)methyl)-l,7-naphthyridin-8-yl)amino)-2,2’-dimethyl-[l ,l’-biphenyl]-3-yl)amino)-l ,7-naphthyridin-3-yl)methyl)pyrrolidine-3-carboxylic acid;
or a pharmaceutically acceptable salt or a stereoisomer thereof.

54. The compound of claim 1 selected from:

1-((8<2-chloro-3’-(l,5-dimethyl-4,5,6,7-tetrahydro-lH-irnidazo[4,5-c]pyridine-2-carboxamido)-2’-methylbiphenyl-3-ylamino)-l,7-naphthyridin-3-yl)methyl)azetidine-3-carboxylic acid;

(i?-l-((5-(2-chloro-3’-(3-(((i?-3-hydroxypyrrolidin-l-yl)methyl)-l,7-naphthyridin-8-yl)amino)-2’-methylbiphenyl-3-ylcarbamoyl)-l-methyl-6-oxo-1,6-dihydropyridin-3-yl)methyl)pyrrolidine-3-carboxylic acid;

(R)-1-((8-2,2’dichloro-3’-(5-3-hydroxyethylamino)methyl)-l,7-naphthyridin-3-yl)methyl)azetidine-3-carboxylic acid;

1-((8-2,2’dichloro-3’-(5-3-hydroxyethylamino)methyl)-l-methyl-2-oxo-1,2-dihydropyridine-3-carboxamido)biphenyl-3-ylamino)-1,7-naphthyridin-3-yl)methyl)azetidine-3-carboxylic acid;

2,2’-(((((2,2’-dimethyl-[l ,l’-biphenyl]-3,3’-diyl)bis(azanediyl))bis(l,7-naphthyridine-8,3-diyl))bis(methylene))bis(ethan-1-ol);

(3i?,3’i ?)-14’-(((((2,2’-dimethyl-[l4’-biphenyl]-3,3’-diyl)bis(azanediyl))bis(1,7-naphthyridine-8,3-diyl))bis(methylene))bis(pyrrolidin-3-ol);

(R)-1-((8-3’-(3-(2-hydroxyethylamino)methyl)-l,7-naphthyridin-8-ylamino)-2,2’-dimethylbiphenyl-3-ylamino)-l,7-naphthyridin-3-yl)methyl)pyrrolidine-3-carboxylic acid;

(3i?,3’i ?)-14’-(((((2,2’-dichloro-[l4’-biphenyl]-3,3’-diyl)bis(azanediyl))bis(1,7-naphthyridine-8,3-diyl))bis(methylene))bis(pyrrolidin-3-ol);
(i?)-l-((4-(3'-(3-(((i?)-3-hydroxypyrrolidin-1-yl)methyl)-l,7-naphthyridin-8-ylamino)-2,2'-dimethylbiphenyl-3-ylamino)pyrido[3,2-d]pyrimidin-7-yl)methyl)pyrrolidin-3-ol;

(i?)-l-((8-(3'-(7-((2-hydroxyethylamino)methyl)pyrido[3,2-d]pyrimidin-4-ylamino)-2,2'-dimethylbiphenyl-3-ylamino)-1,7-naphthyridin-3-yl)methyl)pyrrolidin-3-ol;

(i?)-l-((8-(3'-(7-(((2-hydroxyethyl)(methyl)amino)methyl)pyrido[3,2-d]pyrimidin-4-ylamino)-2,2'-dimethylbiphenyl-3-ylamino)-1,7-naphthyridin-3-yl)methyl)pyrrolidine-3-carboxamide;

(i?)-l-((8-(3'-(7-(((i?)-2-hydroxypropylamino)methyl)pyrido[3,2-d]pyrimidin-4-ylamino)-2,2'-dimethylbiphenyl-3-ylamino)-1,7-naphthyridin-3-yl)methyl)pyrrolidin-3-ol;

(R)-l-((8-(3'-(5-(((i?)-3-hydroxypropyl-1-y1)methyl)-2-oxo-1,2-dihydropyridine-3-carboxamido)-2,2'-dimethylbiphenyl-3-ylamino)-1,7-naphthyridin-3-yl)methyl)pyrrolidine-3-carboxylic acid;

(i?)-l-((8-(3'-(7-(((i?)-2-hydroxypropylamino)methyl)pyrido[3,2-d]pyrimidin-4-ylamino)-2,2'-dimethylbiphenyl-3-ylamino)-1,7-naphthyridin-3-yl)methyl)pyrrolidine-3-carboxylic acid;

(5)-N-(2-chloro-3'-(3-((3-hydroxypyrrolidin-1-yl)methyl)-1,7-naphthyridin-8-yllaridno)-2'-methylbiphenyl-3-yl)-1,5-dimethyl-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridine-2-carboxamido-2-methylbiphenyl-3-ylamino)-1,7-naphthyridin-3-yl)methyl)pyrrolidine-3-carboxylic acid;
The compound of claim 1 selected from:

(i?)-l-(8-(2'-Chloro-2-methyl-3'-(l-methyl-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridin-2-yl)-l,7-naphthyridin-3-yl)methyl)pyrrolidine-3-carboxylic acid; and

(i?)-l-(5-chloro-2-(5-cyanopyridin-3-yl)methoxy)-4-((3'-(3-hydroxy-4-oxoethyl)pyrrolo[3,4-d]oxazol-5-yl)-2-oxoethyl)piperidine-2-carboxylic acid; and

or a pharmaceutically acceptable salt or a stereoisomer thereof.

