Pyrazolopyridazinone Compound, and Pharmaceutical Composition and Use Thereof

TECHNICAL FIELD

The present application relates to a pyrazolopyridazinone compound, particularly a pyrazolopyridazinone derivative with HPK1 inhibitory activity.

BACKGROUND ART

Hematopoietic progenitor kinase 1 (HPK1), belonging to the mitogen-activated protein kinase kinase kinase kinase-4 (MAP4K) family, is a serine/threonine kinase originally cloned from hematopoietic progenitor cells (Hu, M. C. et al., Genes Dev. 1996; 10: 2251-2264; Keifer, F. et al, The EMBO Journal 1996; 15: 7013-7025). HPK1 is mainly distributed in lymphoid organs and lymphoid tissues, such as bone marrow, lymph nodes, thymus, etc., and is expressed predominantly in immune cells (T cells, B cells, dendritic cells, macrophages, etc.) (Hu, M.C. et al., Genes Dev. 1996; 10:2251-2264). This has drawn attention to the immunomodulatory role of HPK1.

Studies have shown that HPK1 is a negative regulator of the T cell receptor (TCR) signaling pathway. TCR signaling causes the activation of HPK1, and subsequently binding to SLP-76 protein (Lasserre, R. et al., J Cell Biol. 2011; 195: 839-853; Shui, J. et al., Nature Immuno. 2007; 8: 84-91). Activated HPK1 phosphorylates the Ser376 residue of SLP-76, promoting the binding of SLP-76 to 14-3-3 protein (Di Bartolo, V. et al., J. Exp. Med. 2007; 204: 681-691; Shui, J. et al, Nature Immuno. 2007; 8: 84-91). The SLP-76/14-3-3 interaction downregulates ERK signaling and calcium flux, and triggers the ubiquitination of SLP-76. The degradation of the SLP-76 complex blocks the TCR activation pathway consequently, thereby inhibiting T cell function (Lasserre, R. et al, J. Cell Biol. 2011; 195: 839-853).

In in vivo experiments, HPK1 knockout mice showed enhanced T cell function under antigen stimulation and produced more cytokines, such as IL-2 and IFN-γ (Shui, J. et al., Nature Immuno. 2007; 8: 84- 91; Alzabin, S. et al, J. Immunol. 2009; 182: 6187-6194; Alzabin, S. et al, Cancer Immunol. Immunother. 2010; 59: 419-429). Further studies demonstrated that the kinase activity of HPK1 plays a key role in the negative regulation of immune cells. Compared with wild-type mice, mice with blockade of the kinase activity of HPK1 showed enhanced CD8+ T cell function, faster clearance of chronic lymphocytic meningitis virus, and better inhibition of tumor growth (Hernandez, S. et al., Cell Reports 2018; 25: 80-94). In Lewis lung cancer (LLC) model, mice transfected with $HPK1^{-/-}$ T cells exhibited stronger antitumor immune responses than wild-type (Sawasdikosol, S. et al., Immunol. Res. 2012; 54: 262-265). Similar studies revealed that the immunosuppressive effects of HPK1 on B cells (Sauer, K. et al., J. Biol. Chem. 2001; 276: 45207-45216; Tsuji, S. et al., J. Exp. Med. 2001; 194: 529-539; Wang, X. et al, J. Biol. Chem. 2012; 287: 34091-34100; Königsberger, S. et al, PLos One, 2010; 5: e12468), dendritic cells (Alzabin, S. et al, J. Immunol. 2009; 182: 6187-6194), NK cells and Treg cells are also derived from its kinase activity (Liu, J. et al., PLos One, 2019; 14: e0212670).

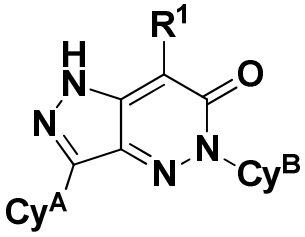
Clinical studies have found that, comparing with health controls, the HPK1 levels were significantly downregulated in tissues from patients of systemic lupus erythematosus (Zhang, Q. et al, J. Autoimmun., 2011; 37: 180-189) and psoriatic arthritis (Stoeckman, A. K. et al, Genes Immun 2006; 7: 583-591; Baltiwalla, F. M. et al., Mol. Med. 2005; 11: 21-29), suggesting that HPK1 downregulation contributes to the enhancement of autoimmune responses. On the other hand, upregulation of HPK1 levels has been observed in various cancers, such as acute myeloid leukemia (Chen-Deutsch, X. et al., Leuk. Res. 2012; 36: 884-888; Chen-Deutsch, X. et al., Cell Cycle 2012; 11: 1364-1373), bladder urothelial carcinoma (Wang. Y et al, Mol. Med. Rep. 2012; 5: 260-265), extramammary Paget's disease (Qian, Y et al, Am J. Dermatopathol. 2011; 33: 681-

686) and colon cancer (Yang, H.S. et al., Mol. Cell Biol. 2006; 26: 1297-1306).

Therefore, HPK1 is a potential target for the treatment of tumors and viral diseases. The development of small-molecule inhibitors of HPK1 kinase holds important clinical promise. Although some patent applications for small molecule HPK1 inhibitors have been published, such as WO2018049191, WO2018049200, WO2018102366, WO2018183964, WO2019090198, WO2019206049, WO2019238067 and WO2020092528, no drug targeting HPK1 has been approved yet. Therefore, the development of novel small-molecule HPK1 inhibitors with good activity is still an urgent need.

SUMMARY

A main purpose of this application is to provide a compound of formula (I), or a pharmaceutically acceptable salt, hydrate, solvate, active metabolite, polymorph, isotope labeled compound, isomer or prodrug thereof,



(I)

wherein, R^1 is selected from:

1) hydrogen, halogen, cyano, -C(=O)NR^aR^b, -OR^a and -NR^aR^b;

2) C_{1-6} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{3-8} cycloalkyl and 3- to 8-membered aliphatic heterocyclyl, unsubstituted or optionally substituted with 1, 2, 3 or 4 substituents independently selected from R^{11};

R^a and R^b are each independently selected from:

1) hydrogen;

2) C_{1-6} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{3-6} monocyclic cycloalkyl, and 3- to 6-membered aliphatic monocyclic heterocyclyl, unsubstituted or optionally substituted with 1, 2, or 3 substituents independently selected from R^{11}; or

R^a and R^b attached to the same nitrogen atom, together with the nitrogen atom, form a 3-6 membered aliphatic monocyclic heterocyclyl unsubstituted or optionally substituted with 1, 2 or 3 substituents independently selected from R^{11};

R^{11} is selected from fluorine, chlorine, C_{1-3} alkyl and hydroxyl;

Cy^A is selected from 6- to 10-membered aryl or 5- to 10-membered heteroaryl, unsubstituted or optionally substituted with 1, 2, 3, 4 or 5 substituents independently selected from R^{12};

R^{12} is selected from:

1) oxo, halogen, cyano, -C(=O)R^{a2}, -C(=O)OR^{a2}, -C(=O)$NR^{a2}R^{b2}$, -C(=NR^{d2})$NR^{a2}R^{b2}$, -OR^{a2}, -OC(=O)R^{a2}, -OC(=O)OR^{c2}, -OC(=O)$NR^{a2}R^{b2}$, -SR^{a2}, -S(=O)R^{c2}, -$S(=O)_2R^{c2}$, sulfonic acid group, -S(=O)$NR^{a2}R^{b2}$, -$S(=O)_2NR^{a2}R^{b2}$, -S(=O)(=NR^{d2})R^{c2}, -$NR^{a2}R^{b2}$, -NR^{a2}C(=O)R^{b2}, -NR^{a2}C(=O)OR^{c2}, -NR^{e2}C(=O)$NR^{a2}R^{b2}$, -NR^{e2}C(=NR^{d2})$NR^{a2}R^{b2}$, -NR^{a2}S(=O)$_2R^{c2}$, -$NR^{e2}S(=O)_2NR^{a2}R^{b2}$, nitro, -$PR^{c2}R^{f2}$, -P(=O)$R^{c2}R^{f2}$ and phosphonic acid group;

2) C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 6- to 10-membered aryl, 5- to 10-membered heteroaryl, C_{3-12} cycloalkyl and 3- to 12-membered aliphatic heterocyclyl, unsubstituted or optionally substituted with 1, 2, 3, 4, 5 or 6 substituents independently selected from R^{22};

3) the two R^{12} substituents attached to two adjacent ring-forming atoms on the aryl or heteroaryl group of Cy^A respectively, together with the two said ring-forming atoms, form a C_{5-12} alicyclyl or a 5- to 12-membered aliphatic heterocyclyl, unsubstituted or optionally substituted

by 1, 2, 3, 4, 5 or 6 substituents independently selected from R^{22};

R^{a2}, R^{b2} and R^{e2} are each independently selected from:

1) hydrogen;

2) C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, phenyl, 5-6 membered heteroaryl, C_{3-12} cycloalkyl and 3-12 membered aliphatic heterocyclyl, unsubstituted or optionally substituted with 1, 2, 3, 4, 5 or 6 substituents independently selected from R^{22};

or,

R^{a2} and R^{b2} attached to the same nitrogen atom, together with the nitrogen, form a 3--12 membered aliphatic heterocyclyl, unsubstituted or optionally substituted with 1, 2, 3, 4 or 5 substituents independently selected from R^{22};

R^{c2} and R^{f2} are each independently selected from the group consisting of C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, phenyl, 5-6 membered heteroaryl, C_{3-12} cycloalkyl and 3--12 membered aliphatic heterocyclyl, unsubstituted or optionally substituted with 1, 2, 3, 4 or 5 substituents independently selected from R^{22};

or,

R^{c2} and R^{f2} attached to the same phosphorous atom, together with the phosphorous, form a 3--12 membered aliphatic heterocyclyl, unsubstituted or optionally substituted with 1, 2, 3, 4 or 5 substituents independently selected from R^{22};

R^{d2} is selected from:

1) hydrogen, cyano, nitro and $-S(=O)_2R^G$;

2) C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, phenyl, 5--6 membered heteroaryl, C_{3-12} cycloalkyl and 3--12 membered aliphatic heterocyclyl, unsubstituted or optionally selected from 1, 2, 3, 4 or 5 substituents independently selected from R^{22};

R^{22} is selected from:

1) oxo, halogen, cyano, $-C(=O)R^{a4}$, $-C(=O)OR^{a4}$, $-C(=O)NR^{a4}R^{b4}$, $-C(=NR^{d4})NR^{a4}R^{b4}$, $-OR^{a4}$, $-OC(=O)R^{a4}$, $-OC(=O)OR^{c4}$, $-OC(=O)NR^{a4}R^{b4}$, $-SR^{a4}$, $-S(=O)R^{c4}$, $-S(=O)_2R^{c4}$, sulphonic acid group, $-S(=O)NR^{a4}R^{b4}$, $-S(=O)_2NR^{a4}R^{b4}$, $-S(=O)(=NR^{d4})R^{c4}$, $-NR^{a4}R^{b4}$, $-NR^{a4}C(=O)R^{b4}$, $-NR^{a4}C(=O)OR^{c4}$, $-NR^{e4}C(=O)NR^{a4}R^{b4}$, $-NR^{e4}C(=NR^{d4})NR^{a4}R^{b4}$, $-NR^{a4}S(=O)_2R^{c4}$, $-NR^{e4}S(=O)_2NR^{a4}R^{b4}$, nitro, $-PR^{c4}R^{f4}$, $-P(=O)R^{c4}R^{f4}$, phosphonic acid group and imino group ($=N-R^{d4}$);

2) C_{1-6} alkyl, C_{1-6} alkylene, C_{2-6} alkenyl, C_{2-6} alkynyl, phenyl, 5--6 membered heteroaryl, C_{3-10} cycloalkyl and 3--10 membered aliphatic heterocyclyl, unsubstituted or optionally substituted with 1, 2, 3, 4 or 5 substituents independently selected from R^{32};

R^{a4}, R^{b4} and R^{e4} are each independently selected from:

1) hydrogen;

2) C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, phenyl, 5--6 membered heteroaryl, C_{3-10} cycloalkyl and 3--10 membered aliphatic heterocyclyl, unsubstituted or optionally substituted with 1, 2, 3, 4 or 5 substituents independently selected from R^{32};

or,

R^{a4} and R^{b4} attached to the same nitrogen atom, together with the nitrogen, form a 3--10 membered aliphatic heterocyclyl, unsubstituted or optionally substituted with 1, 2, 3, 4 or 5 substituents independently selected from R^{32};

R^{c4} and R^{f4} are each independently selected from C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, phenyl, 5-6 membered heteroaryl, C_{3-10} cycloalkyl and 3-10 membered aliphatic heterocyclyl, unsubstituted or optionally substituted with 1, 2, 3, 4 or 5 substituents independently selected from R^{32};

or,

R^{c4} and R^{f4} attached to the same phosphorous atom, together with the phosphorous, form a 3-10 membered aliphatic heterocyclyl, unsubstituted or optionally substituted with 1, 2, 3, 4 or 5 substituents independently selected from R^{32};

R^{d4} is selected from:

1) hydrogen, cyano, nitro and $-S(=O)_2R^G$;

2) C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, phenyl, 5-6 membered heteroaryl, C_{3-10} cycloalkyl and 3-10 membered aliphatic heterocyclyl, unsubstituted or optionally substituted with 1, 2, 3, 4 or 5 substituents independently selected from R^{32};

R^{32} is selected from:

1) oxo, halogen, cyano, $-C(=O)R^{a6}$, $-C(=O)OR^{a6}$, $-C(=O)NR^{a6}R^{b6}$, $-C(=NR^{d6})NR^{a6}R^{b6}$, $-OR^{a6}$, $-OC(=O)R^{a6}$, $-OC(=O)OR^{c6}$, $-OC(=O)NR^{a6}R^{b6}$, $-SR^{a6}$, $-S(=O)R^{c6}$, $-S(=O)_2R^{c6}$, sulphonic acid group, $-S(=O)NR^{a6}R^{b6}$, $-S(=O)_2NR^{a6}R^{b6}$, $-S(=O)(=NR^{d6})R^{c6}$, $-NR^{a6}R^{b6}$, $-NR^{a6}C(=O)R^{b6}$, $-NR^{a6}C(=O)OR^{c6}$, $-NR^{e6}C(=O)NR^{a6}R^{b6}$, $-NR^{e6}C(=NR^{d6})NR^{a6}R^{b6}$, $-NR^{a6}S(=O)_2R^{c6}$, $-NR^{e6}S(=O)_2NR^{a6}R^{b6}$, nitro, $-PR^{c6}R^{f6}$, $-P(=O)R^{c6}R^{f6}$, phosphonic acid group and imino group (=N-R^{d6});

2) C_{1-4} alkyl, C_{1-4} alkylene, C_{2-4} alkenyl, C_{2-4} alkynyl, phenyl, 5-6 membered heteroaryl, C_{3-8} cycloalkyl and 3-8 membered aliphatic heterocyclyl, unsubstituted or optionally substituted with 1, 2, 3 or 4 substituents independently selected from R^G;

R^{a6}, R^{b6} and R^{e6} are each independently selected from:

1) hydrogen;

2) C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, phenyl, 5-6 membered heteroaryl, C_{3-8} cycloalkyl and 3-8 membered aliphatic heterocyclyl, unsubstituted or optionally substituted with 1, 2, 3 or 4 substituents independently selected from R^G;

or,

R^{a6} and R^{b6} attached to the same nitrogen atom, together with the nitrogen, form a 3-8 membered aliphatic heterocyclyl, unsubstituted or optionally substituted with 1, 2, 3 or 4 substituents independently selected from R^G;

R^{c6} and R^{f6} are each independently selected from C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, phenyl, 5-6 membered heteroaryl, C_{3-8} cycloalkyl and 3-8 membered aliphatic heterocyclyl, unsubstituted or optionally substituted with 1, 2, 3 or 4 substituents independently selected from R^G;

or,

R^{c6} and R^{f6} attached to the same phosphorous atom, together with the phosphorous, form a 3-8 membered aliphatic heterocyclyl, unsubstituted or optionally substituted with 1, 2, 3 or 4 substituents independently selected from R^G;

R^{d6} is selected from:

1) hydrogen, cyano, nitro and $-S(=O)_2R^G$;

2) C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, phenyl, 5-6 membered heteroaryl, C_{3-8} cycloalkyl, 3-8 membered aliphatic heterocyclyl, unsubstituted or optionally substituted with 1, 2, 3 or 4 substituents independently selected from R^G;

Cy^B is selected from 6-10 membered aryl or 5-10 membered heteroaryl, unsubstituted or optionally substituted with 1, 2, 3, 4 or 5 substituents independently selected from R^{13};

R^{13} is selected from:

1) oxo, halogen, cyano, $-C(=O)R^{a3}$, $-C(=O)OR^{a3}$, $-C(=O)NR^{a3}R^{b3}$, $-C(=NR^{d3})NR^{a3}R^{b3}$, $-OR^{a3}$, $-OC(=O)R^{a3}$, $-OC(=O)OR^{c3}$, $-OC(=O)NR^{a3}R^{b3}$, $-SR^{a3}$, $-S(=O)R^{c3}$, $-S(=O)_2R^{c3}$, sulphonic acid group, $-S(=O)NR^{a3}R^{b3}$, $-S(=O)_2NR^{a3}R^{b3}$, $-S(=O)(=NR^{d3})R^{c3}$, $-NR^{a3}R^{b3}$, $-NR^{a3}C(=O)R^{b3}$, $-NR^{a3}C(=O)OR^{c3}$, $-NR^{e3}C(=O)NR^{a3}R^{b3}$, $-NR^{e3}C(=NR^{d3})NR^{a3}R^{b3}$, $-NR^{a3}S(=O)_2R^{c3}$, $-NR^{e3}S(=O)_2NR^{a3}R^{b3}$, nitro, $-PR^{c3}R^{f3}$, $-P(=O)R^{c3}R^{f3}$ and phosphonic acid group ;

2) C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 6-10 membered aryl, 5-10 membered heteroaryl, C_{3-12} cycloalkyl and 3-12 membered aliphatic heterocyclyl, unsubstituted or optionally substituted with 1, 2, 3, 4, 5 or 6 substituents independently selected from R^{23};

3) two R^{13} attached to two adjacent ring-forming atoms on the aryl or heteroaryl group of Cy^B respectively, together with the two said ring-forming atoms form a C_{5-12} alicyclyl ring or a

5-12 membered aliphatic heterocyclyl, unsubstituted or optionally substituted with 1, 2, 3, 4 or 5 substituents independently selected from R^{23};

R^{a3}, R^{b3} and R^{e3} are each independently selected from:

1) hydrogen;

2) C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, phenyl, 5-6 membered heteroaryl, C_{3-12} cycloalkyl and 3-12 membered aliphatic heterocyclyl, unsubstituted or optionally substituted with 1, 2, 3, 4, 5 or 6 substituents independently selected from R^{23};

or,

R^{a3} and R^{b3} attached to the same nitrogen atom, together with the nitrogen, form a 3-12 membered aliphatic heterocyclyl, unsubstituted or optionally substituted with 1, 2, 3, 4 or 5 substituents independently selected from R^{23};

R^{c3} and R^{f3} are each independently selected from C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, phenyl, 5-6 membered heteroaryl, C_{3-12} cycloalkyl and 3-12 membered aliphatic heterocyclyl, unsubstituted or optionally substituted with 1, 2, 3, 4 or 5 substituents independently selected from R^{23};

or,

R^{c3} and R^{f3} attached to the same phosphorous atom, together with the phosphorous atom, form a 3-12 membered aliphatic heterocyclyl, unsubstituted or optionally substituted with 1, 2, 3, 4 or 5 substituents independently selected from R^{23};

R^{d3} selected from:

1) hydrogen, cyano, nitro and $S(=O)_2R^G$;

2) C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, phenyl, 5-6 membered heteroaryl, C_{3-12} cycloalkyl and 3-12 membered aliphatic heterocyclyl, unsubstituted or optionally substituted with 1, 2, 3, 4 or 5 substituents independently selected from R^{23};

R^{23} is selected from:

1) oxo, halogen, cyano, $-C(=O)R^{a5}$, $-C(=O)OR^{a5}$, $-C(=O)NR^{a5}R^{b5}$, $-C(=NR^{d5})NR^{a5}R^{b5}$, $-OR^{a5}$, $-OC(=O)R^{a5}$, $-OC(=O)OR^{c5}$, $-OC(=O)NR^{a5}R^{b5}$, $-SR^{a5}$, $-S(=O)R^{c5}$, $-S(=O)_2R^{c5}$, sulphonic acid group, $-S(=O)NR^{a5}R^{b5}$, $-S(=O)_2NR^{a5}R^{b5}$, $-S(=O)(=NR^{d5})R^{c5}$, $-NR^{a5}R^{b5}$, $-NR^{a5}C(=O)R^{b5}$, $-NR^{a5}C(=O)OR^{c5}$, $-NR^{e5}C(=O)NR^{a5}R^{b5}$, $-NR^{e5}C(=NR^{d5})NR^{a5}R^{b5}$, $-NR^{a5}S(=O)_2R^{c5}$, $-NR^{e5}S(=O)_2NR^{a5}R^{b5}$, nitro, $-PR^{c5}R^{f5}$, $-P(=O)R^{c5}R^{f5}$, phosphonic acid group and imino group ($=N-R^{d5}$);

2) C_{1-6} alkyl, C_{1-6} alkylene, C_{2-6} alkenyl, C_{2-6} alkynyl, phenyl, 5-6 membered heteroaryl, C_{3-10} cycloalkyl and 3-10 membered aliphatic heterocyclyl, unsubstituted or optionally substituted with 1, 2, 3, 4 or 5 substituents independently selected from R^{33};

R^{a5}, R^{b5} and R^{e5} are each independently selected from:

1) hydrogen;

2) C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, phenyl, 5-6 membered heteroaryl, C_{3-10} cycloalkyl and 3-10 membered aliphatic heterocyclyl, unsubstituted or optionally substituted with 1, 2, 3, 4 or 5 substituents independently selected from R^{33};

or,

R^{a5} and R^{b5} attached to the same nitrogen atom, together with the nitrogen atom, form a 3-10 membered aliphatic heterocyclyl, unsubstituted or optionally substituted with 1, 2, 3, 4 or 5 substituents independently selected from R^{33};

R^{c5} and R^{f5} are each independently selected from C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, phenyl, 5-6 membered heteroaryl, C_{3-10} cycloalkyl and 3-10 membered aliphatic heterocyclyl, unsubstituted or optionally substituted with 1, 2, 3, 4 or 5 substituents independently selected from R^{33};

or,

R^{c5} and R^{f5} attached to the same phosphorous atom, together with the phosphorous atom, form a 3-10 membered aliphatic heterocyclyl, unsubstituted or optionally substituted with 1, 2, 3,

4 or 5 substituents independently selected from R^{33};

R^{d5} is selected from:

1) hydrogen, cyano, nitro and $-S(=O)_2R^G$;

2) C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, phenyl, 5-6 membered heteroaryl, C_{3-10} cycloalkyl and 3-10 membered aliphatic heterocyclyl, unsubstituted or optionally substituted with 1, 2, 3, 4 or 5 substituents independently selected from R^{33};

R^{33} selected from:

1) oxo, halogen, cyano, $-C(=O)R^{a7}$, $-C(=O)OR^{a7}$, $-C(=O)NR^{a7}R^{b7}$, $-C(=NR^{d7})NR^{a7}R^{b7}$, $-OR^{a7}$, $-OC(=O)R^{a7}$, $-OC(=O)OR^{c7}$, $-OC(=O)NR^{a7}R^{b7}$, $-SR^{a7}$, $-S(=O)R^{c7}$, $-S(=O)_2R^{c7}$, sulphonic acid group, $-S(=O)NR^{a7}R^{b7}$, $-S(=O)_2NR^{a7}R^{b7}$, $-S(=O)(=NR^{d7})R^{c7}$, $-NR^{a7}R^{b7}$, $-NR^{a7}C(=O)R^{b7}$, $-NR^{a7}C(=O)OR^{c7}$, $-NR^{e7}C(=O)NR^{a7}R^{b7}$, $-NR^{e7}C(=NR^{d7})NR^{a7}R^{b7}$, $-NR^{a7}S(=O)_2R^{c7}$, $-NR^{e7}S(=O)_2NR^{a7}R^{b7}$, nitro, $-PR^{c7}R^{f7}$, $-P(=O)R^{c7}R^{f7}$, phosphonic acid group and imino group ($=N-R^{d7}$);

2) C_{1-4} alkyl, C_{1-4} alkylene, C_{2-4} alkenyl, C_{2-4} alkynyl, phenyl, 5-6 membered heteroaryl, C_{3-8} cycloalkyl and 3-8 membered aliphatic heterocyclyl, unsubstituted or optionally substituted with 1, 2, 3 or 4 substituents independently selected from R^G;

R^{a7}, R^{b7} and R^{e7} are each independently selected from:

1) hydrogen;

2) C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, phenyl, 5-6 membered heteroaryl, C_{3-8} cycloalkyl and 3-8 membered aliphatic heterocyclyl, unsubstituted or optionally substituted with 1, 2, 3 or 4 substituents independently selected from R^G;

or,

R^{a7} and R^{b7} attached to the same nitrogen atom, together with the nitrogen atom, form a 3-8 membered aliphatic heterocyclyl, unsubstituted or optionally substituted with 1, 2, 3 or 4 substituents independently selected from R^G;

R^{c7} and R^{f7} are each independently selected from C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, phenyl, 5-6 membered heteroaryl, C_{3-8} cycloalkyl and 3-8 membered aliphatic heterocyclyl, unsubstituted or optionally substituted with 1, 2, 3 or 4 substituents independently selected from R^G;

or,

R^{c7} and R^{f7} attached to the same phosphorous atom, together with the phosphorous atom, form a 3-8 membered aliphatic heterocyclyl, unsubstituted or optionally substituted with 1, 2, 3 or 4 substituents independently selected from R^G;

R^{d7} is selected from:

1) hydrogen, cyano, nitro and $-S(=O)_2R^G$;

2) C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, phenyl, 5-6 membered heteroaryl, C_{3-8} cycloalkyl and 3-8 membered aliphatic heterocyclyl, unsubstituted or optionally substituted with 1, 2, 3 or 4 substituents independently selected from R^G;

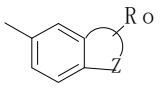
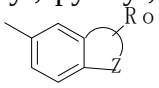
R^G is selected from:

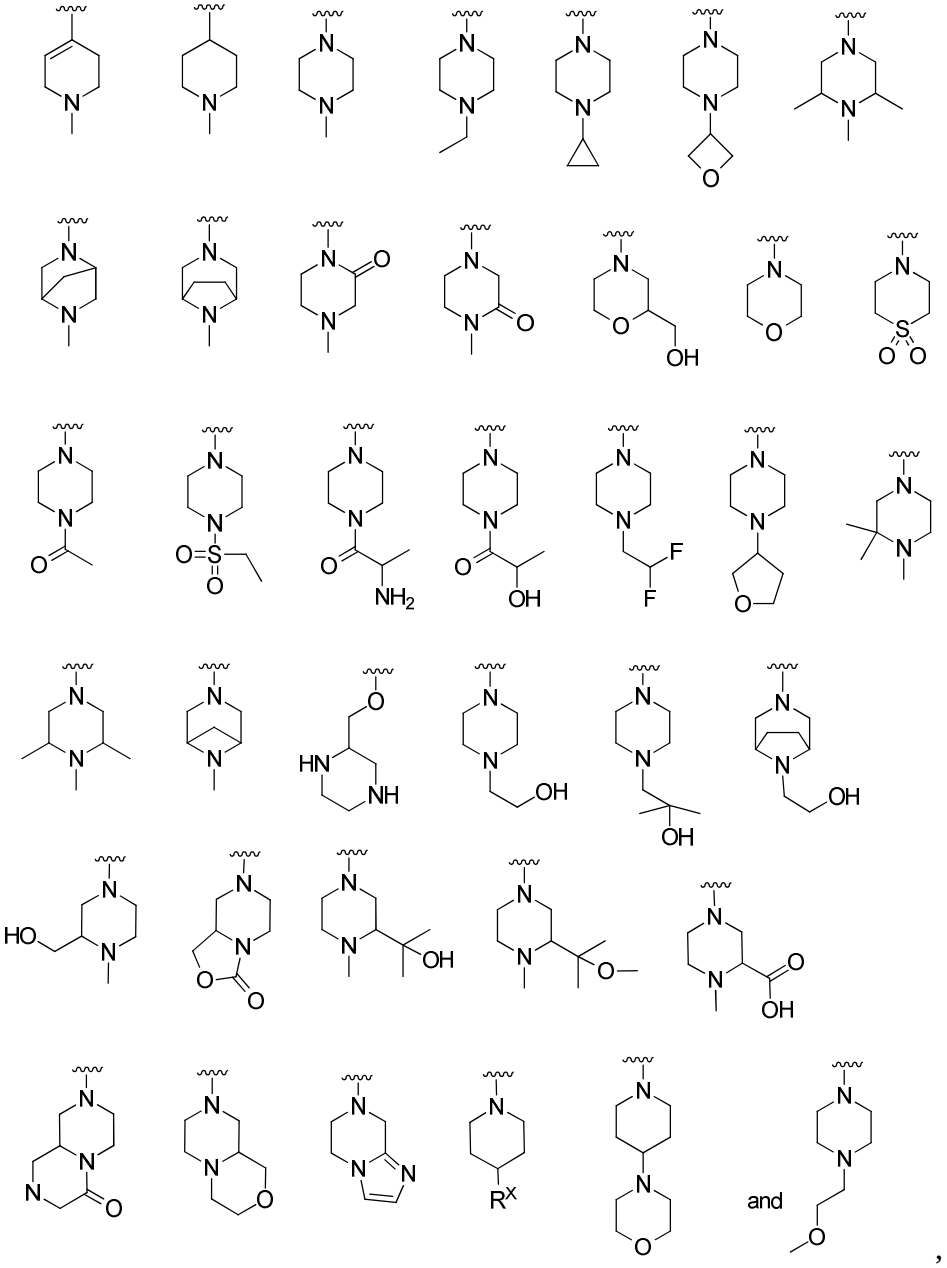
1) halogen, oxo, cyano, carboxyl, hydroxyl, C_{1-4} alkoxy, amino, C_{1-4} alkylamino, nitro, C_{1-4} alkylthio, sulphonic acid group, C_{1-4} alkyl sulfinyl, C_{1-4} alkyl sulfonyl, C_{1-4} alkylaminosulfinyl and C_{1-4} alkylaminosulfonyl;

2) C_{1-4} alkyl, C_{1-4} alkylene, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{3-6} cycloalkyl and 3-8 membered aliphatic heterocyclyl, unsubstituted or optionally substituted with 1, 2, 3 or 4 substituents independently selected from oxo, halogen, hydroxyl, hydroxymethyl, carboxyl, cyano, C_{1-3} alkoxy, amino, C_{1-4} alkylamino, nitro and sulphonic acid group.

In some embodiments, in formula (I), R^1 is selected from hydrogen, fluorine, cyano, methyl and methoxy.

In some embodiments, in formula (I), Cy^A is phenyl, pyridyl, pyrimidyl, pyrazolyl,

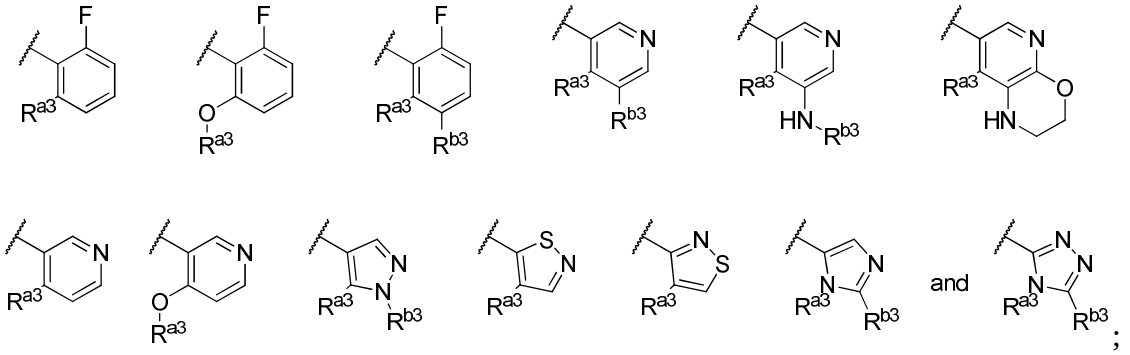
imidazolyl, thiazolyl, isothiazolyl, or a bicyclyl represented by  where a phenyl is fused with a 5-7 membered saturated aliphatic heterocyclyl, wherein Z represents 1-3 heteroatoms optionally selected from nitrogen and oxygen; when Z=N, said N is optionally linked to Ry; Ro is selected from oxo, F, amino, C1-3 alkyl (optionally substituted with F, hydroxyl, amino and C1-3 alkoxy); said aliphatic heterocyclyl may be fused with another 5-6 membered nitrogen-containing saturated aliphatic heterocyclyl to form fused ring; said phenyl, pyridyl, pyrimidyl, pyrazolyl, imidazolyl, thiazolyl, isothiazolyl, or bicyclyl represented by  is unsubstituted or optionally substituted with 1, 2 or 3 substituents independently selected from R^{12}, wherein 1) when Cy^A contains one R^{12}, the R^{12} is selected from one of the followings:



Wherein R^x is selected from -OH, C_{1-6} alkyl (e.g., methyl), C1-6 alkoxy (e.g., methoxy), -NH_2, C_{1-6} alkylamino (e.g., amino, dimethylamino),  , and  ;

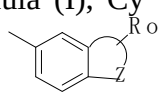
2) when Cy^A contains more than one R^{12}, other R^{12} are each independently selected from fluorine, C_{1-6} alkyl (e.g., methyl), C_{1-6} alkoxy (e.g., methoxy), (C_{1-6} alkylamino)methyl (e.g., (dimethylamino)methyl, (methylamino)methyl);

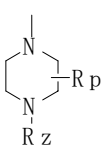
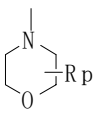
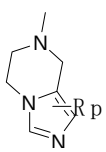
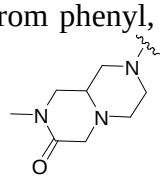
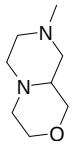
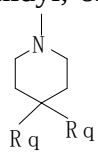
Cy^B is selected from one of the followings:

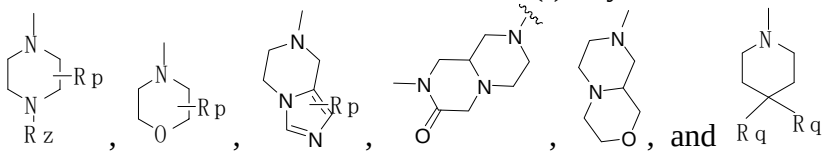


R^{a3} and R^{b3} are each independently selected from hydrogen, C_{1-6} alkyl, and C_{3-6} cycloalkyl, or R^{a3} and R^{b3} together with N atom to to which they are attached form a 4-6 membered saturated aliphatic heterocyclyl; said C_{1-6} alkyl, C_{3-6} cycloalkyl, and 4-6 membered saturated aliphatic heterocyclyl is unsubstituted or optionally substituted with substituent(s) selected from hydroxyl, C_{1-6} alkyl, and fluoro-substituted C_{1-6} alkyl;

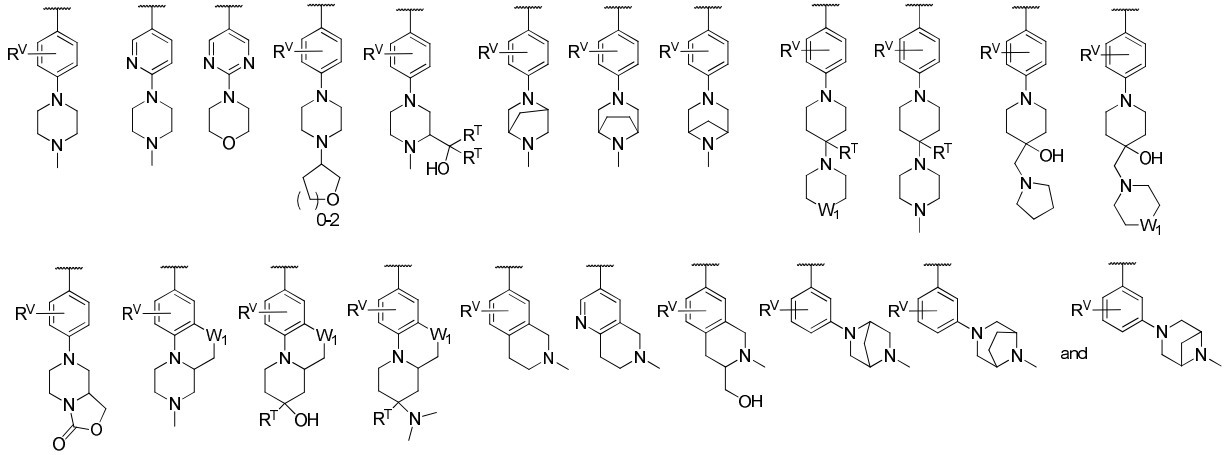
R^y is selected from H, C1-6 alkyl (e.g., methyl), C1-6 alkyl substituted with hydroxyl orhalogen (e.g., hydroxyethyl, hydroxypropyl, difluoroethyl), C3-6 cycloalkyl (e.g., cyclobutanyl, cyclobutanyl substituted with amino), 4-6 membered N-containing saturated aliphatic heterocyclyl, 5-6 membered O-containing saturated aliphatic heterocyclyl, and -C(=O)Rs, Rs is selected from C1-6 alkyl optionally substituted with hydroxyl, amino, and 5-6 membered N-containing aliphatic heterocyclyl.

In some embodiments, In formula (I), Cy^A is selected from phenyl, pyridyl, pyrimidyl, thiazolyl or a bicyclyl represented by  where a phenyl is fused with a 5-7 membered saturated aliphatic heterocyclyl, wherein Z represents 1-3 heteroatoms optionally selected from nitrogen and oxygen; when Z = N, Z is optionally substituted with Ry; Ro is selected from oxo, F, amino, C1-3 alkyl (optionally substituted with F, hydroxyl, amino, and C1-3 alkoxy); said aliphatic heterocyclyl may form fused ring with another 5-6 membered nitrogen-containing saturated aliphatic heterocyclyl heteroatom;

When Cy^A is selected from phenyl, pyridyl, pyrimidyl, or thiazolyl, R^{12} is selected from  ,  ,  ,  ,  , and  , wherein Rz is selected from hydrogen, C_{1-6} alkyl (substituted with cyano, or methoxy), 4-6 membered oxygen-containing aliphatic heterocyclyl, or $-S(=O)_2-C_{1-6}$ alkyl; Rp, single or multiple substituent(s), are each optionally selected from hydrogen, C_{1-6} alkyl (optionally substituted with F, hydroxyl, and amino); Rq is selected from hydroxyl, amino, C_{1-3} alkyl (optionally substituted with 5-6 membered nitrogen-containing aliphatic heterocyclyl, or 5-6 membered nitrogen-containing heteroaryl), spiro heterocyclyl composed of two 4-5 membered nitrogen- and/or oxygen-containing rings, 5-6 membered aliphatic heterocyclyl containing one or two heteroatoms selected from nitrogen and oxygen; said aliphatic heterocyclyl is optionally substituted with F or C_{1-3} alkyl.

In some embodiments, in formula (I), Cy^A is selected from phenyl, R^{12} is selected from  , wherein Rz is selected from hydrogen, C_{1-6} alkyl (substituted with cyano, or methoxy), 4-6 membered oxygen-containing aliphatic heterocyclyl, or $-S(=O)_2-C_{1-6}$ alkyl; Rp, single or multiple substituent(s), are each optionally selected from hydrogen, C_{1-6} alkyl (optionally substituted with F, hydroxyl, or amino); Rq is selected from hydroxyl, amino, C_{1-3} alkyl (optionally substituted with 5-6 membered nitrogen-containing aliphatic heterocyclyl, or 5-6 membered nitrogen-containing heteroaryl), spiro heterocyclyl composed of two 4-5 membered nitrogen- and/or oxygen-containing aliphatic heterocyclyl, 5-6 membered aliphatic heterocyclyl containing one or two heteroatoms selected from nitrogen and oxygen; wherein said aliphatic heterocyclyl is optionally substituted with F or C_{1-3} alkyl.

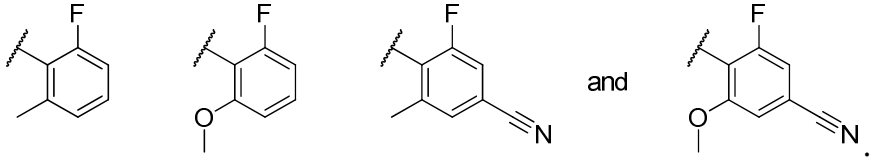
In some embodiments, in formula (I), Cy^A is selected from the followings:



Wherein W_1 is selected from CH_2 or oxygen;
R^T is selected from hydrogen or methyl;
R^V is selected from fluorine or methyl, the amount of R^V is 0, 1 or 2.

In some embodiments, in formula (I), Cy^B is selected from phenyl, optionally substituted with H, F, -CN, C_{1-3} alkyl (substituted with F, and amino), C_{1-3} alkoxy (substituted with F), C_{3-6} cycloalkoxy, and $-C(=O)NR^{a3}R^{b3}$, wherein R^{a3} and R^{b3} are each independently selected from hydrogen, C_{1-6} alkyl, C_{3-6} cycloalkyl (substituted with C1-3 alkyl optionally substituted with F), or R^{a3} and R^{b3} together with the N atom to which they are attached form a 4-5 membered aliphatic heterocyclyl (optionally substituted with hydroxyl and C1-3 alkyl).

In some embodiments, in formula (I), Cy^B is selected from:



In some embodiments, in formula (I), when Cy^A is phenyl, and R^{12} is an aliphatic heterocyclyl, R^{12} is linked to the *meta*- or *para*-position of said phenyl.

In some embodiments, the compounds of formula (I) include isotope labeled compounds wherein ^{1}H is deuterated.

In an aspect, the application provides a pharmaceutical composition including the compound of formula (I) or a pharmaceutically acceptable salt, hydrate, solvate, active metabolite, polymorph, isotope labeled compound, isomer or prodrug thereof, and a pharmaceutically acceptable carrier.