55.
c|pyridine-2-carboxamido)biphenyl-3-ylamino)-l,7-naphthyridin-3-yl)methyl)-3-
methylpyrrolidine-3-carboxylic acid;

(i?)-l-((8<3'<l,5-dimethyl-4,5,6,7-tetrahydro-1 H-imidazo[4,5-c|pyridine-2-
carboxamido)-2',2'-dimethylbiphenyl-3-ylamino)-l,7-naphthyridin-3-yl)methyl|pyrrolidine-3 -
carboxylic acid;

f arab=4-((2-(2-chloro-3'-3-((i?)-3-hydroxy|pyrrolidin-1-yl)methyl)-l,7-naphthyridin-8-
ylamo)-2'-methylbiphenyl-3-ylcarbamoyl)-l-methyl-6,7-dihydro-lH-imidazo[4,5-
c|pyridin-5(4 H)-yl)methyl)cyclohexanecarboxylic acid;

cis=4-((2-(2-chloro-3'-3-((R)-3-hydroxy|pyrrolidin-1-yl)methyl)-l,7-naphthyridin-8-
ylamo)-2'-methylbiphenyl-3-ylcarbamoyl)-l-methyl-6,7-dihydro-lH-imidazo[4,5-
c|pyridin-5(4 H)-yl)methyl)cyclohexanecarboxylic acid;

cis=4-((2-(2-chloro-2'-methyl-3'-3-(pyrrolidin-1-ylmethyl)-l,7-naphthyridin-8-
ylamo)biphenyl-3-ylcarbamoyl)-l-methyl-6,7-dihydro-lH-imidazo[4,5-c|pyridin-5(4H)-
yl)methyl)cyclohexanecarboxylic acid;

cis=4-((2-(2-chloro-2'-methyl-3'-3-(|pyrrolidin-1-ylmethyl)-l,7-naphthyridin-8-
ylamo)biphenyl-3-ylcarbamoyl)-l-methyl-6,7-dihydro-lH-imidazo[4,5-c|pyridin-5(4H)-
yl)methyl)cyclohexanecarboxylic acid;

cis=4-((2-(2-chloro-3'-3-(((5)-l-hydroxypropan-2-ylamino)methyl)-l,7-
naphthyridin-8-ylamo)-2'-methylbiphenyl-3-ylcarbamoyl)-l-methyl-6,7-dihydro-l H-
imidazo[4,5-c|pyridin-5(4 H)-yl)methyl)cyclohexanecarboxylic acid;

fra/75-4-((2-(2-chloro-3'-3-(((IS,2S)-2-hydroxycyclopentylamino)methyl)-l,7-
naphthyridin-8-ylamo)-2'-methylbiphenyl-3-ylcarbamoyl)-l-methyl-6,7-dihydro-l H-
imidazo[4,5-c|pyridin-5(4 H)-yl)methyl)cyclohexanecarboxylic acid;

trans 4-(2-(2-chloro-3'-3-(((i?)-3-hydroxy|pyrrolidin-1-yl)methyl)-1,7-
naphthyridin-8-ylamo)-2'-methylbiphenyl-3-ylcarbamoyl)-l-methyl-6,7-dihydro-l H-imidazo[4,5-
c|pyridin-5(4H)-yl)methyl)cyclohexanecarboxylic acid;

cis 4-(2-(2-chloro-3'-3-(((R)-3-hydroxy|pyrrolidin-1-yl)methyl)-1,7-naphthyridin-8-
ylamo)-2'-methylbiphenyl-3-ylcarbamoyl)-l-methyl-6,7-dihydro-lH-imidazo[4,5-
c|pyridin-5(4H)-yl)methyl)cyclohexanecarboxylic acid;

3-(2-(2-chloro-3'-3-(((i?)-3-hydroxy|pyrrolidin-1-yl)methyl)-1,7-naphthyridin-8-
ylamo)-2'-methylbiphenyl-3-ylcarbamoyl)-l-methyl-6,7-dihydro-l H-imidazo[4,5-
c|pyridin-5(4 H)-yl)butanoic acid;

cis 4-((2-(2-chloro-3'-3-(((5)-3-hydroxy-3-methyl|pyrrolidin-1-yl)methyl)-l,7-
naphthyridin-8-ylamo)-2'-methylbiphenyl-3-ylcarbamoyl)-l-methyl-6,7-dihydro-l H-
naphthyridin-8-ylamo)-2'-methylbiphenyl-3-ylcarbamoyl)-l-methyl-6,7-dihydro-l H-
imidazo[4,5-c]pyridin-5(4 H)-yl)methyl)cyclohexanecarboxylic acid;

(i?)-4-(2-(2-chloro-3'-(3-((3-hydroxy-3-methylpyrrolidin-1-yl)methyl)-1,7-
naphthyridin-8-ylamino)-2'-methylbiphenyl-3-ylcarbamoyl)-1-methyl-6,7-dihydro-1 H-
imidazo[4,5-c]pyridin-5(4 H)-yl)cyclohexanecarboxylic acid;

(5)-4-(2-(2-chloro-3'-(3-((3-hydroxy-3-methylpyrrolidin-1-yl)methyl)-1,7-
naphthyridin-8-ylamino)-2'-methylbiphenyl-3-ylcarbamoyl)-1-methyl-6,7-dihydro-1 H-
imidazo[4,5-c]pyridin-5(4 H)-yl)cyclohexanecarboxylic acid;

trans 4-(2-(2-chloro-3'-(3-(((i?)-l-hydroxypropan-2-ylamino)methyl)-1,7-
naphthyridin-8-ylamino)-2'-methylbiphenyl-3-ylcarbamoyl)-1-methyl-6,7-dihydro-1 H-
imidazo[4,5-c]pyridin-5(4 H)-yl)cyclohexanecarboxylic acid;

trans 4-(2-(2-chloro-3'-(3-(((i?)-3-hydroxy-3-methylpyrrolidin-1-yl)methyl)-1,7-
naphthyridin-8-ylamino)-2,2'-dimethylbiphenyl-3-ylcarbamoyl)-1-methyl-6,7-dihydro-1 H-
imidazo[4,5-c]pyridin-5(4 H)-yl)cyclohexanecarboxylic acid;