In an aspect, the application provides the compound of formula (I) or a pharmaceutically acceptable salt, hydrate, solvate, active metabolite, polymorph, isotope labeled compound, isomer or prodrug thereof, or a pharmaceutical composition thereof, for the prevention or treatment of a disease mediated with HPK1.

In an aspect, the application provides use of the compound of formula (I) or a pharmaceutically acceptable salt, hydrate, solvate, active metabolite, polymorph, isotope labeled compound, isomer or prodrug thereof, or a pharmaceutical composition thereof, in the preparation of a medicament for the prevention or treatment of a disease mediated with HPK1.

In some embodiments, the application provides use of the compound of formula (I) or a pharmaceutically acceptable salt, hydrate, solvate, active metabolite, polymorph, isotope labeled compound, isomer or prodrug thereof, or a pharmaceutical composition thereof, for the treatment or amelioration of one or more diseases selected from the group consisiting of benign or malignant tumors, myelodysplastic syndromes and diseases caused by viruses.

In an aspect, the application provides a method for inhibiting the activity of HPK1 including administering the compound of formula (I) or a pharmaceutically acceptable salt, hydrate, solvate, active metabolite, polymorph, isotope labeled compound, isomer or prodrug thereof to a subject.

In some embodiments, the application provides a method for treating a disease or disorder mediated with HPK1 in a patient, including administering therapeutically effective amount of the compound of formula (I) or a pharmaceutically acceptable salt, hydrate, solvate, active metabolite, polymorph, isotope labeled compound, isomer or prodrug thereof to the patient.

In some embodiments, the compounds of formula (I) has the activity of inhibiting HPK1.

In some embodiments, the disease includes one or more diseases selected from the group consisiting of benign or malignant tumors, myelodysplastic syndromes and diseases caused by viruses.

Embodiments

Typical embodiments embodying the features and advantages of the present application will be described in detail in the following description. It should be understood that the present application may have various variations in different embodiments, none of which is departing from the scope of the present application, and the description therein is essentially for illustrative purposes and not for the purpose of limiting the scope of the application.

In some embodiments, R^1 is selected from:

1) hydrogen, halogen, cyano, acetylenyl, $-OR^a$ and $-NR^aR^b$;

2) C_{1-4} alkyl, C_{3-5} monocyclic cycloalkyl, and 4-7 membered aliphatic heterocyclyl, unsubstituted or optionally substituted with one, two, three or four substituents independently selected from R^{11}.

In some embodiments, R^1 is selected from hydrogen, fluorine, chlorine, bromine, cyano, C_{1-4} alkyl, C_{3-4} cycloalkyl, 3-4 membered aliphatic heterocyclyl and $-OR^a$.

In some embodiments, R^1 is selected from hydrogen, fluorine, cyano, methyl, ethyl, 1-propyl, isopropyl, cyclopropyl, methoxy, ethoxy and cyclopropoxy.

In some embodiments, R^1 is hydrogen.

In some embodiments, R^a and R^b are each independently selected from hydrogen, C_{1-3} alkyl, C_{3-4} cycloalkyl and 3-4 membered aliphatic heterocyclyl;

or, R^a and R^b attached to same nitrogen atom, together with the nitrogen atom, form an unsubstituted 3-6 membered aliphatic heterocyclyl.

In some embodiments, R^a and R^b are each independently selected from hydrogen, methyl, ethyl and cyclopropyl.

In some embodiments, Cy^A is phenyl, naphthyl, or 5, 6, 7, 8, 9 or 10 membered heteroaryl containing 1, 2 or 3 ring-forming heteroatoms selected from N, O, and S, said phenyl, naphthyl and 5, 6, 7, 8, 9 or 10 membered heteroaryl is unsubstituted or optionally substituted with 1, 2, 3 or 4 substituents independently selected from R^{12}.

In some embodiments, the aryl or heteroaryl of Cy^A contains one R^{12} selected from a cyclic group, wherein the cyclic group is selected from 6-10 membered aryl, 5-10 membered heteroaryl, C_{3-7} cycloalkyl, and 3-7 membered aliphatic heterocyclylaliphatic containing 1 or 2 ring-forming heteroatoms optionally selected from N, O, and S, wherein said 6-10 membered aryl, 5-10 membered heteroaryl, C_{3-7} cycloalkyl, and 3-7 membered aliphatic heterocyclyl is unsubstituted or optionally substituted with 1, 2 or 3 substituents independently selected from R^{22};

or,

the aryl or heteroaryl of Cy^A contains 2, 3 or 4 of R^{12}, wherein one of the R^{12} is the above mentioned cyclic group, and other R^{12} are each independently selected from C_{1-6} alkyl, halogen, cyano, $-OR^{a2}$ and $-NR^{a2}R^{b2}$.

In some embodiments, the aryl or heteroaryl of Cy^A contains one R^{12} which is a cyclic group selected from phenyl, 5-6 membered heteroaryl, C_{3-6} cycloalkyl, and 4, 5, 6, and 7 membered aliphatic heterocyclylaliphatic containing 1 or 2 of ring-forming heteroatoms selected from N, O, and S, wherein said phenyl, 5-6 membered heteroaryl, C_{3-6} cycloalkyl, and 4, 5, 6, and 7 membered aliphatic heterocyclyl is unsubstituted or optionally substituted with 1, 2 or 3 subsituents independently selected from R^{22};

or,

the aryl or heteroaryl of Cy^A contains 2 or 3 of R^{12}, wherein one of the R^{12} is the above mentioned cyclic group, and other R^{12} are each independently selected from C_{1-6} alkyl, halogen, cyano, $-OR^{a2}$ and $-NR^{a2}R^{b2}$.

In some embodiments, Cy^A is phenyl or 5-6 membered heteroaryl, optionally substituted with 1, 2, 3 or 4 substituents independently selected from R^{12}.

In some embodiments, Cy^A is phenyl or 5-6 membered heteroaryl, optionally substituted with 1, 2, 3 or 4 subsituents independently selected from R^{12}, wherein two R^{12}, together with two adjacent ring-forming atoms of the phenyl or heteroaryl to which they are attached respectively, form C_5, C_6, C_7 aliphatic monocyclyl or 5, 6, 7 membered aliphatic monocyclic heterocyclyl, said C_5, C_6, C_7 aliphatic monocyclyl or 5, 6, 7 membered aliphatic monocyclic heterocyclyl is unsubstituted or optionally substituted with 1, 2, 3 or 4 subsituents independently selected from R^{22}.

In some embodiments, Cy^A is phenyl, 5 membered or 6 membered heteroaryl containing one or two heteroatoms selected from N and S, for example, one nitrogen atom, two nitrogen atoms, or one nitrogen atom and one sulfur atom, said phenyl, 5 membered or 6 membered heteroaryl is optionally substituted with 1, 2 or 3 substituents independently selected from R^{12}.

In some embodiments, Cy^A is phenyl, pyridyl, pyrimidyl, pyrazolyl, imidazolyl, thiazolyl, isothiazolyl, oxazolyl or isoxazolyl, which is optionally substituted with 1, 2 or 3 substituents independently selected from R^{12}.

In some embodiments, Cy^A is phenyl, pyridyl, pyrazolyl, imidazolyl or thiazolyl, which is optionally substituted with 1, 2 or 3 substituents independently selected from R^{12}.

In some embodiments, the aryl or heteroaryl of Cy^A contains two, three or four of R^{12}, wherein two R^{12}, together with two adjacent ring-forming atoms of the aryl or heteroaryl to which they are attached respectively, form C_{5-8} aliphatic cyclyl (alicycly) or 5-8 membered aliphatic heterocyclyl containing 1, 2 or 3 ring-forming heteroatoms selected from N, O, and S, wherein

said C_{5-8} aliphatic cyclyl (alicycly) or 5-8 membered aliphatic heterocyclyl is unsubstituted or optionally substituted with 1, 2 or 3 substituents independently selected from R^{22}; other not-ring-forming R^{12} are each independently selected from C_{1-6} alkyl, halogen, cyano, $-OR^{a2}$ and $-NR^{a2}R^{b2}$.

In some embodiments, the aryl or heteroaryl of Cy^A contains two, three or four of R^{12}, wherein two R^{12}, together with two adjacent ring-forming atoms of the aryl or heteroaryl to which they are attached respectively, form 5, 6, 7 membered aliphatic monoheterocyclyl containing 1 or 2 ring-forming heteroatoms selected from N and O, wherein said aliphatic monocyclic heterocyclyl is unsubstituted or optionally substituted with 1, 2 or 3 substituents independently selected from oxo, R^H, $-(CH_2)_{0-2}$-OH, $-(CH_2)_{0-2}-OR^H$, $-(CH_2)_{0-2}-NH_2$, $-(CH_2)_{0-2}-NHR^H$ and $-(CH_2)_{0-2}-N(R^H)_2$; other not-ring-forming R^{12} are each independently selected from C_{1-6} alkyl, halogen, cyano, $-OR^{a2}$ and $-NR^{a2}R^{b2}$; R^H is selected from methyl, ethyl, isopropyl, cyclopropyl and 3-oxetanebutyl.

In some embodiments, each R^{12} is independently selected from:

1) oxo, halogen, cyano, $-C(=O)R^{a2}$, $-C(=O)OR^{a2}$, $-C(=O)NR^{a2}R^{b2}$, $-C(=NR^{d2})NR^{a2}R^{b2}$, $-OR^{a2}$, $-OC(=O)R^{a2}$, $-OC(=O)OR^{c2}$, $-OC(=O)NR^{a2}R^{b2}$, $-SR^{a2}$, $-S(=O)R^{c2}$, $-S(=O)_2R^{c2}$, sulphonic acid group, $-S(=O)NR^{a2}R^{b2}$, $-S(=O)_2NR^{a2}R^{b2}$, $-S(=O)(=NR^{d2})R^{c2}$, $-NR^{a2}R^{b2}$, $-NR^{a2}C(=O)R^{b2}$, $-NR^{a2}C(=O)OR^{c2}$, $-NR^{e2}C(=O)NR^{a2}R^{b2}$, $-NR^{e2}C(=NR^{d2})NR^{a2}R^{b2}$, $-NR^{a2}S(=O)_2R^{c2}$, $-NR^{e2}S(=O)_2NR^{a2}R^{b2}$ and nitro;

2) C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 6-10 membered aryl, 5-10 membered heteroaryl, C_{3-12} cycloalkyl and 3-12 membered aliphatic heterocyclyl, unsubstituted or optionally substituted with 1, 2, 3, 4, 5 or 6 subtituents independently selected from R^{22};

3) two R^{12}, together with two adjacent ring-forming atomsring-forming atoms of the aryl or heteroaryl in Cy^A to which they are attached respectively, form C_{5-12} aliphatic cyclyl or 5-12 membered aliphatic heterocyclyl, unsubstituted or optionally substituted with 1, 2, 3, 4, 5 or 6 substituents independently selected from R^{22}.

In some embodiments, each R^{12} is independently selected from:

1) oxo, halogen, cyano, $-C(=O)R^{a2}$, $-C(=O)OR^{a2}$, $-C(=O)NR^{a2}R^{b2}$, $-C(=NR^{d2})NR^{a2}R^{b2}$, $-OR^{a2}$, $-OC(=O)R^{a2}$, $-OC(=O)OR^{c2}$, $-OC(=O)NR^{a2}R^{b2}$, $-NR^{a2}R^{b2}$, $-NR^{a2}C(=O)R^{b2}$, $-NR^{a2}C(=O)OR^{c2}$, $-NR^{e2}C(=O)NR^{a2}R^{b2}$, $-NR^{e2}C(=NR^{d2})NR^{a2}R^{b2}$, $-NR^{a2}S(=O)_2R^{c2}$, $-NR^{e2}S(=O)_2NR^{a2}R^{b2}$ and nitro;

2) C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 6-10 membered aryl, 5-10 membered heteroaryl, C_{3-10} cycloalkyl and 3-10 membered aliphatic heterocyclyl, unsubstituted or optionally substituted with 1, 2, 3, 4, 5 or 6 substituents independently selected from R^{22};

3) two R^{12}, together with two adjacent ring-forming atoms of the aryl or heteroaryl in Cy^A to which they are attached respectively, form C_{5-10} aliphatic cyclyl or 5-10 membered aliphatic heterocyclyl, unsubstituted or optionally substituted with 1, 2, 3, 4 or 5 subtituents independently selected from R^{22}.

In some embodiments, each R^{12} is independently selected from:

1) oxo, halogen, cyano, $-C(=O)R^{a2}$, $-C(=O)OR^{a2}$, $-C(=O)NR^{a2}R^{b2}$, $-C(=NR^{d2})NR^{a2}R^{b2}$, $-OR^{a2}$, $-OC(=O)R^{a2}$, $-OC(=O)OR^{c2}$, $-OC(=O)NR^{a2}R^{b2}$, $-NR^{a2}R^{b2}$, $-NR^{a2}C(=O)R^{b2}$, $-NR^{a2}C(=O)OR^{c2}$, $-NR^{e2}C(=O)NR^{a2}R^{b2}$, $-NR^{e2}C(=NR^{d2})NR^{a2}R^{b2}$, $-NR^{a2}S(=O)_2R^{c2}$, $-NR^{e2}S(=O)_2NR^{a2}R^{b2}$ and nitro;

2) C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 6-10 membered aryl, 5-10 membered heteroaryl, C_{3-10} cycloalkyl and 3-10 membered aliphatic heterocyclyl, unsubstituted or optionally substituted with 1, 2, 3 or 4 substituents independently selected from R^{22};

3) two R^{12}, together with two adjacent ring-forming atoms of the aryl or heteroaryl in Cy^A to which they are attached respectively, form C_{4-8} aliphatic cyclyl or 4-8 membered aliphatic heterocyclyl, unsubstituted or optionally substituted with 1, 2 or 3 substituents independently selected from R^{22}.

In some embodiments, each R^{12} is independently selected from:

1) oxo, halogen, cyano, -C(=O)R^{a2}, -C(=O)$NR^{a2}R^{b2}$, -C(=NR^{d2})$NR^{a2}R^{b2}$, -OR^{a2}, -$NR^{a2}R^{b2}$, -NR^{a2}C(=O)R^{b2}, -NR^{e2}C(=O)$NR^{a2}R^{b2}$, -NR^{e2}C(=NR^{d2})$NR^{a2}R^{b2}$, -NR^{a2}S(=O)$_2R^{c2}$, and -NR^{e2}S(=O)$_2NR^{a2}R^{b2}$;

2) C_{1-6} alkyl, 6-10 membered aryl, 5-10 membered heteroaryl, C_{3-10} cycloalkyl, and 3-10 membered aliphatic heterocyclyl, unsubstituted or optionally substituted with 1, 2, 3, 4, 5 or 6 substituents independently selected from R^{22};

3) two R^{12}, together with two adjacent ring-forming atoms of the aryl or heteroaryl in Cy^A to which they are attached respectively, form C_{4-8} aliphatic cyclyl or 4-8 membered aliphatic heterocyclyl, unsubstituted or optionally substituted with1, 2, 3 or 4 substituents independently selected from R^{22}.

In some embodiments, each R^{12} is independently selected from:

1) oxo, halogen, cyano, -C(=O)R^{a2}, -C(=O)$NR^{a2}R^{b2}$, -C(=NR^{d2})$NR^{a2}R^{b2}$, -OR^{a2}, -$NR^{a2}R^{b2}$, -NR^{a2}C(=O)R^{b2}, -NR^{a2}C(=O)OR^{c2}, -NR^{e2}C(=O)$NR^{a2}R^{b2}$, -NR^{e2}C(=NR^{d2})$NR^{a2}R^{b2}$, -NR^{a2}S(=O)$_2R^{c2}$, and -NR^{e2}S(=O)$_2NR^{a2}R^{b2}$;

2) C_{1-6} alkyl, phenyl, 5-6 membered heteroaryl, C_{3-10} cycloalkyl, and 3-10 membered aliphatic heterocyclyl, unsubstituted or optionally substituted with 1, 2, 3 or 4 substituents independently selected from R^{22};

3) two R^{12}, together with two adjacent ring-forming atoms of the aryl or heteroaryl in Cy^A to which they are attached respectively, form C_5, C_6, C_7 aliphatic monocyclyl or 5 membered, 6 membered, 7 membered aliphatic monocyclic heterocyclyl, unsubstituted or optionally substituted with 1, 2 or 3 substituents independently selected from R^{22}.

In some embodiments, each R^{12} independently selected from:

1) halogen, cyano, -OR^{a2}, -C(=O)$NR^{a2}R^{b2}$, -$NR^{a2}R^{b2}$, -NR^{a2}C(=O)R^{b2}, -NR^{a2}C(=O)OR^{c2}, -NR^{e2}C(=O)$NR^{a2}R^{b2}$, -NR^{e2}(=NR^{d2})$NR^{a2}R^{b2}$, -NR^{a2}S(=O)$_2R^{c2}$, and -NR^{e2}S(=O)$_2NR^{a2}R^{b2}$;

2) C_{1-6} alkyl, phenyl, 5-6 membered heteroaryl, C_{3-7} cycloalkyl, and 3-7 membered aliphatic heterocyclyl, unsubstituted or optionally substituted with 1, 2, 3 or 4 substituents independently selected from R^{22}.

In some embodiments, each R^{12} is independently selected from:

1) halogen, C_{1-6} alkyl, C_{3-6} cycloalkyl, 3-7 membered aliphatic heterocyclyl, cyano, -OR^{a2}, -C(=O)$NR^{a2}R^{b2}$, -$NR^{a2}R^{b2}$, -NR^{a2}C(=O)R^{b2}, -NR^{e2}C(=O)$NR^{a2}R^{b2}$, -NR^{e2}C(=NR^{d2})$NR^{a2}R^{b2}$, -NR^{a2}S(=O)$_2R^{c2}$ and NR^{e2}S(=O)$_2NR^{a2}R^{b2}$;

2) two R^{12}, together with two adjacent ring-forming atoms of the aryl or heteroaryl in Cy^A to which they are attached respectively, form C_{4-8} aliphatic cyclyl, 4-8 membered aliphatic heterocyclyl, unsubstituted or independently optionally substituted with 1, 2, 3 or 4 substituents independently selected from R^{22}.

In some embodiments, two R^{12}, together with two adjacent ring-forming atoms of the aryl or heteroaryl in Cy^A to which they are attached respectively, form C_5, C_6, C_7 aliphatic monocyclyl and 5 membered, 6 membered, 7 membered aliphatic monocyclic heterocyclyl, unsubstituted or independently optionally substituted with1, 2 or 3 substituents independently selected from R^{22}.

In some embodiments, R^{12} is selected from 4 membered, 5 membered, 6 membered, 7 membered aliphatic monocyclic heterocyclyl and 7 membered, 8 membered, 9 membered, 10 membered bicylic aliphatic heterocyclyl, which is unsubstituted or optionally substituted with 1, 2, 3 substituents independently selected from R^{22}.

In some embodiments, R^{12} is unsubstituted or optionally substituted aliphatic monocyclic heterocyclyl or aliphatic bicyclic heterocyclyl, wherein the aliphatic bicyclic heterocyclyl may be, for example, a bridged ring group, or a spiro-ring group; wherein said aliphatic dicyclic heterocyclyl comprises A1 ring and A2 ring, A1 ring is directly connected to the aryl or heteroaryl of Cy^A, and A1 ring can be a 3-6 membered ring, and the total number of ring-forming atoms of the aliphatic bicyclic heterocyclyl is no more than 10.

In some embodiments, aliphatic heterocyclyl of R^{12} contains 1 or 2 ring-forming

heteroatoms selected from N, O, and S.

In some embodiments, each R^{12} is independently selected from C_{1-6} alkyl, halogen, cyano, $-OR^{a2}$ and $-NR^{a2}R^{b2}$.

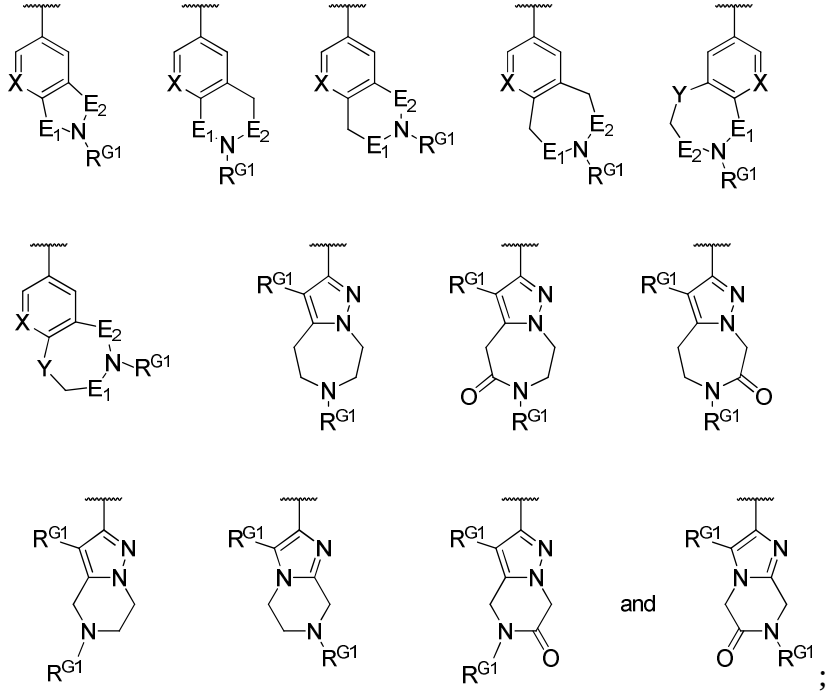
In some embodiments, each R^{12} is independently selected from:

1) C_{1-6} alkyl, C_{1-3} alkoxy, C_{3-8} cycloalkyl, and 3-8 membered aliphatic heterocyclyl, unsubstituted or optionally substituted with 1, 2, 3 or 4 substituents independently selected from R^{22}; wherein 3-8 membered aliphatic heterocyclyl is monocyclic aliphatic heterocyclyl or bicyclic aliphatic heterocyclyl, said aliphatic heterocyclyl may contain ring-forming heteroatoms selected from N and/or O; R^{22} is selected from oxo, hydroxyl, amino, cyano, C_{1-3} alkylamino, C_{1-3} alkoxy, 3-6 membered cycloalkyl and 3-6 membered aliphatic monocyclic heterocyclyl;

2) two R^{12}, together with two adjacent ring-forming atoms of the aryl or heteroaryl in Cy^A to which they are attached respectively, form C_5, C_6, C_7 aliphatic monocyclyl or 5 membered, 6 membered, 7 membered aliphatic monocyclic heterocyclyl, unsubstituted or optionally substituted with1, 2 or 3 substituents each independently selected from R^{22}; R^{22} is selected from oxo, methyl, ethyl, isopropyl, cyclopropyl, oxetanyl, $-N(CH_3)_2$, -OH, -CN, $-OCH_3$, $-C(=O)CH_3$, $-S(=O)_2CH_2CH_3$, $-C(=O)NH_2$, $-S(=O)_2NH_2$, $-CH_2CH_2OH$, $-CH_2OH$, and $-CH_2CH_2N(CH_3)_2$.

In some embodiments, Cy^A is selected from:

1) the following strutures, wherein the "〰" at the end of the chemical bond in each structure means that the structure is connected to the rest of the formula (I) through the bond:



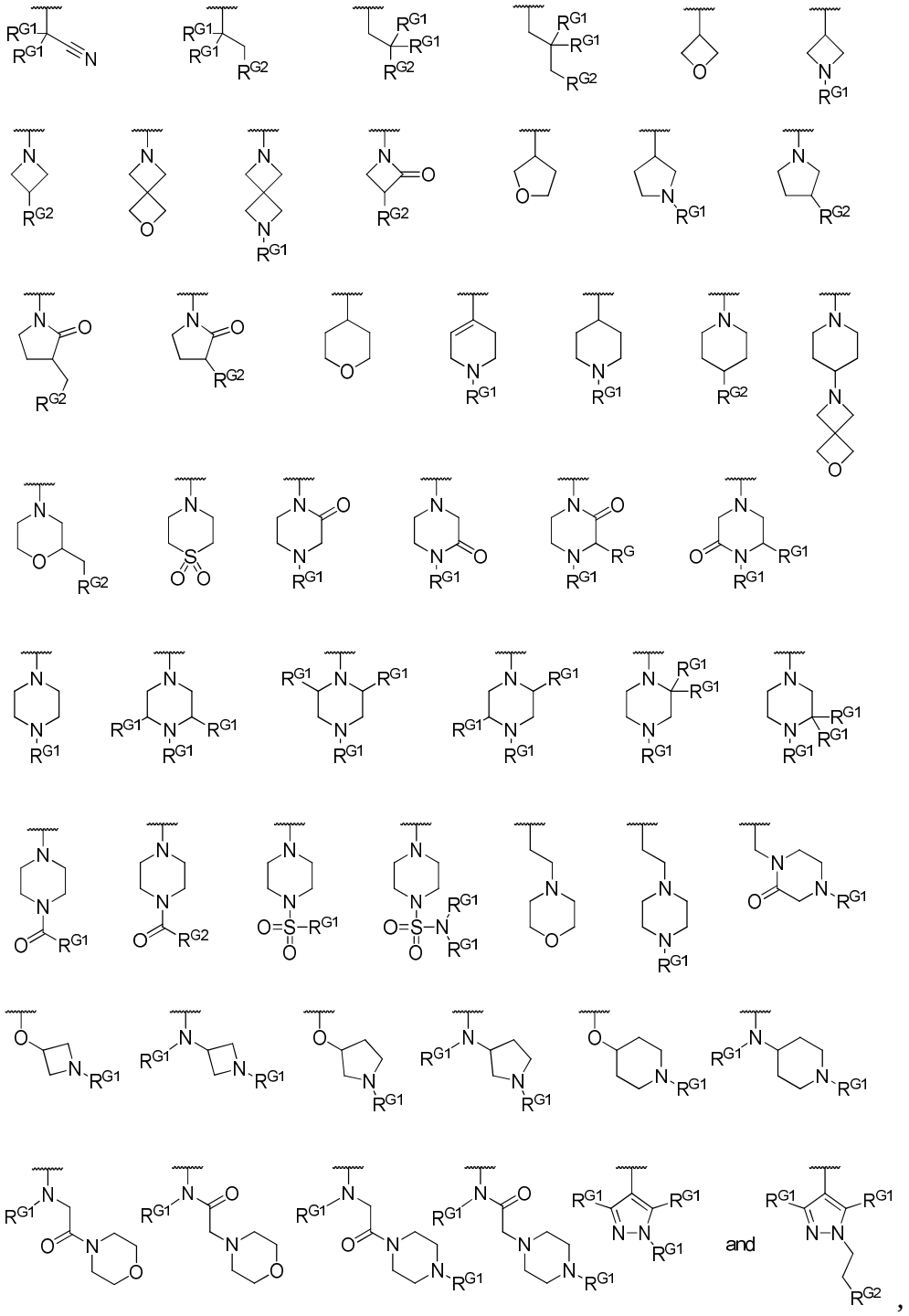
;

2) phenyl, pyridyl, pyrimidyl, pyrazolyl, imidazolyl, thiazolyl, isothiazolyl, oxazolyl or isoxazolyl, unsubstituted or optionally substituted with 1, 2 or 3 substituents each independently selected from R^{12}, wherein:

(a) each R^{12} is independently selected from fluorine, chlorine, non-hydrogen R^{G1}, and $-OR^{G1}$;

or,

(b) Cy^A contains one R^{12} selected from the following strutures, wherein the "〰" at the end of the chemical bond in each structure means that the structure is connected to the rest of formula (I) through the bond:



or,

Cy^A contains two or three R^{12}, wherein one of R^{12} is selected from the above structures and the others of R^{12} are each independently selected from fluorine, chlorine, non-hydrogen R^{G1}, and $-OR^{G1}$;

wherein,

X is selected from CH and N;

Y is selected from $-CH_2-$, NH and O;

E_1 and E_2 are each independently selected from $-CH_2-$ and carbonyl, but E_1 and E_2 cannot be carbonyl simultaneously;

R^{G2} is selected from hydrogen, $-OR^{G1}$ and $-N(R^{G1})_2$;

Each R^{G1} is independently selected from:

1) hydrogen, methyl, ethyl (optionally substituted with C_{1-3} alkylamino), propyl (optionally substituted with hydroxyl and C_{1-3} alkyl, such as 2-hydroxyl-2-methyl-propyl), isopropyl (substituted with cyano), cyclopropyl, 3-oxetanyl and 3-methyl-3-azetidinyl;

2) two R^{G1}, together with the one atom to which they are attached to, form a C_{3-6} monocyclyl or 3-6 membered aliphatic monocyclic heterocyclyl;

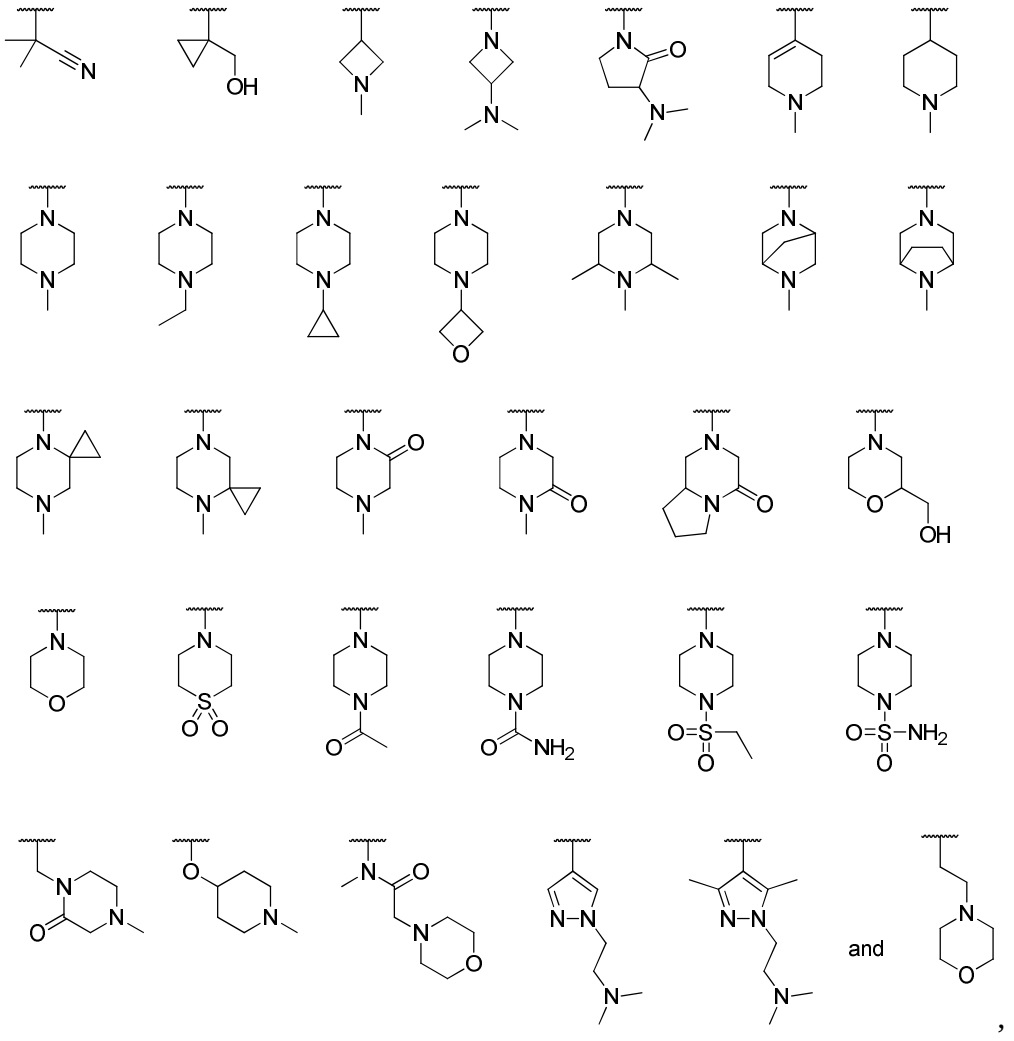
3) two R^{G1} attached to two different ring-forming atoms of the same monocycle are connected to form a ring structure together with part of the ring-forming atoms of said monocycle, wherein the two connected R^{G1} form a C2, C3 or C4 alkylene.

In some embodiments, Cy^A is phenyl, pyridyl, pyrimidyl, pyrazolyl, imidazolyl, thiazolyl or isothiazolyl, unsubstituted or optionally substituted with 1, 2 or 3 substituents each independently selected from R^{12},

1) each R^{12} is independently selected from fluorine, chlorine, non-hydrogen R^{G1}, and $-OR^{G1}$;

or,

2) Cy^A contains one R^{12} selected from the following structures:



,

or,

Cy^A contains two or three R^{12}, wherein one of R^{12} is selected from the above structures and the others of R^{12} are each independently selected from fluorine, chlorine, non-hydrogen R^{G1}, and $-OR^{G1}$;

Each R^{G1} is independently selected from hydrogen, methyl, ethyl, isopropyl, cyclopropyl, 3-oxetanebutyl and 3-methyl-3-azetidinyl.

In some embodiments, R^{22} is selected from oxo, cyano, C_{3-7} cycloalkyl, 3-7 membered

aliphatic heterocyclyl, R^{H1}, $-(CH_2)_{0-2}OH$, $-(CH_2)_{0-2}OR^{H1}$, $-(CH_2)_{0-2}NH_2$, $-(CH_2)_{0-2}NHR^{H1}$, $-(CH_2)_{0-2}N(R^{H1})_2$, aldehyde group, $-C(=O)R^{H1}$, $-C(=O)NH_2$, $-C(=O)NHR^{H1}$, $-C(=O)N(R^{H1})_2$, $-S(=O)_2R^{H1}$, $-S(=O)_2NH_2$, $-S(=O)_2NHR^{H1}$ and $-S(=O)_2N(R^{H1})_2$; R^{H1} is independently selected from methyl, ethyl, isopropyl, cyclopropyl, 3-oxetanebutyl and 3-methyl-3-azetidinyl.

In some embodiments, R^{22} is selected from oxo, cyano, methyl, ethyl, isopropyl, cyclopropyl, oxetanyl, $-N(CH_3)_2$, -OH, -CN, $-OCH_3$, $-C(=O)CH_3$, $-S(=O)_2CH_2CH_3$, $-C(=O)NH_2$, $-S(=O)_2NH_2$, $-CH_2CH_2OH$, $-CH_2OH$, and $-CH_2CH_2N(CH_3)_2$.

In some embodiments, Cy^B is selected from phenyl, naphthyl and 5-10 membered heteroaryl, unsubstituted or optionally substituted with 1, 2, 3 or 4 substituents independently selected from R^{13}; wherein said 5-10 membered heteroaryl contains at least one ring-forming carbon atom and 1, 2, 3 or 4 ring-forming heteroatoms independently selected from N, O and S.

In some embodiments,Cy^B is phenyl or 5-6 membered heteroaryl, optionally substituted with 1, 2, 3 or 4 substituents independently selected from R^{13}.

In some embodiments, Cy^B is phenyl or 5-6 membered heteroaryl containing 1, 2 or 3 ring-forming heteroatoms selected from N and S, said phenyl or 5-6 membered heteroaryl is optionally substituted with 1, 2, or 3 substituents independently selected from R^{13}.

In some embodiments, Cy^B is phenyl, pyridyl, pyrimidyl, pyridazinyl, pyrazolyl, imidazolyl, thiazolyl, isothiazolyl, thienyl, optionally substituted with 1, 2, or 3 substituents independently selected from R^{13}.

In some embodiments, Cy^B is phenyl or 5-6 membered heteroaryl, optionally substituted with 1, 2, 3 or 4 substituents independently selected from R^{13}; wherein two R^{13}, together with two adjacent ring-forming atoms of the phenyl or heteroaryl of Cy^B to which they are connected respectively, form a C_{5-12} aliphatic cyclyl or 5-12 membered aliphatic heterocyclyl, unsubstituted or optionally substituted with 1, 2, 3, 4 or 5 substituents independently selected from R^{23}.

In some embodiments, Cy^B is phenyl or 5-6 membered heteroaryl, optionally substituted with 1, 2, or 3 substituents independently selected from R^{13}; wherein two R^{13}, together with two adjacent ring-forming atoms of the phenyl or heteroaryl of Cy^B together with the two said ring-forming atoms to which they are connected respectively, form a C_{4-8} aliphatic cyclyl or 4-8 membered aliphatic heterocyclyl, unsubstituted or optionally substituted with 1, 2 or 3 subsituents independently selected from R^{23}.

In some embodiments, Cy^B is phenyl or 5-6 membered heteroaryl, optionally substituted with 1, 2, or 3 substituents independently selected from R^{13}; wherein two R^{13}, together with two adjacent ring atoms of the phenyl or heteroaryl of Cy^B to which they are connected respectively, form a C_{5-6} aliphatic monocyclyl or 5-6 membered aliphatic monocyclic heterocyclyl, unsubstituted or optionally substituted with 1, 2 or 3 subsituents independently selected from R^{23};

R^{23} is selected from fluorine, methyl, ethyl, isopropyl, cyclopropyl, ethylene and 3-oxetanyl.

In some embodiments, each R^{13} is independently selected from:

1) oxo, halogen, cyano, $-C(=O)R^{a3}$, $-C(=O)OR^{a3}$, $-C(=O)NR^{a3}R^{b3}$, $-C(=NR^{d3})NR^{a3}R^{b3}$, $-OR^{a3}$, $-OC(=O)R^{a3}$, $-OC(=O)OR^{c3}$, $-OC(=O)NR^{a3}R^{b3}$, $-SR^{a3}$, $-S(=O)R^{c3}$, $-S(=O)_2R^{c3}$, sulphonic acid group, $-S(=O)NR^{a3}R^{b3}$, $-S(=O)_2NR^{a3}R^{b3}$, $-S(=O)(=NR^{d3})R^{c3}$, $-NR^{a3}R^{b3}$, $-NR^{a3}C(=O)R^{b3}$, $-NR^{a3}C(=O)OR^{c3}$, $-NR^{e3}C(=O)NR^{a3}R^{b3}$, $-NR^{e3}C(=NR^{d3})NR^{a3}R^{b3}$, $-NR^{a3}S(=O)_2R^{c3}$, $-NR^{e3}S(=O)_2NR^{a3}R^{b3}$ and nitro;

2) C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 6-10 membered aryl, 5-10 membered heteroaryl, C_{3-12} cycloalkyl and 3-12 membered aliphatic heterocyclyl, unsubstituted or optionally substituted with 1, 2, 3, 4, 5 or 6 substituents independently selected from R^{23};

3) two R^{13}, together with two adjacent ring atoms of the phenyl or heteroaryl of Cy^B to which they are connected respectively, form a C_{5-12} aliphatic cyclyl or 5-12 membered aliphatic heterocyclyl, unsubstituted or optionally substituted with 1, 2, 3, 4 or 5 substituents independently selected from R^{23}.

In some embodiments, each R^{13} is independently selected from:

1) oxo, halogen, cyano, -C(=O)R^{a3}, -C(=O)OR^{a3}, -C(=O)$NR^{a3}R^{b3}$, -C(=NR^{d3})$NR^{a3}R^{b3}$, -OR^{a3}, -OC(=O)R^{a3}, -OC(=O)OR^{c3}, -OC(=O)$NR^{a3}R^{b3}$, -$NR^{a3}R^{b3}$, -NR^{a3}C(=O)R^{b3}, -NR^{a3}C(=O)OR^{c3}, -NR^{e3}C(=O)$NR^{a3}R^{b3}$, -NR^{e3}C(=NR^{d3})$NR^{a3}R^{b3}$, -$NR^{a3}S(=O)_2R^{c3}$, -$NR^{e3}S(=O)_2NR^{a3}R^{b3}$ and nitro;

2) C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 6-10 membered aryl, 5-10 membered heteroaryl, C_{3-10} cycloalkyl and 3-10 membered aliphatic heterocyclyl, unsubstituted or optionally substituted with 1, 2, 3, 4, 5 or 6 substituents independently selected from R^{23};

3) two R^{13}, together with two adjacent ring-forming atoms of the aryl or heteroaryl of Cy^B to which they are connected respectively, form a C_{5-10} aliphatic cyclyl or 5-10 membered aliphatic heterocyclyl, unsubstituted or optionally substituted with 1, 2, 3, 4 or 5 substituents independently selected from R^{23}.

In some embodiments, each R^{13} is independently selected from:

1) oxo, halogen, cyano, -C(=O)R^{a3}, -C(=O)OR^{a3}, -C(=O)$NR^{a3}R^{b3}$, -C(=NR^{d3})$NR^{a3}R^{b3}$, -OR^{a3}, -OC(=O)R^{a3}, -OC(=O)OR^{c3}, -OC(=O)$NR^{a3}R^{b3}$, -$NR^{a3}R^{b3}$, -NR^{a3}C(=O)R^{b3}, -NR^{a3}C(=O)OR^{c3}, -NR^{e3}C(=O)$NR^{a3}R^{b3}$, -NR^{e3}C(=NR^{d3})$NR^{a3}R^{b3}$, -$NR^{a3}S(=O)_2R^{c3}$, -$NR^{e3}S(=O)_2NR^{a3}R^{b3}$ and nitro;

2) C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 6-10 membered aryl, 5-10 membered heteroaryl, C_{3-10} cycloalkyl and 3-10 membered aliphatic heterocyclyl, unsubstituted or optionally substituted with 1, 2, 3 or 4 substituents independently selected from R^{23};

3) two R^{13}, together with two adjacent ring-forming atoms of the aryl or heteroaryl of Cy^B to which they are connected respectively, form a C_{4-8} aliphatic cyclyl or 4-8 membered aliphatic heterocyclyl, unsubstituted or optionally substituted with 1, 2 or 3 substituents independently selected from R^{23}.

In some embodiments, each R^{13} is independently selected from:

1) oxo, halogen, cyano, -C(=O)R^{a3}, -C(=O)$NR^{a3}R^{b3}$, -C(=NR^{d3})$NR^{a3}R^{b3}$, -OR^{a3}, -$NR^{a3}R^{b3}$, -NR^{a3}C(=O)R^{b3}, -NR^{e3}C(=O)$NR^{a3}R^{b3}$, -NR^{e3}C(=NR^{d3})$NR^{a3}R^{b3}$, -$NR^{a3}S(=O)_2R^{c3}$ and -$NR^{e3}S(=O)_2NR^{a3}R^{b3}$;

2) C_{1-6} alkyl, 6-10 membered aryl, 5-10 membered heteroaryl, C_{3-10} cycloalkyl and 3-10 membered aliphatic heterocyclyl, unsubstituted or optionally substituted with 1, 2, 3, 4, 5 or 6 substituents independently selected from R^{23};

3) two R^{13}, together with two adjacent ring-forming atoms of the aryl or heteroaryl of Cy^B to which they are connected respectively, form a C_{4-8} aliphatic cyclyl or 4-8 membered aliphatic heterocyclyl, unsubstituted or optionally substituted with 1, 2, 3 or 4 substituents independently selected from R^{23}.