(i?)-4-(2-(3'-(3-((3-hydroxy-3-methylpyrrolidin-1-yl)methyl)-1,7-naphthyridin-8-ylamino)-2,2'-dimethylbiphenyl-3-ylcarbamoyl)-1-methyl-6,7-dihydro-1 H-imidazo[4,5-c]pyridin-5(4 H)-yl)cyclohexanecarboxylic acid;

trans 4-(2-(2'-chloro-3'-(3-(((i?)-3-hydroxy-3-methylpyrrolidin-1-yl)methyl)-1,7-
naphthyridin-8-ylamino)-2-methylbiphenyl-3-ylcarbamoyl)-1-methyl-6,7-dihydro-1 H-imidazo[4,5-c]pyridin-5(4 H)-yl)cyclohexanecarboxylic acid;

trans 4-(2-(2'-chloro-3'-(3-(((i?)-1-hydroxypropan-2-ylamino)methyl)-1,7-
naphthyridin-8-ylamino)-2-methylbiphenyl-3-ylcarbamoyl)-1-methyl-6,7-dihydro-1 H-imidazo[4,5-c]pyridin-5(4 H)-yl)cyclohexanecarboxylic acid;

trans 4-(2-(2'-chloro-3'-(3-(((i?)-3-hydroxy-3-methylpyrrolidin-1-yl)methyl)-1,7-
naphthyridin-8-ylamino)-2-methylbiphenyl-3-ylcarbamoyl)-1-methyl-6,7-dihydro-1 H-imidazo[4,5-c]pyridin-5(4 H)-yl)cyclohexanecarboxylic acid;

trans 4-(2-(2'-chloro-3'-(3-(((i?)-3-hydroxy-3-methylpyrrolidin-1-yl)methyl)-1,7-
naphthyridin-8-ylamino)-2-methylbiphenyl-3-ylcarbamoyl)-1-methyl-6,7-dihydro-1 H-imidazo[4,5-c]pyridin-5(4 H)-yl)cyclohexanecarboxylic acid;

trans 4-(2-(2'-dichloro-3'-(3-(((i?)-3-hydroxy-3-methylpyrrolidin-1-yl)methyl)-1,7-
naphthyridin-8-ylamino)biphenyl-3-ylcarbamoyl)-1-methyl-6,7-dihydro-1 H-imidazo[4,5-c]pyridin-5(4 H)-yl)cyclohexanecarboxylic acid;

trans 4-(2-(2'-dichloro-3'-(3-(((i?)-3-hydroxy-3-methylpyrrolidin-1-yl)methyl)-1,7-
naphthyridin-8-ylamino)biphenyl-3-ylcarbamoyl)-1-methyl-6,7-dihydro-1 H-imidazo[4,5-c]pyridin-5(4 H)-yl)cyclohexanecarboxylic acid;

trans 4-(2-(2'-dichloro-3'-(3-(((i?)-3-hydroxy-3-methylpyrrolidin-1-yl)methyl)-1,7-
naphthyridin-8-ylamino)biphenyl-3-ylcarbamoyl)-1-methyl-6,7-dihydro-1 H-imidazo[4,5-c]pyridin-5(4 H)-yl)cyclohexanecarboxylic acid;

trans 4-(2-(2'-dichloro-3'-(3-(((i?)-3-hydroxy-3-methylpyrrolidin-1-yl)methyl)-1,7-
naphthyridin-8-ylamino)biphenyl-3-ylcarbamoyl)-1-methyl-6,7-dihydro-1 H-imidazo[4,5-c]pyridin-5(4 H)-yl)cyclohexanecarboxylic acid;

trans 4-(2-(2'-dichloro-3'-(3-(((i?)-3-hydroxy-3-methylpyrrolidin-1-yl)methyl)-1,7-
naphthyridin-8-ylamino)biphenyl-3-ylcarbamoyl)-1-methyl-6,7-dihydro-1 H-imidazo[4,5-c]pyridin-5(4 H)-yl)cyclohexanecarboxylic acid;

trans 4-(2-(2'-dichloro-3'-(3-(((i?)-3-hydroxy-3-methylpyrrolidin-1-yl)methyl)-1,7-
naphthyridin-8-ylamino)biphenyl-3-ylcarbamoyl)-1-methyl-6,7-dihydro-1 H-imidazo[4,5-c]pyridin-5(4 H)-yl)cyclohexanecarboxylic acid;

trans 4-(2-(2'-dichloro-3'-(3-(((i?)-3-hydroxy-3-methylpyrrolidin-1-yl)methyl)-1,7-
naphthyridin-8-ylamino)biphenyl-3-ylcarbamoyl)-1-methyl-6,7-dihydro-1 H-imidazo[4,5-c]pyridin-5(4 H)-yl)cyclohexanecarboxylic acid;
(i?)-4-(2-(2-chloro-3'-(7-((3-hydroxypyrrolidin-l^\text{H})-methyl)pyrido[3,2-d]pyrimidin-4-ylamino)-2'-methylbiphenyl-3-ylcarbamoyl)-l-methyl-6,7-dihydro-1H-imidazo[4,5-c]pyridin-5(4H)-yl)-1-methylcyclohexanecarboxylic acid;

trans 4-((2-(2-chloro-3'-(7-((i?)-3-hydroxypyrrolidin-l-yl)methyl)pyrido[3,2-d]pyrimidin-4-ylamino)-2'-methylbiphenyl-3-ylcarbamoyl)-l-methyl-6,7-dihydro-1H-imidazo[4,5-c]pyridin-5(4H)-yl)methyl)cyclohexanecarboxylic acid;

(i?)-l-((5-(3'-(((i?)-3-hydroxypyrrolidin-l-yl)methyl)-3-hydroxy2',2'-dimethylbiphenyl-3-ylamino)pyrido[4,3-Z]pyrazin-2-yl)methyl)pyrrolidine-3-carboxylic acid;

(3i?)-l-((8-(2,2'-dimethyl-3'-(3-((pyrrolidin-2-yl)methyl)pyrido[4,3-Z]pyrazin-2-yl)methyl)pyrrolidine-3-carboxylic acid;

(i?)-l-((8-(2,2'-dichloro-3'-(3-hydroxyethylamino)methyl)imidazo[1,2-a]pyrazin-8-yl)methyl)biphenyl-3-ylamino)-1,7-naphthyridin-3-yl)methyl)pyrrolidin-3-ol;

(i?)-l-((8-(2,2'-dime%l-3'-(3-((2-hydroxyethyl)amino)methyl)-l,7-naphthyridin-8-yl)amino)-2-methyl-[1,1'-biphenyl]-3-yl)amino)-1,7-naphthyridin-3-yl)methyl)pyrrolidin-3-ol;

(i?)-l-((8-(2-chloro-3'-(7-((3-hydroxypyrrolidin-l-yl)methyl)-1,7-naphthyridin-3-yl)-methyl)pyrrolidin-3-yl)methyl)pyrrolidin-3-ol;

(i?)-l-((8-(2,2'-dichloro-3'-(3-((i?)-3-hydroxypyrrolidin-l-yl)methyl)-1,7-naphthyridin-8-yl)amino)-2'-methyl-[1,1'-biphenyl]-3-yl)amino)-1,7-naphthyridin-3-yl)methyl)pyrrolidin-3-ol;

(i?)-l-((8-(2-chloro-3'-(7-((3-hydroxypyrrolidin-l-yl)methyl)-1,7-naphthyridin-3-yl)amino)-1,7-naphthyridin-3-yl)methyl)pyrrolidin-3-ol;
carboxylic acid;

(i?)-3-(((8-((2-chloro-3'-(3-((3-hydroxypyrrolidin-1-yl)methyl)-1,7-naphthyridin-8-yl)amino)-2'-methyl-[1,1'-biphenyl]-3-yl)amino)-1,7-naphthyridin-3-yl)methyl)amino)propanoic acid;

(i?)-l-((8-((2,2'-dichloro-3'-(3-((S)-3-hydroxypyrrolidin-1-yl)methyl)-1,7-naphthyridin-8-y)amino)-[1,1'-biphenyl]-3-yl)methyl)pyrrolidine-3-carboxylic acid;

(S)-l-((8-((2,2'-dichloro-3'-(3-(((5)-3-hydroxypyrrolidin-1-yl)methyl)-1,7-naphthyridin-8-y)amino)-[1,1'-biphenyl]-3-yl)methyl)pyrrolidine-3-carboxylic acid;

(i?)-l-((8-((3'-((5-(dimethylglycyl)-5,6-dihydro-4H-pyrrolo[3,4-cf]oxazol-2-yl)-2,2'-dimethyl-[1,r-biphenyl]-3-yl)amino)-1,7-naphthyridin-3-yl)methyl)pyrrolidine-3-carboxylic acid;

(i?)-l-((8-((3'-((5-(dimethylglycyl)-5,6-dihydro-4H-pyrrolo[3,4-cf]thiazol-2-yl)-2,2'-dimethyl-[1,r-biphenyl]-3-yl)amino)-1,7-naphthyridin-3-yl)methyl)pyrrolidine-3-carboxylic acid;

2-((i?)-3-hydroxypyrrolidin-1-yl)-l-(2-(3'-(5-(dimethylglycyl)-5,6-dihydro-4,6-dihydro-5H-pyrrolo[3,4-cf]thiazol-5-yl)ethan-1-one);
2-(8-((2-chloro-3’-(5-(dimethylglycyl)-5,6-dihydro-4H-pyrrolo[3,4-cf|thiazol-2-yl)-2’-methyl-1,1’-biphenyl-3-yl)amino)-1,7-naphthyridin-3-yl)methyl)pyrrolidin-3-yl)acetic acid;  
(i?)-(1-((8-(2-chloro-3’-(5-(2-(ethyl(methyl)amino)acetyl)-5,6-dihydro-4H-pyrrolo[3,4-d]thiazol-2-yl)-2’-methylbiphenyl-3-ylamino)-1,7-naphthyridin-3-yl)methyl)pyrrolidin-3-yl)acetic acid;  
2-(8-(2-chloro-3’-(5-(2-(ethyl(methyl)amino)acetyl)-5,6-dihydro-4H-pyrrolo[3,4-d]thiazol-2-yl)-2’-methylbiphenyl-3-ylamino)-1,7-naphthyridin-3-yl)methyl)pyrrolidin-3-yl)acetic acid;  
(i?)-(1-((8-(2-chloro-3’-(5-(2-((i?)-3-hydroxypyrrolidin-1-yl)acetyl)-5,6-dihydro-4H-pyrrolo[3,4-d]thiazol-2-yl)-2’-methylbiphenyl-3-ylamino)-1,7-naphthyridin-3-yl)methyl)pyrrolidin-3-yl)acetic acid;  
(i?)-(1-((8-(2-chloro-3’-(5-(2-((i?)-3-hydroxypyrrolidin-1-yl)acetyl)-5,6-dihydro-4H-pyrrolo[3,4-d]thiazol-2-yl)-2’-methylbiphenyl-3-ylamino)-1,7-naphthyridin-3-yl)methyl)pyrrolidin-3-yl)acetic acid;  
(i?)-(1-((8-(2-chloro-3’-(5-((S)-3-hydroxyazetidin-1-yl)acetyl)-5,6-dihydro-4H-pyrrolo[3,4-d]thiazol-2-yl)-2’-methylbiphenyl-3-ylamino)-1,7-naphthyridin-3-yl)methyl)pyrrolidin-3-yl)acetic acid;  
(i?)-(1-((8-(2-chloro-3’-(5-((S)-3-hydroxyazetidin-1-yl)acetyl)-5,6-dihydro-4H-pyrrolo[3,4-d]thiazol-2-yl)-2’-methylbiphenyl-3-ylamino)-1,7-naphthyridin-3-yl)methyl)pyrrolidin-3-yl)acetic acid; and  
Cis-4-((2-(3’-(3-((R)-3-hydroxyazetidin-1-yl)methyl)-1,7-naphthyridin-8-ylamino)2,2’-dimethylbiphenyl-3-ylcarbamoyl)-1-methyl-6,7-dihydro-1H-imidazo[4,5-c]pyridin-5(4H)-yl)methyl)cyclohexanecarboxylic acid; or a pharmaceutically acceptable salt or a stereoisomer thereof.

56. The compound of any one of claims 1-7, or a pharmaceutically acceptable salt or a stereoisomer thereof, wherein:

ring A is 5- to 10-membered heteroaryl, 4- to 11-membered heterocycloalkyl, or C_{6-10} aryl, wherein the 5- to 10-membered heteroaryl and 4- to 11-membered heterocycloalkyl each has 1-4 heteroatoms as ring members selected from N, O and S, wherein the N or S atom as ring members is optionally oxidized and one or more carbon atoms as ring members are each optionally replaced by a carbonyl group; and wherein ring A is optionally substituted with 1, 2 or 3 R^6 substituents;
L is a bond, -C(0)NR\textsubscript{13}, -NR\textsubscript{13}C(0)-, -(CR\textsubscript{14}R\textsubscript{15})\textsubscript{0}-, -O(CR\textsubscript{14}R\textsubscript{15})\textsubscript{0}, -0(CR\textsubscript{14}R\textsubscript{15})\textsubscript{0}, -NR\textsubscript{13}, or CH=CH-;