In some embodiments, each R^{13} is independently selected from:

1) oxo, halogen, cyano, -C(=O)R^{a3}, -C(=O)$NR^{a3}R^{b3}$, -C(=NR^{d3})$NR^{a3}R^{b3}$, -OR^{a3}, -$NR^{a3}R^{b3}$, -NR^{a3}C(=O)R^{b3}, -NR^{a3}C(=O)OR^{c3}, -NR^{e3}C(=O)$NR^{a3}R^{b3}$, -NR^{e3}C(=NR^{d3})$NR^{a3}R^{b3}$, -$NR^{a3}S(=O)_2R^{c3}$, and -$NR^{e3}S(=O)_2NR^{a3}R^{b3}$;

2) C_{1-6} alkyl, phenyl, 5-6 membered heteroaryl, C_{3-10} cycloalkyl and 3-10 membered aliphatic heterocyclyl, unsubstituted or optionally substituted with 1, 2, 3 or 4 substituents independently selected from R^{23};

3) two R^{13}, together with two adjacent ring-forming atoms of the aryl or heteroaryl of Cy^B to which they are connected respectively, form a C_5, C_6, C_7 aliphatic monocyclyl or 5 membered, 6 membered, 7 membered aliphatic monocyclic heterocyclyl, unsubstituted or optionally substituted with 1, 2 or 3 substituents independently selected from R^{23}.

In some embodiments, each R^{13} is independently selected from:

1) oxo, halogen, cyano, C_{1-4} alkyl, C_{3-6} cycloalkyl, -C(=O)R^{a3}, -C(=O)$NR^{a3}R^{b3}$, -OR^{a3}, -$NR^{a3}R^{b3}$, -NR^{a3}C(=O)R^{b3}, -NR^{e3}C(=O)$NR^{a3}R^{b3}$ and -NR^{e3}C(=NR^{d3})$NR^{a3}R^{b3}$;

2) two R^{13}, together with two adjacent ring-forming atoms of the aryl or heteroaryl of Cy^B to which they are connected respectively, form a C_{4-8} aliphatic cyclyl or 4-8 membered aliphatic

heterocyclyl, unsubstituted or optionally substitutedwith 1, 2, 3 or 4 substituents independently selected from R^{23}.

In some embodiments, each R^{13} is independently selected from:

1) oxo, fluorine, chlorine, cyano, C_{1-3} alkyl, C_{3-4} cycloalkyl, $-C(=O)R^{a3}$, $-C(=O)NR^{a3}R^{b3}$, $-OR^{a3}$, $-NR^{a3}R^{b3}$, $-NR^{a3}C(=O)R^{b3}$, $-NR^{e3}C(=O)NR^{a3}R^{b3}$ and $-NR^{e3}C(=NR^{d3})NR^{a3}R^{b3}$;

2) two R^{13}, together with two adjacent ring-forming atoms of the aryl or heteroaryl of Cy^B to which they are connected respectively, form a C_{5-6} aliphatic monocyclyl or 5-6 membered aliphatic monocyclic heterocyclyl, unsubstituted or optionally substituted with 1, 2 or 3 substituents independently selected from R^{23}.

In some embodiments, each R^{13} independently selected from:

1) halogen and cyano;

2) C_{1-4} alkyl, C_{3-6} cycloalkyl and 3-6 membered aliphatic heterocyclyl, unsubstituted or optionally substituted with 1, 2 or 3 substituents each independently selected from fluorine, cyano, $-OR^{a5}$ and $-NR^{a5}R^{b5}$; wherein R^{a5} and R^{b5} are each independently selected from hydrogen and C_{1-6} alkyl, or, R^{a5} and R^{b5} attached to the same N atom, together with the N atom, form a 3-6 membered aliphatic heterocyclyl.

In some embodiments, each R^{13} is independently selected from halogen, cyano, $-OR^{a3}$ and $-NR^{a3}R^{b3}$; wherein R^{a3} and R^{b3} are each independently selected from:

1) hydrogen;

2) C_{1-6} alkyl, C_{3-6} cycloalkyl, and 3-6 membered aliphatic heterocyclyl, unsubstituted or optionally substituted with 1, 2 or 3 substituents independently selected from fluorine, cyano, $-OR^{a5}$ and $-NR^{a5}R^{b5}$; wherein R^{a5} and R^{b5} are each independently selected from hydrogen and C_{1-4} alkyl, or, R^{a5} and R^{b5} attached to the same N atom, together with said N atom, form a 3-6 membered aliphatic heterocyclyl.

In some embodiments, R^{13} is independently selected from:

1) fluorine, chlorine, cyano, C_{1-3} alkyl, C_{3-4} cycloalkyl, $-OR^{a3}$ and $-NR^{a3}R^{b3}$;

2) two R^{13}, together with two adjacent ring-forming atoms of the aryl or heteroaryl of Cy^B to which they connected respectively, form a C_{5-6} aliphatic monocyclyl or 5-6 membered aliphatic monocyclic heterocyclyl, unsubstituted or optionally substituted with 1, 2 or 3 substituents independently selected from R^{23};

R^{a3} and R^{b3} are each independently selected from hydrogen, C_{1-4} alkyl and C_{3-6} cycloalkyl, or, R^{a3} and R^{b3} attached to the same N atom, together said N atom, form a 3-6 membered aliphatic heterocyclyl; R^{23} selected from C_{1-6} alkyl and C_{3-6} cycloalkyl.

In some embodiments, two R^{13}, together with two adjacent ring-forming atoms of the aryl or heteroaryl of Cy^B to which they attached respectively, form a C_{3-7} aliphatic cyclyl or 3-7 membered aliphatic heterocyclyl, unsubstituted or optionally substituted with 1, 2 or 3 substituents independently selected from oxo, fluorine, cyano, $-OR^{a5}$ and $-NR^{a5}R^{b5}$; wherein said 3-7 membered aliphatic heterocyclyl contains 1 or 2 ring-forming heteroatoms selected from N, O and S; R^{a5} and R^{b5} are each independently selected from hydrogen and C_{1-4} alkyl, or, R^{a5} and R^{b5} attached to the same N atom, together with said N atom, form a 3-6 membered aliphatic heterocyclyl.

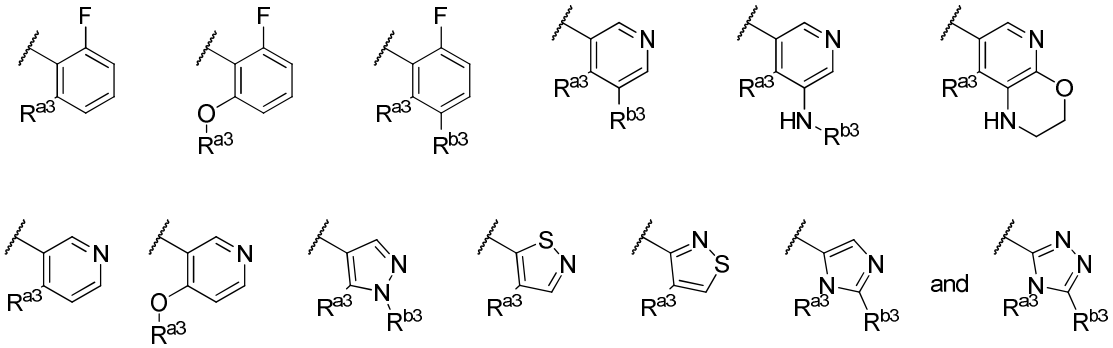
In some embodiments, each R^{13} independently selected from halogen, amino, C_{1-3} alkyl, substituted C_{1-3} alkyl, C_{1-3} alkoxy, substituted C_{1-3} alkoxy, C_{3-6} cycloalkoxy, C_{1-3} alkylamino and $-C(=O)NR^{a3}R^{b3}$; wherein the substituent of substituted C_{1-3} alkyl is selected from one, two or three of halogen, hydroxyl, C_{1-3} alkoxy, and C_{1-3} alkyl; the substituent of substituted C_{1-3} alkoxy is selected from one, two or three halogens; R^{a3} and R^{b3} are each independently selected from hydrogen and C_{1-3} alkyl, or, R^{a3}, R^{b3} attached to the same N atom, together with said N atom, form a 3-6 membered aliphatic heterocyclyl, unsubstituted or optionally substituted with one or two substituents selected from C_{1-3} alkyl, C_{1-3} alkoxy, and hydroxyl.

In some embodiments, each R^{13} is independently selected from -F, -Cl, $-NH_2$, $-CH_3$, -

CH_2CH_3, $-CH(CH_3)CH_3$, $-CF_3$, $-CHF_2$, $-CH_2OCH_3$, $-OCH_3$, $-OCH_2CH_3$, $-OCH(CH_3)CH_3$, $-OCHF_2$, $-O(C_3H_5)$(cyclopropoxy), $-CH_2NHCH_3$, $-CH_2N(CH_3)_2$, $-NHCH_3$, $-N(CH_3)_2$, $-NHCH_2CH_3$, $-N(CH_3)(CH_2CH_3)$, $-N(CH_2CH_3)_2$, $-NR^{a3}R^{b3}$, $-C(=O)NHCH_3$, $-C(=O)N(CH_3)_2$, and $-C(=O)NR^{a3}R^{b3}$; in $-NR^{a3}R^{b3}$ and $-C(=O)NR^{a3}R^{b3}$, R^{a3}, R^{b3} attached to the same N atom, together with said N atom, form a 4 or 5 membered saturated aliphatic monocyclic heterocyclyl, unsubstituted or optionally substituted with one or two substituents selected from methyl, hydroxyl, and methoxy.

In some embodiments, two R^{13}, together with two adjacent ring-forming atoms of the aryl or heteroaryl of Cy^B to which they connected respectively, form a 5 membered or 6 membered aliphatic monocyclic heterocyclyl containing one or two ring-forming heteroatoms selected from N and O, said aliphatic monocyclic heterocyclyl is unsubstituted or optionally substituted with 1 or 2 subsituents independently selected from R^{23}; R^{23} may be oxo, fluorine, methyl, $-CH_2OH$, $-NHCH_3$.

In some embodiments, Cy^B is selected from the following structures, wherein the "〰" at the end of the chemical bond in each structure means that the structures are connected to the rest of formula (I) through the bond:



wherein, R^{a3} and R^{b3} are each independently selected from hydrogent and C_{1-6} alkyl, or, R^{a3} and R^{b3}, together with two adjacent ring-forming atoms to which they are attached respectively, form a 5-6 membered aliphatic monocyclyl or 5-6 membered aliphatic monocyclic heterocyclyl.

In some embodiments, R^1 is hydrogen;

Cy^A is selected from phenyl, naphthyl and 5-10 membered heteroaryl, unsubstituted or optionally substituted with 1, 2, 3 or 4 substituents independently selected from R^{12}; wherein 5-10 membered heteroaryl contains at least two ring-forming carbon atoms and 1, 2, 3 or 4 ring-forming heteroatoms independently selected from N, O and S;

R^{12} is selected from:

1) oxo, halogen, cyano, $-C(=O)R^{a2}$, carboxyl, $-C(=O)NR^{a2}R^{b2}$, $-OR^{a2}$, $-NR^{a2}R^{b2}$, $-NR^{a2}C(=O)R^{c2}$, $-NR^{e2}C(=O)NR^{a2}R^{b2}$, $-NR^{e2}C(=NR^{d2})NR^{a2}R^{b2}$, $-NR^{a2}S(=O)_2R^{c2}$ and $-NR^{e2}S(=O)_2NR^{a2}R^{b2}$;

2) C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, phenyl, 5-6 membered heteroaryl, C_{3-7} monocyclic cycloalkyl, C_{6-10} bicyclic cycloalkyl, 3-7 membered aliphatic monocyclic heterocyclyl and 6-10 membered biocyclic aliphatic heterocyclyl, unsubstituted or optionally substituted with 1, 2, 3 or 4 substituents independently selected from R^{22};

3) two R^{12}, together with two adjacent ring-forming atoms of the aryl or heteroaryl in Cy^A to which they connected respectively, form a C_{5-10} aliphatic cyclyl or 5-10 membered aliphatic heterocyclyl, unsubstituted or optionally substituted with 1, 2 or 3 subsituens independently selected from R^{22}; wherein 5-10 membered aliphatic heterocyclyl contains one or two ring-forming heteroatoms independently selected from N, O and S;

R^{a2}, R^{b2} and R^{e2} are each independently selected from:

1) hydrogen;

2) C_{1-4} alkyl, phenyl, 5-6 membered heteroaryl, C_{3-6} cycloalkyl and 3-6 membered aliphatic heterocyclyl, unsubstituted or optionally substituted with 1, 2 or 3 subsituents independently selected from R^{22};

or,

R^{a2} and R^{b2}, togehter with the same N atom to which they are attached, form a 3-8 membered aliphatic heterocyclyl, unsubstituted or optionally substituted with 1, 2 or 3 substituents independently selected from R^{22}; wherein 3-8 membered aliphatic heterocyclyl contains 1 or 2 ring-forming heteroatoms, for example, contains only said N atom, or contains said N atom and another heteroatom independently selected from N, O and S atom;

R^{c2} is selected from C_{1-4} alkyl, C_{2-3} alkenyl, phenyl, 5-6 membered heteroaryl, C_{3-6} cycloalkyl and 3-6 membered aliphatic heterocyclyl, unsubstituted or optionally substituted with 1, 2 or 3 substituents independently selected from R^{22};

R^{d2} is selected from hydrogen, C_{1-4} alkyl, C_{3-6} cycloalkyl, 3-6 membered aliphatic heterocyclyl, cyano, nitro and $-S(=O)_2R^G$;

R^{22} is selected from:

1) oxo, halogen, cyano, carboxyl, $-C(=O)R^{a4}$, $-C(=O)NR^{a4}R^{b4}$, $-C(=NR^{d4})NR^{a4}R^{b4}$, $-OR^{a4}$, $-S(=O)R^{c4}$, $-S(=O)_2R^{c4}$, $-S(=O)_2NR^{a4}R^{b4}$, $-S(=O)(=NR^{d4})R^{c4}$, $-NR^{a4}R^{b4}$, $-NR^{a4}C(=O)R^{b4}$, $-NR^{e4}C(=O)NR^{a4}R^{b4}$, $-NR^{e4}C(=NR^{d4})NR^{a4}R^{b4}$, $-NR^{a4}S(=O)_2R^{c4}$, $-NR^{e4}S(=O)_2NR^{a4}R^{b4}$ and imino group ($=N-R^{d4}$);

2) C_{1-4} alkyl, C_{1-4} alkylene, phenyl, 5-6 membered heteroaryl, C_{3-7} cycloalkyl and 3-7 membered aliphatic heterocyclyl, unsubstituted or optionally substituted with 1, 2 or 3 substituents independently selected from R^{32};

R^{a4}, R^{b4} and R^{e4} are each independently selected from:

1) hydrogen;

2) C_{1-4} alkyl, C_{3-6} monocyclic cycloalkyl and 3-6 membered aliphatic monocyclic heterocyclyl, unsubstituted or optionally substituted with 1, 2 or 3 substituents independently selected from R^{32};

or,

R^{a4} and R^{b4}, together with the same N atom to which they are attached, form a 3-6 membered aliphatic monocyclic heterocyclyl or 6-7 membered bicyclic aliphatic heterocyclyl, unsubstituted or optionally substituted with 1, 2 or 3 substituents independently selected from R^{32}; wherein 3-6 membered aliphatic monocyclic heterocyclyl and 6-7 membered bicyclic aliphatic heterocyclyl contain one or two ring-forming heteroatoms, for example, contains only said N atom, or contains said N atom and another heteroatonm independently selected from N, O and S atom;

R^{c4} is selected from C_{1-4} alkyl, C_{2-3} alkenyl, C_{3-6} monocyclic cycloalkyl and 3-6 membered aliphatic monocyclic heterocyclyl, unsubstituted or optionally substituted with 1, 2 or 3 substituents independently selected from R^{32};

R^{d4} is selected from hydrogen, C_{1-4} alkyl, C_{3-6} monocyclic cycloalkyl, 3-6 membered aliphatic monocyclic heterocyclyl, cyano, nitro and $-S(=O)_2R^G$;

R^{32} is selected from oxo, halogen, cyano, hydroxyl, $-OR^G$, amino, $-NHR^G$, $-N(R^G)_2$, aldehyde group, $-C(=O)R^G$, $-S(=O)_2R^G$, carboxyl, $-C(=O)OR^G$, $-C(=O)NH_2$, $-C(=O)-NHR^G$, $-C(=O)N(R^G)_2$, $-S(=O)_2NH_2$, $-S(=O)_2-NHR^G$ and $-S(=O)_2N(R^G)_2$;

Cy^B selected from phenyl, naphthyl and 5-10 membered heteroaryl, unsubstituted or optionally substituted with 1, 2, 3 or 4 substituents independently selected from R^{13}; wherein 5-10 membered heteroaryl contains at least two ring-forming carbon atoms and 1, 2, 3 or 4 ring-forming heteroatoms independently selected from N, O and S;

R^{13} is selected from:

1) oxo, halogen, cyano, $-C(=O)R^{a3}$, carboxyl, $-C(=O)NR^{a3}R^{b3}$, $-OR^{a3}$, $-NR^{a3}R^{b3}$, $-NR^{a3}C(=O)R^{b3}$, $-NR^{e3}C(=O)NR^{a3}R^{b3}$, $-NR^{e3}C(=NR^{d3})NR^{a3}R^{b3}$, $-NR^{a3}S(=O)_2R^{c3}$ and $-NR^{e3}S(=O)_2NR^{a3}R^{b3}$;

2) C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, phenyl, 5-6 membered heteroaryl, C_{3-7} monocyclic cycloalkyl, C_{6-10} bicyclic cycloalkyl, 3-7 membered aliphatic monocyclic heterocyclyl and 6-10 membered bicyclic aliphatic heterocyclyl, unsubstituted or optionally substituted with 1, 2, 3 or 4 substituents independently selected from R^{23};

3) two R^{13}, together with two adjacent ring-forming atoms of the aryl or heteroaryl in Cy^B to which they are attached respectively, form a C_{5-10} aliphatic cyclyl or 5-10 membered aliphatic heterocyclyl, unsubstituted or optionally substituted with 1, 2 or 3 substituents independently selected from R^{23}; wherein said 5-10 membered aliphatic heterocyclyl contains 1 or 2 ring-forming heteroatoms independently selected from N, O and S;

R^{a3}, R^{b3} and R^{e3} are each independently selected from:

1) hydrogen;

2) C_{1-4} alkyl, phenyl, 5-6 membered heteroaryl, C_{3-6} cycloalkyl and 3-6 membered aliphatic heterocyclyl, unsubstituted or optionally substituted with 1, 2 or 3 substituents independently selected from R^{23};

or,

R^{a3} and R^{b3} together with the same N atom to which they are attached form a 3-8 membered aliphatic heterocyclyl, unsubstituted or optionally substituted with 1, 2 or 3 substituents independently selected from R^{23}; wherein 3-8 membered aliphatic heterocyclyl contains one or two ring-forming heteroatoms, for example, contains only said N atom, or contains said N atom and another heteroatom independently selected from N, O and S;

R^{c3} is selected from C_{1-4} alkyl, C_{2-3} alkenyl, phenyl, 5-6 membered heteroaryl, C_{3-6} cycloalkyl and 3-6 membered aliphatic heterocyclyl, unsubstituted or optionally substituted with 1, 2 or 3 substituents independently selected from R^{23};

R^{d3} is selected from hydrogen, C_{1-4} alkyl, C_{3-6} cycloalkyl, 3-6 membered aliphatic heterocyclyl, cyano, nitro and $-S(=O)_2R^G$;

R^{23} is selected from:

1) oxo, halogen, cyano, carboxyl, $-C(=O)R^{a5}$, $-C(=O)NR^{a5}R^{b5}$, $-C(=NR^{d5})NR^{a5}R^{b5}$, $-OR^{a5}$, $-S(=O)R^{c5}$, $-S(=O)_2R^{c5}$, $-S(=O)_2NR^{a5}R^{b5}$, $-S(=O)(=NR^{d5})R^{c5}$, $-NR^{a5}R^{b5}$, $-NR^{a5}C(=O)R^{b5}$, $-NR^{e5}C(=O)NR^{a5}R^{b5}$, $-NR^{e5}C(=NR^{d5})NR^{a5}R^{b5}$, $-NR^{a5}S(=O)_2R^{c5}$, $-NR^{e5}S(=O)_2NR^{a5}R^{b5}$ and imino group ($=N-R^{d5}$);

2) C_{1-5} alkyl, C_{1-5} alkylene, phenyl, 5-6 membered heteroaryl, C_{3-7} cycloalkyl and 3-7 membered aliphatic heterocyclyl, unsubstituted or optionally substituted with 1, 2 or 3 substituens independently selected from R^{33};

R^{a5}, R^{b5} and R^{e5} are each independently selected from:

1) hydrogen;

2) C_{1-4} alkyl, C_{3-6} monocyclic cycloalkyl and 3-6 membered aliphatic monocyclic heterocyclyl, unsubstituted or optionally substituted with 1, 2 or 3 substituents independently selected from R^{33};

or,

R^{a5} and R^{b5} together with the same N atom to which they are attached form a 3-6 membered aliphatic monocyclic heterocyclyl or 6-7 membered bicyclic aliphatic heterocyclyl, unsubstituted or optionally substituted with 1, 2 or 3 substitents independently selected from R^{33}; wherein 3-6 membered aliphatic monocyclic heterocyclyl and 6-7 membered bicyclic aliphatic heterocyclyl contains one or two ring-forming heteroatoms, for example, contains only said N atom, or contains said N atom and another heteroatom independently selected from N, O and S;

R^{c5} is selected from C_{1-4} alkyl, C_{2-3} alkenyl, C_{3-6} monocyclic cycloalkyl and 3-6 membered aliphatic monocyclic heterocyclyl, unsubstituted or optionally substituted with 1, 2 or 3 substituents independently selected from R^{33};

R^{d5} is selected from hydrogen, C_{1-4} alkyl, C_{3-6} monocyclic cycloalkyl, 3-6 membered aliphatic monocyclic heterocyclyl, cyano, nitro and $-S(=O)_2R^{GA}$;

R^{33} is selected from oxo, halogen, cyano, hydroxyl, -OR^{GA}, amino, -NHR^{GA} and -$N(R^{GA})_2$;

Each R^{GA} are each independently selected from:

C_{1-4} alkyl, C_{1-4} alkylene, C_{3-6} cycloalkyl and 4-6 membered aliphatic heterocyclyl, unsubstituted or optionally substituted with 1, 2 or 3 fluorine atoms;

or,

two R^{GA} together with the same N atom to which they are attached form a 4-6 membered aliphatic monocyclic heterocyclyl, unsubstituted or optionally substituted with 1, 2 or 3 fluorine atoms; wherein 4-6 membered aliphatic monocyclic heterocyclyl contains one or two ring-forming heteroatoms, for example, contains only said N atom, or contains said N atom and another heteroatom indenpendently selected from N, O and S.

In some embodiments, the application provides a pharmaceutical composition including the compound of formula (I) or a pharmaceutically acceptable salt, hydrate, solvate, active metabolite, polymorph, isotope labeled compound, isomer or prodrug thereof and a pharmaceutically acceptable carrier.

The pharmaceutical combination may be prepared in a manner well known in the pharmaceutical field, and may be administered by various routes. The mode of administration may be topical (including transdermal, epidermal, ocular and mucosal, including intranasal, vaginal, and rectal delivery), pulmonary (e.g., by inhalation or insufflation of powders or aerosols, including by nebulizer; intratracheal or intranasal), oral or parenteral.

In some embodiments, the composition is suitable for parenteral administration, including intravenous, intraarterial, subcutaneous, intraperitoneal, intramuscular or infusion; or intracranial, such as intrathecal or intraventricular administration. Parenteral administration may be in the form of a single bolus dose, or (e.g.) continuous perfusion pump.

In some embodiments, the composition is suitable for topical administration, which .may include transdermal patches, ointments, lotions, creams, gels, drops, suppositories, sprays, liquids and powders. Conventional pharmaceutical carriers, aqueous, powdered or oily matrices, thickeners and the like may be necessary or desired.

In some embodiments, the application provides use of the compound of formula (I) or a pharmaceutically acceptable salt, hydrate, solvate, active metabolite, polymorph, isotope labeled compound, isomer or prodrug thereof, or a pharmaceutical composition thereof, for the prevention or treatment of a disease mediated with HPK1.

In some embodiments, the application provides a method for regulating, for example, inhibiting, the activity of HPK1, including administering the compound of formula (I) or a pharmaceutically acceptable salt, hydrate, solvate, active metabolite, polymorph, isotope labeled compound, isomer or prodrug thereof, or a pharmaceutical composition thereof to a patient, in order to stimulate and/or boost immunity to cancers or viral diseases.

In some embodiments, the application provides a method for preventing, ameliorating or treating a disease mediated with HPK1 in a patient, including administering therapeutically effective amount of the compound of formula (I) or a pharmaceutically acceptable salt, hydrate, solvate, active metabolite, polymorph, isotope labeled compound, isomer or prodrug thereof, or a pharmaceutical composition thereof to the patient.

In some embodiments, the application provides use of the compound of formula (I) or a pharmaceutically acceptable salt, hydrate, solvate, active metabolite, polymorph, isotope labeled compound, isomer or prodrug thereof, or a pharmaceutical composition thereof, for the treatment or amelioration of benign or malignant tumors, myelodysplastic syndromes and diseases caused by viruses.

In some embodiments, the application provides use of the compound of formula (I) or a pharmaceutically acceptable salt, hydrate, solvate, active metabolite, polymorph, isotope labeled compound, isomer or prodrug thereof, or a pharmaceutical composition thereof, for the treatment or amelioration of benign or malignant tumors.

In some embodiments, the application provides use of the compound of formula (I) or a pharmaceutically acceptable salt, hydrate, solvate, active metabolite, polymorph, isotope labeled compound, isomer or prodrug thereof, or a pharmaceutical composition thereof, for the treatment or amelioration of diseases caused by viruses.

In some embodiments, the application provides use of the compound of formula (I) or a pharmaceutically acceptable salt, hydrate, solvate, active metabolite, polymorph, isotope labeled compound, isomer or prodrug thereof, or a pharmaceutical composition thereof, in the preparation of a medicament for the treatment or amelioration of one or more particular diseases selected from benign or malignant tumors, myelodysplastic syndromes and diseases caused by viruses.

In some embodiments, the application provides use of the compound of formula (I) or a pharmaceutically acceptable salt, hydrate, solvate, active metabolite, polymorph, isotope labeled compound, isomer or prodrug thereof, or a pharmaceutical composition thereof, in the preparation of a medicament for the treatment or amelioration of benign or malignant tumors.

In some embodiments, the application provides use of the compound of formula (I) or a pharmaceutically acceptable salt, hydrate, solvate, active metabolite, polymorph, isotope labeled compound, isomer or prodrug thereof, or a pharmaceutical composition thereof, in the preparation of a medicament for the treatment or amelioration of diseased caused by viruses.

In some embodiments, the malignant tumors include one or more of leukemia, lymphoma, multiple myeloma, lung cancer, hepatocellular carcinoma, cholangiocarcinoma, gallbladder cancer, gastric cancer, colorectal cancer, intestinal leiomyosarcoma, breast cancer, ovarian cancer, cervical cancer, endometrial cancer, vaginal cancer, malignant teratoma, pancreatic cancer, pancreatic ductal adenocarcinoma, nasopharyngeal cancer, oral cancer, laryngeal cancer, esophageal squamous cell carcinoma, thyroid cancer, kidney cancer, bladder cancer, malignant brain tumor, rhabdomyosarcoma, osteosarcoma, chondrosarcoma, osteofibrosarcoma, malignant thymoma, malignant peripheral nerve sheath tumor, prostate cancer, testicular cancer, penile cancer and other malignant tumors, as well as benign and malignant tumors of the skin (including but not limited to melanoma, basal cell carcinoma, squamous cell carcinoma).

In some embodiments, the tumor is a tumor producing PGE2 (e.g., COX-2 overexpressed tumor) and/or an adenosine-producing tumor (e.g., CD39 and CD73 overexpressed tumor), such as colorectal cancer, breast cancer, pancreatic cancer, lung cancer and ovarian cancer.

In some embodiments, the virus includes one or more of hepatitis virus, human immunodeficiency virus, human papillomavirus, herpes simplex virus, measles virus, norovirus, Boca virus, Coxsackie virus, Ebola virus, enterovirus, lymphocytic meningitis virus, influenza virus, SARS virus and novel coronavirus.

Definition of Terms

In this disclosure, unless otherwise specified, a definition of a certain group applies to all groups containing this group. For example, the definition of alkyl is applicable to C1-C6 alkyl, C1-C3 alkyl, etc.; the definition of C1-C6 alkyl is applicable to "C1-C6 alkoxy", etc., and the following definitions are applicable to the claims and the description.

When a structure contains multiple substituents represented by the same symbol, the substituents may be the same or different; For example, the Cy^B contains two R^{13} as substituents, wherein the two R^{13} may be both methoxy, or one may be methoxy, and the other may be methyl.

The term "halogen" includes fluorine, chlorine, bromine, and iodine.

The term "C_{m-n}" (where m and n is an integer, and indicates the range that includes the end point) represents corresponding groups containing m-n carbon atoms, for example, C_{1-6} alkyl represents an alkyl containing 1-6 carbon atoms, and C_{2-6} alkenyl represents an alkenyl containing 2-6 carbon atoms.

The term "n membered" (where n is an integer) usually describes the number of ring-forming atoms, where the number of ring-forming atoms is n. "m-n membered" indicates the range that

includes the end point, representing that the corresponding ring structure contains m-n ring-forming atoms. For example, piperidinyl is an example of a 6-membered heterocyclyl, and pyrazolyl is an example of a 5-membered heteroaryl.

The term "substituted" refers to a hydrogen of a structure is displaced by a "substituent". Unless otherwise indicated, the term "substituted" means any degree of substitution as long as said substitution is permitted. The choice of substituents is independent and the substitution may be in any chemically accessible position. It should be understood that substitution on a given atom is limited by chemical valence. It should be understood that substitution on a given atom produces chemically stable molecules. One divalent substituent (e.g., oxo) will displace two hydrogen atoms.

"The rest of the compound" refers to the portion of the whole molecular structure except for the "substituent" described. The rest of the compound is connected to the substituent by one or more unsaturated valences. The rest of the compound may contain one or more "junctions", and two or more junctions may be on the same atom or different atoms.

The term "alkyl" refers to a straight-chain or branched-chain saturated hydrocarbon group. Alkyl is a group formed by the loss of a hydrogen of an alkane. The examples of alkyl include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, n-pentyl, isopentyl, 2-methylbutyl, neopentyl, 1-ethylpropyl, n-hexyl, 1,2,2-trimethylpropyl and the like.

The term "alkenyl" refers to a straight or branched chain hydrocarbon group having one or more carbon - carbon double bonds. Alkenyl are a group formed by the loss of a hydrogen atom in an olefin. The examples of the alkenyl may be vinyl, 1-propenyl, 2-propenyl, allyl, 1-butenyl, 2-butenyl, (*E*)-but-2-ene-1-yl, (*Z*)-but-2-ene-1-yl, 2-methyl-propy-1-ene-1-yl, 1,3-butadiene-1-yl, 1,3-butadiene-2-yl and the like.

The term "alkynyl" refers to a straight or branched chain hydrocarbon group having one or more carbon-carbon triple bonds. Alkynyl is a group formed by the loss of one hydrogen atom from an alkyne. Examples of alkynyl may be ethynyl, 1-propynyl, propargyl, 1-butynyl, but-2-yn-1-yl, but-3-yn-1-yl, but-3-ene-1-alkynyl, 3-methylpent-2-ene-4-yn-1-yl and the like.

The term "alkylene" refers to a divalent group formed by losing two hydrogen atoms on the carbon atom of an alkane at the same time, wherein the two valences may be connected to the same atom, or connected to two atoms respectively. For example, methylene ($-CH_2-$ or $=CH_2$), 1,1-ethylene ($-CH(CH_3)-$ or $=CH-CH_3$), 1,2-ethylene ($-CH_2CH_2-$), but-1,4-diyl, but-1,3-diyl, 2,2-dimethyl-prop-1,3-diyl, etc.

The term "alkoxy" refers to a group with formula "-O-alkyl", wherein the alkyl group is as defined above. Alkoxy may be, for example, methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, tert-butoxy and n-hexoxy and the like.

The term "alkylthio" refers to a group of formula "-S-alkyl", wherein the alkyl group is as defined above. "alkylthio" may be, for example, methylthio, ethylthio, n-propylthio, isopropylthio, n-butylthio, tert-butylthio and n-hexylthio and the like.

The term "alkylamino" includes a group of formula "-NH-alkyl" and a group of formula "-N-$(alkyl)_2$", wherein the alkyl group is as defined above. The group of formula "-NH-alkyl" may be, for example, methylamino, ethylamino, isopropylamino and n-hexylamino and the like; The group of formula "-N-$(alkyl)_2$" may be, for example, dimethylamino, diethylamino, methylethylamino, methylisopropylamino and ethyl-n-hexylamino and the like.

The term "alkyl sulfinyl" refers to a group of formula "-S (=O)-alkyl", wherein the alkyl group is as defined above. For example, it may be methyl sulfinyl, ethyl sulfinyl, isopropyl sulfinyl and the like.

The term “alkyl sulfonyl” refers to a group of formula “$-S(=O)_2$-alkyl”, wherein the alkyl group is as defined above. For example, it may be methyl sulfonyl, ethyl sulfoyl, isopropyl sulfonyl and the like.

The term "alkylaminosulfinyl" comprises a group of formula "-S(=O)-NH-alkyl" and a

group of formula "-S(=O)-N(alkyl)$_2$", wherein the alkyl group is as defined above. The group of formula "-S(=O)-NH-alkyl" may be, for example, methylaminosulfinyl, ethylaminosulfinyl, isopropylaminosulfinyl, tert-butylaminosulfinyl and the like. The group of formula "-S(=O)-N(alkyl)$_2$" may be, for example, dimethylaminosulfinyl, diethylaminosulfinyl, methylethylaminosulfinyl, ethyl isobutylaminosulfinyl and the like.

The term "alkylaminosulfonyl" comprises a group of formula "-S(=O)$_2$-NH-alkyl" and a group of formula "-S(=O)$_2$-N(alkyl)$_2$", wherein the alkyl group is as defined above. The group of formula "-S(=O)$_2$-NH-alkyl" may be, for example, methylaminosulfonyl, ethylaminosulfonyl, isopropylaminosulfonyl, tert-butylaminosulfonyl, etc. The group of formula "-S(=O)$_2$-N(alkyl)$_2$" may be, for example, dimethylaminosulfonyl, diethylaminosulfonyl, methyl isopropylaminosulfonyl, ethyl tert-butylaminosulfonyl and the like.

The term “carbonyl” refers to a group of formula “-(C=O)-”, which may also be represented by “-C(O)-”.

The term “cyano” refers to a group of formula “-C≡N”, which may also be represented by “-CN”.

The term “hydroxymethyl”refers to a group of formula “-CH$_2$OH”.

The term "oxo" refers to an oxygen atom as a divalent substituent, when connected to a carbon atom to form a carbonyl group, or to the heteroatom to form a sulfinyl or sulfonyl, or N-oxide group and the like. In some embodiments, cycloalkyl and heterocyclyl may optionally be substituted by one or two oxo groups.

The term "imino group" or "=N-R", refers to an amino group as a divalent substituent, wherein two valents of the same nitrogen atom are connected to one atom selected from the rest of the compound to form a double bond, and the third valence of the nitrogen atom is connected to the R group defined by the context. The nitrogen atom may form imide, amidine or guanidine when connected to a carbon atom, or forms a sulfinyl imide or the like when connected to a heteroatom.

The term "cyclyl" includes aliphatic and aromatic monocyclyl or polycyclyl. The aliphatic monocyclyl contains a cyclyl, including cyclized alkyl and alkenyl. Aliphatic polycyclyl contains two or more cyclyls wherein at least one cyclyl is an aliphatic monocyclyl (including cyclized alkyl and alkenyl), the other cyclyls may be aliphatic and/or aromatic cyclyls. In aliphatic polycyclyl, any one of the rings is connected to at least one another ring to form a spiro ring (two rings share a ring-forming atom) or a bridged ring (two rings share two or more ring-forming atoms). The polycyclyl is connected to the rest of the compound by a ring carbon atom. It may be, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclopentenyl, cyclohexadienyl, dicyclo[3.1.0]hexyl, norbornyl, norpinanyl, dicyclo[1.1.1] pentyl, 1*H*-inden-1-yl, 2,3-dihydro-1*H*-inden-2-yl and the like. When a cyclyl only contains saturated rings, the cyclyl is a saturated cyclyl, also named as the "cycloalkyl".

The term "cycloalkoxy" refers to a group of formula "-O-cycloalkyl", wherein the cycloalkyl is as defined above. It may be, for example, cyclopropoxy.

The cyclyl includes a "cyclylene", i.e., the cyclyl is connected by two chemical valences to two connection points of the rest of the compound, and the two chemical valences described may be on the same carbon atom of the cyclylene, or may be on two different carbon atoms of the cyclylene. The two connection points may be located on the same atom of the rest of the compound, or located on two different atoms of the rest of the compound. For example, it may be 1,1-cyclobutylene, 1,3-cyclobutylene, and the like.

The term "aryl" refers to an aromatic monocyclyl or polycyclyl. For example, it may be phenyl, naphthyl, and the like.

The term "heterocyclyl" refers to a monocyclylic or polycyclic group having at least one ring-forming heteroatom selected from oxygen, nitrogen, sulfur and phosphorus. The poly-

heterocyclyl contains two or more rings, wherein at least one ring has at least one ring-forming heteroatom selected from oxygen, nitrogen, sulfur and phosphorus, and the other ring may have ring-forming heteroatoms or not. In poly-heterocyclyl, any one of the rings is connected to at least one other ring to form a spiro ring (two rings share a ring-forming atom) or a bridged ring (two rings share two or more ring-forming atoms). The heterocyclyl may be connected to the rest of the compound by an optional ring-forming carbon atom, or by an optional ring-forming heteroatom. In some embodiments, any of the ring carbon atoms in the heterocyclyl may be substituted by an oxo group to form a carbonyl group. In some embodiments, any ring nitrogen atom in the heterocyclyl may be *N*-oxide. In some embodiments, any ring nitrogen atom in the heterocyclyl may be quaternary ammonium ion.

Heterocyclyl includes aromatic heterocyclyl (i.e., "heteroaryl") and aliphatic heterocyclyl.

The term "heteroaryl" refers to an aromatic monoheterocyclyl or polyheterocyclyl having at least one ring-forming heteroatom selected from oxygen, nitrogen and sulfur. The heteroaryl group may be connected to the rest of the compound by an optional carbon atom, or by an optional heteroatom, provided that the chemical valence of the carbon atom or heteroatom allows. In some embodiments, any of the ring-forming carbon atoms in the heteroaryl may be substituted by an oxo group to form a carbonyl group. In some embodiments, any ring-forming nitrogen atom in the heteroaryl may be *N*-oxide. In some embodiments, any ring nitrogen atom in the heteroaryl may be quaternary ammonium ion. For example, the heteroaryl may be pyrrolyl (including pyrrol-1-yl, pyrrol-2-yl and pyrrol-3-yl), pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, triazolyl, tetrazolyl, pyridyl, pyridin-2(1*H*)-one-1-yl, pyridin-4(1*H*)-one-1-yl, pyrazinyl, pyrimidinyl, pyridazinyl, pyrazin-3(2*H*)-one-2-yl, 1,2,4-triazinyl, 1,3,5-triazinyl, indolyl, benzofuranyl, benzothienyl, indazolyl, benzoimidazolyl, benzisothiazolyl, quinolinyl, isoquinolinyl, naphthyridinyl, imidazo[1,2-b]thiazolyl, purinyl, etc..

The term "aliphatic heterocyclyl" includes monocyclic or polycyclic aliphatic heterocyclyl. The monocyclic aliphatic heterocyclyl (aliphatic monoheterocyclyl) may not contain double bond or contain one or more double bonds in the rings. The polycyclic aliphatic heterocyclyl (aliphatic polyheterocyclyl) contains at least one alicycle, and other rings may be aliphatic or aromatic rings. The polycyclic aliphatic heterocyclyl may not contain a double bond or contain one or more double bonds in the rings. For example, it may be azetidinyl, oxetanyl, tetrahydropyrrolyl, tetrahydrofuranyl, 2-oxo-oxazolidinyl, piperidinyl, 3-oxo-piperidinyl, piperazinyl, morpholinyl, azepanyl, 2-oxa-6-azaspiro[3.3]heptyl, 1,2,3,4-tetrahydroquinolinyl, etc.

The term “heterocyclyl” includes a heterocyclylene, i.e., a heterocyclyl is connected to two points of attachment to the rest of the compound through two valences, and the two valences may be in the same ring-forming atom of the heterocyclylene. It may also be located on the two ring-forming atoms of the heterocyclylene group. The two connection points may be located on the same atom in the rest of the compound, or may be located on two atoms in the rest of the compound. For example, 1,1-(3-oxetanylene), 1,3-(2-azacyclopentylene), and the like.

The term "fused rings" refers to a bridged ring system formed by two rings sharing two adjacent ring-forming atoms. The two rings may be saturated alicyclic, unsaturated alicyclic or aromatic rings. The two adjacent ring-forming atoms are optionally carbon atoms or heteroatoms.

The term "n-membered oxaalkylene" refers to a divalent group formed by replacing one or more carbon atoms in the main chain of an n-membered alkylene with oxygen atom(s). The two valences as described may be on the same atom of the rest of the compound, or may be on two atoms of the rest of the compound. For example, 2-oxa-1,3-propylene (-CH2OCH2-) is an example of 3-membered oxaalkylene. 2-oxa-1,4-butylene (-CH2OCH2CH2-) is an example of a 4-membered oxaalkylene and the like. An alkylene group in which only branched-chain carbon atom(s) is replaced by oxygen atom(s) should not be considered "oxaalkylene"; for example, in 2-methyl-1,3-propylene, when the branched-chain methyl is replaced by oxygen, and the resulted group (-CH2CH(OH)CH2-) should be regarded as 2-hydroxy substituted 1,3-propylene.

The term "n-membered azaalkylene" refers to a divalent group formed by replacing one or more carbon atoms in the main chain of an n-membered alkylene with nitrogen atom(s), and the two valences described may be on the same atom of the rest of the compound, or on two separate atoms of the rest of the compound. For example, 2-aza-1,3-propylene (-CH2NHCH2-) is an example of 3-membered azaalkylene, and aza-1,2-ethylene (-CH2NH-) is an example of a 2-membered azaalkylene, and the like. An alkylene group in which only branched-chain carbon atom(s) is substituted with nitrogen atom(s) should not be considered "azaalkylene"; for example, in 2-methyl-1,3-propylene, when the branched-chain methyl is replaced by nitrogen, and the resulted group (-CH2CH(NH2)CH2-) should be regarded as 2-amino substituted 1,3-propylene.

The term "isomer" refers to isomers that result from different spatial arrangements of atoms in a molecule. "Stereoisomers" of the compounds described herein refers to all stereoisomers. For example, when the compound has asymmetric carbon atoms, enantiomers and diastereomers are produced; when the compound has carbon-carbon double bonds, carbon-nitrogen double bonds, or ring structures, cis- or trans- isomers are produced. Unless otherwise indicated, the compounds described herein include all isomers thereof, such as optical isomers, geometric isomers, rotational isomers, tautomers, stably existing conformational isomers, and the like; and the compounds may exist as a mixture of isomers or as isolated isomers.

Methods for preparing optically active products from optically inactive starting materials are known in the art, e.g., by resolution of racemic mixtures or by stereoselective synthesis.

Resolution of racemic mixtures of compounds may be carried out by any of a number of methods known in the art. One method involves fractional recrystallization using a chiral resolving acid that is an optically active salt-forming organic acid. Suitable resolving agents for fractional recrystallization may be optically active acids such as D-tartaric acid, L-tartaric acid, diacetyltartaric acid, dibenzoyltartaric acid, mandelic acid, malic acid, camphorsulfonic acid, etc. Other suitable resolving agents for fractional recrystallization include, for example, methylbenzylamine, 2-phenylglycinol, cyclohexylethylamine and the like in stereoisomerically pure form.

Methods for resolution of racemic mixtures also include, for example, the separation of diastereomers obtained by reaction with appropriate optically active species such as chiral alcohols or Mosher's acid chlorides, and then conversion (such as hydrolysis) to the corresponding single optical isomer. For example, it may be performed by elution on a chromatographic column packed with an optically active resolving agent. Suitable chromatographic column and elution solvents may be determined by those skilled in the art.

The term "isotope labeled compounds" refers to a compound of the present application in which one or more atoms are replaced by a particular isotopic atom thereof. For example, the isotopic atom in the compound of the present application may include various isotopes of elements H, C, N, O, F, P, S, Cl and I, such as ^{2}H, ^{3}H, ^{13}C, ^{14}C, ^{15}N, ^{17}O, ^{18}O, ^{18}F, ^{30}P, ^{32}P, ^{35}S, ^{36}S, ^{123}I, ^{124}I and ^{125}I, etc. This application includes various isotope labeled compounds as defined. For example, they may be those compounds in which radioactive isotopes such as ^{3}H and ^{14}C are present, or those in which non-radioactive isotopes such as ^{2}H and ^{13}C are present. Such isotope labeled compounds are suitable for metabolic studies (using ^{14}C), reaction kinetic studies (using e.g, ^{2}H or ^{3}H), detection or imaging techniques such as positron emission tomography (PET) or single photon emission computed tomography (SPECT), including drug or substrate tissue distribution analysis; or radiotherapy for patients, etc.

In particular, ^{18}F compounds may be particularly desirable for PET or SPECT studies. Isotope labeled compounds of formula (I) may generally be prepared by conventional techniques known to those skilled in the art or by methods analogous to those described in the accompanying examples and preparations using an appropriate isotope labeled reagent in place of the unlabeled reagents.

Furthermore, substitution with heavier isotopes, especially deuterium (i.e, ^{2}H or D), may

yield certain therapeutic advantages resulting from greater metabolic stability, such as increased in vivo half-life or reduced dose requirements or improved therapeutic index, and thus in some cases it may be preferred.

The term "pharmaceutically acceptable" refers to those compounds, materials, compositions and/or dosage forms, which are within the scope of sound medical judgment, suitable for use in contact with human and animal tissue without excessive of toxicity, irritation, allergic reactions or other problems or complications commensurate with a reasonable benefit/risk ratio.

The term "a pharmaceutically acceptable salt" refers to a salt that retains the biological activity and properties of the compounds of the present application and generally have no biologically or otherwise undesirable effects. In many cases, the compounds of the present application are capable of forming acid and/or base addition salts via the presence of amino and/or carboxyl groups or the like.

The term “pharmaceutically acceptable acid addition salts” may be formed with inorganic and organic acids.

The term “pharmaceutically acceptable base addition salts” may be formed with inorganic and organic bases.

All compounds and pharmaceutically acceptable salts thereof may be found (e.g., hydrates and solvates) with other substances (e.g., solvents, including water and other solvents, etc.) or may be isolated. When in the solid state, the compounds described herein and salts thereof may exist in various forms, including hydrates and solvates. Hydrates and solvates of compounds and salts thereof described herein include those in which water and solvents may be isotopically labeled, such as D_2O, methanol-d_3, methanol-d_4, acetone-d_6, DMSO-d_6. The presence of hydrates and solvates may be identified by those skilled in the art using means such as nuclear magnetic resonance (NMR).

The term "polymorph" refers to compounds of the present application that exist in different crystal lattice forms, as well as in amorphous form. Polymorphs of the compounds of the present application and salts thereof also include mixtures of various lattice forms, as well as mixtures of one or several lattice forms and amorphous form. The presence of polymorphs may be identified by those skilled in the art using means such as X-ray diffraction.

Therefore, unless expressly stated otherwise, references to compounds and salts thereof in this specification are to be understood to encompass any solid state form of the compounds.

The term "active metabolite" refers to an active derivative of a compound that is formed when the compound is metabolized.

The term "a pharmaceutically acceptable prodrug" refers to any pharmaceutically acceptable ester, salt of the ester, amide or other derivative of the compound of the present application, which, upon administration to a subject, is capable of directly or indirectly providing the compound of the present application or its pharmacologically active metabolites or residues. Particularly preferred derivatives or prodrugs are those that increase the bioavailability of the compound of the present application when administered to a patient (e.g., make orally administered compounds more readily absorbed into the blood), or promote the delivery of the compound to biological organs or the site of action.

The term "a pharmaceutical composition" refers to a biologically active compound optionally in admixture with at least one pharmaceutically acceptable chemical component or agent, which is a "carrier" that facilitates for introducing the active compound into cells or tissues, include but are not limited to stabilizers, diluents, suspending agents, thickening agents and/or excipients. The pharmaceutical composition includes, but are not limited to, the following forms: tablets, pills, powders, lozenges, sachets, cachets, elixirs, suspensions, emulsions, solutions, syrups, aerosols (solid or dissolved in liquid vehicles), ointments, soft and hard gelatin capsules, suppositories, transdermal patches, sterile injectable solutions and sterile packaged powders, etc.

The term "pharmaceutically acceptable carriers" includes solvents, dispersion media,

coatings, surfactants, antioxidants, preservatives (e.g., antibacterial, antifungal), isotonic agents, absorption delaying agents, salts, preservatives, pharmaceutical stabilizers, binders, excipients, disintegrants, lubricants, sweeteners, flavoring agents, dyes, and the like, well known to those skilled in the art, and combinations thereof. Unless being incompatible with the active compound, any conventional carrier is included in the therapeutic or pharmaceutical compositions.

The term "therapeutically effective amount" refers to the amount of the compound of the present application that induces a biological or medical response in a subject, such as reducing or inhibiting activity of enzyme or protein or ameliorating symptoms, alleviating a condition, slowing or delaying disease progression, or preventing disease, etc. .

The term "subject" or "patient" refers to an individual, including mammals and non-mammals, suffering from a disease, disorder, condition, or the like. Examples of mammal include, but are not limited to, any member of the class mammalia: humans; non-human primates (e.g., chimpanzees and other apes and monkeys); livestock, such as cattle, horses, sheep, goats, pigs; other domesticated animals, such as rabbits, dogs, and cats; laboratory animals, including rodents, such as rats, mice, and guinea pigs, and the like. Examples of non-mammals include, but are not limited to, birds, fish, and the like.

Synthesis

The compounds of the present application and their salts may be prepared using known organic synthesis techniques and may be prepared according to any of some synthetic routes such as those in the schemes below.

The reactions used to prepare the compounds of the present application may be carried out in suitable solvents. Suitable solvents may be substantially unreactive with the starting materials (reactants), intermediates or products at temperatures at which the reaction is carried out (e.g., temperatures that may range from the melting point to the boiling point of the solvent). A given reaction may be carried out in one solvent or a mixture of solvents. Depending on a particular reaction step, one skilled in the art may select an appropriate solvent for a particular reaction step.

The preparation of the compounds of the present application may involve the protection and deprotection of various chemical groups. The need for protection and deprotection and the selection of appropriate protecting groups may be readily determined by those skilled in the art.

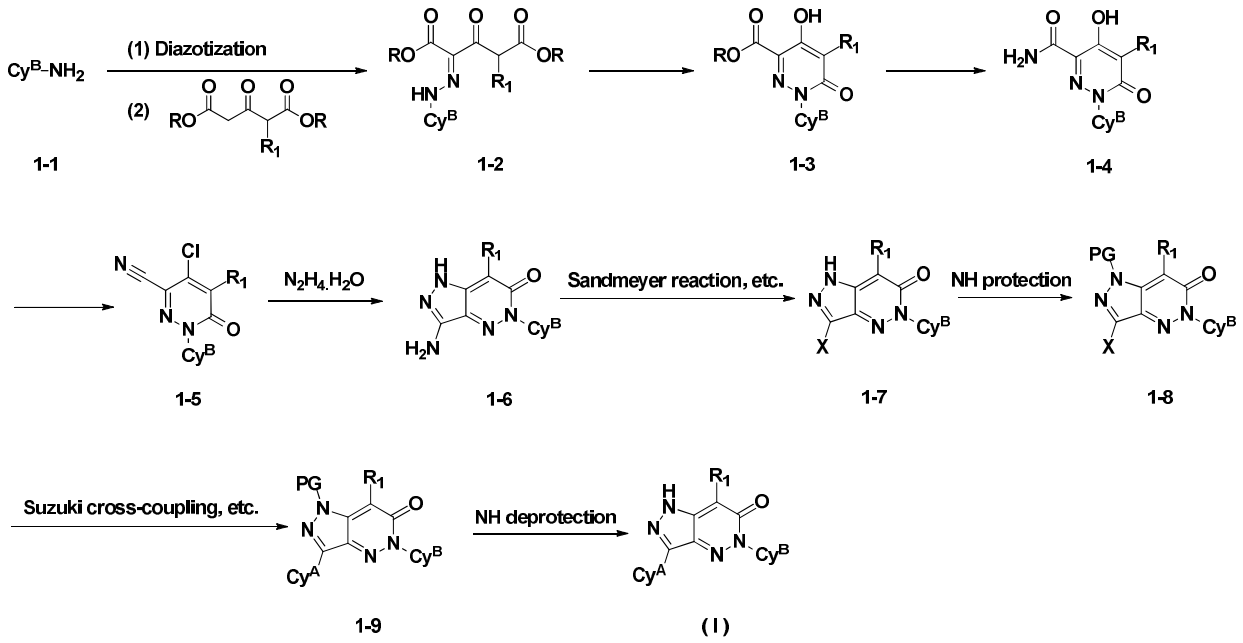
The following schemes provide general guidance related to the preparation of the compounds of the present application. Those skilled in the art will appreciate that general knowledge of organic chemistry may be used to modify or optimize the methods shown in the schemes to prepare the various compounds of the present application.

Compounds of formula (I) may be prepared according to the methods as illustrated in the schemes below.

Various compounds of formula (I) may be prepared using the methods illustrated in Scheme 1. In the method shown in Scheme 1, the compound of formula 1-1 is transformed by diazotization and coupling reaction to the compound of formula 1-2. The compound of formula 1-2 is converted to the compound of formula 1-3 by ring closure reactions such as thermal ring closure, as well as acid or base catalyzed ring closure reactions. The compound of formula 1-3 is amidated to form the compound of formula 1-4. The compound of formula 1-4 is chlorinated and dehydrated (e.g., chlorination and dehydration in the presence of phosphorus oxychloride) to form the compound of formula 1-5. The compound of formula 1-5 is converted to the compound of formula 1-6 bycondensation and ring-closing with hydrazine (or hydrazine hydrate). The compound of formula 1-6 undergoes Sandmeyer or similar reactions to form the halogenated (e.g., chloro, bromo, or iodo) compound of formula 1-7. The NH group of the pyrazolyl of formula 1-7 is protected by a suitable protecting group to form the compound of formula 1-8. The compound of formula 1-8 is then transformed by various cross-coupling reactions (e.g., Suzuki reaction, Stille reaction, etc.) to the compound of formula 1-9. Finally, the compound of formula (I) is

generated by deprotection. By selection of suitable catalyst (e.g. SPhos-Pd-G2), the compound of formula 1-7 may directly undergo various cross-coupling reactions (e.g. Suzuki reaction, Stille reaction, etc.) and subsequent reactions (such as reductive amination, carboxylic acid-amine condensation, etc.) to form the desired compound of formula (I).

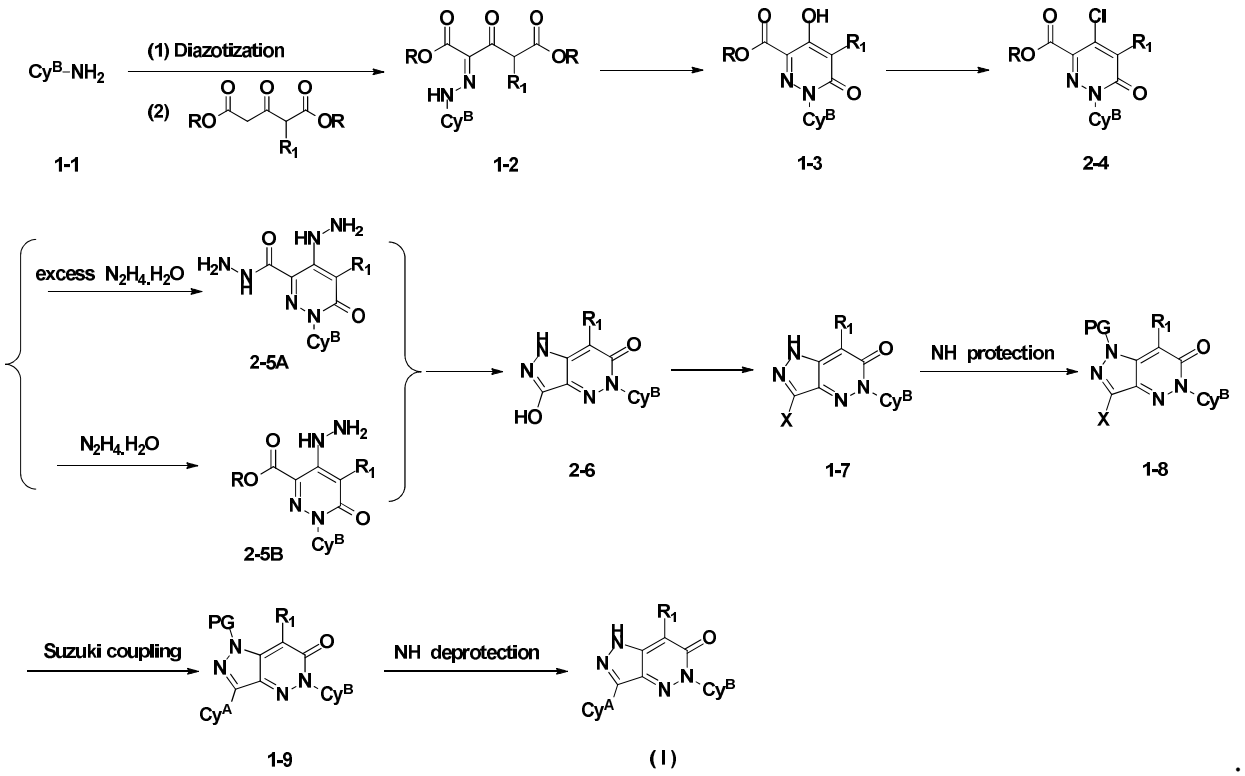
Scheme 1:



.

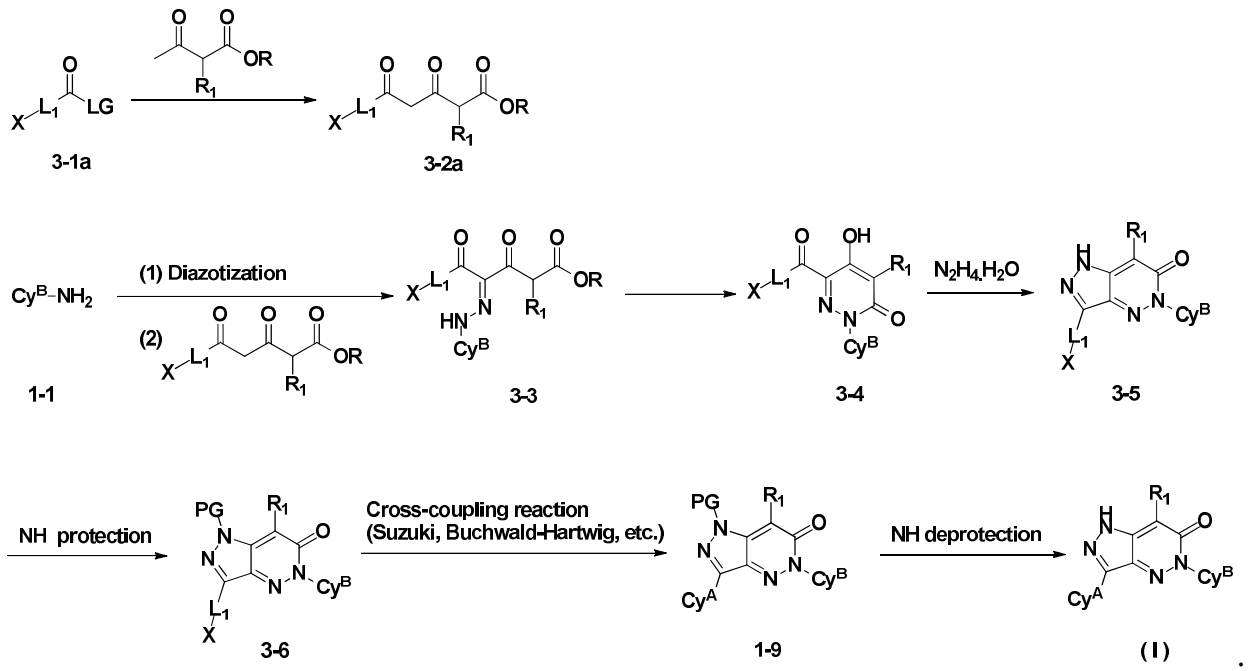
Alternatively, the compounds of formula (I) may be prepared using the methods illustrated in Scheme 2. In the method shown in Scheme 2, firstly, the compound of formula 1-1 is transformed to the compound of formula 1-3 by the same method as shown in Scheme 1. The compound of formula 1-3 is then chlorinated to form the compound of formula 2-4. The compound of formula 2-4 is condensed with excessive hydrazine (or hydrazine hydrate) to form the compound of formula 2-5A; or the compound of formula 2-4 is condensed with one equivalent of hydrazine (or hydrazine hydrate) to form the compound of formula 2-5B. The compound of formula 2-5A or 2-5B may undergo ring closure reactions (e.g., thermal ring closure, and acid- or base-catalyzed ring closure reactions) to form the compound of formula 2-6. The compound of formula 2-6 is halogenated (e.g., chloro, bromo, etc.) to form the compound of formula 1-7. The compound of formula 1-7 may be transformed in a manner as shown in Scheme 1 to form the desired compound of formula (I). Scheme 2 is subdivided into Scheme 2A and Scheme 2B according to different intermediates of formula 2-5A or formula 2-5B.

Scheme 2:



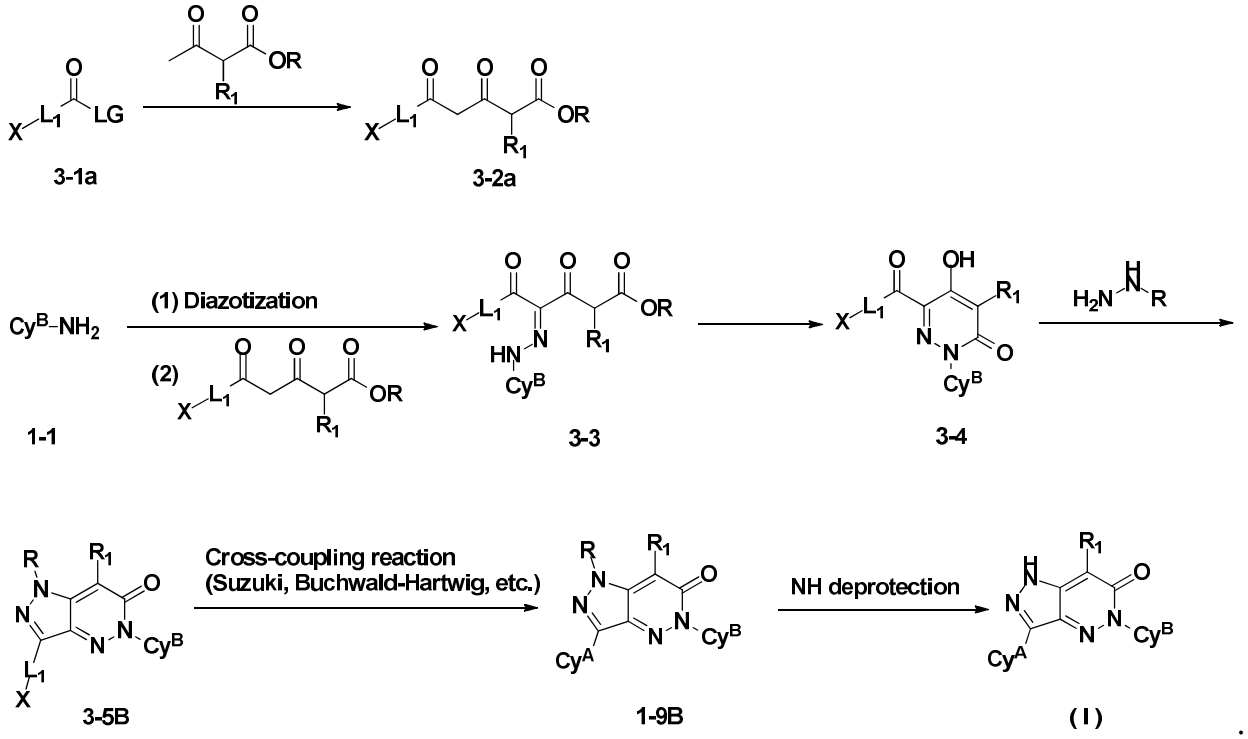
Alternatively, the compounds of formula (I) may be prepared using the method illustrated in Scheme 3A. In the method shown in Scheme 3A, the carboxylic acid derivative compound of formula 3-1a (wherein X is a halogen or a halogen-like group, such as bromine, iodine, etc.; L1 is an aromatic or heteroaromatic ring; LG is a leaving group such as halogen, alkoxy, -N(Me)OMe, etc.) is converted to the compound of formula 3-2a by condensation. The compound of formula 1-1 is diazotizated and coupled with the compound of formula 3-2a to form the compound of formula 3-3. The compound of formula 3-3 is trnasformed to the compound of formula 3-4 by ring closure reaction. The compound of formula 3-4 is condensed with hydrazine (or hydrazine hydrate) to form the compound of formula 3-5A. The NH group of pyrazolyl in the compound of formula 3-5A is protected with an appropriate protecting group to form the compound of formula 3-6. The compound of formula 3-6 undergoes various cross-coupling reactions (e.g., Suzuki reaction, Stille reaction, Buchwald-Hartwig amination, ect.) to form the compound of formula 1-9. Finally, the compound of formula (I) is formed by deprotection of compound 1-9. By selection of suitable catalyst, the compound of formula 3-5A can then be converted to the desired compound of formula (I) through various cross-coupling reactions (e.g. Suzuki reaction, Stille reaction, Buchwald-Hartwig amination, ect.).

Scheme 3A:



Alternatively, the compound of formula (I) may be prepared by the method illustrated in Scheme 3B. The compound of formula 3-4 is condensed with a substituted hydrazine to form the compound of formula 3-5B. The compound of formula 3-5B undergoes various cross-coupling reactions (e.g. Suzuki reaction, Stille reaction, Buchwald-Hartwig amination, etc.) to form the compound of formula 1-9B. Finally, the compound of formula (I) is formed by deprotection of the compound 1-9B.

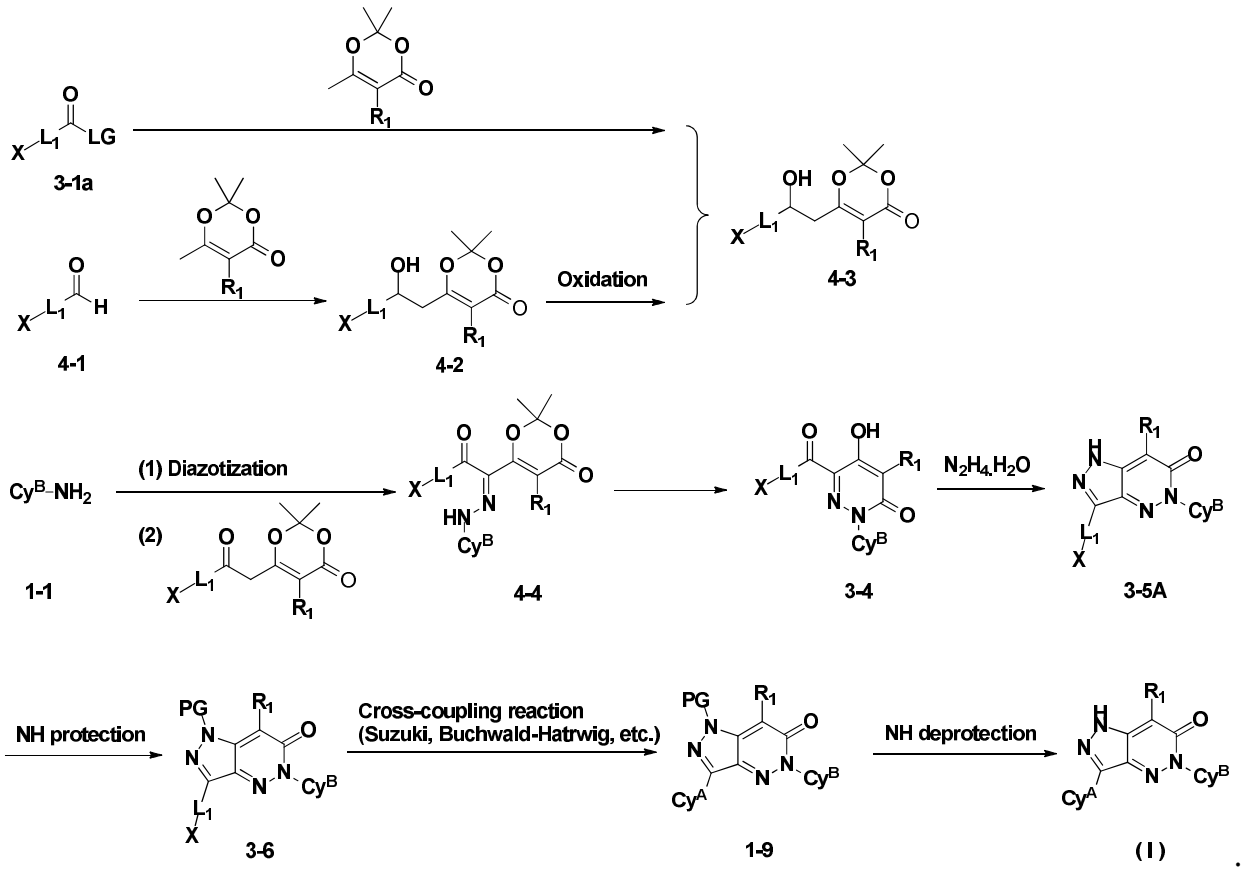
Scheme 3B:



Alternatively, the compound of formula (I) may be prepared using the method illustrated in Scheme 4. In the method shown in Scheme 4, the carboxylic acid derivative compound of formula 3-1a (wherein X is a halogen or a halogen-like group, such as bromine, iodine, etc.; L1 is an aromatic or heteroaromatic ring; LG is a leaving group such as halogen, alkoxy, -N(Me)OMe,

etc.) is converted to the compound of formula 4-3 by condensation; or the aldehyde compound of formula 4-1 is converted to the compound of formula 4-3 by addition reaction and then oxidation (such as using Dess-Martin periodinane). The compound of formula 1-1 is diazotized and then coupled with the compound of formula 4-3 to form the compound of formula 4-4. The compound of formula 4-4 is subjected to ring closure reaction to generate the compound of formula 3-4. The compound of formula 3-4 can then be converted to the desired compound of formula (I) in a manner as shown in Schemes 3A or 3B.

Scheme 4



All methods described in this specification may be performed in any suitable order unless otherwise indicated or clearly contradicted by context. All examples or exemplary language (e.g., "such as") provided in this specification are used only to better clarify the invention, and are not intended to limit the scope of the application as otherwise claimed.

Hereinafter, the preparation and properties of the compounds of formula (I) in some embodiments will be further described with reference to specific examples. Among them, the starting materials used are known and commercially available, or may be synthesized using or according to methods known in the art.

Unless otherwise specified, all reactions in the examples were carried out under continuous magnetic stirring, and the reaction temperature was in degrees Celsius.

The reactions may be monitored according to any suitable method known in the art, such as nuclear magnetic resonance spectroscopy (NMR), infrared spectroscopy (IR), spectrophotometry (e.g., UV-Vis spectroscopy), liquid mass spectrometry (LC-MS), mass spectrometry, high performance liquid chromatography, thin layer chromatography and so on. The products may be purified by any suitable method known in the art, such as column chromatography (normal or reverse phase), preparative thin layer chromatography, trituration, recrystallization, and the like. Generally, 100-200 mesh silica gel from Qingdao Haiyang Chemical Co., Ltd. is used as carrier (stationary phase) in normal phase column chromatography. Silica gel 60 F254 silica gel plate

from Merck Ltd. is used in thin layer chromatography (TLC), and GF254 preparative silica gel plate from Anhui Liangchen Silicon Material Co., Ltd. is used in preparative thin layer chromatography (pre-TLC).

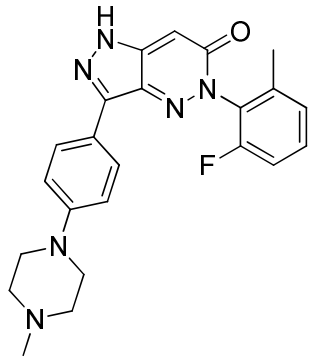
The structures of the compounds in the examples were determined by nuclear magnetic resonance spectroscopy (NMR) and/or liquid chromatography-mass spectrometry (LC-MS). The nuclear magnetic resonance spectrum was measured by Bruker AVANCE-400 nuclear magnetic resonance apparatus, and the solvent was usually deuterated dimethyl sulfoxide (DMSO-d_6) or deuterated chloroform ($CDCl_3$). NMR chemical shifts (δ) were given in parts per million (ppm) using tetramethylsilane (TMS) as the internal standard. LC-MS was performed on an Agilent 1100 series liquid chromatograph and a Bruker HCT-Ultra ion trap mass spectrometer.

Abbreviation Table

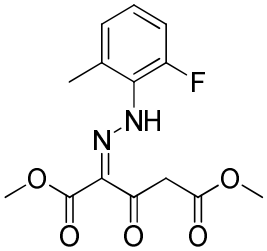
DIPEA	*N*,*N*-diisopropylethylamine
BINAP	1,1'-binaphthalene-2,2'-bisdiphenylphosphine
$Pd_2(dba)_3$	tris(dibenzylideneacetone)dipalladium
$Pd(dppf)Cl_2$	(1,1'-bis(diphenylphosphino)ferrocene)palladium dichloride
$Pd(dppf)Cl_2$-DCM	(1,1'-bis(diphenylphosphino)ferrocene)palladium dichloride-dichloromethane adduct
SPhos-Pd-G2	chloro(2-dicyclohexylphosphino-2',6'-dimethoxy-1,1'-biphenyl)(2'-amino)-1,1'-biphenyl-2-yl)palladium(II)

Example 1

Compound 1: Preparation of 5-(2-fluoro-6-methylphenyl)-3-(4- (4-methylpiperazin-1-yl)phenyl)-1*H*-pyrazolo[4,3-c]pyridazin-6(5*H*)-one (Scheme 1)



Step 1: Preparation of dimethyl 2-(2-(2-fluoro-6-methylphenyl)hydrazino)-3-oxo-glutarate

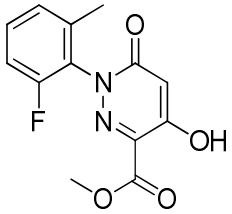


To a there-necked flask containing 2-fluoro-6-methylaniline (5.0 g, 40 mmol) was added hydrochloric acid (4M, 54 mL). The mixture was cooled to 0 ℃. An aqueous solution (30 mL) of sodium nitrite (2.8 g, 40 mmol) was added dropwise, while keeping the temperature of the reaction mixture at 5-10 °C. After stirring for additional 2 hours at 5-10 °C, the mixture formed

was then added rapidly to a vigorously stirred solution of dimethyl 3-oxo-glutarate (7.0 g, 40 mmol) and sodium acetate (21.0 g, 264 mmol) in a solvent mixture of ethanol (30 mL) and water (60 mL) at room temperature, the product precipitated. The reaction mixture was further stirred at room temperature for 2 hours and then filtered with suction. The filter cake was dried to give crude dimethyl 2-(2-(2-fluoro-6-methylphenyl)hydrazino)-3-oxo-glutarate (6.0 g) as a yellow solid. The crude product was directly used in the next step.

ESI-MS: m/z = 310.9 ($[M+H]^+$).

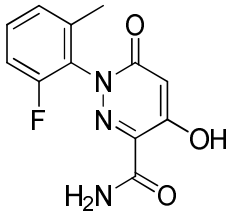
Step 2: Preparation of methyl 1-(2-fluoro-6-methylphenyl)-4-hydroxy-6-oxo-1,6-dihydropyridazine-3-carboxylate



Dimethyl 2-(2-(2-fluoro-6-methylphenyl)hydrazino)-3-oxo-glutarate (6.0 g, 19 mmol) was dissolved in 1,2-dichlorobenzene (100 mL) in a sealed tube, and was heated to reflux. After heating for 4 hours, the reaction mixture was cooled to room temperature, and cyclohexane (300 mL) was added dropwise. The product was crystallized and filtered with suction. The filter cake was dried to give methyl 1-(2-fluoro-6-methylphenyl)-4-hydroxy-6-oxo-1,6-dihydropyridazine-3-carboxylate as a brown solid (2.0 g, 7.2 mmol).Yield: 37%.

ESI-MS: m/z = 279.1 ($[M+H]^+$).

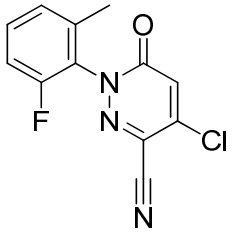
Step 3: Preparation of 1-(2-fluoro-6-methylphenyl)-4-hydroxy-6-oxo-1,6-dihydropyridazine-3-carboxamide



Methyl 1-(2-fluoro-6-methylphenyl)-4-hydroxy-6-oxo-1,6-dihydropyridazine-3-carboxylate (2.0 g, 7.2 mmol) was dissolved in ammonia in methanol (7N, 20 mL) in a sealed tube, and was heated to reflux overnight. The reaction mixture was cooled to room temperature and concentrated to dryness to give the crude product of 1-(2-fluoro-6-methylphenyl)-4-hydroxy-6-oxo-1,6-dihydropyridazine-3-carboxamide (1.6 g) as oil. The crude product was directly used in the next step.

ESI-MS: m/z = 264.1 ($[M+H]^+$).

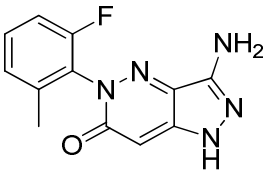
Step 4: Preparation of 4-chloro-1-(2-fluoro-6-methylphenyl)-6-oxo-1,6-dihydropyridazine-3-carbonitrile



To a solution of 4-chloro-1-(2-fluoro-6-methylphenyl)-6-oxo-1,6-dihydropyridazine-3-carbonitrile (1.6 g) in acetonitrile (16 mL) was added phosphorus oxychloride (8 mL) and heated to reflux overnight. The reaction mixture was poured into ice and stirred for 1 hour, and then extracted with ethyl acetate for three times (30 mL × 3). The organic phases were combined, dried, filtered and concentrated to dryness. The residue was purified by column chromatography (petroleum ether/ethyl acetate: 20/1 to 10/1) to give 4-chloro-1-(2-fluoro-6-methylphenyl)-6-oxo-1,6-dihydropyridazine-3-carbonitrile as a white solid (800 mg, 3.04 mmol). Overall yield for two steps: 50%.

ESI-MS: m/z = 264.0 ($[M+H]^+$).

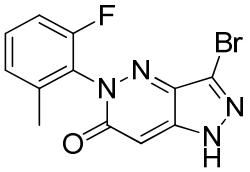
Step 5: Preparation of 3-amino-5-(2-fluoro-6-methylphenyl)-1*H*-pyrazolo[4,3-c]pyridazin-6(5*H*)-one



4-Chloro-1-(2-fluoro-6-methylphenyl)-6-oxo-1,6-dihydropyridazine-3-carbonitrile (800 mg, 3.04 mmol) was dissolved in ethanol (8 mL), and 98% hydrazine hydrate (760 mg, 15 mmol) was added. The reaction tube was sealed and heated to 100°C overnight. The reaction mixture was cooled to room temperature, and the product was precipitated and filtered. The filter cake was dried to give 3-amino-5-(2-fluoro-6-methylphenyl)-1H-pyrazolo[4,3-c]pyridazin-6(5*H*)-one (600 mg, 2.3 mmol) as a red solid. Yield: 75%.

ESI-MS: m/z = 260.1 ($[M+H]^+$).

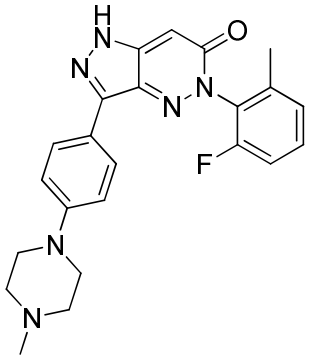
Step 6. Preparation of 3-bromo-5-(2-fluoro-6-methylphenyl)-1*H*-pyrazolo[4,3-c]pyridazin-6(5*H*)-one



3-Amino-5-(2-fluoro-6-methylphenyl)-1*H*-pyrazolo[4,3-c]pyridazin-6(5*H*)-one (600 mg, 2.3 mmol) was dissolved in acetonitrile (12 mL), and tert-butyl nitrite (240 mg) was added dropwise at 0°C. The reaction mixture was stirred at 0°C for 10 minutes, then copper bromide (510 mg) was added and further stirred for 20 minutes. The reaction mixture was poured into water (20 mL) and filtered. The filtrate was extracted with ethyl acetate (20 mL×3) for three times. The combined organic phase was washed with brine, dried, filtered, and concentrated to give crude 3-bromo-5-(2-fluoro-6-methylphenyl)-1*H*-pyrazolo[4,3-c]pyridazine-6(5*H*)-one (400 mg). The crude product was directly used in the next step.

ESI-MS: m/z = 323.0 ($[M+H]^+$).

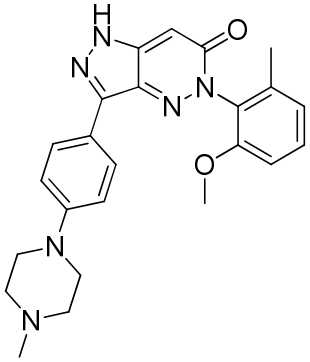
Step 7: Preparation of Compound 1



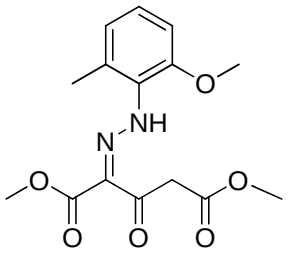
To a single-necked flask was added crude 3-bromo-5-(2-fluoro-6-methylphenyl)-1*H*-pyrazolo[4,3-c]pyridazin-6(5*H*)-one (400 mg, 1.24 mmol), (4-(4-methylpiperazin-1-yl)phenyl)boronic acid pinacol ester (376 mg, 1.24 mmol), potassium carbonate (340 mg, 2.48 mmol), Pd(dppf)Cl_2-DCM (108 mg, 0.147 mmol), 1,4-dioxane (2 mL) and water (2 mL). The mixture was heated to 80°C under nitrogen and stirred for 3 hours. The reaction mixture was cooled to room temperature and concentrated. The residue was purified by preparative high pressure liquid chromatography (pre-HPLC) to give compound 1 (as the trifluoroacetate salt, 5.3 mg, 0.010 mmol) as a brown solid.

Example 2

Compound 2: Preparation of 5-(2-methoxy-6-methylphenyl)-3-(4-(4-methylpiperazin-1-yl)phenyl)-1*H*-pyrazolo[4,3-c]pyridazin-6(5*H*)-one (Scheme 2A)



Step 1: Preparation of dimethyl 2-(2-(2-methoxy-6-methylphenyl)hydrazino)-3-oxo-glutarate

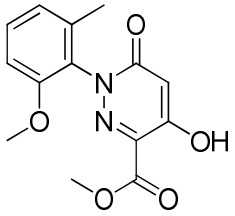


This compound was prepared according to the procedure described in Example 1 (step 1) using 2-methoxy-6-methylaniline instead of 2-fluoro-6-methylaniline as the starting material.

Yield: 79%.

ESI-MS: m/z = 323.2 ($[M+H]^+$).