X is N or CR\textsubscript{17}, wherein R\textsubscript{17} is H, Ci-4 alkyl, Ci-4 alkoxy, Ci-4 haloalkyl, Ci-4 haloalkoxy, CN, halo, or OH, wherein the Ci-4 alkyl and Ci-4 alkoxy are each optionally substituted with 1 or 2 substituents independently selected from CN, halo and -(C(0)NH\textsubscript{2});

one of R\textsubscript{1} and R\textsubscript{2} is -(CR\textsubscript{9}R\textsubscript{8})\textsubscript{p}-NR\textsubscript{10}R\textsubscript{11} and the other is H, Ci M alkyl, Ci M alkoxy, Ci M haloalkyl, Ci M haloalkoxy, CN, halo, or OH, wherein the Ci M alkyl and Ci M alkoxy of R\textsubscript{1} or R\textsubscript{2} is optionally substituted with 1 or 2 substituents independently selected from Ci M alkoxy, Ci M haloalkyl, Ci M haloalkoxy, CN, halo, and OH;

R\textsubscript{3} is methyl, halo, CN or Ci M haloalkyl;

R\textsubscript{4} is Ci-4 alkyl, Ci-4 alkoxy, or Ci M haloalkyl;

R\textsubscript{5} is Ci-4 alkyl, Ci M alkoxy, Ci M haloalkyl, Ci M haloalkoxy, CN, halo, or OH;

each R\textsubscript{6} is independently selected from H, halo, Ci-6 alkyl, C\textsubscript{2}6 alkkenyl, C\textsubscript{2}6 alkynyl, Ci-6 haloalkyl, C\textsubscript{16}haloalkoxy, 5-14 membered heteroaryl, 4-10 membered heterocycloalkyl, (5-14 membered heteroaryl)-Ci-4 alkyl-, (4-10 membered heterocycloalkyl)-Ci-4 alkyl-, CN, NO\textsubscript{2}, OR\textsubscript{a}, C(OR\textsubscript{a})\textsubscript{a}, C(0)NR\textsubscript{a} R\textsubscript{a}, C(0)OR\textsubscript{a}, OC(0)R\textsubscript{a}, OC(0)NR\textsubscript{a} R\textsubscript{a}, NHR\textsubscript{a}, NR\textsubscript{a} R\textsubscript{a}, NR\textsubscript{a}C(0)R\textsubscript{a}, or NR\textsubscript{a}C(0)OR\textsubscript{a}, wherein the Ci-e alkyl, C\textsubscript{2}6 alkkenyl, C\textsubscript{2}6 alkynyl, 5-14 membered heteroaryl, 4-10 membered heterocycloalkyl, (5-14 membered heteroaryl)-Ci-4 alkyl- and (4-10 membered heterocycloalkyl)-Ci-4 alkyl- of R\textsubscript{6} are each optionally substituted with 1, 2, or 3 R\textsubscript{b} substituents;

R\textsubscript{7} is H, Ci-4 alkyl, Ci M alkoxy, Ci M haloalkyl, Ci M haloalkoxy, CN, halo, or OH;

R\textsubscript{8} and R\textsubscript{9} are each independently selected from H, halo, CN, OH, -COOH, Ci M alkyl, Ci-4 alkoxy, -NH Ci-4 alkyl, -N(Ci M alkyl)\textsubscript{2}, and Ci-4 haloalkyl;

R\textsubscript{10} and R\textsubscript{11} are each independently selected from H, Ci-6 alkyl, Ci-6 haloalkyl, -(C(0)R\textsubscript{a})\textsubscript{a}, -C(0)OR\textsubscript{a}, and -(C(0)NR\textsubscript{a} R\textsubscript{a}), wherein the Ci-e alkyl and Ci-e haloalkyl of R\textsubscript{10} or R\textsubscript{11} are each optionally substituted with 1 or 2 independently selected R\textsubscript{f} substituents;

or R\textsubscript{10} and R\textsubscript{11} taken together with the nitrogen atom to which they are attached form 4-, 5-, 6- or 7-membered heterocycloalkyl, wherein the 4-, 5-, 6- or 7-membered heterocycloalkyl is optionally substituted with 1, 2 or 3 R\textsubscript{b} substituents;

R\textsubscript{12} is H, Ci M alkyl, Ci M alkoxy, Ci M haloalkyl, Ci M haloalkoxy, CN, halo, or OH;

each R\textsubscript{13} is independently H, Ci-6 haloalkyl or Ci-6 alkyl;

R\textsubscript{14} and R\textsubscript{15} are each independently selected from H, halo, or Ci M alkyl;

each R\textsubscript{a} is independently selected from H, CN, Ci-6 alkyl, C\textsubscript{14}haloalkyl, C\textsubscript{2}6 alkkenyl, C\textsubscript{2}6 alkynyl, (5-14 membered heteroaryl)-Ci-4 alkyl-, and (4-14 membered heterocycloalkyl)-Ci-4 alkyl-, wherein the Ci-6 alkyl, C\textsubscript{2}6 alkkenyl, C\textsubscript{2}6 alkynyl, (5-14 membered heteroaryl)-Ci-4 alkyl-
and (4-14 membered heterocycloalkyl)-Ci-4 alkyl- of R^a are each optionally substituted with 1, 2, 3 or independently selected R^d substituents;

each R^d is independently selected from Ci-6 alkyl, Ci-6 haloalkyl, halo, CN, NH2, OR^e, C(0)R^e, C(0)NR^e, C(0)OR^e, OC(0)R^e, OC(0)NR(0)R^e, NHR^e, NR^eR^e, and NR^eC(0)R^e;
each R^e is independently selected from H, Ci-6 alkyl, Ci-6 haloalkyl, C2-6 alkenyl, and C2-6 alkynyl;
each R^b substituent is independently selected from halo, Ci-6 alkyl, Ci-6 haloalkyl, Ci-6 haloalkoxy, CN, OH, NH2, NO2, OR^e, C(0)R^e, C(0)NR^e, C(0)OR^e, OC(0)R^e, OC(0)NR(0)R^e, C(=NR)^eNR^e, NR^eC(=NR)^eNR^e, NHR^e, NR^eR^e, NR^eC(0)R^e, and NR^eC(0)OR^e; wherein the Ci-4 alkyl, Ci-4 haloalkyl, and Ci-4 haloalkoxy of R^b are each further optionally substituted with 1 or 2 independently selected R^d substituents;
each R^f is independently selected from H, Ci-6 alkyl, Ci-4 haloalkyl, C2-6 alkenyl, C2-6 alkynyl, C6-10 aryl, C3-10 cycloalkyl, C6-10 aryl-Ci-4 alkyl-, and C3-10 cycloalkyl-Ci-4 alkyl-, wherein the Ci-6 alkyl, C2-6 alkenyl, C2-6 alkynyl, C6-10 aryl, C3-10 cycloalkyl, C6-10 aryl-Ci-4 alkyl-, and C3-10 cycloalkyl-Ci-4 alkyl- of R^f are each optionally substituted with 1, 2, or 3 R^i substituents;
each R^i is independently selected from C1-4 alkyl, C1-4 haloalkyl, C2-6 alkenyl, C2-6 alkynyl, halo, CN, OR^e, C(0)R^e, C(0)NR^eR^e, C(0)OR^e, OC(0)Rg, OC(0)NRgRg, NHR^e, NR^eR^e, NR^eC(0)Rg, and NRgC(0)OR^e;
each R^g is independently selected from H, Ci-6 alkyl, Ci-4 haloalkyl, C2-6 alkenyl, and C2-6 alkynyl; each R^h is independently selected from Ci-6 alkyl, Ci-6 haloalkyl, Ci-6 haloalkoxy, C2-6 alkenyl, C2-6 alkynyl, halo, CN, OR^i, C^0R^i, C(0)NR^iR^i, C(0)OR^i, OC(0)R^i, OC(0)NR^iR^i, NHR^i, NR^iR^i, NR^iO); and NRC(0)OR^i, wherein the Ci-e alkyl, C2-6 alkenyl, and C2-6 alkynyl of R^h are each further optionally substituted by 1, 2, or 3 R^i substituents; each R^i is independently selected from C2-4 alkenyl, C2-4 alkynyl, halo, C1-4 alkyl, C1-4 haloalkyl, and CN; or any two R^e substituents together with the nitrogen atom to which they are attached form a 4-, 5-, 6-, or 7-membered heterocycloalkyl group optionally substituted with 1, 2, or 3 independently selected R^h substituents;
each R^j is independently selected from H, C1-4 alkyl, Ci-6 haloalkyl, Ci-6 haloalkoxy, C2-4 alkenyl, and C2-4 alkynyl; the subscript m is an integer of 0, 1, or 2; the subscript n is an integer of 0, 1, or 2; and the subscript p is an integer of 1, 2, or 3.
57. The compound of any one of claims 1-7, or a pharmaceutically acceptable salt or a stereoisomer thereof, wherein:

    ring A is 5- to 10-membered heteroaryl or 4- to 11-membered heterocycloalkyl, wherein the 5- to 10-membered heteroaryl and 4- to 11-membered heterocycloalkyl each has 1-4 heteroatoms as ring members selected from N, O and S, wherein the N or S atom as ring members is optionally oxidized and one or more carbon atoms as ring members are each optionally replaced by a carbonyl group; and wherein ring A is optionally substituted with 1, 2 or 3 R^6 substituents;

    L is a bond, -C(0)NR^{13}, -NR^{13}C(0)-, -NR^{13}, or CH=CH-;

    X is N or CR^{17}, wherein R^{17} is H, Ci-4 alkyl, Ci-4 alkoxy, Ci-4 haloalkyl, Ci-4 haloalkoxy, CN, halo, or OH, wherein the Ci-4 alkyl and Ci-4 alkoxy are each optionally substituted with 1 or 2 substituents independently selected from CN, halo and -C(0)NH2;

    one of R^1 and R^2 is -(CR^8R^9)p-NR^{10}R^{11} and the other is H, CM alkyl, CM alkoxy, CM haloalkyl, Ci-4 haloalkoxy, CN, halo, or OH, wherein the CM alkyl and Ci-4 alkoxy of R^1 or R^2 is optionally substituted with 1 or 2 substituents independently selected from CN, halo, and OH;

    R^3 is methyl, halo, CN or Ci-4 haloalkyl;

    R^4 is Ci-4 alkyl, Ci-4 alkoxy, or CM haloalkyl;

    R^5 is Ci-4 alkyl, Ci-4 alkoxy, CM haloalkyl, Ci-4 haloalkoxy, CN, halo, or OH;

    each R^6 is independently selected from H, halo, Ci-6 alkyl, C_{26} alkenyl, C_{26} alkynyl, Ci-6 haloalkyl, C_{14} haloalkoxy, 5-14 membered heteroaryl, 4-10 membered heterocycloalkyl, (5-14 membered heteroaryl)-Ci-4 alkyl-, (4-10 membered heterocycloalkyl)-Ci-4 alkyl-, CN, NO2, OR^a, C(0)R^a, C(0)NR^a, C(0)OR^a, OC(0)R^a, OC(0)NR^a, R^a, NR^aR^a, NR^aC(0)R^a, or NR^aC(0)OR^a, wherein the Ci-e alkyl, C_{26} alkenyl, C_{26} alkynyl, 5-14 membered heteroaryl, 4-10 membered heterocycloalkyl, (5-14 membered heteroaryl)-Ci-4 alkyl- and (4-10 membered heterocycloalkyl)-Ci-4 alkyl- of R^6 are each optionally substituted with 1, 2, or 3 R^b substituents;

    R^7 is H, Ci-4 alkyl, CM alkoxy, C_{14} haloalkyl, CM haloalkoxy, CN, halo, or OH;

    R^8 and R^9 are each independently selected from H, halo, CN, OH, -COOH, CM alkyl, Ci-4 alkoxy, -NHCl-4 alkyl, -N(CM alkyl)_2, and Ci-4 haloalkyl;

    R^{10} and R^{11} are each independently selected from H, Ci-6 alkyl, Ci-6 haloalkyl, -C(0)R^a, -C(0)OR^a, and -C(0)NR^aR^a, wherein the Ci-e alkyl and Ci-e haloalkyl of R^{10} or R^{11} are each optionally substituted with 1 or 2 independently selected R^f substituents;
or R^{10} and R^{11} taken together with the nitrogen atom to which they are attached form 4-, 5-, 6- or 7-membered heterocycloalkyl, wherein the 4-, 5-, 6- or 7-membered heterocycloalkyl is optionally substituted with 1, 2 or 3 R^{h} substituents;