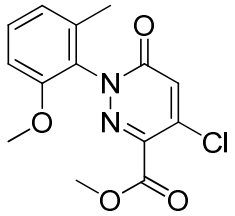
Step 2: Preparation of methyl 4-hydroxy-1-(2-methoxy-6-methylphenyl)-6-oxo-1,6-dihydropyridazine-3-carboxylate



This compound was prepared according to the procedure described in Example 1 (step 2) using dimethyl 2-(2-(2-(2-methoxy-6-methylphenyl)hydrazino)-3-oxo-glutarate instead of dimethyl 2-(2-(2-fluoro-6-methylphenyl)hydrazino)-3-oxo-glutarate as starting material. Yield: 83%.

ESI-MS: m/z = 291.2 ($[M+H]^+$).

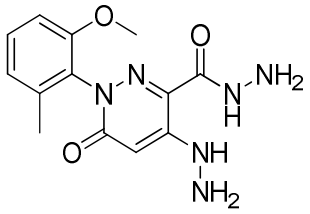
Step 3: Preparation of methyl 4-chloro-1-(2-methoxy-6-methylphenyl)-6-oxo-1,6-dihydropyridazine-3-carboxylate



To phosphorus oxychloride (15 mL) was added methyl 4-hydroxy-1-(2-methoxy-6-methylphenyl)-6-oxo-1,6-dihydropyridazine-3-carboxylate (3.12 g, 10.8 mmol) , and heated to 100°C under nitrogen for 14 hours. The reaction was complete. The reaction mixture was cooled to room temperature, concentrated to dryness, and the residue was purified by column chromatography (petroleum ether/ethyl acetate: 3/1) to obtain methyl 4-chloro-1-(2-methoxy-6-methylphenyl)-6-oxo-1,6-dihydropyridazine-3-carboxylate (2.39 g, 7.74 mmol) as an orange solid. Yield: 72%.

ESI-MS: m/z = 309.1 ($[M+H]^+$).

Step 4: Preparation of 4-hydrazino-1-(2-methoxy-6-methylphenyl)-6-oxo- 1,6-dihydropyridazine-3-carbohydrazide

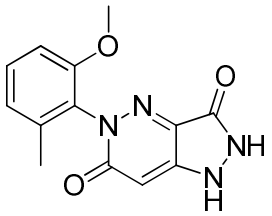


Methyl 4-chloro-1-(2-methoxy-6-methylphenyl)-6-oxo-1,6-dihydropyridazine-3-carboxylate (2.39 g, 7.74 mmol), hydrazine hydrate (1.45 g, 23.2 mmol) and DIPEA (3.84 mL, 23.2 mmol) were added into absolute ethanol (24 mL), and was heated to 80°C under nitrogen for 2 hours. The reaction was complete. The reaction mixture was cooled to 0°C. A precipitate was formed, and collected by filtration. The filter cake was rinsed with cold absolute ethanol

(about 0°C) and dried in vacuo to give 4-hydrazino-1-(2-methoxy-6-methylphenyl)-6-oxo-1,6-dihydropyridazine-3-carbohydrazide (2.06 g, 6.77 mmol) as a yellow solid. Yield: 88%.

ESI-MS: m/z = 305.2 ($[M+H]^+$).

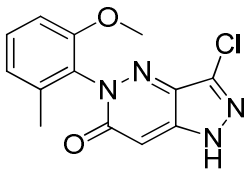
Step 5: Preparation of 5-(2-methoxy-6-methylphenyl)-1*H*-pyrazolo[4,3-c]pyridazin-3,6(2*H*,5*H*)-dione



Methyl 4-hydrazino-1-(2-methoxy-6-methylphenyl)-6-oxo-1,6-dihydropyridazine-3-carboxylate (2.06 g, 6.78 mmol), glacial acetic acid (2.33 mL, 40.7 mmol) and DIPEA (5.60 mL, 33.9 mmol) were added into n-butanol (20 mL), and heated to 120 °C under nitrogen for 15 hours. The reaction was complete. The reaction mixture was cooled to room temperature and concentrated to dryness. The residue was purified by column chromatography (dichloromethane/methanol: 40/1 to 8/1) to give 5-(2-methoxy-6-methylphenyl)-1*H*-pyrazolo[4,3-c]pyridazin-3,6(2*H*,5*H*)-dione (1.67 g, 6.14 mmol) as a reddish-brown solid. Yield: 90%.

ESI-MS: m/z = 273.1 ($[M+H]^+$).

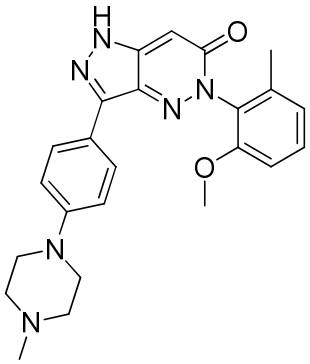
Step 6: Preparation of 3-chloro-5-(2-methoxy-6-methylphenyl)-1*H*-pyrazolo[4,3-c]pyridazin-6(5*H*)-one



To a solution of 5-(2-methoxy-6-methylphenyl)-1,2-dihydro-3*H*-pyrazolo[4,3-c]pyridazine-3,6(5*H*)-dione (200 mg, 0.74 mmol) in acetonitrile (100 mL) was added phosphorus oxychloride (334 uL, 3.67 mmol) and benzyltrimethylammonium chloride (136 mg, 0.74 mmol). The mixture was heated to 70 ℃ under nitrogen, and stirred for 18 hours. The reaction mixture was cooled to room temperature, and concentrated to dryness. The residue was purified by thin layer chromatography (dichloromethane/methanol: 20/1) to give 3-chloro-5-(2-methoxy-6-methylphenyl)-1*H*-pyrazolo[4,3-c]pyridazin-6(5*H*)-one (95 mg, 0.33 mmol) as a yellow solid. Yield: 44%.

ESI-MS: m/z = 291.2 ($[M+H]^+$).

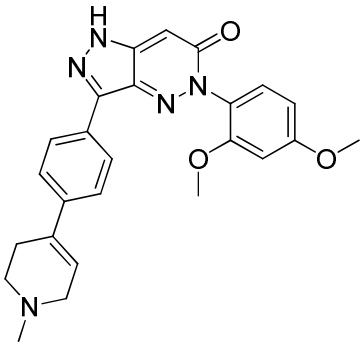
Step 7: Preparation of Compound 2



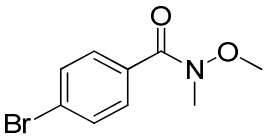
3-Chloro-5-(2-methoxy-6-methylphenyl)-1,5-dihydro-6H-pyrazolo[4,3-c]pyridazin-6-one (50 mg, 0.17 mmol), 4-(4-methyl-1-piperazinyl)phenylboronic acid (76 mg, 0.34 mmol), SPhos-Pd-G2 (10 mg, 0.014 mmol) and potassium phosphate (110 mg, 0.52 mmol) were added to a mixture of 1,4-dioxane (4 mL) and water (1 mL). The mixture was heated to 100° C under nitrogen for 14 hours to complete the reaction. The reaction mixture was cooled to room temperature and concentrated to dryness. The residue was purified by thin layer chromatography (dichloromethane/methanol: 20/1) to give a crude product, which was slurried with methanol (1 mL) in ice-water bath to give compound 2 (61 mg, 0.14 mmol) as a yellow solid. Yield: 82%.

Example 4

Compound 4: 5-(2,4-dimethoxyphenyl)-3-(4-(1-methyl-1,2,3,6-tetrahydropyridin- 4-yl)phenyl)-1*H*-pyrazolo[4,3-c]pyridazin-6(5*H*)-one (Scheme 3A)



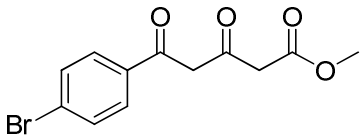
Step 1: Preparation of 4-bromo-*N*-methoxy-*N*-methylbenzamide



To a solution of 4-bromobenzoyl chloride (5.0 g, 22.8 mmol) in dichloromethane (50 mL) cooled in ice-water bath under nitrogen Was added *N*,*O*-dimethylhydroxylamine hydrochloride (2.667 g, 27.34 mmol) and triethylamine (6.32 mL, 45.6 mmol) successively. The mixture was warmed to room temperature gradually and further stirred for 2 hours. Dilute hydrochloric acid (0.1M, 100 mL) was added to quench the reaction. The reaction mixture was extracted with dichloromethane for three times (100 mL×3). The combined organic phase was washed with brine, dried and filtered. The filtrate was concentrated to dryness under reduced pressure to give 4-bromo-*N*-methoxy-*N*-methylbenzamide (5.46 g, 22.4 mmol) as a yellow oil. Yield: 98%.

ESI-MS: m/z = 244.0 ($[M+H]^+$).

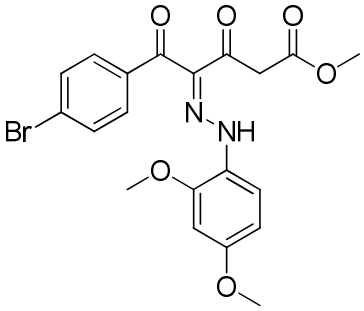
Step 2: Preparation of methyl 5-(4-bromophenyl)-3,5-dioxopentanoate



To an ice water bath-cooled suspension of sodium hydride (360 mg, 9.01 mmol) in dry tetrahydrofuran (20 mL) under nitrogen was added methyl acetoacetate (951 mg, 8.19 mmol) dropwise with stirring. The mixture was stirred for 0.5 hour at the same temperature. The reaction was then cooled to -70°C in a dry ice-acetone bath, and *n*-butyllithium (2.5M in n-hexane, 3.3 mL, 8.2 mmol) was added dropwise. The mixture was stirred for 10 minutes with the temperature maintained. Then, a solution of 4-bromo-*N*-methoxy-*N*-methylbenzamide (2.00 g, 8.19 mmol) in tetrahydrofuran (10 mL) was added dropwise, and then stirred for 1 hour. The reaction was warmed to 0°C, and quenched with saturated ammonium chloride solution (100 mL). The reaction mixture was extracted with ethyl acetate (100 mL × 2). The combined organic phase was washed with saturated brine (100 mL), dried over anhydrous sodium sulfate, and then filtered. The filtrate was concentrated under reduced pressure, and the residue was purified by column chromatography (petroleum ether/ethyl acetate: 10/1) to give methyl 5-(4-bromophenyl)-3,5-dioxopentanoate (1.346 g, 4.5 mmol)) as a yellow oil. Yield: 54%.

ESI-MS: m/z = 299.0 ($[M+H]^+$).

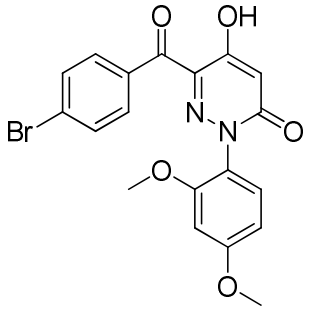
Step 3: Preparation of methyl 5-(4-bromophenyl)-4-(2-(2,4-dimethoxyphenyl)hydrazino)-3,5-dioxopentanoate



To an ice bath-cooled mixture of 2,4-dimethoxyaniline (200 mg, 1.31 mmol) in water (1.6 mL) was added concentrated hydrochloric acid (0.8 mL) and aqueous solution (1.2 mL) of sodium nitrite (90 mg, 1.31 mmol) dropwise, successively. The resultant solution was stirred for 0.5 hours with the temperature maintained to obtain a diazonium salt solution. To a solution of methyl 5-(4-bromophenyl)-3,5-dioxopentanoate (391 mg, 1.31 mmol) and sodium acetate (643 mg, 7.83 mmol) in absolute ethanol (1.2 mL) and water (2.4 mL) was added the above obtained diazonium salt solution dropwise. After the addition, the mixture was stirred at room temperature for 2 hours. The reaction mixture was extracted with dichloromethane for three times(20 mL×3), dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure, and the residue was purified by column chromatography (petroleum ether/ethyl acetate: 10/1 to 1/8) to give methyl 5-(4-bromophenyl)-4-(2-(2,4)-dimethoxyphenyl)hydrazino)-3,5-dioxopentanoate (325 mg, 0.70 mmol) as an orange solid. Yield: 54%.

ESI-MS: m/z = 463.1 ($[M+H]^+$).

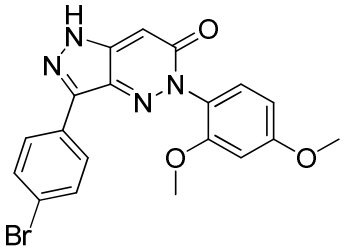
Step 4: Preparation of 6-(4-bromobenzoyl)-2-(2,4-dimethoxyphenyl)-5-hydroxypyridazin-3(2*H*)-one



Methyl 5-(4-bromophenyl)-4-(2-(2,4-dimethoxyphenyl)hydrazinomethylene)-3,5-dioxopentanoate (100 mg, 0.22 mmol) was dissolved in *o*-dichlorobenzene (2 mL), heated to 175°C and stirred for 5 hours under nitrogen. The reaction mixture was cooled to room temperature, diluted with ethyl acetate (10 mL), and extracted with saturated sodium bicarbonate solution for three times (10 mL×3). The combined aqueous phases was adjusted to pH = 4-5 with saturated citric acid solution, and extracted with ethyl acetate twice (20 mL×2). The organic phases were combined, dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated to dryness under reduced pressure to give 6-(4-bromobenzoyl)-2-(2,4-dimethoxyphenyl)-5-hydroxypyridazin-3(2*H*)-one (67 mg, 0.16 mmol) as a yellow solid. Yield: 72%.

ESI-MS: m/z = 431.1 ($[M+H]^+$).

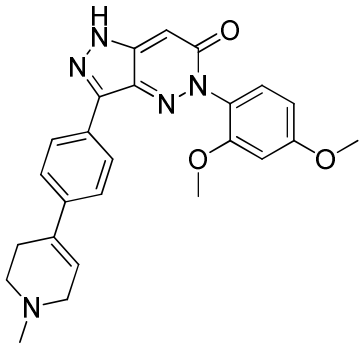
Step 5: Preparation of 3-(4-bromophenyl)-5-(2,4-dimethoxyphenyl)-1*H*-pyrazolo[4,3-c]pyridazin-6(5*H*)-one



To a solution of 6-(4-bromobenzoyl)-2-(2,4-dimethoxyphenyl)-5-hydroxypyridazin-3(2*H*)-one (47 mg, 0.11 mmol) in *n*-butanol (2 mL) was added glacial acetic acid (31 uL, 0.55 mmol) and hydrazine hydrate (33 uL, 0.55 mmol). The mixture was heated to 120° C under nitrogen and stirred for 15 hours. The reaction mixture was cooled to room temperature. Precipitate formed. The solid was collected by filtration and dried in vacuo to give 3-(4-bromophenyl)-5-(2,4-dimethoxyphenyl)-1*H*-pyrazolo[4,3-c]pyridazine-6(5*H*)-one (27 mg, 0.063 mmol) as a yellow solid. Yield: 58%.

ESI-MS: m/z = 427.1 ($[M+H]^+$).

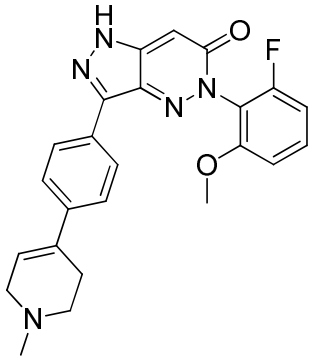
Step 6: Preparation of Compound 4



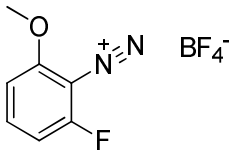
3-(4-Bromophenyl)-5-(2,4-dimethoxyphenyl)-1*H*-pyrazolo[4,3-c]pyridazin-6(5*H*)-one (10.0 mg, 0.023 mmol), 1-methyl-1,2,3,6-tetrahydropyridine-4-boronic acid pinacol ester (10.4 mg, 0.047 mmol), SPhos-Pd-G2 (1.7 mg, 0.002 mmol) and potassium phosphate (14.9 mg, 0.070 mmol) were added to a solvent mixture of 1,4-dioxane (1.6 mL) and water (0.4 mL). The resultant mixture was heated to 100°C under nitrogen and stirred for 15 hours. The reaction mixture was cooled to room temperature, concentrated to dryness, and the residue was purified by thin layer chromatography (dichloromethane/methanol: 10/1) to obtain the crude product, which was slurried with methanol (0.5 mL) at room temperature to obtain compound 4 (3.4 mg, 0.0077 mmol) as a yellow solid. Yield: 33%.

Example 23

Compound 23: 5-(2-fluoro-6-methoxyphenyl)-3-(4-(1-methyl-1,2,3,6-tetrahydro-pyridin-4-yl)phenyl)-1*H*-pyrazolo[4,3-c]pyridazin-6(5*H*)-one (Scheme 4)



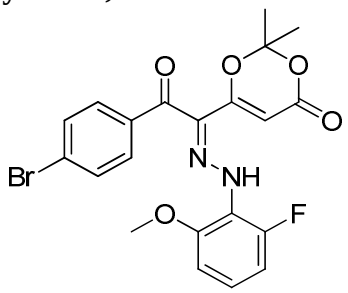
Step 1: Preparation of 2-methoxy-6-fluorophenyldiazonium tetrafluoroborate



To dry methyl *tert*-butyl ether (8 mL) cooled to -5°C under nitrogen was added boron trifluoride diethyl ether complex (1.1 mL, 8.9 mmol) and a solution of 2-fluoro-6-methoxyaniline (614 mg, 4.35 mmol) in dry methyl *tert*-butyl ether (3 mL) successively. After stirring for 15 minutes, the reaction mixture was cooled to -15°C. A solution of *tert*-butyl nitrite (0.62 mL, 5.2 mmol) in dry methyl *tert*-butyl ether (3 mL) was added dropwise. After the addition, the reaction mixture was gradually warmed to 0°C. Dry tetrahydrofuran (5 mL) was added, and stirring was continued at 0°C for 2 hours. The reaction mixture was filtered, and the filter cake was washed

with methyl *tert*-butyl, collected, and dried at room temperature to give 2-methoxy-6-fluorophenyldiazonium tetrafluoroborate (955 mg, 3.98 mmol) as a gray solid, Yield: 91%.

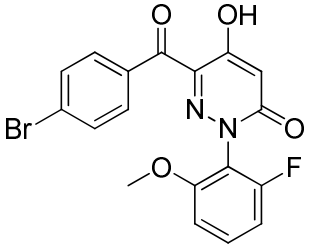
Step 2: Preparation of 6-(2-(4-bromophenyl)-1-(2-(2-fluoro-6-methoxyphenyl)-hydrazino)-2-oxo-ethyl)-2,2-dimethyl-4*H*-1,3-dioxin-4-one



To a solution of 6-(2-(4-bromophenyl)-2-oxo-ethyl)-2,2-dimethyl-4*H*-1,3-dioxin-4-one (694 mg, 2.13 mmol) in ethanol (20 mL) was added sodium acetate (506 mg, 6.16 mmol), and cooled to -5°C. To the above mixture was added a solution of 2-methoxy-6-fluorophenyldiazonium tetrafluoroborate (539 mg, 2.25 mmol) in acetonitrile (3 mL) dropwise, and stirred for 20 minutes. The reaction mixture was poured into a mixture of ethyl acetate and aqueous ammonium chloride solution with stirring. After pahse separation, the aqueous phase was extracted with ethyl acetate. The combined organic phase was dried and concentrated to give the crude product of 6-(2-(4-bromophenyl)-1-(2-(2-fluoro-6-methoxyphenyl)hydrazino)-2-oxo-ethyl)-2,2-dimethyl-4*H*-1,3-dioxin-4-one. The crude product was used directly in the next step without purification.

ESI-MS: m/z = 477.1 ($[M+H]^+$).

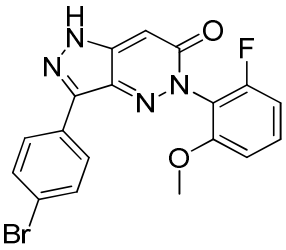
Step 3: Preparation of 6-(4-bromobenzoyl)-2-(2-fluoro-6-methoxyphenyl)-5-hydroxypyridazin-3(2*H*)-one



To a solution of 6-(2-(4-bromophenyl)-1-(2-(2-fluoro-6-methoxyphenyl)hydrazino)-2-oxo-ethyl)-2,2-dimethyl-4*H*-1,3-dioxin-4-one (970 mg, 2.03 mmol) in 1,2-dichlorobenzene (4 mL) was added glacial acetic acid (485 μL), and heated to 130°C for 1 hour. The reaction mixture was cooled to room temperature, and poured into *n*-heptane (120 mL) cooled in an ice-water bath with stirring. The resultant precipitate was collected by filtration, dried in vacuo to give 6-(4-bromobenzoyl)-2-(2-fluoro-6-methoxyphenyl)-5-hydroxypyridazin-3(2*H*)-one (518 mg, 1.23 mmol) as an orange-red solid. Yield: 61%.

ESI-MS: m/z = 419.1 ($[M+H]^+$).

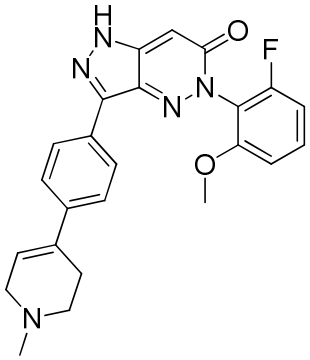
Step 4: Preparation of 3-(4-bromophenyl)-5-(2-fluoro-6-methoxyphenyl)-1*H*-pyrazolo[4,3-c]pyridazin-6(5*H*)-one



This compound was prepared according to the procedure described in Example 4 (step 5) using 6-(4-bromobenzoyl)-2-(2-fluoro-6-methoxyphenyl)-5-hydroxypyridazine-3(2*H*)-one instead of 6-(4-bromobenzoyl)-2-(2,4-dimethoxyphenyl)-5-hydroxypyridazin-3(2*H*)-one as starting material. Yield: 70%.

ESI-MS: m/z = 415.1 ($[M+H]^+$).

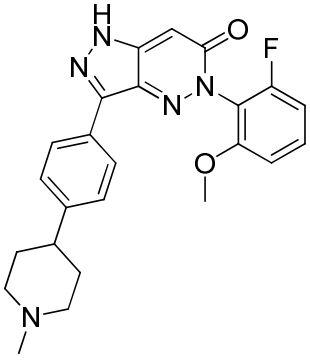
Step 5: Preparation of Compound 23



This compound was prepared according to the procedure described in Example 4 (step 6) using 3-(4-bromophenyl)-5-(2-fluoro-6-methoxyphenyl)-1H-pyrazolo[4,3-c]pyridazin-6(5H)-one instead of 3-(4-bromophenyl)-5-(2,4-dimethoxyphenyl)-1H-pyrazolo[4,3-c]pyridazin-6(5H)-one as starting material with yield of 58%.

Example 24

Compound 24: 5-(2-fluoro-6-methoxyphenyl)-3-(4-(1-methylpiperidin-4-yl)phenyl)-1H-pyrazolo[4,3-c]pyridazin-6(5H)-one

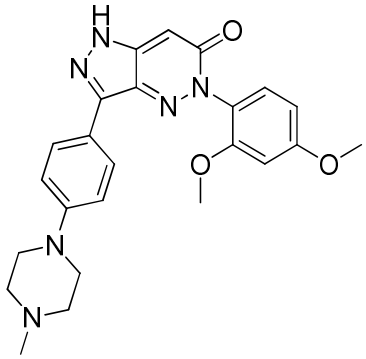


To a solution of compound 23 (60 mg, 014 mmol) in a solvent mixture of anhydrous methanol (6 mL) and tetrahydrofuran (6 mL) was added 10% Pd/C(12 mg), and stirred at room temperature overnight under a hydrogen atmosphere. The Pd/C was removed by filtration, and the filtrate was concentrated to dryness. The residue was purified by thin layer chromatography (dichloromethane/anhydrous methanol: 10/1) to give 5-(2-fluoro-6-methoxyphenyl)-3-(4-(1-methylpiperidin-4-yl)phenyl)-1H-pyrazolo[4,3-c]pyridazin-6(5H)-one (32 mg, 0.074 mmol).

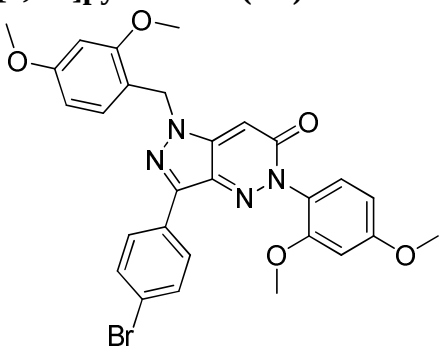
Yield: 53%.

Example 25

Compound 25: 5-(2,4-dimethoxyphenyl)-3-(4-(4-methylpiperazin-1-yl)phenyl)-1H-pyrazolo[4,3-c]pyridazin-6(5H)-one (Scheme 3B)



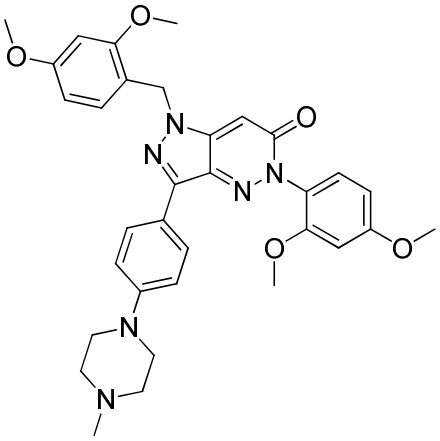
Step 1: Preparation of 3-(4-Bromophenyl)-1-(2,4-dimethoxybenzyl)-5-(2,4-dimethoxyphenyl)-1H-pyrazolo[4,3-c]pyridazin-6(5H)-one



6-(4-bromobenzoyl)-2-(2,4-dimethoxyphenyl)-5-hydroxypyridazin-3(2H)-one was prepared according to the procedure described in Example 4 (step 4). 6-(4-bromobenzoyl)-2-(2,4-dimethoxyphenyl)-5-hydroxypyridazin-3(2H)-one (840 mg, 1.95 mmol), 2,4-dimethoxyphenylhydrazine dihydrochloride (646 mg, 2.53 mmol) and anhydrous sodium acetate (479 mg, 5.84 mmol) were added to n-butanol (10 mL), heated to 100° C for 1 hour. The reaction mixture was cooled to room temperature, and the precipitate was collected by filtration. The solid was purified by column chromatography (petroleum ether/ethyl acetate: 1/9 to 0/10) to give 3-(4-bromophenyl)-1-(2,4-dimethoxybenzyl)-5-(2,4-dimethoxyphenyl)-1H-pyrazolo[4,3-c]pyridazin-6(5H)-one (532 mg, 0.92 mmol). Yield: 36%.

ESI-MS: m/z = 577.2 ([M+H]$^+$).

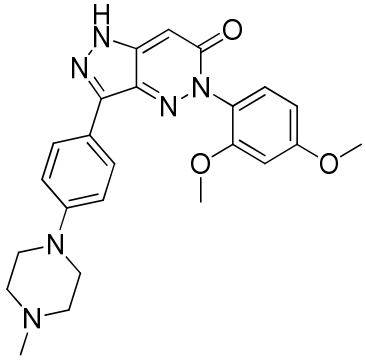
Step 2: Preparation of 1-(2,4-dimethoxybenzyl)-5-(2,4-dimethoxyphenyl)-3-(4-(4-methylpiperazin-1-yl)phenyl)-1H-pyrazolo[4,3-c] pyridazin-6(5H)-one



To a mixture of 3-(4-bromophenyl)-1-(2,4-dimethoxybenzyl)-5-(2,4-dimethoxyphenyl)-1H-pyrazolo[4,3-c]pyridazin-6(5H)-one (450 mg, 0.78 mmol), methylpiperazine (390 mg, 3.9 mmol), $Pd_2(dba)_3$ (71 mg, 0.078 mmol) and BINAP (121 mg, 0.195 mmol) in toluene (9 mL) was added a solution of sodium *tert*-pentoxide in toluene (3.5M, 1.1 mL) under nitrogen. The resultant mixture was heated to 100°C and stirred overnight. The reaction mixture was diluted with dichloromethane and washed with water. The organic phase was dried and concentrated. The residue was purified by column chromatography (dichloromethane/methanol: 100/1 to 30/1) to give 1-(2,4-dimethoxybenzyl)-5-(2,4-dimethoxyphenyl)-3-(4-(4-methylpiperazin-1-yl)phenyl)-1H-pyrazolo[4,3-c]pyridazin-6(5H)-one (203 mg , 0.34 mmol) as an orange-red solid. Yield: 44%.

ESI-MS: m/z = 597.4 ($[M+H]^+$).

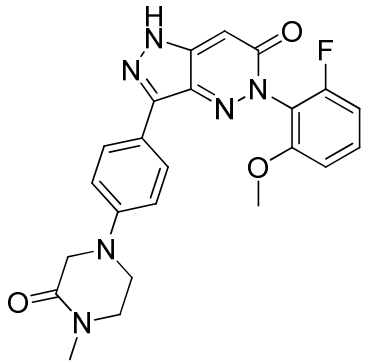
Step 3: Preparation of Compound 25



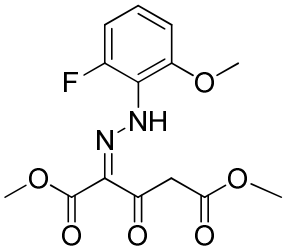
To a solution of 1-(2,4-dimethoxybenzyl)-5-(2,4-dimethoxyphenyl)-3-(4-(4-methylpiperazin-1-yl)phenyl)-1H-pyrazolo[4,3-c]pyridazin-6(5H)-one (200 mg, 0.34 mmol) in trifluoroacetic acid (6 mL) was added anisole (0.3 mL), and heated to 80 °C for 2 hours. The reaction mixture was cooled to room temperature, diluted with water (20 mL), and extracted with ethyl acetate for three times. The aqueous phase was adjusted to pH = 8 with sodium carbonate solution, and solid precipitated. The solid was collected by filtration, dried, and slurried with methanol to give compound 25 (90 mg, 0.20 mmol) as an orange solid. Yield: 60%.

Example 29

Compound 33: 5-(2-fluoro-6-methoxyphenyl)-3-(4-(4-methyl-3-oxo-piperazin-1-yl)phenyl)-1H-pyrazolo [4,3-c]pyridazin-6(5H)-one (Scheme 2B)



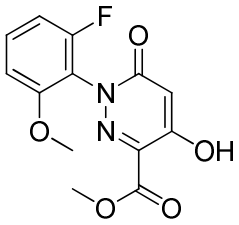
Step 1: Preparation of dimethyl 2-(2-(2-(2-fluoro-6-methoxyphenyl)hydrazino)-3-oxo-glutarate



This compound was prepared according to the procedure described in Example 2 (step 1) using 2-fluoro-6-methoxyaniline instead of 2-methoxy-6-methylaniline as the starting material. Yield: 94%.

ESI-MS: m/z = 327.2 ([M+H]$^+$).

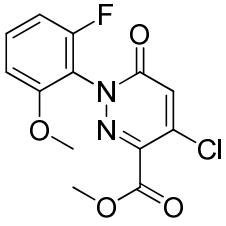
Step 2: Preparation of methyl 4-hydroxy-1-(2-fluoro-6-methoxyphenyl)-6-oxo-1,6-dihydropyridazine-3-carboxylate



This compound was prepared according to the procedure described in Example 2 (step 2) using dimethyl 2-(2-(2-(2-fluoro-6-methoxyphenyl)hydrazino)-3-oxo-glutarate instead of dimethyl 2-(2-(2-(2-methoxy-6-methylphenyl)hydrazino)-3-oxo-glutarate as starting material. Yield: 90%.

ESI-MS: m/z = 295.2 ([M+H]$^+$).

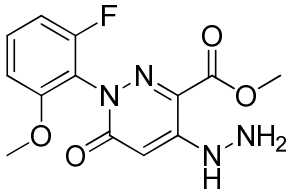
Step 3: Preparation of methyl 4-chloro-1-(2-fluoro-6-methoxyphenyl)-6-oxo-1,6-dihydropyridazine-3-carboxylate



This compound was prepared according to the procedure described in Example 2 (step 3) using methyl 4-hydroxy-1-(2-fluoro-6-methoxyphenyl)-6-oxo-1,6-dihydropyridazine-3-carboxylate instead of methyl 4-hydroxy-1-(2-methoxy-6-methylphenyl)-6-oxo-1,6-dihydropyridazine-3-carboxylate as starting material. Yield: 84%.

ESI-MS: m/z = 313.2 ($[M+H]^+$).

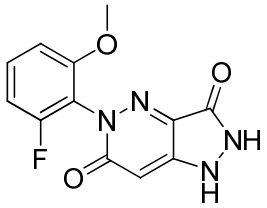
Step 4: Preparation of methyl 4-hydrazino-1-(2-fluoro-6-methoxyphenyl)-6-oxo-1,6-dihydropyridazine-3-carboxylate



To a suspension of methyl 4-chloro-1-(2-fluoro-6-methoxyphenyl)-6-oxo-1,6-dihydropyridazine-3-carboxylate (4.0 g, 12.8 mmol, 1.0 eq) and DIPEA (8.4 mL, 51.3 mmol, 4.0 eq) in ethanol (40 mL)was added a solution of 98% hydrazine hydrate (785 mg, 15.4 mmol, 1.2 eq) in ethanol (40 mL) at room temperature. After the addition, the mixture was stirred at room temperature for 4 hours. The reaction mixture was diluted with water (150 mL) and extracted with ethyl acetate for three times. The organic phases were combined, washed with brine, dried, filtered and concentrated to dryness. The residue was purified by column chromatography (dichloromethane/methanol: 100/1) to give methyl 4-hydrazino-1-(2-fluoro-6-methoxyphenyl)-6-oxo-1,6-dihydropyridazine-3-carboxylate (2.3 g) as a yellow solid. Yield: 59%.

ESI-MS: m/z = 309.1 ($[M+H]^+$).

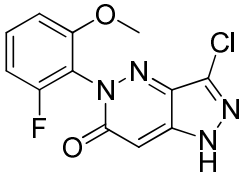
Step 5: Preparation of 5-(2-fluoro-6-methoxyphenyl)-1H-pyrazolo[4,3-c]pyridazine-3,6(2H,5H)-dione



To a solution of methyl 4-hydrazino-1-(2-fluoro-6-methoxyphenyl)-6-oxo-1,6-dihydropyridazine-3-carboxylate (1.6 g, 5.19 mmol, 1.0 eq) in a solvent mixture of methanol (15 mL) and tetrahydrofuran (15 mL) was added aqueous solution (15 mL) of lithium hydroxide monohydrate (436 mg, 10.38 mmol, 2.0 eq), and the mixture was stirred at room temperature for 2 hours. The reaction mixture was concentrated to dryness. The residue was purified by column chromatography (dichloromethane/methanol: 15/1) to give methyl 4-hydrazino-1-(2-fluoro-6-methoxyphenyl)-6-oxo-1,6-dihydropyridazine-3-carboxylate (1.4 g) as a brown-red solid. Yield: 99%.

ESI-MS: m/z = 277.2 ($[M+H]^+$).

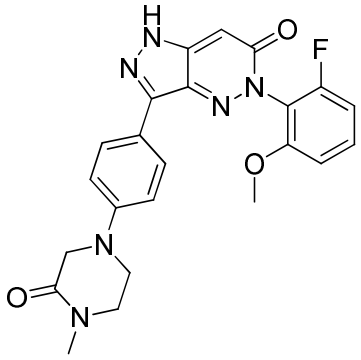
Step 6: Preparation of 3-chloro-5-(2-fluoro-6-methoxyphenyl)-1H-pyrazolo[4,3-c]pyridazin-6(5H)-one



This compound was prepared according to the procedure described in Example 2 (step 6) using 5-(2-fluoro-6-methoxyphenyl)-1H-pyrazolo[4,3-c]pyridazine-3,6(2H,5H)-dione instead of 5-(2-methoxy-6-methylphenyl)-1H-pyrazolo[4,3-c]pyridazine-3,6(2H,5H)-dione as starting material. Yield: 28%.

ESI-MS: m/z = 295.1 ($[M+H]^+$).

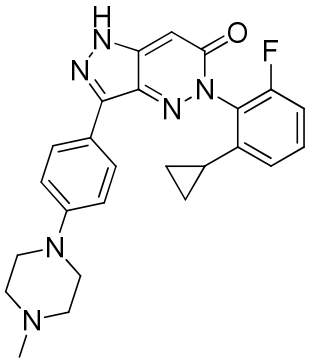
Step 7: Preparation of Compound 33



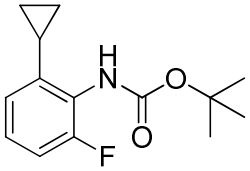
This compound was prepared according to the procedure described in Example 2 (step 7) using 3-chloro-5-(2-fluoro-6-methoxyphenyl)-1H-pyrazolo[4,3-c]pyridazine-6(5H)-one instead of 3-chloro-5-(2-methoxy-6-methylphenyl)-1H-pyrazolo[4,3-c]pyridazine-6(5H)-one, and using (4-(4-methyl-3-oxo-piperazin-1-yl)phenyl)boronic acid pinacol ester instead of 4-(4-methyl-1-piperazinyl)phenylboronic acid as starting materials. Yield: 25%.

Example 30

Compound 34: 5-(2-fluoro-6-cyclopropylphenyl)-3-(4-(4-methylpiperazin-1-yl)phenyl)-1H-pyrazolo[4,3-c]pyridazin-6(5H)-one (Scheme 3A)



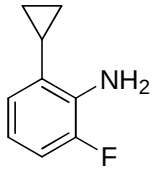
Step 1: Preparation of tert-butyl (2-fluoro-6-cyclopropylphenyl)carbamate



This compound was prepared according to the procedure described in Example 29 (step 2) using cyclopropylboronic acid instead of 4,4,5,5-tetramethyl-2-(prop-1-en-2-yl)-1,3,2-dioxaborane as the starting material. Yield: 65%.

ESI-MS: m/z = 196.1 ($[M+H-C_4H_8]^+$).

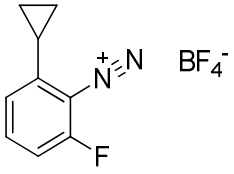
Step 2: Preparation of 2-fluoro-6-cyclopropylaniline



This compound was prepared according to the procedure described in Example 29 (step 4) using *tert*-butyl (2-fluoro-6-cyclopropylphenyl)carbamate as starting material. Yield: 87%.

ESI-MS: m/z = 152.1 ($[M+H]^+$).

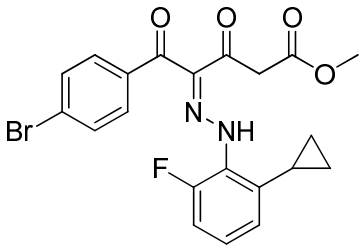
Step 3: Preparation of 2-cyclopropyl-6-fluorophenyldiazonium tetrafluoroborate



To a solvent mixture of dry methyl *tert*-butyl ether (3 mL) and dry tetrahydrofuran (3 mL) cooled to -5°C was added boron trifluoride ether complex (489 μL, 3.97 mmol) and a solution of 2-fluoro-6-cyclopropylaniline (300 mg, 1.98 mmol) in dry tetrahydrofuran (3 mL) successively, under nitrogen. After stirring for 15 minutes, the reaction mixture was cooled to -15°C. A solution of *tert*-butyl nitrite (246 mg, 2.38 mmol) in dry methyl *tert*-butyl ether (3 mL) was added dropwise. After the addition, the reaction mixture was gradually warmed to 0°C, and further stirred for 1.5 hours. The reaction mixture was filtered, and the filter cake was washed with methyl *tert*-butyl (50 mL) and dried at room temperature to give 2-cyclopropyl-6-fluorophenyldiazonium tetrafluoroborate (426 mg, 1.70 mmol) was a white solid. Yield: 86%.

ESI-MS: m/z = 163.1 ($[M+H-BF_4]^+$).

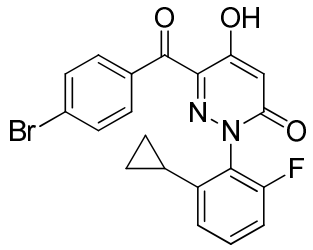
Step 4: Preparation of methyl 5-(4-bromophenyl)-4-(2-(2-fluoro-6-cyclopropylphenyl)hydrazino)-3,5-dioxopentanoate



To a mixture of methyl 5-(4-bromophenyl)-3,5-dioxopentanoate (920 mg, 3.07 mmol) and anhydrous sodium acetate (757 mg, 9.22 mmol) in absolute ethanol (20 mL) cooled to -15°C was added a solution of 2-cyclopropyl-6-fluorophenyldiazonium tetrafluoroborate (384 mg, 1.54 mmol) in acetonitrile (4 mL) dropwise. After the addition, the reaction mixture was gradually warmed to 0°C and further stirred for 1.5 hours. The reaction mixture was concentrated under reduced pressure, diluted with water (60 mL), and extracted with ethyl acetate (20 mL*3). The combined organic phase was washed with saturated brine (60 mL), dried over anhydrous sodium sulfate, and filtered with suction. The filtrate was concentrated to dryness. The residue was purified by column chromatography (petroleum ether/ethyl acetate:15/1) to give methyl 5-(4-bromophenyl)-4-(2-(2-fluoro-6-cyclopropylphenyl)hydrazino)-3,5-dioxopentanoate (435 mg, 0.94 mmol) as a yellow solid. Yield: 61%.

ESI-MS: m/z = 461.0 ([M+H]$^+$).

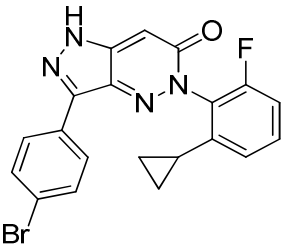
Step 5: Preparation of 6-(4-bromobenzoyl)-2-(2-fluoro-6-cyclopropylphenyl)-5-hydroxypyridazin-3(2H)-one



This compound was prepared according to the procedure described in Example 4 (step 4) using methyl 5-(4-bromophenyl)-4-(2-(2-fluoro-6-cyclopropylphenyl)hydrazinomethylene)-3,5-dioxopentanoate instead of methyl 5-(4-bromophenyl)-4-(2-(2,4-dimethoxyphenyl)hydrazinomethylene)-3,5-dioxopentanoate as the starting material. Yield: 38%.

ESI-MS: m/z = 429.0 ([M+H]$^+$).