R^{12} is H, C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} haloalkoxy, C_{1-4} haloalkoxy, CN, halo, or OH;

each R^{13} is independently H, C_{1-6} haloalkyl or C_{1-6} alkyl;

each R^{a} is independently selected from H, CN, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl;

each R^{d} is independently selected from C_{1-6} alkyl, C_{1-6} haloalkyl, halo, CN, NH_{2}, OR^{e}, C(O)R^{e}, C(O)NR^{e}, C(O)OR^{e}, OC(O)R^{e}, OC(O)NR^{e}, NHR^{e}, NR^{e}R^{e}, and NR^{e}C(O)R^{e};

each R^{e} is independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl;

each R^{b} substituent is independently selected from halo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, CN, OH, NH_{2}, NO_{2}, OR^{e}, C(O)R^{e}, C(O)NR^{e}, C(O)OR^{e}, OC(O)R^{e}, OC(O)NR^{e}, C(=NR^{e})NR^{e}R^{e}, NR^{e}C(=NR^{e})NR^{e}R^{e}, NHR^{e}, NR^{e}R^{e}, NR^{e}C(O)R^{e}, and NR^{e}C(O)OR^{e}; wherein the C_{1-4} alkyl, C_{1-4} haloalkyl, and C_{1-4} haloalkoxy of R^{b} are each further optionally substituted with 1 or 2 independently selected R^{d} substituents;

each R^{c} is independently selected from H, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, C_{6-10} aryl-C_{1-4} alkyl-, and C_{3-10} cycloalkyl-C_{1-4} alkyl-, wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, C_{6-10} aryl-C_{1-4} alkyl-, and C_{3-10} cycloalkyl-C_{1-4} alkyl- of R^{c} are each optionally substituted with 1, 2, or 3 R^{f} substituents;

each R^{f} is independently selected from C_{1-4} alkyl, C_{1-4} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, halo, CN, OR^{e}, C(O)R^{e}, C(O)NR^{e}, C(O)OR^{e}, OC(O)R^{e}, OC(O)NR^{e}, NHR^{e}, NR^{e}R^{e}, NR^{e}C(O)R^{e}, and NR^{e}C(O)OR^{e};

each R^{g} is independently selected from H, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl;

each R^{h} is independently selected from C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{2-6} alkenyl, C_{2-6} alkynyl, halo, CN, OR^{e}, C(=NR^{e})R^{e}, C(O)NR^{e}, C(O)OR^{e}, OC(O)R^{e}, OC(O)NR^{e}, NHR^{e}, NR^{e}R^{e}, NR^{e}C(O)R^{e}, and NR^{e}C(O)OR^{e}; wherein the C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl of R^{h} are each further optionally substituted by 1, 2, or 3 R^{f} substituents;

each R^{i} is independently selected from C_{2-4} alkenyl, C_{2-4} alkynyl, halo, C_{1-4} alkyl, C_{1-4} haloalkyl, and CN;

or any two R^{e} substituents together with the nitrogen atom to which they are attached form a 4-, 5-, 6-, or 7-membered heterocycloalkyl group optionally substituted with 1, 2, or 3 independently selected R^{h} substituents;
each \( R^1 \) is independently selected from \( \text{H, C}1-4 \text{ alkyl, C}1-6 \text{ haloalkyl, C}1-6 \text{ haloalkoxy, C}2-4 \text{ alkenyl, and C}2-4 \text{ alkylnyl;}
\)

the subscript \( m \) is an integer of 0, 1, or 2;

the subscript \( n \) is an integer of 0, 1, or 2; and

the subscript \( p \) is an integer of 1, 2, or 3.

58. The compound of any one of claims 1-7, or a pharmaceutically acceptable salt or a stereoisomer thereof, wherein:

- ring \( A \) is 5- to 10-membered heteroaryl or 4- to 11-membered heterocycloalkyl, wherein the 5- to 10-membered heteroaryl and 4- to 11-membered heterocycloalkyl each has 1-4 heteroatoms as ring members selected from N, O and S, wherein the N or S atom as ring members is optionally oxidized and one or more carbon atoms as ring members are each optionally replaced by a carbonyl group; and wherein ring \( A \) is optionally substituted with 1, 2 or 3 \( R^6 \) substituents;

- \( L \) is a bond, \( -\text{C(=O)}\text{NR}^{13}, -\text{NR}^{13}, \) or \( -\text{NR}^{13}\text{C(=O)}; \)
- \( X \) is \( \text{CR}^{17}, \) wherein \( R^{17} \) is \( \text{H} \) or \( \text{C}m \) alkyl;
- one of \( R^1 \) and \( R^2 \) is \( -(\text{CR}^5\text{R}^9)_p\text{-NR}^{10}\text{R}^{11} \) and the other is \( \text{H, C}m \text{ alkyl, or C}m \text{ alkoxy;}
- \( R^3 \) is methyl, or halo;
- \( R^4 \) is \( \text{C}1-4 \text{ alkyl or C}1-4 \text{ alkoxy;}
- \( R^5 \) is \( \text{C}1-4 \text{ alkyl, C}1-4 \text{ alkoxy, or halo;}
- each \( R^6 \) is independently selected from \( \text{H, halo, C}1-6 \text{ alkyl, C}2-6 \text{ alkenyl, C}2-6 \text{ alkynyl, 5-14 membered heteroaryl, 4-10 membered heterocycloalkyl, (5-14 membered heteroaryl)-C}4 \text{ alkyl,}
\)

and (4-10 membered heterocycloalkyl)-C4 alkyl-, wherein the C1-6 alkyl, C2-6 alkenyl, C2-6 alkynyl, 5-14 membered heteroaryl, 4-10 membered heterocycloalkyl, (5-14 membered heteroaryl)-C4 alkyl- and (4-10 membered heterocycloalkyl)-C4 alkyl- of \( R^6 \) are each optionally substituted with 1, 2, or 3 \( R^b \) substituents;

- \( R^7 \) is \( \text{H or C}1-4 \text{ alkyl;}
- \( R^8 \) and \( R^9 \) are each independently selected from \( \text{H and C}1-4 \text{ alkyl;}
- \( R^{10} \) and \( R^{11} \) are each independently selected from \( \text{H and C}1-6 \text{ alkyl optionally substituted with 1 or 2 independently selected R}^f \text{ substituents;}
\)

or \( R^{10} \) and \( R^{11} \) taken together with the nitrogen atom to which they are attached form 4-, 5-, 6- or 7-membered heterocycloalkyl, wherein the 4-, 5-, 6- or 7-membered heterocycloalkyl is optionally substituted with 1, 2 or 3 \( R^b \) substituents;