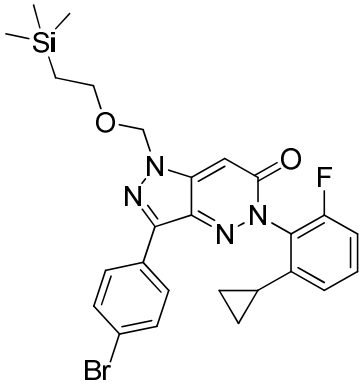
Step 6: Preparation of 3-(4-bromophenyl)-5-(2-fluoro-6-cyclopropylphenyl)-1H-pyrazolo[4,3-c]pyridazin-6(5H)-one



This compound was prepared according to the procedure described in Example 4 (step 5) using 6-(4-bromobenzoyl)-2-(2-fluoro-6-cyclopropylphenyl)-5-hydroxypyridazine-3(2H)-one instead of 6-(4-bromobenzoyl)-2-(2,4-dimethoxyphenyl)-5-hydroxypyridazin-3(2H)-one as starting material. Yield: 71%.

ESI-MS: m/z = 425.1 ([M+H]$^+$).

Step 7: Preparation of 3-(4-bromophenyl)-5-(2-cyclopropyl-6-fluorophenyl)-1-(2-(trimethylsilyl)ethoxymethyl)-1H-pyrazolo[4,3-c]pyridazin-6(5H)-one

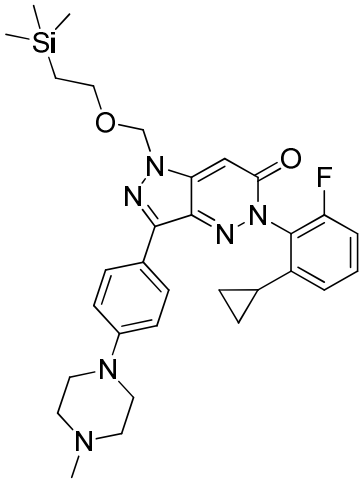


To a solution of 3-(4-bromophenyl)-5-(2-fluoro-6-cyclopropylphenyl)-1H-pyrazolo[4,3-c]pyridazin-6(5H)-one (92 mg, 0.22 mmol) in dry dimethylformamide (5 mL) at 0 °C was added sodium hydride (26 mg, 0.65 mmol) under nitrogen, and the mixture was stirred at 0°C for 20 min. 2-(Trimethylsilyl)ethoxymethyl chloride (111 mg, 0.67 mmol) was then added dropwise,

and the mixture was warmed to room temperature and stirred for 2 hours. The reaction mixture was poured into water (50 mL), extracted with ethyl acetate for three times (15 mL*3). The combined organic phase was washed with saturated brine (50 mL*3), dried over anhydrous sodium sulfate, and filtered with suction. The filtrate was concentrated to dryness, and the residue was purified by column chromatography (petroleum ether/ethyl acetate: 5/1) to give 3-(4-bromophenyl)-5-(2-cyclopropyl-6-fluorophenyl)-1-(2-(trimethylsilyl)ethoxymethyl)-1H-pyrazolo[4,3-c]pyridazin-6(5H)-one (82 mg, 0.15 mmol) as a yellow solid. Yield: 67%.

ESI-MS: m/z = 555.0 ($[M+H]^+$).

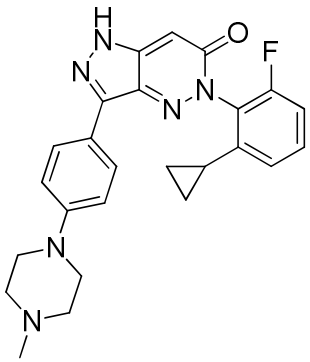
Step 8: Preparation of 5-(2-cyclopropyl-6-fluorophenyl)-3-(4-(4-methylpiperazin-1-yl)phenyl)-1-(2-(trimethylsilyl)ethoxymethyl)-1H-pyrazolo[4,3-c]pyridazin-6(5H)-one



To a mixture of 3-(4-bromophenyl)-5-(2-cyclopropyl-6-fluorophenyl)-1-(2-(trimethylsilyl)ethoxymethyl)-1H-pyrazolo[4,3-c]pyridazin-6(5H)-one (82 mg, 0.15 mmol), methylpiperazine (74 mg, 0.74 mmol), $Pd_2(dba)_3$ (13 mg, 0.015 mmol) and BINAP (23 mg , 0.037 mmol) in toluene (7 mL) was added a solution of sodium *tert*-pentoxide in toluene (3.5 M, 0.21 mL) under nitrogen. The mixture was heated to 100 °C and stirred overnight. The reaction mixture was poured into saturated aqueous ammonium chloride solution (60 mL), and extracted with ethyl acetate for three times (20 mL*3). The combined organic phase was washed with saturated brine, dried over anhydrous sodium sulfate, and filtered with suction. The filtrate was concentrated to dryness, and the residue was purified by column chromatography (ethyl acetate/triethylamine: 100/3) to give 5-(2-cyclopropyl-6-fluorophenyl)-3-(4-(4-methylpiperazin-1-yl)phenyl)-1-(2-(trimethylsilyl)ethoxymethyl)-1H-pyrazolo[4,3-c]pyridazin-6(5H)-one (36 mg, 0.063 mmol) as a red solid. Yield: 42%.

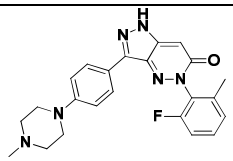
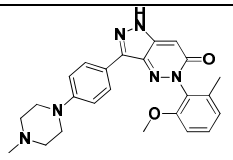
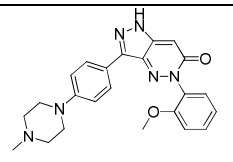
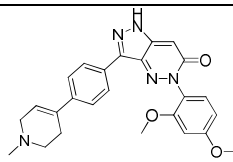
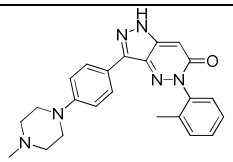
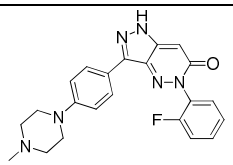
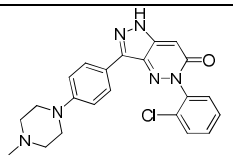
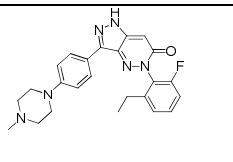
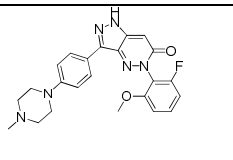
ESI-MS: m/z = 575.2 ($[M+H]^+$).

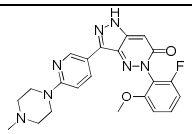
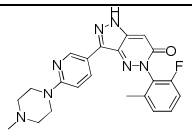
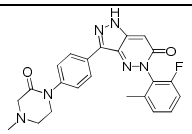
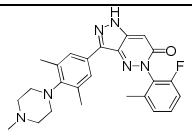
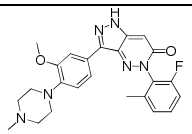
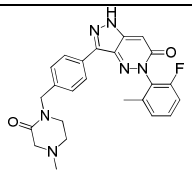
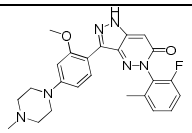
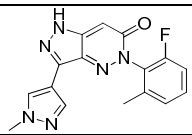
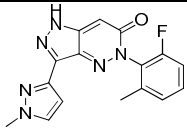
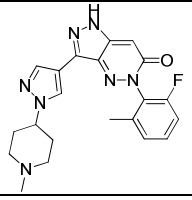
Step 9: Preparation of Compound 34

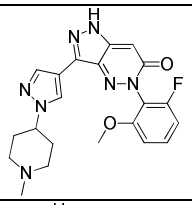
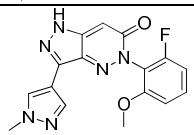
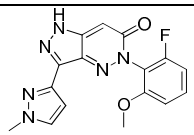
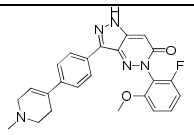
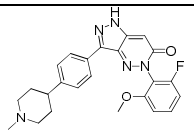
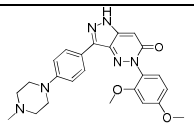
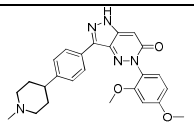
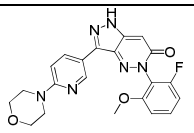
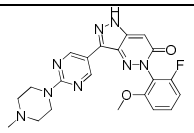
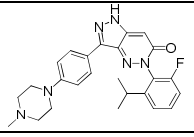


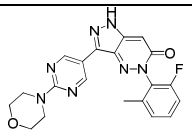
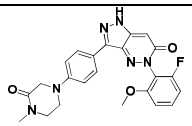
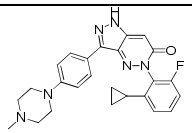
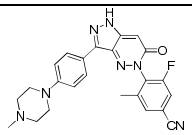
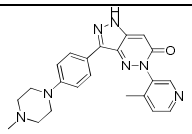
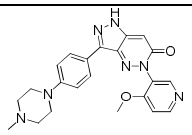
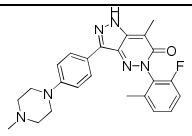
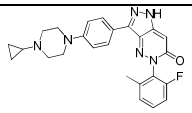
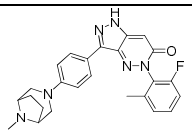
To a solution of 5-(2-cyclopropyl-6-fluorophenyl)-3-(4-(4-methylpiperazin-1-yl)phenyl)-1-(2-(trimethylsilyl)ethoxymethyl)-1H-pyrazolo[4,3-c]pyridazin-6(5H)-one (36 mg, 0.063 mmol) in dichloromethane (10 mL) was added trifluoroacetic acid (2.5 mL) at 0°C. The reaction mixture was warmed to room temperature and stirred for 2 hours. The reaction mixture was neutralized with saturated aqueous sodium carbonate solution, extracted with dichloromethane for three times (30 mL*3). The combined organic phase was washed with saturated brine, dried over anhydrous sodium sulfate, and filtered with suction. The filtrate was concentrated to dryness. The residue was re-dissolved in methanol (5 mL), and a small amount of aqueous ammonia was added. After stirring at room temperature for 1 hour, the mixture was concentrated to dryness, and the residue was purified by thin layer chromatography (DCM/MeOH: 10/1) to give compound 34 (10 mg, 0.022 mmol) as a red solid. Yield: 36%.

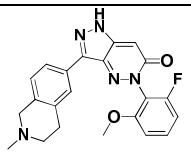
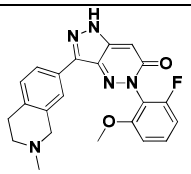
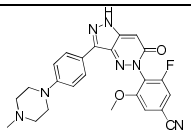
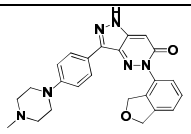
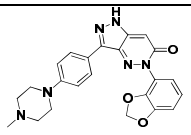
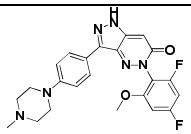
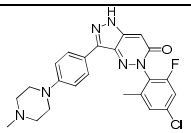
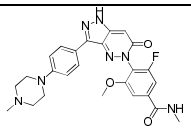
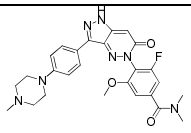
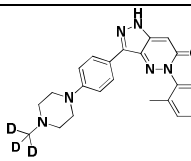
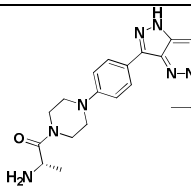
Other compounds in the Examples were synthesized by methods similar to those described in the above synthetic schemes, and their characterization data are listed in the table below.

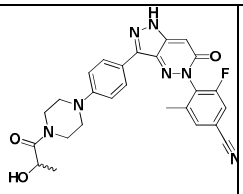
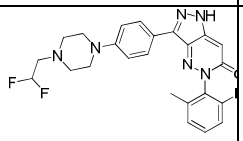
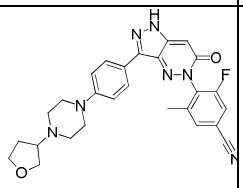
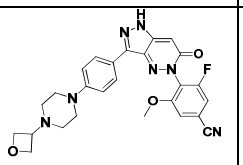
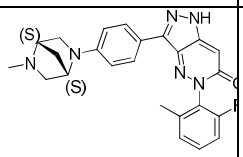
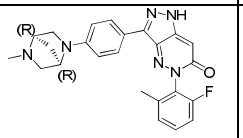
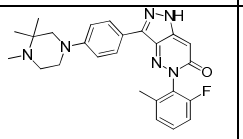
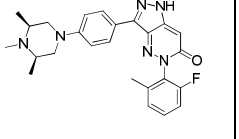
Example	Compound	Structural Formula	Spectrum Data	Synthetic Scheme
Example 1	Compound 1		ESI-MS: m/z = 419.2 ([M+H]$^+$). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.91 (s, 1H), 9.65 (s, 1H), 8.01 (d, J = 8.8 Hz, 2H), 7.52-7.46 (m, 1H), 7.30 (t, J = 7.8 Hz, 2H), 7.13 (d, J = 9.2 Hz, 1H), 6.71 (s, 1H), 3.96-3.92 (m, 2H), 3.55-3.52 (m, 2H), 3.18-3.10 (m, 2H), 3.04-2.98 (m, 2H), 2.85 (s, 3H), 2.10 (s, 3H).	1
Example 2	Compound 2		ESI-MS: m/z = 431.2 ([M+H]$^+$). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.71 (s, 1H), 7.95 (d, J = 9.0 Hz, 2H), 7.39 (t, J = 8.0 Hz, 1H), 7.10-6.96 (m, 4H), 6.59 (s, 1H), 3.69 (s, 3H), 3.24-3.16 (m, 4H), 2.47-2.37 (m, 4H), 2.21 (s, 3H), 1.99 (s, 3H).	2A
Example 3	Compound 3		ESI-MS: m/z = 417.3 ([M+H]$^+$). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.68 (s, 1H), 7.97 (d, J = 9.0 Hz, 2H), 7.52-7.48 (m, 1H), 7.41 (dd, J = 7.7, 1.6 Hz, 1H), 7.24 (dd, J = 8.4, 0.8 Hz, 1H), 7.11 (td, J = 7.6, 1.0 Hz, 1H), 7.02 (d, J = 9.0 Hz, 2H), 6.55 (s, 1H), 3.74 (s, 3H), 3.24-3.17 (m, 4H), 2.46-2.40 (m, 4H), 2.21 (s, 3H).	2A
Example 4	Compound 4		ESI-MS: m/z = 444.3 ([M+H]$^+$). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.90 (s, 1H), 8.09 (d, J = 8.5 Hz, 2H), 7.56 (d, J = 8.5 Hz, 2H), 7.32 (d, J = 8.6 Hz, 1H), 6.76 (d, J = 2.5 Hz, 1H), 6.66 (dd, J = 8.6, 2.5 Hz, 1H), 6.59 (s, 1H), 6.27-6.22 (m 1H), 3.86 (s, 3H), 3.73 (s, 3H), 3.05-3.00 (m, 2H), 2.60-2.54 (m, 2H), 2.50-2.45 (m, 2H), 2.28 (s, 3H).	3A
Example 5	Compound 5		ESI-MS: m/z = 401.3 ([M+H]$^+$). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.73 (s, 1H), 7.98 (d, J = 9.0 Hz, 2H), 7.45-7.35 (m, 4H), 7.02 (d, J = 9.0 Hz, 2H), 6.62 (s, 1H), 3.30 (s, 3H), 3.23-3.18 (m, 4H), 2.46-2.40 (m, 4H), 2.07 (s, 3H).	2A
Example 6	Compound 6		ESI-MS: m/z = 405.3 ([M+H]$^+$). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.77 (s, 1H), 7.99 (d, J = 9.0 Hz, 2H), 7.69-7.55 (m, 2H), 750-7.38 (m, 2H), 7.03 (d, J = 9.0 Hz, 2H), 6.63 (s, 1H), 3.24-3.19 (m, 4H), 2.46-2.40 (m, 4H), 2.21 (s, 3H).	2A
Example 7	Compound 7		ESI-MS: m/z = 421.3 ([M+H]$^+$). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.78 (s, 1H), 7.97 (d, J = 9.0 Hz, 2H), 7.73-7.69 (m, 1H), 7.68-7.64 (m, 1H), 7.61-7.53 (m, 2H), 7.03 (d, J = 9.0 Hz, 2H), 6.64 (s, 1H), 3.23-3.18 (m, 4H), 2.46-2.40 (m, 4H), 2.21 (s, 3H).	2A
Example 8	Compound 8		ESI-MS: m/z = 433.3 ([M+H]$^+$). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.82 (s, 1H), 7.96 (d, J = 9.0 Hz, 2H), 7.57-7.50 (m, 1H), 7.34-7.26 (m, 2H), 7.03 (d, J = 9.0 Hz, 1H), 6.67 (s, 1H), 3.24-3.16 (m, 2 H), 2.45-2.35 (m, 6H), 2.21 (s, 3H), 1.06 (t, J = 7.6 Hz, 3H).	2A
Example 9	Compound 9		ESI-MS: m/z = 435.3 ([M+H]$^+$). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.77 (s, 1H), 9.75 (d, J = 9.0 Hz, 2H), 7.59-7.52 (m, 1H), 7.12 (d, J = 8.6 Hz, 1H), 7.09-7.02 (m, 3H), 6.61 (s, 1H), 3.78 (s, 3H), 3.24-3.17 (m, 4H), 2.46-2.40 (m, 4H), 2.21 (s, 3H).	2A

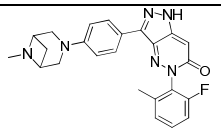
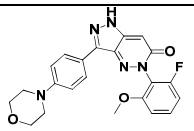
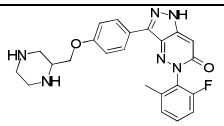
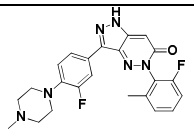
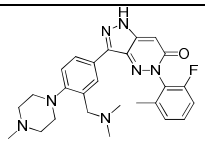
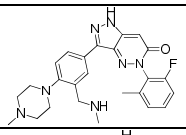
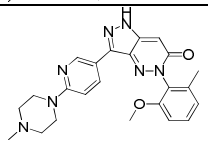
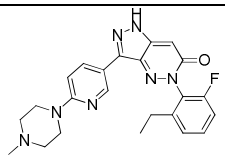
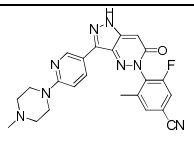
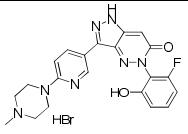
Example 10	Compound 10		ESI-MS: m/z = 436.3 ([M+H]$^+$). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.84 (s, 1H), 8.82 (d, J = 2.2 Hz, 1H), 8.13 (dd, J = 9.0, 2.4 Hz, 1H), 7.60-7.521 (m, 1H), 7.12 (d, J = 8.6 Hz, 1H), 7.09-7.03 (m, 1H), 6.96 (d, J = 9.0 Hz, 1H), 6.64 (s, 1H), 3.79 (s, 3H), 3.60-3.52 (m, 4H), 2.42-2.35 (m, 4H), 2.21 (s, 3H).	2A
Example 11	Compound 11		ESI-MS: m/z = 420.3 ([M+H]$^+$). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.89 (s, 1H), 8.83 (d, J = 2.2 Hz, 1H), 8.13 (dd, J = 9.0, 2.4 Hz, 1H), 7.53-7.45 (m, 1H), 7.33-7.25 (m, 2H), 6.96 (d, J = 9.0 Hz, 1H), 6.70 (s, 1H), 3.60-3.52 (m, 4H), 2.41-2.34 (m, 4H), 2.21 (s, 3H), 2.10 (s, 3H).	2A
Example 12	Compound 12		ESI-MS: m/z = 433.3 ([M+H]$^+$). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.89 (s, 1H), 8.83 (d, J = 2.2 Hz, 1H), 8.13 (dd, J = 9.0, 2.4 Hz, 1H), 7.53-7.45 (m, 1H), 7.33-7.25 (m, 2H), 6.96 (d, J = 9.0 Hz, 1H), 6.70 (s, 1H), 3.60-3.52 (m, 4H), 2.41-2.34 (m, 4H), 2.21 (s, 3H), 2.10 (s, 3H).	2A
Example 13	Compound 13		ESI-MS: m/z = 447.3 ([M+H]$^+$). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.97 (s, 1H), 7.70 (s, 2H), 7.52-7.46 (m, 1H), 7.32-7.26 (m, 2H), 6.71 (s, 1H), 3.60-3.52 (m, 4H), 2.41-2.34 (m, 4H), 2.28 (s, 6H), 2.23 (s, 3H), 2.11 (s, 3H).	2A
Example 14	Compound 14		ESI-MS: m/z = 449.3 ([M+H]$^+$). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.92 (s, 1H), 7.70 (dd, J = 8.2, 1.8 Hz, 1H), 7.61 (d, J = 1.8 Hz, 1H), 7.53-7.45 (m, 1H), 7.33-7.25 (m, 2H), 6.98 (d, J = 8.3 Hz, 1H), 6.71 (s, 1H), 3.80 (s, 3H), 3.02 (br, 4H), 2.47 (br, 4H), 2.22 (s, 3H), 2.11 (s, 3H).	2A
Example 15	Compound 15		ESI-MS: m/z = 447.3 ([M+H]$^+$). ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.08 (s, 1H), 8.08 (d, J = 8.3 Hz, 2H), 7.53-7.45 (m, 1H), 7.37-7.26 (m, 4H), 6.76 (s, 1H), 4.54 (s, 2H), 3.21 (t, J = 5.5 Hz, 2H), 3.01 (s, 2H), 2.56 (t, J = 5.4 Hz, 2H), 2.20 (s, 3H), 2.10 (s, 3H).	2A
Example 16	Compound 16		ESI-MS: m/z = 449.3 ([M+H]$^+$). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.78 (s, 1H), 7.48-7.39 (m, 2H), 7.28-7.22 (m, 2H), 6.63 (s, 1H), 6.61-6.56 (m, 2H), 3.71 (s, 3H), 3.25-3.20 (m, 4H), 2.46-2.41 (m, 4H), 2.21 (s, 3H), 2.07 (s, 3H).	2A
Example 17	Compound 17		ESI-MS: m/z = 325.3 ([M+H]$^+$). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.77 (s, 1H), 8.21 (s, 1H), 7.93 (s, 1H), 7.52-7.45 (m, 2H), 7.32-7.25 (m, 2H), 6.66 (s, 1H), 3.89 (s, 3H), 2.09 (s, 3H).	2A
Example 18	Compound 18		ESI-MS: m/z = 325.3 ([M+H]$^+$). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.95 (s, 1H), 7.79 (d, J = 2.2 Hz, 1H), 7.52-7.45 (m, 1H), 7.32-7.24 (m, 2H), 6.74 (d, J = 2.2 Hz, 1H), 6.70 (s, 1H), 3.90 (s, 3H), 2.07 (s, 3H).	2A
Example 19	Compound 19		ESI-MS: m/z = 408.2 ([M+H]$^+$). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.77 (s, 1H), 8.26 (s, 1H), 7.97 (s, 1H), 7.52-7.44 (m, 1H), 7.32-7.26 (m, 2H), 6.66 (s, 1H), 4.31-4.22 (m, 1H), 2.90-2.84 (m, 2H), 2.22 (s, 3H), 2.12-1.90 (m, 9H).	2A

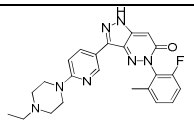
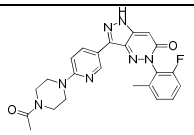
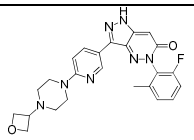
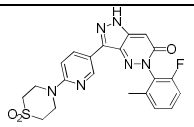
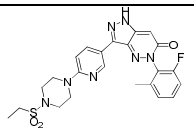
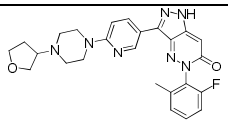
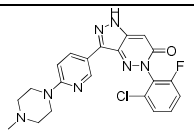
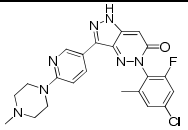
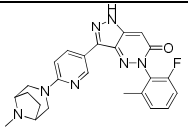
Example 20	Compound 20		ESI-MS: m/z = 424.2 ([M+H]$^+$). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.73 (s, 1H), 8.24 (s, 1H), 7.96 (s, 1H), 7.60-7.50 (m, 1H), 7.12 (d, J = 8.6 Hz, 1H), 7.06 (t, J = 8.7 Hz, 1H), 6.60 (s, 1H), 4.31-4.21 (m, 1H), 3.78 (s, 3H), 2.90-2.81 (m, 2H), 2.20 (s, 3H), 2.08-1.90 (m, 6H).	2A
Example 21	Compound 21		ESI-MS: m/z = 341.2 ([M+H]$^+$). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.73 (s, 1H), 8.20 (s, 1H), 7.93 (s, 1H), 7.59-7.51 (m, 1H), 7.12 (d, J = 8.6 Hz, 1H), 7.05 (t, J = 8.7 Hz, 1H), 6.61 (s, 1H), 3.89 (s, 3H), 3.78 (s, 3H).	2A
Example 22	Compound 22		ESI-MS: m/z = 341.2 ([M+H]$^+$). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.91 (s, 1H), 7.79 (d, J = 1.9 Hz, 1H), 7.60-7.51 (m, 1H), 7.14-7.02 (m, 2H), 6.73 (d, J = 1.9 Hz, 1H), 6.64 (s, 1H), 3.90 (s, 3H), 3.78 (s, 3H).	2A
Example 23	Compound 23		ESI-MS: m/z = 432.4 ([M+H]$^+$). ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.04 (br, 1H), 8.07 (d, J = 8.4 Hz, 2H), 7.61-7.53 (m 3H), 7.15-7.03 (m, 2H), 6.70 (s, 1H), 6.25 (s, 1H), 3.79 (s, 3H), 3.12 (s, 2H), 2.70-2.62 (m, 2H), 2.56-2.50 (m, 2H), 2.34 (s, 3H).	4
Example 24	Compound 24		ESI-MS: m/z = 434.4 ([M+H]$^+$). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.96 (br, 1H), 8.02 (d, J = 8.2 Hz, 1H), 7.60-7.52 (m, 1H), 7.37 (d, J = 8.2 Hz, 1H), 7.12 (d, J = 8.6 Hz, 1H), 7.06 (t, J = 8.92 Hz, 1H), 6.68 (s, 1H), 2.86 (d, J =11.2 Hz, 2H), 2.50-2.42 (m, 1H), 2.19 (s, 3H), 1.97 (t, J = 10.6 Hz, 2H), 1.77-1.60 (m, 4H).	4
Example 25	Compound 25		ESI-MS: m/z = 447.3 ([M+H]$^+$). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.65 (s, 1H), 9.78 (d, J = 9.0 Hz, 2H), 7.30 (d, J = 8.6 Hz, 1H), 7.02 (d, J = 9.0 Hz, 2H), 6.76 (d, J = 2.5 Hz, 1H), 6.65 (dd, J = 8.6, 2.6 Hz, 1H), 6.51 (s, 1H), 3.85 (s, 3H), 3.73 (s, 3H), 3.23-3.18 (m, 4H), 2.45-2.41 (m, 4H), 2.21 (s, 3H).	3B
Example 26	Compound 26		ESI-MS: m/z = 446.3 ([M+H]$^+$). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.88 (s, 1H), 8.05 (d, J = 8.3 Hz, 2H), 7.37 (d, J = 8.4 Hz, 2H), 7.31 (d, J = 8.6 Hz, 1H), 6.76 (d, J = 2.5 Hz, 1H), 6.66 (dd, J = 8.6, 2.5 Hz, 1H), 6.59 (s, 1H), 3.86 (s, 3H), 373 (s, 3H), 3.08-2.98 (m, 2H), 2.62-2.52 (m, 1H), 2.40-2.20 (m, 5H), 1.84-1.68 (m, 4H).	3A
Example 27	Compound 27		ESI-MS: m/z = 423.3 ([M+H]$^+$). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.88 (s, 1H), 8.84 (d, J = 2.2 Hz, 1H), 8.16 (dd, J = 9.0, 2.4 Hz, 1H), 7.60-7.52 (m, 1H), 7.12 (d, J = 8.6 Hz, 1H), 7.06 (t, J = 8.8 Hz, 1H), 6.97 (d, J = 9.0 Hz, 1H), 6.65 (s, 1H), 3.79 (s, 3H), 3.72-3.66 (m, 4H), 3.54-3.50 (m, 4H).	2A
Example 28	Compound 28		ESI-MS: m/z = 437.3 ([M+H]$^+$). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.97 (br, 1H), 8.94 (s, 2H), 7.60-7.52 (m, 1H), 7.12 (d, J = 8.6 Hz, 1H), 7.06 (t, J = 8.8 Hz, 1H), 6.68 (s, 1H), 3.82-3.76 (m, 7H), 3.38-3.32 (m, 4H), 2.20 (s, 3H).	2A
Example 29	Compound 29		ESI-MS: m/z = 447.3 ([M+H]$^+$). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.83 (s, 1H), 7.96 (d, J = 9.0 Hz, 2H), 7.57-7.50 (m, 1H), 7.39 (d, J = 7.9 Hz, 1H), 7.31-7.25 (m, 1H), 7.03 (d, J = 9.0 Hz, 2H),	2A

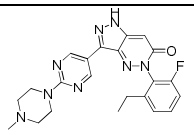
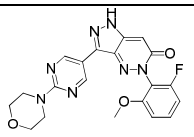
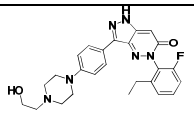
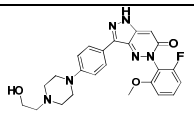
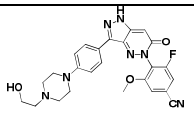
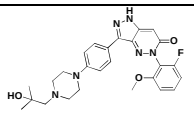
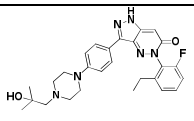
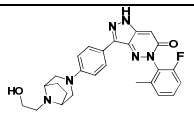
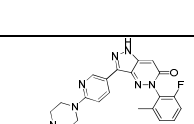
			6.66 (s, 1H), 3.24-3.16 (m, 4H), 2.61 (sept, 1H), 2.45-2.35 (m, 4H), 2.21 (s, 3H), 1.15-1.11 (m, 6H).	
Example 30	Compound 32		ESI-MS: 408.1 $[M+H]^+$ ^{1}H NMR (400MHz, DMSO-d_6) δ 13.04 (s, 1H), 8.98 (s, 2H), 7.52-7.46 (m, 1H), 7.32-7.27 (m, 2H), 6.75 (s, 1H), 3.77 (t, J = 4.4 Hz, 4H), 3.66 (t, J = 4.4 Hz, 4H), 2.10 (s, 3H).	2A
Example 31	Compound 33		ESI-MS: m/z = 449.1 ($[M+H]^+$). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.81 (brs, 1H), 7.98 (d, *J* = 8.9 Hz, 2H), 7.56 (q, *J* = 7.9 Hz, 1H), 7.15-7.02 (m, 4H), 6.63 (s, 1H), 3.83 (s, 2H), 3.79 (s, 3H), 3.59-3.53 (m, 2H), 3.47-3.41 (m, 2H), 3.32 (s, 3H).	2B
Example 32	Compound 34		ESI-MS: m/z = 445.2 ($[M+H]^+$). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.83 (s, 1H), 7.96 (d, *J* = 9.0 Hz, 2H), 7.51-7.44 (m, 1H), 7.26 (t, *J* = 8.8 Hz, 1H), 7.06-6.96 (m, 3H), 6.67 (s, 1H), 3.24-3.18 (m, 4H), 2.45-2.39 (m, 4H), 2.21 (s, 3H), 1.61-1.52 (m, 1H), 0.82-0.62 (m, 4H).	3A
Example 33	Compound 42		ESI-MS: 444.3 $[M+H]^+$ ^{1}H NMR (400MHz, DMSO-d_6) δ 12.89 (s, 1H), 8.01 (d, J = 9.2 Hz, 1H), 7.95 (d, J = 8.8 Hz, 2H),7.89 (s, 1H), 7.03 (d, J = 8.8 Hz, 2H), 6.71 (s, 1H), 3.23-3.20 (m, 4H), 2.45-2.41 (m, 4H), 2.21 (s, 3H), 2.17 (s, 3H).	2A
Example 34	Compound 47		ESI-MS: m/z = 402.2 ($[M+H]^+$). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.81 (brs, 1H), 8.59-8.55 (m, 2H), 7.98 (d, *J* = 8.8 Hz, 2H), 7.49 (d, *J* = 4.2, 1H), 7.03 (d, *J* = 8.0 Hz, 2H), 6.66 (s, 1H), 3.32-3.21 (m, 4H), 2.58-2.42 (m, 4H), 2.25 (s, 3H), 2.15 (s, 3H).	4
Example 35	Compound 48		ESI-MS: m/z = 418.1 ($[M+H]^+$). ^{1}H NMR (400MHz, DMSO-d_6) δ 12.76 (brs, 1H), 8.68-8.48 (m, 2H), 7.97 (d, *J* = 8.4 Hz, 2H), 7.33 (d, *J* = 5.6 Hz, 1H), 7.02 (d, *J* = 8.4 Hz, 2H), 6.59 (s, 1H), 3.85 (s, 3H), 3.29-3.08 (m, 4H), 2.48-2.31 (m, 4H), 2.21 (s, 3H).	4
Example 36	Compound 55		ESI-MS: 433.2 $[M+H]^+$ ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.90 (s, 1H), 7.98 (d, J = 8.8 Hz, 2H), 7.51-7.45 (m, 1H), 7.32-7.27 (m, 2H), 7.03 (d, J = 9.2 Hz, 2H), 3.20 (t, J = 4.8 Hz, 4H), 2.43 (t, J = 4.8 Hz, 4H), 2.28 (s, 3H), 2.21 (s, 3H), 2.07 (s, 3H).	3A
Example 37	Compound 58		ESI-MS: 445.3 $[M+H]^+$ ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.84 (s, 1H), 7.96 (d, J= 8.9 Hz, 2H), 7.55 – 7.44 (m, 1H),, 7.35 – 7.25 (m, 2H), 7.04 (d, J = 8.6 Hz, 2H), 6.68 (s, 1H), 3.17 (br, 4H), 2.67 (br, 4H), 2.10 (s, 3H), 1.65 (br, 1H), 0.56-0.30 (m, 4H).	4
Example 38	Compound 61		ESI-MS: 445.3$[M+H]^+$ ^{1}H NMR (700MHz, DMSO-d_6) δ 12.82 (s, 1H), 7.94 (d, J = 8.9 Hz, 2H), 7.51-7.46 (m, 1H), 7.32-7.28 (m, 2H), 6.95 – 6.89 (m, 2H), 6.67 (s, 1H), 3.51-3.44 (m, 2H), 3.42-3.35 (m, 2H), 3.06 – 2.84 (m, 2H), 2.33 (brs, 3H), 2.09 (s, 3H), 2.06 – 1.94 (m, 2H), 1.79 – 1.52 (m, 2H).	2A

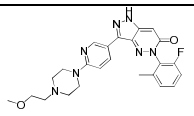
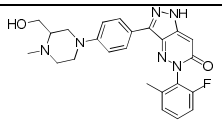
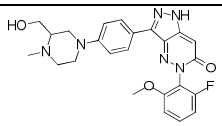
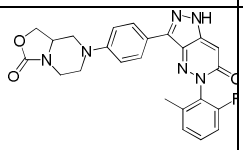
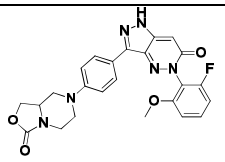
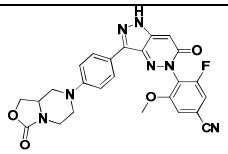
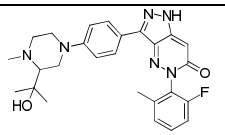
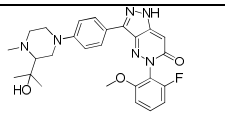
Example 39	Compound 72		ESI-MS: 406.3 $[M+H]^+$ ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.01 (s, 1H), 8.05-7.75 (m, 2H), 7.63-7.45 (m, 1H), 7.22 – 6.99 (m, 3H), 6.69 (s, 1H), 3.79 (s, 3H), 3.53 (s, 2H), 2.86 (s, 2H), 2.62 (s, 2H), 2.35 (s, 3H).	2A
Example 40	Compound 73		ESI-MS: m/z = 406.2 ($[M+H]^+$). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.80 (brs, 1H), 7.77 (s, 1H), 7.61-7.51 (m, 1H), 7.12 (d, J = 8.6 Hz, 1H), 7.06 (t, J = 8.9 Hz, 1H), 6.63 (s, 1H), 3.79 (s, 3H), 3.75-3.68 (m, 4H), 3.51-3.44 (m, 4H).	2A
Example 41	Compound 74		ESI-MS: m/z = 460.2 ($[M+H]^+$). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.91 (brs, 1H), 7.96 (d, J = 8.7 Hz, 2H), 7.85-7.70 (m, 2H), 7.08 (d, J = 8.7 Hz, 2H), 6.85 (s, 1H), 3.87 (s, 3H), 3.39-3.30 (m, 4H), 3.02-2.78 (m, 4H), 2.55 (s, 3H).	4
Example 42	Compound 75		ESI-MS: m/z = 429.2 ($[M+H]^+$). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.76 (brs, 1H), 8.01 (d, J = 8.8 Hz, 2H), 7.53-7.42 (m, 3H), 7.04 (d, J = 8.9 Hz, 2H), 6.62 (s, 1H), 5.11 (s, 2H), 4.95 (s, 2H), 3.27-3.17 (m, 4H), 2.48-2.41 (m, 4H), 2.22 (s, 3H).	4
Example 43	Compound 76		ESI-MS: m/z = 431.2 ($[M+H]^+$). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.75 (brs, 1H), 8.01 (d, J = 8.8 Hz, 2H), 7.15-6.96 (m, 5H), 6.60 (s, 1H), 6.10 (s, 2H), 3.28-3.17 (m, 4H), 2.47-2.36 (m, 4H), 2.22 (s, 3H).	4
Example 44	Compound 77		ESI-MS: 453.2 $[M+H]^+$ ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.81 (s, 1H), 7.95 (d, J = 9.0 Hz, 2H), 7.17 – 7.08 (m, 2H), 7.04 (d, J = 9.0 Hz, 2H), 6.62 (s, 1H), 3.80 (s, 3H), 3.25-3.19 (m, 4H), 2.47-2.42 (m, 4H), 2.22 (s, 3H).	2A
Example 45	Compound 78		ESI-MS: 453.1 $[M+H]^+$	2A
Example 46	Compound 79		ESI-MS: 492.2 $[M+H]^+$ ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.83 (s, 1H), 8.70 (d, J = 4.3 Hz, 1H), 7.95 (d, J = 8.3 Hz, 2H), 7.54 (s, 1H), 7.47 (d, J = 10.0 Hz, 1H), 7.03 (d, J = 8.4 Hz, 2H), 6.64 (s, 1H), 3.85 (s, 3H), 3.23 – 3.18 (m, 4H), 2.85 (d, J = 3.5 Hz, 3H), 2.46-2.40 (m, 4H), 2.21 (s, 3H).	4
Example 47	Compound 80		ESI-MS: 506.1 $[M+H]^+$ ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.83 (s, 1H), 7.95 (d, J = 8.6 Hz, 2H), 7.17-7.11 (m, 2H), 7.04 (d, J = 8.6 Hz, 2H), 6.64 (s, 1H), 3.81 (s, 3H), 3.24-3.17 (m, 4H), 3.03 (s, 3H), 3.00 (s, 3H), 2.46-2.40 (m, 4H), 2.21 (s, 3H).	4
Example 48	Compound 81		ESI-MS: 422.3 $[M+H]^+$ ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.81 (s, 1H), 7.96 (d, J = 8.8 Hz, 2H), 7.52-7.46 (m, 1H), 7.32-7.26 (m, 2H), 7.03 (d, J = 9.0 Hz, 1H), 6.67 (s, 1H), 3.23-3.19 (m, 2H), 2.46-2.42 (m, 4H), 2.10 (s, 3H).	2A
Example 49	Compound 82		ESI-MS: 501.3 $[M+H]^+$ ^{1}H NMR (700 MHz, DMSO-d_6) δ 8.02-8.00 (m, 1H), 8.00 – 7.95 (m, 2H), 7.90 (s, 1H), 7.08-7.04 (m, 2H), 6.73 – 6.71 (m, 1H), 3.83 – 3.78 (m, 1H), 3.70 – 3.54 (m, 4H), 3.28 – 3.15 (m, 6H), 2.17 (s, 3H), 1.10-1.09 (m, 3H).	2B

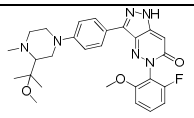
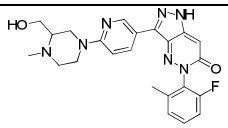
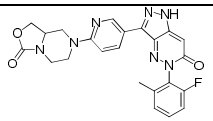
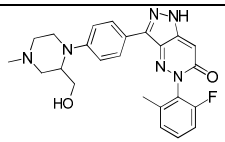
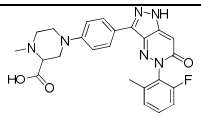
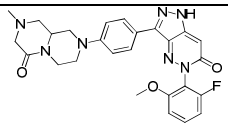
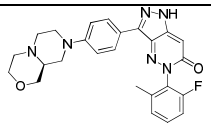
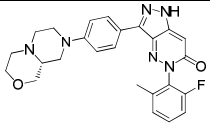
Example 50	Compound 83		ESI-MS: 502.2 $[M+H]^+$ ^{1}H NMR (700 MHz, DMSO-d_6) δ 12.93 (s, 1H), 8.02 (dd, *J* = 9.2, 1.7 Hz, 1H), 7.98 (d, *J* = 9.0 Hz, 2H), 7.90 (s, 1H), 7.07 (d, *J* = 9.0 Hz, 2H), 6.73 (s, 1H), 4.98 (d, *J* = 6.9 Hz, 1H), 4.48-4.44 (m, 1H), 3.73 – 3.62 (m, 3H), 3.58-3.52 (m, 1H), 3.30-3.16 (m, 4H), 2.17 (s, 3H), 1.20 (d, *J* = 6.6 Hz, 3H).	2B
Example 51	Compound 84		ESI-MS: 469.1 $[M+H]^+$ ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.86 (s, 1H), 7.97 (d, J = 9.0 Hz, 2H), 7.54-7.45 (m, 1H), 7.35-7.26 (m, 2H), 7.04 (d, J = 9.0 Hz, 2H), 6.68 (s, 1H), 6.18 (tt, J = 55.6, 4.3 Hz, 1H), 3.26 – 3.20 (m, 4H), 2.78 (td, J = 15.6, 4.1 Hz, 2H), 2.69 – 2.62 (m, 4H), 2.10 (s, 3H).	4
Example 52	Compound 85		ESI-MS: 500.3 $[M+H]^+$ ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.91 (s, 1H), 8.04-7.98 (m, 1H), 7.95 (d, J = 8.9 Hz, 2H), 7.88 (s, 1H), 7.02 (d, J = 8.9 Hz, 2H), 6.71 (s, 1H), 3.83-3.75 (m, 2H), 3.68-3.62 (m, 1H), 3.54-3.49 (m, 1H), 3.21 (t, J = 5.0 Hz, 4H), 2.95-2.87 (m, 1H), 2.60-2.42 (m, 4H), 2.17 (m, 3H), 2.03-1.94 (m, 1H), 1.81-1.71 (m, 1H).	2B
Example 53	Compound 86		ESI-MS: 502.2 $[M+H]^+$ ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.87 (s, 1H), 7.94 (d, J = 8.9 Hz, 2H), 7.79 (d, J = 8.9 Hz, 1H), 7.73 (s, 1H), 7.04 (d, J= 8.9 Hz, 2H), 6.67 (s, 1H), 4.56 (t, J = 6.5 Hz, 2H), 4.47 (t, J = 6.5 Hz, 2H), 3.87 (s, 3H), 3.47-3.40 (m, 1H), 3.26-3.23 (m, 4H), 2.41-2.37 (m, 4H).	2A
Example 54	Compound 87		ESI-MS: 431.2 $[M+H]^+$ ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.72 (s, 1H), 7.93 (d, J = 8.8 Hz, 2H), 7.53 – 7.44 (m, 1H), 7.33-7.27 (m, 2H), 6.68 (d, J = 8.9 Hz, 2H), 6.64 (s, 1H), 4.35 (s, 2H), 3.46 (br, 1H), 3.30-3.28 (m, 1H), 3.21 (d, J = 9.3 Hz, 2H), 2.79 (d, J = 9.4 Hz, 1H), 2.52-2.50 (m, 1H), 2.27 (brs, 3H), 2.10 (s, 3H), 1.93-1.86 (m, 1H), 1.81-1.75 (s, 1H).	4
Example 55	Compound 88		ESI-MS: 431.2 $[M+H]^+$ ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.72 (s, 1H), 7.93 (d, J = 8.8 Hz, 2H), 7.53 – 7.44 (m, 1H), 7.33-7.27 (m, 2H), 6.68 (d, J = 8.9 Hz, 2H), 6.64 (s, 1H), 4.35 (s, 2H), 3.46 (br, 1H), 3.30-3.28 (m, 1H), 3.21 (d, J = 9.3 Hz, 2H), 2.79 (d, J = 9.4 Hz, 1H), 2.52-2.50 (m, 1H), 2.27 (brs, 3H), 2.10 (s, 3H), 1.93-1.86 (m, 1H), 1.81-1.75 (s, 1H).	4
Example 56	Compound 89		ESI-MS: 447.1 $[M+H]^+$ ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.85 (s, 1H), 7.95 (d, J = 8.9 Hz, 2H), 7.53-7.44 (m, 1H), 7.34-7.25 (m, 2H), 7.02 (d, J = 8.9 Hz, 2H), 6.67 (s, 1H), 3.20 (br, 2H), 2.99 (br, 2H), 2.63 – 2.52 (m, 2H), 2.16 (br, 3H), 2.10 (s, 3H), 1.01 (s, 6H).	4
Example 57	Compound 90		ESI-MS: 447.1 $[M+H]^+$ ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.81 (s, 1H), 7.96 (d, J = 9.0 Hz, 2H), 7.58-7.42 (m, 1H), 7.36-7.25 (m, 2H), 7.03 (d, J = 9.0 Hz, 2H), 6.67 (s, 1H), 3.66 (d, J = 11.7 Hz, 2H), 2.48-2.42 (m, 2H), 2.29 – 2.14 (m, 5H), 2.10 (s, 3H), 1.06 (d, J = 6.1 Hz, 6H).	4

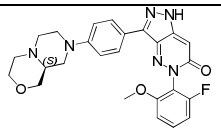
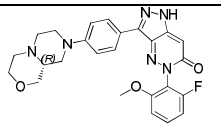
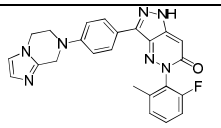
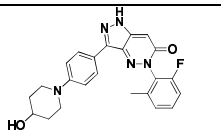
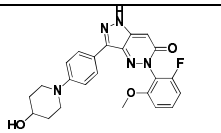
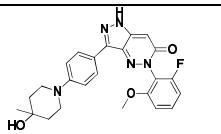
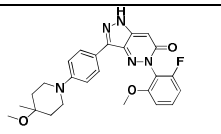
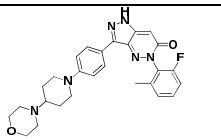
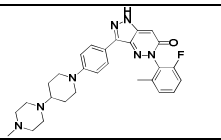
Example 58	Compound 91		ESI-MS: 431.2 $[M+H]^+$ ^{1}H NMR (400MHz, DMSO-d_6) δ 12.74 (br, 1H), 7.99 (d, J = 9.0 Hz, 2H), 7.52-7.46 (m, 1H), 7.32-7.26 (m, 2H), 6.84 (d, J = 9.0 Hz, 2H), 6.64 (s, 1H), 3.56 (d, J = 5.8 Hz, 2H), 3.47 (d, J = 11.2 Hz, 2H), 3.30-3.27 (m, 2H), 2.42 (q, J = 6.7 Hz, 1H), 2.10 (s, 3H), 1.99 (s, 3H), 1.50 (d, J = 8.2 Hz, 1H).	4
Example 59	Compound 92		ESI-MS: 422.2 $[M+H]^+$ ^{1}H NMR (400MHz, DMSO-d_6) δ 12.81 (s,1H), 7.97 (d, J = 8.8 Hz, H), 7.59-7.53 (m, 1H), 7.12 (d, J = 8.4 Hz, 1H), 7.09-7.04 (m, 3H), 6.63 (s, 1H), 3.78 (s, 3H), 3.73 (t, J = 4.8 Hz, 4H), 3.18 (t, J = 4.8 Hz, 4H).	2A
Example 60	Compound 93		ESI-MS: 435.2 $[M+H]^+$ ^{1}H NMR (400MHz, DMSO-d_6) δ 13.05 (s, 1H), 9.79 (br, 3H), 8.10 (d, J = 8.5 Hz, 2H), 7.54-7.45 (m, 1H), 7.34-7.26 (m, 2H), 7.17 (d, J = 8.6 Hz, 2H), 6.74 (s, 1H), 4.38-4.28 (m, 2H), 4.01-3.92 (m, 1H), 3.66-3.17 (m, 4H), 2.10 (s, 3H).	4
Example 61	Compound 94		ESI-MS: 437.2 $[M+H]^+$ ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.89 (br, 1H), 7.87 (dd, J = 8.4, 2.0 Hz, 1H), 7.75 (dd, J = 14.2, 2.0 Hz, 1H), 7.55 – 7.46 (m, 1H), 7.33 – 7.27 (m, 2H), 7.15 (t, J = 8.9 Hz, 1H), 6.72 (s, 1H), 3.10-3.04 (m, 4H), 2.48-2.43 (m, 4H), 2.21 (s, 3H), 2.10 (s, 3H).	2A
Example 62	Compound 95		ESI-MS: 476.4 $[M+H]^+$ ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.04 (s, 1H), 8.18 (s, 1H), 8.00 (d, J = 8.1 Hz, 1H), 7.49 (q, J = 7.0 Hz, 1H), 7.35-7.19 (m, 3H), 6.74 (s, 1H), 3.59 (br, 2H), 3.00 (s, 4H), 2.70 (br, 4H), 2.39 (s, 3H), 2.27 (s, 6H), 2.12 (s, 3H).	2A
Example 63	Compound 96		ESI-MS: 462.4 $[M+H]^+$	2A
Example 64	Compound 97		ESI-MS: 432.2 $[M+H]^+$ 1HNMR (DMSO-d6, 400MHz), δ 12.79 (s, 1H), 8.82 (d, J = 2.2 Hz, 1H), 8.12 (dd, J = 9.0, 2.4 Hz, 1H), 7.39 (t, J = 8.0 Hz, 1H), 7.06 (d, J = 8.2 Hz, 1H), 6.99 (d, J = 7.6 Hz, 1H), 6.95 (d, J = 9.0 Hz, 1H), 6.62 (s, 1H), 3.70 (s, 3H), 3.60 – 3.50 (m, 4H), 2.42 – 2.32 (m, 4H), 2.20 (s, 3H), 2.00 (s, 3H).	2A
Example 65	Compound 98		ESI-MS: 434.2 $[M+H]^+$ ^{1}HNMR (400MHz, DMSO-d_6) δ 12.92 (s, 1H), 8.83 (d, J = 2.4 Hz, 1H), 8.14 (dd, J = 9.2, 2.4 Hz, 1H), 7.57-7.51 (m, 1H), 7.33-7.28 (m, 2H), 6.97 (d, J = 9.2 Hz, 1H), 6.71 (s, 1H), 3.59-3.52 (m, 4H), 2.47-2.34 (m, 6H), 2.22 (s, 3H), 1.06 (t, J = 7.6 Hz, 3H).	2A
Example 66	Compound 99		ESI-MS: 445.2 $[M+H]^+$ ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.99 (br, 1H), 8.82 (s, 1H), 8.13 (d, J = 8.0 Hz, 1H), 8.01 (d, J = 9.2 Hz, 1H), 7.89 (s, 1H), 6.96 (d, J = 9.2 Hz, 1H), 6.74 (s, 1H), 3.56 (s, 4H), 2.38 (s, 4H), 2.21 (s, 3H), 2.17 (s, 3H).	2A
Example 67	Compound 100		ESI-MS: 422.1 $[M+H]^+$ ^{1}H NMR (400MHz, DMSO-d_6) δ 12.82 (s,1H), 10.37 (s, 1H), 8.85 (d, J = 2.4 Hz, 1H), 8.14 (dd, J = 8.8, 2.4 Hz, 1H), 7.40-7.33 (m, 1H), 6.97 (d, J = 9.2 Hz, 1H), 6.83-6.89 (m, 2H), 6.64 (s, 1H), 3.60-3.54 (m, 4H),	2A

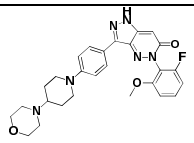
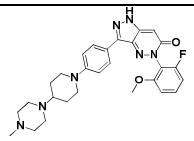
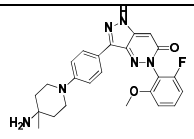
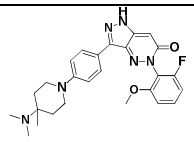
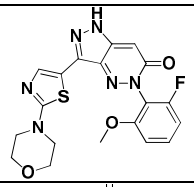
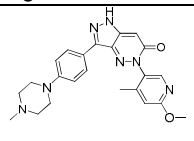
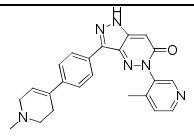
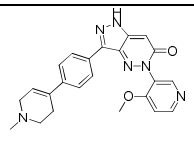
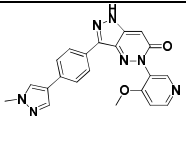
			2.44-2.37 (m, 4H), 2.22 (s, 3H).	
Example 68	Compound 101		ESI-MS: m/z = 434.2 ([M+H]$^+$). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.96 (brs, 1H), 8.83 (s, 1H), 8.14 (d, *J* = 8.9 Hz, 1H), 7.55-7.42 (m, 1H), 7.35-7.22 (m, 2H), 6.95 (d, *J* = 9.0 Hz, 1H), 6.67 (s, 1H), 3.65-3.46 (m, 4H), 2.46-2.38 (m, 4H), 2.38-2.26 (m, 2H), 2.10 (s, 3H), 1.02 (t, *J* = 7.0 Hz, 3H).	2B
Example 69	Compound 102		ESI-MS: m/z = 448.2 ([M+H]$^+$). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.93 (brs, 1H), 8.85 (d, *J* = 2.2 Hz, 2H), 8.17 (d, *J* = 9.2 Hz, 1H), 7.54-7.46 (m, 1H), 7.34-7.26 (m, 2H), 6.99 (d, *J* = 9.1 Hz, 1H), 6.71 (s, 1H), 3.67-3.60 (m, 2H), 3.59-3.49 (m, 6H), 2.10 (s, 3H), 2.04 (s, 3H).	2B
Example 70	Compound 103		ESI-MS: m/z = 462.2 ([M+H]$^+$). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.92 (brs, 1H), 8.85 (s, 1H), 8.15 (d, *J* = 9.2 Hz, 1H), 7.55-7.45 (m, 1H), 7.35-7.26 (m, 2H), 6.99 (d, *J* = 8.6 Hz, 1H), 6.71 (s, 1H), 4.64-4.39 (m, 4H), 3.69-3.49 (m, 4H), 3.48-3.36 (m, 1H), 2.41-2.24 (m, 4H), 2.11 (s, 3H).	2B
Example 71	Compound 104		ESI-MS: m/z = 455.1 ([M+H]$^+$). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.97 (brs, 1H), 8.88 (d, *J* = 2.2 Hz, 1H), 8.21 (d, *J* = 9.0, 2.3 Hz, 1H), 7.55-7.44 (m, 1H), 7.35-7.25 (m, 2H), 7.17 (d, *J* = 9.0 Hz, 1H), 6.73 (s, 1H), 4.20-3.99 (m, 4H), 3.19-3.05 (m, 4H), 2.10 (s, 3H).	2B
Example 72	Compound 105		ESI-MS: 498.1 [M+H]$^+$ ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.94 (s, 1H), 8.86 (d, J = 2.0 Hz, 1H), 8.18 (dd, J = 9.2, 2.4 Hz, 1H), 7.52-7.47 (m, 1H), 7.34-7.26 (m, 2H), 7.03 (d, J = 8.8 Hz, 1H), 6.72 (s, 1H), 3.71-3.65 (m, 4H), 3.29-3.22 (m, 4H), 3.08 (q, J = 7.6 Hz, 2H), 2.10 (s, 3H), 1.21 (t, J = 7.2 Hz, 3H).	2B
Example 73	Compound 106		ESI-MS: 476.2 [M+H]$^+$ ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.91 (s, 1H), 8.83 (d, J = 2.0 Hz, 1H), 8.14 (dd, J = 9.2, 2.4Hz, 1H), 7.52-7.47 (m, 1H), 7.34-7.26 (m, 2H), 6.96 (d, J = 8.8 Hz, 1H), 6.70 (s, 1H), 3.83-3.74 (m, 2H), 3.64 (q, J = 7.6 Hz, 1H), 3.58-3.48 (m, 5H), 2.94-2.87 (m, 1H), 2.55-2.47 (m, 1H), 2.43-2.38 (m, 2H), 2.10 (s, 3H), 2.02-1.94 (m, 1H), 1.80-1.71 (m, 1H).	2A
Example 74	Compound 107		ESI-MS: 440.1 [M+H]$^+$ ^{1}H NMR (400MHz, DMSO-d_6) δ 12.97 (s, 1H), 8.83 (d, J = 2.2 Hz, 1H), 8.13 (dd, J = 9.0, 2.4 Hz, 1H), 7.70-7.60 (m, 2H), 7.57-7.52 (m, 1H), 6.98 (d, J = 9.0 Hz, 2H), 6.74 (s, 1H), 3.62-3.52 (m, 4H), 2.48-2.38 (m, 4H), 2.24 (s, 3H).	2A
Example 75	Compound 108		ESI-MS: 454.3 [M+H]$^+$ ^{1}H NMR (400MHz, DMSO-d_6) δ 12.82 (br, 1H), 8.83 (d, *J* = 2.3 Hz, 1H), 8.13 (dd, *J* = 9.0, 2.4 Hz, 1H), 7.58 (dd, *J* = 9.3, 2.3 Hz, 1H), 7.46 (s, 1H), 6.96 (d, *J* = 9.0 Hz, 1H), 6.72 (s, 1H), 3.58-3.54 (m, 4H), 2.39-2.36 (m, 4H), 2.21 (s, 3H), 2.11 (s, 3H).	2A
Example 76	Compound 109		ESI-MS: 446.3 [M+H]$^+$ ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.88 (s, 1H), 8.81 (s, 1H) 8.12-8.10 (m, 1H), 7.52-7.48 (m, 1H), 7.31-7.28 (m, 2H), 6.82 (d, J = 9.2 Hz, 1H), 6.69 (s, 1H), 3.86 (d, J = 11.2 Hz, 2H), 3.23 (s, 2H), 2.99 (d, J = 11.2 Hz, 2H),	2A

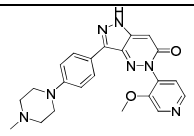
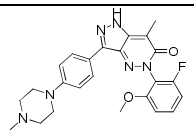
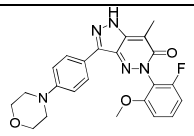
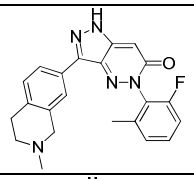
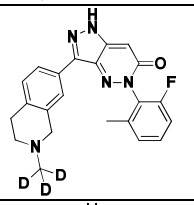
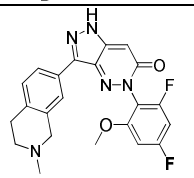
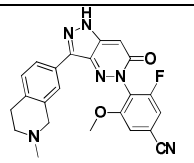
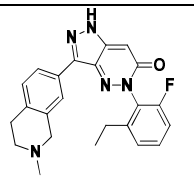
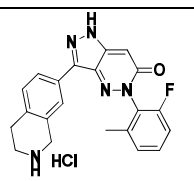
			2.24 (s, 3H), 2.10 (s, 3H), 1.94-1.92 (m, 2H), 1.57-1.46 (m, 2H).	
Example 77	Compound 110		ESI-MS: 435.2 $[M+H]^+$ ^{1}H NMR (400MHz, DMSO-d_6,) δ 13.03 (s, 1H), 8.95 (s, 2H), 7.57-7.51 (m, 1H), 7.33-7.25 (m, 2H), 6.74 (s, 1H), 3.79 (t, J = 4.4 Hz, 4H), 2.45-2.38 (m, 2H), 2.35 (t, J = 4.4 Hz, 4H), 2.20 (s, 3H), 1.05 (t, J = 7.6 Hz, 3H).	2A
Example 78	Compound 111		ESI-MS: m/z = 424.1 ($[M+H]^+$). ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.00 (brs, 1H), 8.97 (s, 2H), 7.56 (q, *J* = 8.0 Hz, 1H), 7.12 (d, *J* = 8.6 Hz, 1H), 7.06 (t, *J* = 8.9 Hz, 1H), 6.70 (s, 1H), 3.80-3.74 (m, 7H), 3.70-3.61 (m, 4H).	2B
Example 79	Compound 112		ESI-MS: 463.4 $[M+H]^+$ ^{1}H NMR (700 MHz, DMSO-d_6) δ 12.86 (s, 1H), 7.97 (d, J = 9.0 Hz, 2H), 7.56-7.52 (m, 1H), 7.33-7.30 (m, 2H), 7.03 (d, J = 9.0 Hz, 2H), 6.68 (s, 1H), 4.44 (s, 1H), 3.53 (q, J = 5.8 Hz, 2H), 3.22-3.19 (m, 4H), 2.56-2.52 (m, 4H), 2.45-2.37 (m, 4H), 1.06 (t, J = 7.6 Hz, 3H).	2A
Example 80	Compound 113		ESI-MS: 465.3 $[M+H]^+$ ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.77 (s, 1H), 7.95 (d, J = 8.9 Hz, 2H), 7.60-7.51 (m, 1H), 7.17 – 6.98 (m, 4H), 6.61 (s, 1H), 4.41 (t, J = 5.3 Hz, 1H), 3.78 (s, 3H), 3.53 (q, J = 6.0 Hz, 2H), 3.24-3.17 (m, 4H), 2.60 – 2.52 (m, 4H), 2.42 (t, J = 6.2 Hz, 2H).	2A
Example 81	Compound 114		ESI-MS: 490.2 $[M+H]^+$ ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.88 (s, 1H), 7.93 (d, *J* = 8.9 Hz, 2H), 7.78 (dd, *J* = 8.9, 1.5 Hz, 1H), 7.73 (s, 1H), 7.03 (d, *J* = 8.9 Hz, 2H), 6.66 (s, 1H), 4.43 (s, 1H), 3.87 (s, 3H), 3.26-3.12 (m, 6H), 2.60-2.52 (m, 4H), 2.47-2.40 (m, 2H).	2B
Example 82	Compound 115		ESI-MS: 493.3 $[M+H]^+$ ^{1}H NMR (400 MHz, DMSO-d_6) δ 1 2.78 (s, 1H), 7.95 (d, J = 9.0 Hz, 2H), 7.61-7.50 (m, 1H), 7.12 (d, J = 8.6 Hz, 1H), 7.09 – 6.96 (m, 3H), 6.62 (s, 1H), 4.12 (s, 1H), 3.78 (s, 3H), 3.27 – 3.12 (m, 4H), 2.72 – 2.59 (m, 4H), 2.23 (s, 2H), 1.10 (s, 6H).	2A
Example 83	Compound 116		ESI-MS: 494.3 $[M+H]^+$ ^{1}H NMR (700 MHz, DMSO-d_6) δ 12.83 (s, 1H), 7.96 (d, J = 8.9 Hz, 2H), 7.56-7.51 (m, 1H), 7.33-7.28 (m, 2H), 7.02 (d, J = 9.0 Hz, 2H),6.67 (s, 1H), 4.12 (s, 1H), 3.24-3.18 (m, 4H), 2.68-2.60 (m, 4H), 2.45-2.37 (m, 2H), 2.24 (s, 2H), 1.10 (s, 6H), 1.06 (t, J = 7.6 Hz, 3H).	2A
Example 84	Compound 117		ESI-MS: 475.1 $[M+H]^+$ ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.77 (s, 1H), 7.94 (d, J = 8.9 Hz, 2H), 7.53-7.46 (m, 1H), 7.33-7.25 (m, 2H), 6.89 (d, J = 9.0 Hz, 2H), 6.66 (s, 1H), 4.36 (t, J = 5.3 Hz, 1H), 3.50 (q, J = 5.9 Hz, 2H), 3.45 – 3.33 (m, 4H), 2.88 (d, J = 9.8 Hz, 2H), 2.43 (t, J = 6.2 Hz, 2H), 2.09 (s, 3H), 1.95 – 1.83 (m, 2H), 1.65-1.54 (m, 2H).	2A
Example 85	Compound 118		ESI-MS: 450.2 $[M+H]^+$ ^{1}H NMR (400MHz, CD_3OD) δ 8.98 (d, J = 2.0 Hz, 1H), 8.31 (dd, J = 8.8, 2.4 Hz, 1H), 7.52-7.46 (m, 1H), 7.28 (d, J = 8.0 Hz, 1H), 7.21 (t, J = 8.8 Hz, 1H), 6.92 (d, J = 8.8 Hz, 1H), 6.74 (s, 1H), 3.74 (t, J = 5.6 Hz, 2H), 3.66 (t, J = 5.2 Hz, 4H), 2.66 (t, J = 5.2 Hz, 4H), 2.61 (t, J = 5.6 Hz, 2H), 2.18 (s, 3H).	2A

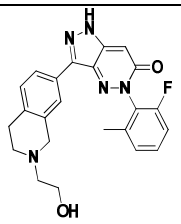
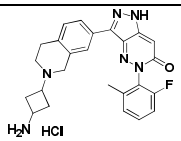
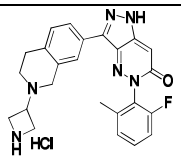
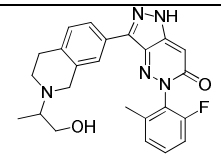
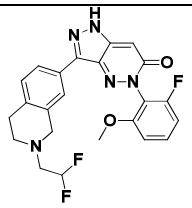
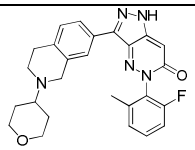
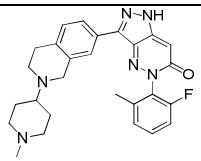
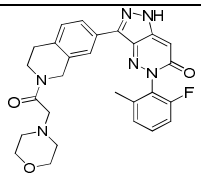
Example 86	Compound 119		ESI-MS: 464.2 $[M+H]^+$ ^{1}H NMR (400MHz, DMSO-d_6) δ 12.90 (s, 1H), 8.83 (d, J = 2.4 Hz, 1H), 8.14 (dd, J = 9.2, 2.4 Hz, 1H), 7.52-7.47 (m, 1H), 7.33-7.26 (m, 2H), 6.96 (d, J = 8.8 Hz, 1H), 6.70 (s, 1H), 3.58-3.51 (m, 4H), 3.46 (t, J = 6.0 Hz, 2H), 3.24 (s, 3H), 2.52-2.45 (m, 6H), 2.10 (s, 3H).	2A
Example 87	Compound 120		ESI-MS: 449.2 $[M+H]^+$ ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.83 (s, 1H), 7.97 (d, J = 8.9 Hz, 2H), 7.53-7.45 (m, 1H), 7.34-7.25 (m, 2H), 7.02 (d, J = 9.0 Hz, 2H), 6.67 (s, 1H), 4.60-4.54 (m, 2H), 3.75 (d, J = 11.6 Hz, 1H), 3.69 – 3.57 (m, 2H), 3.40-3.34 (m, 1H), 2.89 – 2.73 (m, 2H), 2.62-2.53 (m, 1H), 2.30 – 2.19 (m, 4H), 2.14 – 2.06 (m, 4H).	4
Example 88	Compound 121		ESI-MS: 465.2 $[M+H]^+$ ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.75 (br, 1H), 7.95 (d, J = 8.9 Hz, 2H), 7.59-7.51 (m, 1H), 7.14 – 6.99 (m, 4H), 6.60 (s, 1H), 4.56 (s, 1H), 3.78 (s, 3H), 3.77-3.71 (m, 1H), 3.69 – 3.56 (m, 2H), 3.40-3.34 (m, 1H), 2.88 – 2.74 (m, 2H), 2.58 (dd, J = 12.0, 10.2 Hz, 1H), 2.28 – 2.20 (m, 4H), 2.15 – 2.06 (m, 1H).	2A
Example 89	Compound 122		ESI-MS: 461.2 $[M+H]^+$ ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.87 (s, 1H), 7.99 (d, J = 8.9 Hz, 2H), 7.53-7.45 (m, 1H), 7.35-7.25 (m, 2H), 7.13 – 7.04 (m, 2H), 6.69 (s, 1H), 4.41 (t, J = 8.1 Hz, 1H), 4.01 – 3.90 (m, 3H), 3.85 – 3.75 (m, 1H), 3.62 (dd, J = 13.3, 3.2 Hz, 1H), 3.16-3.07 (m, 1H), 2.85 – 2.62 (m, 2H), 2.10 (s, 3H).	4
Example 90	Compound 123		ESI-MS: 477.2 $[M+H]^+$ ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.81 (s, 1H), 7.97 (d, J = 8.9 Hz, 2H), 7.66 – 7.47 (m, 1H), 7.15-7.01 (m, 4H), 6.63 (s, 1H), 4.46-4.36 (m, 1H), 4.03 – 3.89 (m, 3H), 3.84-3.75 (m, 4H), 3.62 (dd, J = 13.1, 2.6 Hz, 1H), 3.17-3.07 (m, 1H), 2.82 – 2.65 (m, 2H).	2A
Example 91	Compound 124		ESI-MS: 502.2 $[M+H]^+$ ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.89 (s, 1H), 7.96 (d, J = 9.0 Hz, 2H), 7.78 (dd, J = 8.9, 1.4 Hz, 1H), 7.74-7.70 (m, 1H), 7.08 (d, J = 9.0 Hz, 2H), 6.67 (s, 1H), 4.41 (t, J = 8.1 Hz, 1H), 4.02 – 3.91 (m, 3H), 3.86 (s, 3H), 3.83-3.76 (m, 1H), 3.62 (dd, J = 13.1, 2.7 Hz, 1H), 3.12 (td, J = 12.7, 3.6 Hz, 1H), 2.82-2.65 (m, 2H).	2B
Example 92	Compound 125		ESI-MS: 477.1 $[M+H]^+$ ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.79 (s, 1H), 7.96 (d, J = 8.8 Hz, 2H), 7.59-7.52 (m, 1H), 7.33-7.26 (m, 2H), 6.93 (d, J = 8.8 Hz, 2H), 6.66 (s, 1H), 4.29 (s, 1H), 3.65-3.58 (m, 1H), 3.56-3.49 (m, 1H), 2.98-2.81 (m, 3H), 2.62-2.55 (m, 1H), 2.41 (s, 3H), 2.28-2.20 (m, 1H), 2.10 (s, 3H), 1.13 (s, 3H), 1.11 (s, 3H).	2A
Example 93	Compound 126		ESI-MS: 493.3$[M+H]^+$ ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.74 (s, 1H), 7.95 (d, J = 8.9 Hz, 2H), 7.65-7.50 (m, 1H), 7.12 (d, J = 8.6 Hz, 1H), 7.06 (t, J = 8.8 Hz, 1H), 6.93 (d, J = 9.0 Hz, 2H), 6.61 (s, 1H), 4.29 (s, 1H), 3.78 (s, 3H), 3.61 (dd, J = 12.8, 3.9 Hz, 1H), 3.58 – 3.48 (m, 1H), 3.01 – 2.77 (m, 3H), 2.63-5.52 (m, 1H), 2.40 (s, 3H), 2.24 (dd, J = 9.1, 3.9 Hz, 1H), 1.13 (s, 3H) , 1.11 (s, 3H).	2A

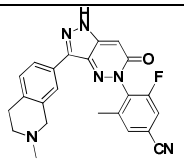
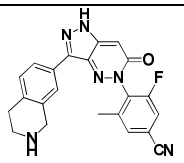
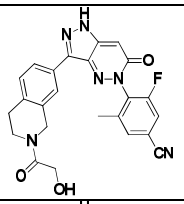
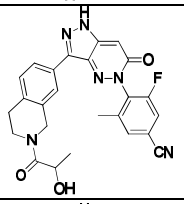
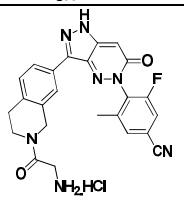
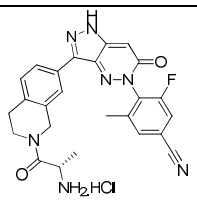
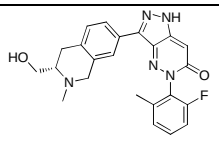
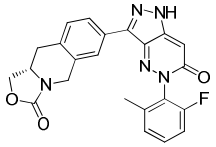
Example 94	Compound 127		ESI-MS: 507.3 $[M+H]^+$ ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.73 (s, 1H), 7.95 (d, J = 8.8 Hz, 2H), 7.59-7.52 (m, 1H), 7.12 (d, J = 8.6 Hz, 1H), 7.06 (t, J = 8.8 Hz, 1H), 6.93 (d, J = 8.8 Hz, 2H), 6.60 (s, 1H), 3.78 (s, 3H), 3.60-3.52 (m, 2H), 3.11 (s, 3H), 2.95-2.80 (m, 3H), 2.62-2.55 (m, 1H), 2.44 (dd, J = 9.0, 3.6 Hz, 1H), 2.39 (s, 3H), 1.15 (s, 3H), 1.11 (s, 3H).	2A
Example 95	Compound 128		ESI-MS: 450.3 $[M+H]^+$ ^{1}H NMR (400MHz, DMSO-d_6) δ 12.83 (br, 1H), 8.83 (d, J = 2.2 Hz, 1H), 8.13 (dd, J = 9.0, 2.4 Hz, 1H), 7.54-7.44 (m, 1H), 7.34-7.25 (m, 2H), 6.93 (d, J = 9.1 Hz, 1H), 6.69 (s, 1H), 4.60 (br, 1H), 4.29 (d, J = 12.0 Hz, 1H), 4.10 (d, J = 12.2 Hz, 1H), 3.65 (dd, J = 11.0, 3.6 Hz, 1H), 3.02 – 2.94 (m, 1H), 2.81 – 2.69 (m, 2H), 2.23 (s, 3H), 2.19-2.13 (m, 1H), 2.10 (s, 3H), 2.07 – 1.92 (m, 1H).	2A
Example 96	Compound 129		ESI-MS: 436.1 $[M+H]^+$ ^{1}H NMR (400MHz, DMSO-d_6) δ 12.95 (s, 1H), 8.85 (d, J = 2.2 Hz, 1H), 8.17 (dd, J = 9.0, 2.4 Hz, 1H), 7.54-7.45 (m, 1H), 7.35-7.26 (m, 2H), 7.04 (d, J = 9.1 Hz, 1H), 6.72 (s, 1H), 4.58 (dd, J = 13.0, 2.8 Hz, 1H), 4.44-4.35 (m, 2H), 3.99 (dd, J = 8.8, 5.6 Hz, 1H), 3.92 – 3.79 (m, 1H), 3.65-3.58 (m, 1H), 3.07-2.99 (m, 1H), 2.96 – 2.79 (m, 2H), 2.10 (s, 3H).	2A
Example 97	Compound 130		ESI-MS: 449.2 $[M+H]^+$ ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.92 (s, 1H;NH), 8.02-7.90 (m, 2H), 7.55 – 7.43 (m, 1H), 7.35-7.24 (m, 2H), 7.03-6.94 m, 2H), 6.66 (s, 1H), 3.84-3.78 (m, 1H), 3.74-3.65 (m, 1H), 3.52-3.44 (m, 1H), 3.07-3.01 (m, 1H), 3.00-2.90 (m, 1H), 2.84-2.77(m, 1H), 2.20 (s, 3H), 2.10 (d, J = 3.5 Hz, 3H), 2.06 – 1.93 (m, 3H).	4
Example 98	Compound 131		ESI-MS: 463.3 $[M+H]^+$ ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.97 (s, 1H), 10.58 (br, 1H), 8.02 (d, J = 8.8 Hz, 2H), 7.52-7.46 (m, 1H), 7.34-7.28 (m, 2H), 7.15 (d, J = 8.4 Hz, 2H), 6.71 (s, 1H), 4.34-4.24 (m, 1H), 4.18-4.04 (m, 1H), 3.94-3.80 (m, 1H), 3.36-3.20 (m, 4H), 2.92 (s, 3H), 2.10 (s, 3H).	2A
Example 99	Compound 132		ESI-MS: 504.3 $[M+H]^+$ ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.80 (s, 1H), 7.97 (d, J = 9.0 Hz, 2H), 7.59-7.53 (m, 1H), 7.14-7.04 (m, 4H), 6.62 (s, 1H), 4.44-4.36 (m, 1H), 3.84-3.77 (m, 5H), 3.65-3.56 (m, 1H), 3.07 (d, J = 15.6 Hz, 1H), 2.92-2.87 (m, 1H), 2.84-2.75 (m, 2H), 2.71-2.56 (m, 2H), 2.26 (dd, J = 11.8, 8.0 Hz, 1H), 2.21 (s, 3H).	2A
Example 100	Compound 133		ESI-MS: 461.3 $[M+H]^+$ ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.81 (s, 1H), 7.96 (d, J = 8.9 Hz, 2H), 7.52-7.46 (m, 1H), 7.32-7.27 (m, 2H), 7.03 (d, J = 8.9 Hz, 2H), 6.67 (s, 1H), 3.79-3.69 (m, 3H), 3.60 (d, J = 11.5 Hz, 1H), 3.56-3.49 (m, 1H), 3.15 (t, J = 10.4 Hz, 1H), 2.85-2.76 (m, 2H), 2.67 (d, J = 11.5 Hz, 1H), 2.36-2.16 (m, 4H), 2.10 (s, 3H).	2A
Example 101	Compound 134		ESI-MS: 461.3 $[M+H]^+$ ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.81 (s, 1H), 7.96 (d, J = 8.9 Hz, 2H), 7.52-7.46 (m, 1H), 7.32-7.27 (m, 2H), 7.03 (d, J = 8.9 Hz, 2H), 6.67 (s, 1H), 3.79-3.69 (m, 3H), 3.60 (d, J = 11.5 Hz, 1H), 3.56-3.49 (m, 1H),	2A

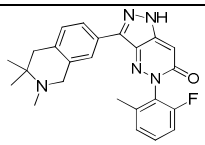
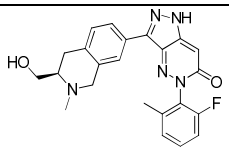
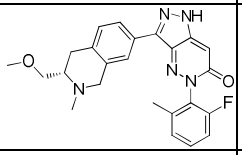
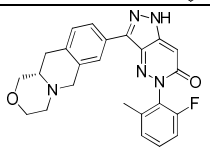
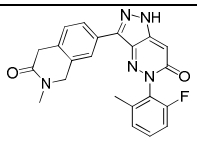
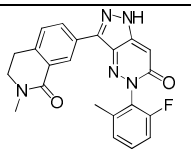
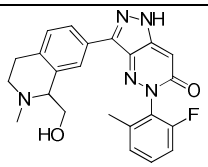
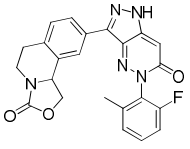
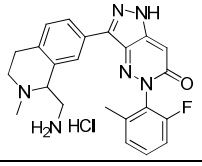
			3.15 (t, J = 10.4 Hz, 1H), 2.85-2.76 (m, 2H), 2.67 (d, J = 11.5 Hz, 1H), 2.36-2.16 (m, 4H), 2.10 (s, 3H).	
Example 102	Compound 135		ESI-MS: 477.2 $[M+H]^+$ ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.78 (s, 1H), 7.95 (d, J = 8.9 Hz, 2H), 7.59-7.52 (m, 1H), 7.12 (d, J = 8.6 Hz, 1H), 7.09-7.02 (m, 3H), 6.61 (s, 1H), 3.78-3.69 (m, 6H), 3.60 (d, J = 11.5 Hz, 1H), 3.56-3.49 (m, 1H), 3.15 (t, J = 10.4 Hz, 1H), 2.85-2.76 (m, 2H), 2.67 (d, J = 11.5 Hz, 1H), 2.36-2.16 (m, 4H).	2A
Example 103	Compound 136		ESI-MS: 477.2 $[M+H]^+$ ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.80 (s, 1H), 7.95 (d, J = 8.9 Hz, 2H), 7.59-7.52 (m, 1H), 7.12 (d, J = 8.6 Hz, 1H), 7.09-7.02 (m, 3H), 6.62 (s, 1H), 3.78-3.69 (m, 6H), 3.60 (d, J = 11.5 Hz, 1H), 3.56-3.49 (m, 1H), 3.15 (t, J = 10.4 Hz, 1H), 2.85-2.76 (m, 2H), 2.67 (d, J = 11.5 Hz, 1H), 2.36-2.16 (m, 4H).	2A
Example 104	Compound 137		ESI-MS: 442.2 $[M+H]^+$ ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.85 (s, 1H), 8.03-8.00 (m, 2H), 7.53-7.46 (m, 1H), 7.33-7.27 (m, 2H), 7.19-7.16 (m, 2H), 7.10 (d, J = 1.0 Hz, 1H), 6.88 (d, J = 1.2 Hz, 1H), 6.69 (s, 1H), 4.47 (s, 2H), 4.09 (t, J = 5.3 Hz, 2H), 3.79 (t, J = 5.3 Hz, 2H), 2.10 (s, 3H).	4
Example 105	Compound 138		ESI-MS: 420.2 $[M+H]^+$ ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.80 (s, 1H), 7.95 (d, J = 8.9 Hz, 2H), 7.52 – 7.46 (m, 1H), 7.33-7.27 (m, 2H), 7.02 (d, J = 8.9 Hz, 2H), 6.67 (s, 1H), 4.67 (d, J = 4.2 Hz, 1H), 3.69 – 3.59 (m, 3H), 2.98-2.88 (m, 2H), 2.10 (s, 3H), 1.84 – 1.72 (m, 2H), 1.47-1.36 (m, 2H).	4
Example 106	Compound 139		ESI-MS: 436.2 $[M+H]^+$ ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.77 (s, 1H), 7.93 (d, J = 8.8 Hz, 2H), 7.59-7.53 (m, 1H), 7.13-7.01 (m, 4H), 6.61 (s, 1H), 4.68 (d, J = 4.4 Hz, 1H), 3.78 (s, 3H), 3.68-3.60 (m, 3H), 2.97-2.90 (m, 2H), 1.84-1.74 (m, 2H), 1.48-1.36 (m,2H).	2A
Example 107	Compound 140		ESI-MS: 450.2 $[M+H]^+$ ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.77 (br, 1H), 7.93 (d, J = 8.8 Hz, 2H), 7.59-7.52 (m,1H), 7.12 (d, J = 8.8 Hz, 1H), 7.09-7.00 (m, 3H) , 6.61 (s, 1H), 4.32 (s, 1H), 3.78 (s, 3H), 3.44-3.30 (m, 2H), 3.22-3.16 (m, 2H), 1.54-1.50 (m, 4H), 1.13 (s, 3H).	2A
Example 108	Compound 141		ESI-MS: 464.3 $[M+H]^+$ ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.77 (s, 1H), 7.93 (d, J = 8.8 Hz, 2H), 7.59-7.52 (m, 1H), 7.12 (d, J = 8.6 Hz, 1H), 7.09-7.00 (m, 3H), 6.61 (s, 1H), 3.79 (s, 3H), 3.46-3.39 (m, 2H), 3.12 (s, 3H), 3.12-3.04 (m, 2H), 1.77-1.70 (m, 2H), 1.57-1.48 (m, 2H), 1.12 (s, 3H).	2A
Example 109	Compound 142		ESI-MS: 489.2 $[M+H]^+$ ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.81 (s, 1H), 7.95 (d, J = 9.0 Hz, 2H), 7.52 – 7.46 (m, 1H), 7.33-7.26 (m, 2H), 7.03 (d, J = 9.1 Hz, 2H), 6.67 (s, 1H), 3.88 – 3.77 (m, 2H), 3.60 – 3.51 (m, 4H), 2.79 – 2.69 (m, 2H), 2.48 – 2.42 (m, 4H), 2.35 – 2.27 (m, 1H), 2.10 (s, 3H), 1.87 – 1.78 (m, 2H), 1.50 – 1.38 (m, 2H).	4
Example 110	Compound 143		ESI-MS: 502.2 $[M+H]^+$ ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.80 (s, 1H), 7.95 (d, J = 9.0 Hz, 2H), 7.53-7.45 (m, 1H), 7.34-7.25 (m, 2H), 7.02 (d, J = 9.0 Hz, 2H), 6.67 (s, 1H), 3.82 (d, J =	4