- \( R^{12} \) is \( \text{H or C}m \text{ alkyl;}

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each R_{13} is independently H or C1-6 alkyl;
each R_b substituent is independently selected from halo, C1-6 alkyl, OH, NH2, C(0)OR, NHR, and NR_2R_c;
each R_c is independently selected from H, C1-6 alkyl, C2-6 alkenyl, C2-6 alkynyl, C3-10 cycloalkyl, and C3-10 cycloalkyl-C1-4 alkyl-, wherein the C1-6 alkyl, C2-6 alkenyl, C2-6 alkynyl, C3-10 cycloalkyl, and C3-10 cycloalkyl-C1-4 alkyl- of R_c are each optionally substituted with 1 or 2 R_f substituents;
each R_f is independently selected from C1-4 alkyl, C2-6 alkenyl, C2-6 alkynyl, halo, OR_g, and C(0)OR_g;
each R_g is independently selected from H and C1-6 alkyl;
each R_h is independently selected from C1-6 alkyl, C2-6 alkenyl, C2-6 alkynyl, halo, CN, OR_l, and 0(0)O_{0a};
or any two R_c substituents together with the nitrogen atom to which they are attached form a 4-, 5-, 6-, or 7-membered heterocycloalkyl group optionally substituted with 1, 2, or 3 independently selected R_h substituents;
each R_i is independently selected from H and C1-4 alkyl;
the subscript m is an integer of 0 or 1;
the subscript n is an integer of 0 or 1; and
the subscript p is an integer of 1 or 2.

59. The compound of any one of claims 1-7, or a pharmaceutically acceptable salt or a stereoisomer thereof, wherein:

ring A is 5- to 10-membered heteroaryl, wherein the 5- to 10-membered heteroaryl has 1-4 heteroatoms as ring members selected from N, O and S, wherein the N or S atom as ring members is optionally oxidized and one or more carbon atoms as ring members are each optionally replaced by a carbonyl group; and wherein ring A is optionally substituted with 1 or 2 R_6 substituents;

L is a bond, -C(0)NR_{13}^-, -NR_{13}^-, or -NR_{13}^3C(0)-;
X is CR_{17}^-, wherein R_{17} is H;
one of R^1 and R^2 is -(CR_{8}R_{9})_p-NR_{10}R_{11}^4 and the other is H;
R^3 is methyl, or halo;
R^4 is C1-4 alkyl or C1-4 alkoxy;
R^5 is C1-4 alkyl or halo;
each $R^6$ is independently selected from H, Ci-6 alkyl, and (4-10 membered heterocycloalkyl)-Ci-4 alkyl-, wherein the Ci-6 alkyl and (4-10 membered heterocycloalkyl)-Ci-4 alkyl- of $R^6$ are each optionally substituted with 1 or 2 $R^b$ substituents;

$R^7$ is H;

$R^8$ and $R^9$ are each independently selected from H and Ci-4 alkyl;

$R^{10}$ and $R^{11}$ are each independently selected from H and Ci-6 alkyl optionally substituted with 1 or 2 independently selected $R^f$ substituents;

or $R^{10}$ and $R^{11}$ taken together with the nitrogen atom to which they are attached form 4-, 5-, 6- or 7-membered heterocycloalkyl, wherein the 4-, 5-, 6- or 7-membered heterocycloalkyl is optionally substituted with 1, 2 or 3 $R^b$ substituents;

$R^{12}$ is H;

$R^{13}$ is H;

each $R^b$ substituent is independently selected from OH, C(0)OR', NHR', and NR'R';

each $R^c$ is independently selected from H, Ci-6 alkyl, and C$_3$-$C_{10}$ cycloalkyl, wherein the Ci-6 alkyl, and C$_3$-$C_{10}$ cycloalkyl of $R^c$ are each optionally substituted with 1 or 2 $R^f$ substituents;

each $R^f$ is independently selected from OR', C(0)OR';

$R^g$ is H;

each $R^h$ is independently selected from OR' and C(0)OR';

or any two $R^c$ substituents together with the nitrogen atom to which they are attached form a 4-, 5-, 6-, or 7-membered heterocycloalkyl group optionally substituted with 1, 2, or 3 independently selected $R^b$ substituents;

$R^i$ is H;

the subscript $m$ is an integer of 0 or 1;

the subscript $n$ is an integer of 0 or 1; and

the subscript $p$ is an integer of 1 or 2.

60. A pharmaceutical composition comprising a compound of any one of claims 1-59, or a pharmaceutically acceptable salt or a stereoisomer thereof, and one or more pharmaceutically acceptable excipient or carrier.

61. A method of inhibiting PD-1/PD-L1 interaction, said method comprising administering to a patient a compound of any one of claims 1-59, or a pharmaceutically acceptable salt or a stereoisomer thereof.
62. A method of treating a disease or disorder associated with inhibition of PD-1/PD-L1 interaction, said method comprising administering to a patient in need thereof a therapeutically effective amount of a compound of any one of claims 1-59, or a pharmaceutically acceptable salt or a stereoisomer thereof.

63. A method of enhancing, stimulating and/or increasing the immune response in a patient, said method comprising administering to the patient in need thereof a therapeutically effective amount of a compound of any one of claims 1-59, or a pharmaceutically acceptable salt or a stereoisomer thereof.
INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07D401/04 C07D519/00 A61P37/00 A61K31/519 A61K31/4375

ADD.

According to International Patent Classification (IPC) and to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category" Citation of document, with indication, where appropriate, of the relevant passages Relevant to claim No.


Date of the actual completion of the international search
15 March 2018

Date of mailing of the international search report
22/03/2018

Name and mailing address of the ISA:
European Patent Office, P.B. 5818 Patentliaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040,
Fax: (+31-70) 340-3016

Authorized officer
Marzi, Elena

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<td>WO 2017/112730 A1 (INCYTE CORP [US]) 29 June 2017 (2017-06-29) claims 1-32 page 1, lines 6-9 examples 1-13, 16-21</td>
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