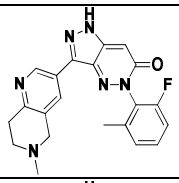
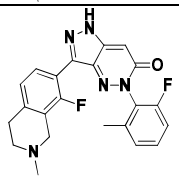
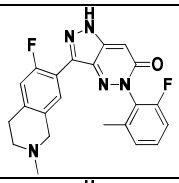
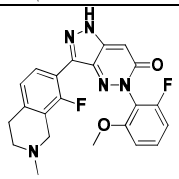
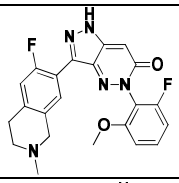
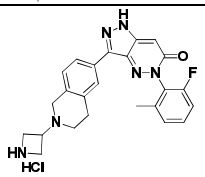
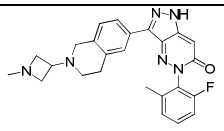
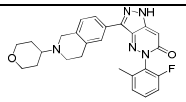
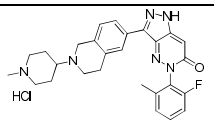
			12.5 Hz, 2H), 3.32 (s, 2H), 2.79 – 2.69 (m, 2H), 2.52-2.43 (m, 2H), 2.40-2.21 (m, 5H), 2.15 (s, 3H), 2.10 (s, 3H), 1.84 – 1.75 (m, 2H), 1.51 – 1.38 (m, 2H).	
Example 111	Compound 144		ESI-MS: 505.3 $[M+H]^+$ ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.75 (s, 1H), 7.93 (d, J = 9.0 Hz, 2H), 7.59-7.52 (m, 1H), 7.12 (d, J = 8.6 Hz, 1H), 7.09-7.01 (m, 3H), 6.61 (s, 1H), 3.85-3.77 (m, 5H), 3.57-3.53 (m, 4H), 2.78-2.70 (m, 2H), 2.48-2.43 (m, 4H), 2.36-2.26 (m, 1H), 1.87-1.80 (m, 2H), 1.50-1.39 (m, 2H).	2A
Example 112	Compound 145		ESI-MS: 518.3 $[M+H]^+$ ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.77 (s, 1H), 7.93 (d, J = 9.0 Hz, 2H), 7.59-7.52 (m, 1H), 7.12 (d, J = 8.6 Hz, 1H), 7.09-7.01 (m, 3H), 6.61 (s, 1H), 3.85-3.77 (m, 5H), 2.78-2.70 (m, 2H), 2.50-2.43 (m, 2H), 2.40-2.26 (m, 5H), 2.15 (s, 3H), 1.84-1.76 (m, 2H), 1.50-1.39 (m, 2H).	2A
Example 113	Compound 146		ESI-MS: 449.3 $[M+H]^+$ ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.95 (d, J = 8.9 Hz, 2H), 7.59-7.52 (m, 1H), 7.12 (d, J = 8.6 Hz, 1H), 7.09-7.02 (m, 3H), 6.61 (s, 1H), 3.78 (s, 3H), 3.55-3.46 (m, 2H), 3.23-3.15 (m, 2H), 1.70-1.58 (m, 4H), 1.24 (s, 3H).	4
Example 114	Compound 147		ESI-MS: 477.3 $[M+H]^+$ ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.81 (s, 1H), 7.96 (d, J = 8.9 Hz, 2H), 7.59-7.52 (m, 1H), 7.14-7.02 (m, 4H), 6.62 (s, 1H), 3.90-3.60 (m, 5H), 2.97 (br, 2H), 2.61 (br, 6H), 1.83 (br, 4H), 1.26 (br, 3H).	4
Example 115	Compound 148		ESI-MS: m/z = 429.1 ($[M+H]^+$). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.80 (brs, 1H), 7.77 (s, 1H), 7.61-7.51 (m, 1H), 7.12 (d, *J* = 8.6 Hz, 1H), 7.06 (t, *J* = 8.9 Hz, 1H), 6.63 (s, 1H), 3.79 (s, 3H), 3.75-3.68 (m, 4H), 3.51-3.44 (m, 4H).	2A
Example 116	Compound 149		ESI-MS: m/z = 432.2 ($[M+H]^+$). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.78 (brs, 1H), 8.20 (s, 1H), 7.99 (d, *J* = 8.8 Hz, 2H), 7.03 (d, *J* = 8.8, 2H), 6.90 (s, 1H), 6.63 (s, 1H), 3.91 (s, 3H), 3.26-3.12 (m, 4H), 2.54-2.48 (m, 4H), 2.24 (s, 3H), 2.08 (s, 3H).	4
Example 117	Compound 150		ESI-MS: 399.2 $[M+H]^+$ ^{1}H NMR (400MHz, DMSO-d_6,) δ 13.07 (s, 1H), 8.66 – 8.54 (m, 2H), 8.11 (d, J = 8.0 Hz, 2H), 7.58 (d, J = 8.1 Hz, 2H), 7.50 (d, J = 4.8 Hz, 1H), 6.74 (s, 1H), 6.26 (s, 1H), 3.32 (s, 2H), 3.06 (s, 2H), 2.64-2.56 (m, 2H), 2.30 (s, 3H), 2.16 (s, 3H).	4
Example 118	Compound 151		ESI-MS: 415$[M+H]^+$ 1H NMR (400 MHz, DMSO-d_6) δ 13.01 (s, 1H), 8.61 (d, J = 5.8 Hz, 1H), 8.53 (s, 1H), 8.09 (d, J = 8.5 Hz, 2H), 7.57 (d, J = 8.5 Hz, 2H), 7.34 (d, J = 5.8 Hz, 1H), 6.67 (s, 1H), 6.25 (s, 1H), 3.85 (s, 3H), 3.36-3.32 (m, 2H), 3.07-2.99 (m, 2H), 2.58 (t, J = 5.5 Hz, 2H), 2.28 (s, 3H).	4
Example 119	Compound 152		ESI-MS: 400.1$[M+H]^+$ ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.99 (s, 1H), 8.61 (d, J = 5.8 Hz, 1H), 8.54 (s, 1H), 8.16 (s, 1H), 8.11 (d, J = 8.5 Hz, 2H), 7.89 (s, 1H), 7.69 (d, J = 8.5 Hz, 2H), 7.34 (d, J = 5.8 Hz, 1H), 6.67 (s, 1H), 3.87 (s, 3H), 3.86	4

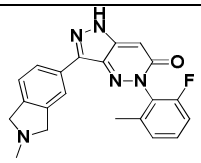
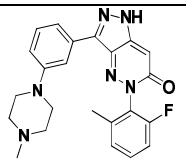
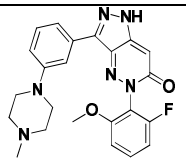
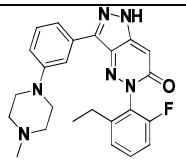
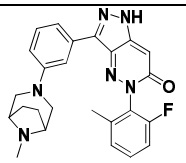
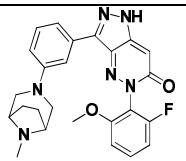
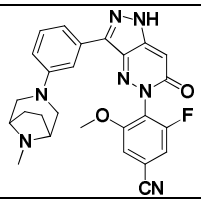
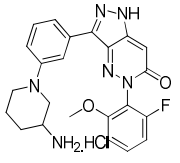
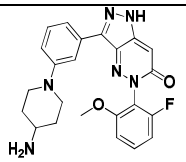
			(s, 3H).	
Example 120	Compound 153		ESI-MS: m/z = 418.2 ([M+H]$^+$). ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.78 (brs, 1H), 8.65 (s, 1H), 8.42 (d, J = 2.7 Hz, 1H), 7.97 (d, J = 9.0 Hz, 2H), 7.56 (d, J = 4.8 Hz, 1H), 7.03 (d, J = 9.0 Hz, 2H), 6.60 (s, 1H), 3.89 (s, 3H), 3.28-3.18 (m, 4H), 2.48-2.38 (m, 4H), 2.23 (s, 3H).	4
Example 121	Compound 154		ESI-MS: 449.2 [M+H]$^+$ ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.86 (s, 1H), 7.96 (d, J = 9.2 Hz, 2H), 7.58-7.52 (m, 1H), 7.11 (d, J = 8.8 Hz, 1H), 7.08-7.01 (m, 1H), 3.77 (s, 3H), 3.22-3.18 (m, 4H), 2.46-2.42 (m, 4H), 2.25 (s, 3H), 2.21 (s, 3H).	3A
Example 122	Compound 155		ESI-MS: 436.2 [M+H]$^+$ ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.88 (s, 1H), 7.99 (d, J = 8.8 Hz, 2H), 7.58-7.51 (m, 1H), 7.13-7.02 (m, 4H), 3.77 (s, 3H), 3.76-3.70 (m, 4H), 3.20-3.14 (m, 4H), 2.26 (s, 3H).	3A
Example 123	Compound 156		ESI-MS: 390.3 [M+H]$^+$ ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.11 (s, 1H), 7.93 (d, J = 8.1 Hz, 1H), 7.81 (s, 1H), 7.54-7.44 (m, 1H), 7.35-7.23 (m, 3H), 6.76 (s, 1H), 3.91 (br, 2H), 2.97 (br, 4H), 2.58 (s, 3H), 2.10 (s, 3H).	2A
Example 124	Compound 157		ESI-MS: 393.2 [M+H]$^+$ ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.02 (s, 1H), 7.87 (dd, J = 8.0, 1.4 Hz, 1H), 7.76 (s, 1H), 7.52-7.46 (m, 1H), 7.32-7.26 (m, 2H), 7.22 (d, J = 8.0 Hz, 1H), 6.74 (s, 1H), 3.52 (br, 2H), 2.83 (t, J = 5.7 Hz, 2H), 2.61 (d, J = 5.7 Hz, 2H), 2.10 (s, 3H).	2A
Example 125	Compound 158		ESI-MS: 424.2 [M+H]$^+$ 1H NMR (400 MHz, DMSO-d_6) δ 13.05 (s, 1H), 7.85 (dd, J = 8.0, 1.5 Hz, 1H), 7.75 (s, 1H), 7.23 (d, J = 8.0 Hz, 1H), 7.17 – 7.09 (m, 2H), 6.69 (s, 1H), 3.80 (s, 3H), 3.52 (s, 2H), 2.84 (t, J = 5.8 Hz, 2H), 2.60 (t, J = 5.9 Hz, 2H), 2.34 (s, 3H).	2A
Example 126	Compound 159		ESI-MS: 431.1 [M+H]$^+$ ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.07 (s, 1H), 7.84 (dd, J = 8.0, 1.8 Hz, 1H), 7.79 (dd, J = 9.0, 1.3 Hz, 1H), 7.76 – 7.72 (m, 2H), 7.22 (d, J = 8.0 Hz, 1H), 6.73 (s, 1H), 3.87 (s, 3H), 3.52 (s, 2H), 2.84 (t, J = 5.9 Hz, 2H), 2.61 (t, J = 5.9 Hz, 2H), 2.34 (s, 3H).	2B
Example 127	Compound 160		ESI-MS: 404.3 [M+H]$^+$ ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.05 (s, 1H), 7.87 (dd, J = 8.0, 1.6 Hz, 1H), 7.77 (s, 1H), 7.57-7.51 (m, 1H), 7.34-7.28 (m, 2H), 7.22 (d, J = 8.0 Hz, 1H), 6.73 (s, 1H), 3.50 (s, 2H), 2.83 (t, J = 5.6 Hz, 2H), 2.59 (t, J = 6.0 Hz, 2H), 2.47-2.36 (m, 2H), 2.33 (s, 3H), 1.07 (t, J = 7.6 Hz, 3H).	2A
Example 128	Compound 161		ESI-MS: 376.3 [M+H]$^+$ ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.19 (s, 1H), 9.25 (s, 2H), 8.00 (dd, J = 8.0, 1.5 Hz, 1H), 7.94-7.91 (m, 1H), 7.54-7.46 (m, 1H), 7.36 (d, J = 8.1 Hz, 1H), 7.33 – 7.27 (m, 2H), 6.78 (s, 1H), 4.33 (t, J = 4.0 Hz, 2H), 3.41-3.33 (m, 2H), 3.03 (t, J = 6.2 Hz, 2H), 2.10 (s, 3H).	2A

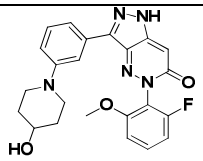
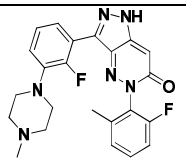
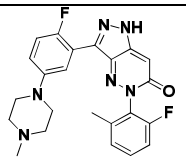
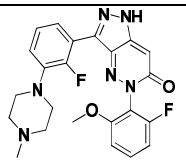
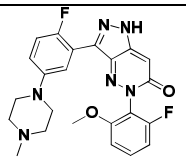
Example 129	Compound 162		ESI-MS: 420.2 $[M+H]^+$ ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.04 (s, 1H), 7.91-7.83 (m, 1H), 7.75 (s, 1H), 7.54-7.45 (m, 1H), 7.36 – 7.26 (m, 2H), 7.21 (d, J = 8.0 Hz, 1H), 6.74 (s, 1H), 4.44 (t, J = 5.2 Hz, 1H), 3.63 (s, 2H), 3.58 (q, J = 5.7 Hz, 2H), 2.82 (t, J = 5.5 Hz, 2H), 2.71 (t, J = 5.5 Hz, 2H), 2.56 (t, J = 6.2 Hz, 2H), 2.10 (s, 3H).	2A
Example 131	Compound 163		ESI-MS: 445.3 $[M+H]^+$ ^{1}H NMR (400MHz, DMSO-d_6) δ 13.22 (s, 1H), 11.70 (br, 1H), 8.41 (br, 3H), 8.02 (d, J = 8.2 Hz, 1H), 7.92 (s, 1H), 7.54-7.45 (m, 1H), 7.39 (d, J = 8.1 Hz, 1H), 7.35 – 7.25 (m, 2H), 6.78 (s, 1H), 4.66-4.54 (m, 1H), 4.30-4.18 (m, 1H), 3.77 – 3.58 (m, 2H), 3.33 – 3.16 (m, 2H), 3.13-3.01 (m, 1H), 2.78-2.60 (m, 4H), 2.11-2.09 (m, 3H).	2A
Example 132	Compound 164		ESI-MS: 431.3 $[M+H]^+$ ^{1}H NMR (400MHz, DMSO-d_6) δ 13.21 (s, 1H), 12.80 (br, 1H), 9.63 (s, 1H), 9.17 (s, 1H), 8.01 (d, J = 8.0 Hz, 1H), 7.85 (s, 1H), 7.54 – 7.45 (m, 1H), 7.38 (d, J = 8.2 Hz, 1H), 7.34 – 7.26 (m, 2H), 6.77 (s, 1H), 4.84-4.08 (m, 8H), 3.32-3.04 (m, 3H), 2.10 (s, 3H).	2A
Example 133	Compound 165		ESI-MS: 434.3 $[M+H]^+$ ^{1}H NMR (400MHz, DMSO-d_6) δ 13.02 (s, 1H), 7.85 (d, J = 8.0 Hz, 1H), 7.76 (s, 1H), 7.52-7.46 (m, 1H), 7.32-7.27 (m, 2H), 7.20 (d, J = 8.0 Hz, 1H), 6.73 (s, 1H), 4.31 (s, 1H), 3.82-3.69 (m, 2H), 3.58-3.48 (m, 1H), 3.40-3.30 (m, 1H), 2.90-2.60 (m, 5H), 2.10 (s, 3H), 1.00 (d, J = 6.4 Hz, 3H).	2A
Example 134	Compound 166		ESI-MS: 456.2 $[M+H]^+$ ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.01 (s, 1H), 7.87 (dd, J = 8.0, 1.5 Hz, 1H), 7.74 (d, J = 1.3 Hz, 1H), 7.60-7.52 (m, 1H), 7.23 (d, J = 8.0 Hz, 1H), 7.13 (d, J = 8.6 Hz, 1H), 7.10 – 7.03 (m, 1H), 6.69 (s, 1H), 6.22 (tt, J = 55.7, 4.3 Hz, 1H), 3.78 (s, 3H), 3.76 (s, 2H), 2.91 (td, J = 15.6, 4.3 Hz, 2H), 2.84 (s, 4H).	2A
Example 135	Compound 167		ESI-MS: 460.4 $[M+H]^+$ ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.06 (s, 1H), 7.86 (dd, J = 8.0, 1.6 Hz, 1H), 7.77 (s, 1H), 7.52-7.47 (m, 1H), 7.32-7.28 (m, 2H), 7.21 (d, J = 8.0 Hz, 1H), 6.74 (s, 1H), 3.91 (dd, J = 10.8, 3.2 Hz, 2H), 3.74 (s, 2H), 3.32-3.26 (m, 2H), 2.84-2.74 (m, 2H), 2.67-2.56 (m, 1H), 2.10 (s, 3H), 1.76 (d, J = 12.0 Hz, 2H), 1.56-1.46 (m, 2H)	2A
Example 136	Compound 168		ESI-MS: 473.4 $[M+H]^+$ ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.12 (br, 1H), 7.86 (dd, J = 7.6, 1.6 Hz, 1H), 7.76 (s, 1H), 7.52-7.47 (m, 1H), 7.32-7.28 (m, 2H), 7.20 (d, J = 8.0 Hz, 1H),6.74 (s, 1H), 3.72 (s, 2H), 2.87 (d, J = 10.4 Hz, 2H), 2.82-2.72 (m, 4H), 2.42-2.36 (m, 1H), 2.21 (s, 1H), 2.10 (s, 1H), 2.04-1.94 (m. 2H), 1.79 (d, J = 11.6 Hz, 2H), 1.60-1.51 (m, 2H).	2A
Example 137	Compound 169		ESI-MS: 503.4 $[M+H]^+$ ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.12 (s, 1H), 7.94-7.88 (m, 2H), 7.51-7.48 (m, 1H), 7.32-7.28 (m, 3H), 6.77 (s, 0.4H), 6.76 (s, 0.6H), 4.81 (s, 0.8H), 4.63 (s, 1.2H), 3.79-3.74 (m, 1.2H), 3.67 (t, J = 4.0 Hz, 0.8H), 3.58-3.54 (m, 2.4H), 3.40-3.36 (m, 1.6H), 3.25-3.23	2A

			(m, 1H), 2.92 (t, J = 3.6 Hz, 1.2H), 2.80 (t, J = 3.6 Hz, 0.8H), 2.4 (s, 2.4H), 2.34 (s, 1.6H), 2.11 (s, 3H).	
Example 138	Compound 170		ESI-MS: 415.3 $[M+H]^+$ ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.12 (s, 1H), 8.02 (d, J = 8.8 Hz, 1H),7.90 (s, 1H), 7.86 (d, J = 7.6 Hz, 1H), 7.76 (s, 1H), 7.23 (d, J = 7.6 Hz, 1H), 6.79 (s, 1H), 3.54 (s, 2H), 2.85 (t, J = 5.2 Hz, 2H), 2.63 (t, J = 5.2 Hz, 2H), 2.36 (s, 3H), 2.17 (s, 3H).	2A
Example 139	Compound 171		ESI-MS: 401.3 $[M+H]^+$ ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.01 (d, J = 8.8 Hz, 1H), 7.89 (s, 1H), 7.85 (d, J = 7.6 Hz, 1H), 7.75 (s, 1H), 7.19 (d, J = 8.0 Hz, 1H), 6.78 (s, 1H), 3.92 (s, 2H), 3.00 (t, J = 5.6 Hz, 2H), 2.75 (t, J = 5.6 Hz, 2H), 2.17 (s, 3H).	2A
Example 140	Compound 172		ESI-MS: 459.3 $[M+H]^+$ ^{1}H NMR (400MHz, DMSO-d_6) δ 13.15 (s, 1H), 8.01 (d, J = 9.2 Hz, 1H), 7.92-7.87 (m, 3H), 7.30 (d, J = 8.0 Hz, 1H), 6.80 (s, 1H), 4.68-4.55 (m, 3H), 4.19-4.16 (m, 2H), 3.74-3.66 (m, 0.8H), 3.62-3.58 (m, 1.2H), 2.90-2.81 (m, 2H), 2.18 (s,3H).	2B
Example 141	Compound 173		ESI-MS: 473.3 $[M+H]^+$ ^{1}H NMR (400MHz, DMSO-d_6) δ 13.14 (s, 1H), 8.01 (d, J = 9.5 Hz, 1H), 7.93-7.89 (m, 3H), 7.30 (d, J = 7.9 Hz, 1H), 6.80 (s, 1H), 5.00-4.90 (m, 1H), 4.88-4.58 (m, 3H), 4.56-4.46 (m, 1H), 3.82-3.61 (m, 2H), 2.90-2.80 (m, 2H), 2.18 (s, 3H), 1.23-1.16 (m, 3H).	2B
Example 142	Compound 174		ESI-MS: 458.3 $[M+H-HCl]^+$ ^{1}H NMR (400MHz, DMSO-d_6) δ 13.19 (br, 1H), 8.10 (br, 3H), 8.02 (d, J = 9.2 Hz, 1H), 7.96-7.91 (m, 3H), 7.36-7.31 (m, 1H), 6.82-6.79 (m, 1H), 4.71-4.68 (m, 2H), 3.98-3.95 (m, 2H), 3.74 (t, J = 6.0 Hz, 0.9H), 3.64 (t, J = 6.0 Hz, 1.1H), 2.94 (t, J = 6.0 Hz, 1.1H), 2.84 (t, J = 6.0 Hz, 0.9H), 2.18 (s, 3H).	2B
Example 143	Compound 175		ESI-MS: 472.3 $[M+H-HCl]^+$ ^{1}H NMR (400MHz, DMSO-d_6) δ 13.22 (br, 1H), 8.19 (br, 3H), 8.02 (d, J = 9.2 Hz, 1H), 7.96-7.90 (m, 3H), 7.34-7.31 (m, 1H), 6.82-6.79 (m, 1H), 4.89-4.38 (m, 3H), 3.92-3.76 (m, 1H), 3.74-3.58 (m, 1H), 2.96-2.90 (m, 1H), 2.88-2.83 (m, 1H), 2.18 (s, 3H), 1.38-1.30 (m, 3H).	2B
Example 144	Compound 176		ESI-MS: 420.2 $[M+H]^+$ ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.07 (s, 1H), 7.89 (d, *J* = 8.0 Hz, 1H), 7.77 (s, 1H), 7.50 (td, *J* = 8.1, 5.6 Hz, 1H), 7.34 – 7.27 (m, 2H), 7.24 (d, *J* = 8.0 Hz, 1H), 6.74 (s, 1H), 4.64 (br, 1H), 3.83 (d, *J* = 15.8 Hz, 1H), 3.66 – 3.54 (m, 2H), 3.48 – 3.38 (m, 1H), 2.88 – 2.69 (m, 2H), 2.68 – 2.56 (m, 1H), 2.40 (s, 3H), 2.10 (s, 3H).	2A
Example 145	Compound 177		ESI-MS: 432.2 $[M+H]^+$ ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.09 (br, 1H), 8.00 – 7.88 (m, 2H), 7.53-7.46 (m, 1H), 7.38 – 7.23 (m, 3H), 6.76 (s, 1H), 4.67 (d, *J* = 17.0 Hz, 1H), 4.54 (t, *J* = 8.2 Hz, 1H), 4.40 (d, *J* = 17.0 Hz, 1H), 4.14 (dd, *J* = 8.6, 5.2 Hz, 1H), 4.08 – 3.92 (m, 1H), 2.99 (dd, *J* = 16.0, 4.0 Hz, 1H), 2.81 (dd, *J* = 15.9, 10.9 Hz, 1H), 2.12-2.10 (m, 3H).	2A

Example 146	Compound 178		ESI-MS: 418.2 $[M+H]^+$ ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.07 (s, 1H), 7.88 (d, J = 7.7 Hz, 1H), 7.78 (s, 1H), 7.53-7.46 (m, 1H), 7.33-7.26 (m, 2H), 7.19 (d, J = 8.0 Hz, 1H), 6.74 (s, 1H), 3.67 (br, 2H), 2.67 (br, 2H), 2.27 (br, 3H), 1.02 (s, 6H).	2A
Example 147	Compound 179		ESI-MS: 420.2 $[M+H]^+$ ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.03 (s, 1H), 7.88 (d, J = 8.0 Hz, 1H), 7.76 (s, 1H), 7.53 – 7.45 (m, 1H), 7.34 – 7.26 (m, 2H), 7.23 (d, J = 8.1 Hz, 1H), 6.74 (s, 1H), 4.60 – 4.52 (m, 1H), 3.78 (d, J = 15.7 Hz, 1H), 3.64 – 3.48 (m, 2H), 3.44 – 3.35 (m, 1H), 2.85 – 2.67 (m, 2H), 2.60-2.50 (m, 1H), 2.36 (s, 3H), 2.10 (s, 3H).	2A
Example 148	Compound 180		ESI-MS: 434.2 $[M+H]^+$	2A
Example 149	Compound 181		ESI-MS: 432.2 $[M+H]^+$ ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.03 (s, 1H), 7.90-7.86 (m, 1H), 7.78 (s, 1H), 7.52-7.46 (m, 1H), 7.32-7.26 (m, 2H), 7.21 (d, J = 8.0 Hz, 1H), 6.74 (s, 1H), 3.88-3.77 (m, 3H), 3.61-3.53 (m, 1H), 3.36-3.30 (m, 1H), 3.21-3.15 (m, 1H), 2.85 (d, J = 11.6 Hz, 1H), 2.66 (d, J = 12.7 Hz, 1H), 2.46-2.40 (m, 2H), 2.32-2.24 (m, 1H), 2.11-2.09 (m, 3H).	2A
Example 150	Compound 182		ESI-MS: 404.2 $[M+H]^+$ ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.12 (s, 1H), 8.01-7.96 (m, 2H),7.53-7.46 (m, 1H), 7.36-7.26 (m, 2H), 6.77 (s, 1H), 4.56 (s, 2H), 3.56 (s, 2H), 2.96 (s, 3H), 2.11 (s, 3H).	2A
Example 151	Compound 183		ESI-MS: 404.2 $[M+H]^+$ 1H NMR (400 MHz, DMSO-d_6) δ 13.15 (s, 1H), 8.64 (d, J = 1.9 Hz, 1H), 8.17 (dd, J = 7.9, 1.8 Hz, 1H), 7.55 – 7.46 (m, 1H), 7.42 (d, J = 8.0 Hz, 1H), 7.36 – 7.26 (m, 2H), 6.78 (s, 1H), 3.56 (t, J = 6.6 Hz, 2H), 3.07 – 2.98 (m, 5H), 2.12 (s, 3H).	2A
Example 152	Compound 184		ESI-MS: 420.2 $[M+H]^+$ ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.04 (s, 1H), 7.98 (d, *J* = 11.2 Hz, 1H), 7.86 (d, *J* = 7.9 Hz, 1H), 7.49 (q, *J* = 7.6 Hz, 1H), 7.34-7.26 (m, 2H), 7.20 (d, *J* = 8.0 Hz, 1H), 6.74 (s, 1H), 4.47 (br, 1H), 3.68 – 3.60 (m, 1H), 3.58 – 3.46 (m, 2H), 3.10 – 3.00 (m, 1H), 2.85 – 2.75 (m, 1H), 2.74 – 2.64 (m, 1H), 2.64 – 2.55 (m, 1H), 2.45 (s, 3H), 2.11 – 2.09 (m, 3H).	2A
Example 153	Compound 185		ESI-MS: 432.2 $[M+H]^+$ ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.38 (s, 1H), 7.97 (d, *J* = 8.0 Hz, 1H), 7.88 (s, 1H), 7.54 – 7.46 (m, 1H), 7.35 – 7.25 (m, 3H), 6.77 (s, 1H), 5.20 – 5.06 (m, 1H), 4.85 (td, *J* = 8.5, 3.4 Hz, 1H), 4.20 – 4.16 (m, 1H), 3.89 – 3.71 (m, 1H), 3.31 – 3.21 (m, 1H), 2.96 – 2.86 (m, 1H), 2.82 – 2.72 (m, 1H), 2.12 – 2.08 (m, 3H).	2A
Example 154	Compound 186		ESI-MS: 419.2 $[M+H-HCl]^+$ ^{1}H NMR (700MHz, DMSO-d_6) δ 13.29 (s, 1H), 11.76 (br, 1H), 8.58 (br, 3H), 8.15-7.95 (m, 2H), 7.53-7.38 (m, 2H), 7.33-7.23 (m, 2H), 6.79 (s, 1H), 3.90-3.60 (m, 3H), 3.30-3.00 (m, 4H), 3.00-2.70 (m, 3H), 2.13-2.08	2A

			(m, 3H).	
Example 155	Compound 187		ESI-MS: 391.2 $[M+H]^+$ ^{1}H NMR (700MHz, DMSO-d_6) δ 13.22 (s, 1H), 9.04 (s, 1H), 8.05 (s, 1H), 7.52-7.48 (m, 1H), 7.32-7.28 (m, 2H), 6.80 (s, 1H), 3.57 (s, 2H), 2.93 (t, J = 5.5 Hz, 2H), 2.71 (t, J = 5.6 Hz, 2H), 2.36 (s, 3H), 2.11 (s, 3H).	2A
Example 156	Compound 188		ESI-MS: 408.1$[M+H]^+$ ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.20 (s, 1H), 7.66 (t, J = 7.6 Hz, 1H), 7.50-7.44 (m, 1H), 7.29-7.25 (m, 1H), 7.10 (d, J = 8.0 Hz, 1H), 6.77 (s, 1H), 3.53 (s, 2H), 2.86 (t, J = 5.6 Hz, 2H), 2.60 (t, J = 5.6 Hz, 2H), 2.38 (s, 3H), 2.07 (s, 3H).	2A
Example 157	Compound 189		ESI-MS: 408.1 $[M+H]^+$ ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.24 (s, 1H), 7.56 (d, J = 7.1 Hz, 1H), 7.51-7.43 (m, 1H), 7.31 – 7.23 (m, 2H), 7.18 (d, J = 11.1 Hz, 1H), 6.78 (s, 1H), 3.76 (s, 2H), 3.00 – 2.80 (m, 4H), 2.51 (s, 3H), 2.07 (s, 3H).	2A
Example 158	Compound 190		ESI-MS: 424.2 $[M+H]^+$ ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.15 (s, 1H), 7.65 (t, J = 7.6 Hz, 1H), 7.57-7.51 (m, 1H), 7.11-7.08 (m, 2H), 7.04 (t, J = 8.4 Hz, 1H), 6.71 (s, 1H), 3.76 (s, 3H), 3.52 (s, 2H), 2.86 (t, J = 5.6 Hz, 2H), 2.60 (t, J = 5.6 Hz, 2H), 2.38 (s,3H).	2A
Example 159	Compound 191		ESI-MS: 410.1$[M+H]^+$ ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.14 (s, 1H), 7.60 – 7.46 (m, 2H), 7.15 – 7.07 (m, 2H), 7.03 (t, J = 8.8 Hz, 1H), 6.71 (s, 1H), 3.77 (s, 3H), 3.46 (s, 2H), 2.85 (t, J = 5.7 Hz, 2H), 2.58 (t, J = 5.9 Hz, 2H), 2.32 (s, 3H).	2A
Example 160	Compound 193		ESI-MS: 431.3 $[M+H]^+$ ^{1}H NMR (400MHz, DMSO-d_6) δ 13.22 (s, 1H), 12.92 (br, 1H), 9.71 (s, 1H), 9.19 (s, 1H), 8.02-7.97 (m, 1H), 7.95 (s, 1H), 7.53 – 7.46 (m, 1H), 7.34 – 7.26 (m, 3H), 6.77 (s, 1H), 4.76 – 3.98 (m, 8H), 3.17 (br, 3H), 2.11 (s, 3H).	2A
Example 161	Compound 194		ESI-MS: 445.3$[M+H]^+$ ^{1}H NMR (700 MHz, DMSO-d_6) δ 13.06 (br, 1H), 7.86 (d, J = 8.0 Hz, 1H), 7.83 (s, 1H), 7.53-7.45 (m, 1H), 7.34-7.27 (m, 2H), 7.17 (d, J = 8.0 Hz, 1H), 6.74 (s, 1H), 3.46 (t, J = 6.4 Hz, 2H), 3.43 (s, 2H), 3.02 – 2.97 (m, 1H), 2.86-2.79 (m, 4H), 2.50-2.48 (m, 2H), 2.23 (s, 3H), 2.10 (s, 3H).	2A
Example 162	Compound 195		ESI-MS: 460.3 $[M+H]^+$ ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.04 (s, 1H), 7.86 (dd, J = 8.0, 1.4 Hz, 1H), 7.83 – 7.80 (m, 1H), 7.52-7.46 (m, 1H), 7.34-7.26 (m, 2H), 7.18 (d, J = 8.1 Hz, 1H), 6.74 (s, 1H), 3.91 (dd, J = 11.2, 2.9 Hz, 2H), 3.72 (s, 2H), 3.31-3.26 (m, 2H), 2.85-2.71 (m 4H), 2.64-2.54 (m, 1H), 2.10 (s, 3H), 1.81-1.72 (m, 2H), 1.57-1.43 (m, 2H).	2A
Example 163	Compound 196		ESI-MS: 473.3$[M+H]^+$ ^{1}H NMR (700 MHz, DMSO-d_6) δ 13.08 (s, 1H), 10.01 (s, 1H), 7.92-7.79 (m, 2H), 7.55-7.44 (m, 1H), 7.34-7.25 (m, 2H), 7.22-7.14 (m, 1H), 6.74 (s, 1H), 3.73 (br, 2H), 3.46 – 3.34 (m, 4H), 2.89 – 2.76 (m, 4H), 2.61-2.57 (m, 1H), 2.49 (s, 3H), 2.10 (s, 3H), 2.01 – 1.90 (m, 2H), 1.85-1.62 (m, 2H).	2A

Example 164	Compound 197		ESI-MS: 376.1 $[M+H]^+$ ^{1}H NMR (400MHz, DMSO-d_6) δ 13.08 (s, 1H), 8.00-7.96 (m, 1H), 7.95 (s, 1H), 7.52-7.46 (m, 1H), 7.36 (d, J = 8.0 Hz, 1H), 7.33-7.27 (m, 2H), 6.75 (s, 1H), 3.90 (s, 2H), 3.88 (s, 2H), 2.51 (s, 3H), 2.10 (s, 3H).	2A
Example 165	Compound 198		ESI-MS: 419.3 $[M+H]^+$ ^{1}H NMR (700 MHz, DMSO-d_6) δ 7.65-7.64 (m, 1H), 7.54 (d, J = 7.7 Hz, 1H), 7.51-7.47 (m, 1H), 7.29-7.32 (m, 3H), 7.04 (dd, J = 8.4, 2.1 Hz,1H), 6.74 (s, 1H), 3.16-3.14 (m, 4H), 2.44-2.42 (m, 4H), 2.21 (s, 3H), 2.11 (s, 3H).	2A
Example 166	Compound 199		ESI-MS: 435.2 $[M+H]^+$ ^{1}H NMR (400MHz, DMSO-d_6) δ 7.66-7.63 (m, 1H), 7.59-7.51 (m, 2H), 7.31 (t, J = 8.0 Hz, 1H), 7.12 (d, J = 8.0 Hz, 1H), 7.08-7.01 (m, 2H), 6.68 (s, 1H), 3.79 (s, 3H), 3.15 (t, J = 4.8 Hz, 4H), 2.44 (t, J = 4.8 Hz, 4H), 2.21 (s, 3H).	2A
Example 167	Compound 200		ESI-MS: 433.4 $[M+H]^+$ ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.05 (s, 1H), 7.65-7.63 (m, 1H), 7.57-7.50 (m, 2H), 7.33-7.28 (m, 3H), 7.04 (dd, J = 8.4, 2.0 Hz, 1H), 6.74 (s, 1H), 3.16-3.11 (m, 4H), 2.47-2.36 (m, 6H), 2.21 (s, 3H), 1.06 (t, J = 7.6 Hz, 3H).	2A
Example 168	Compound 201		ESI-MS: 445.3 $[M+H]^+$ ^{1}H NMR (700 MHz, DMSO-d_6) δ 13.06 (br, 1H), 7.52-7.46 (m, 3H), 7.32-7.26 (m, 3H), 6.91 (dd, J =8.4,2.1 Hz, 1H), 6.75 (s, 1H), 3.38 – 3.34 (m, 2H), 3.19 (s, 2H), 2.85 (d, J = 10.5 Hz,2H), 2.22 (s, 3H), 2.11 (s, 3H), 1.97 – 1.92 (m, 2H), 1.62-1.59 (m, 2H).	2A
Example 169	Compound 202		ESI-MS: 461.2 $[M+H]^+$ ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.00 (s, 1H), 7.59 – 7.50 (m, 2H), 7.47 (d, J = 7.6 Hz, 1H), 7.28 (t, J = 8.0 Hz, 1H), 7.13 (d, J = 8.4 Hz, 1H), 7.06 (t, J = 8.8 Hz, 1H), 6.92 (dd, J = 8.4, 2.1 Hz, 1H), 6.68 (s, 1H), 3.79 (s, 3H), 3.38 (d, J = 10.4 Hz, 2H), 2.90 (d, J = 10.4 Hz, 2H), 2.28 (s, 3H), 2.03 – 1.93 (m, 2H), 1.65-1.63 (m, 2H).	2A
Example 170	Compound 203		ESI-MS: 486.2 $[M+H]^+$	2B
Example 171	Compound 204		ESI-MS: 435.2 $[M+H]^+$ ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.15 (s, 1H), 8.26 (s, 3H), 7.67 (s, 1H), 7.64 – 7.51 (m, 2H), 7.36 (t, J = 8.0 Hz, 1H), 7.15 – 7.03 (m, 3H), 6.71 (s, 1H), 3.79 (s, 3H), 3.71-3.62 (m, 1H), 3.43 – 3.27 (m, 2H), 3.12 – 3.02 (m, 1H), 3.00 – 2.90 (m, 1H), 2.02-1.92 (m, 1H), 1.88-1.78 (m, 1H), 1.70 – 1.54 (m, 2H).	2A
Example 172	Compound 205		ESI-MS: 435.2 $[M+H]^+$ ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.68-7.65 (m, 1H), 7.59-7.53 (m, 1H), 7.49 (d, J = 8.0 Hz, 1H), 7.31 (t, J = 8.0 Hz, 1H), 7.12 (d, J = 8.8 Hz, 1H), 7.09-7.02 (m, 2H), 6.69 (s, 1H), 3.79 (s, 3H), 3.72-3.65 (m, 2H), 2.98-2.89 (m, 1H), 2.83-2.74 (m, 2H), 1.86-1.76 (m, 2H), 1.48-1.36 (m, 2H).	2A

Example 173	Compound 206		ESI-MS: 436.2 $[M+H]^+$ ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.99 (s, 1H), 7.68-7.66 (m, 1H), 7.59-7.53 (m, 1H), 7.47 (d, J = 8.0 Hz, 1H), 7.29 (t, J = 8.0 Hz, 1H), 7.13 (d, J = 8.8 Hz, 1H), 7.09-7.01 (m, 2H), 6.69 (s, 1H), 4.66 (d, J = 4.0 Hz, 1H), 3.79 (s, 3H), 3.67-3.59 (m, 1H), 3.57-3.50 (m, 2H), 2.92-2.85 (m, 2H), 1.78-1.74 (m, 2H), 1.49-1.39 (m, 2H).	2A
Example 174	Compound 207		ESI-MS: 437.2 $[M+H]^+$ ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.22 (br, 1H), 7.50 – 7.40 (m, 2H), 7.31 – 7.14 (m, 4H), 6.78 (s, 1H), 3.05-3.00 (m, 4H), 2.49-2.44 (m, 4H), 2.22 (s, 3H), 2.08 (s, 3H).	2A
Example 175	Compound 208		ESI-MS: 437.2 $[M+H]^+$ ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.17 (br, 1H), 7.50 – 7.43 (m, 1H), 7.39-7.34 (m, 1H), 7.30 – 7.27 (m, 2H), 7.19 (t, J = 9.5 Hz, 1H), 7.10 – 7.05 (m, 1H), 6.78 (s, 1H), 3.10-3.06 (m, 4H), 2.42-2.39 (m, 4H), 2.19 (s, 3H), 2.09 (s, 3H).	2A
Example 176	Compound 209		ESI-MS: 453.2 $[M+H]^+$ ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.13 (br, 1H), 7.57 – 7.49 (m, 1H), 7.43-7.38 (m, 1H), 7.21 (t, J = 7.9 Hz, 1H), 7.17 – 7.07 (m, 2H), 7.03 (t, J = 8.8 Hz, 1H), 6.70 (s, 1H), 3.76 (s, 3H), 3.05-3.00 (m, 4H), 2.50-2.44 (m, 4H), 2.22 (s, 3H).	2A
Example 177	Compound 210		ESI-MS: 453.2 $[M+H]^+$ ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.13 (br, 1H), 7.57 – 7.50 (m, 1H), 7.40 – 7.36 (m, 1H), 7.19 (t, J = 9.5 Hz, 1H), 7.13 – 7.00 (m, 3H), 6.71 (s, 1H), 3.77 (s, 3H), 3.10-3.04 (m, 4H), 2.43-2.38 (m, 4H), 2.19 (s, 3H).	2A

Biological Activity Test and Results:

1. HPK1 Kinase Activity Inhibition Test

The kinase activity of HPK1 is manifested as activity of autophosphorylation and phosphorylation of downstream substrates. In the process of autophosphorylation, additional substrates are not required, and ATP is consumed to generate ADP. The amount of the product was measured by ADP-Glo reagent and luminescence method to reflect kinase activity.

Test compounds: compounds prepared in the examples of this application.

Prepare compound stock solution: dissolve the compound to be tested in 100% DMSO to make a 10 mM stock solution;

Prepare 4×Kinase Reaction Buffer:

Material	Concentration of Stock Solution	Volume	Final Concentration
Tris	1 M (25X)	240μL	40 mM
$MgCl_2$	1 M (50X)	120μL	20 mM
BSA	7.5%(75X)	80μL	0.1%
DTT	1M(500X)	3μL	0.5 mM
ddH_2O		5557μL	

Prepare 2×HPK1 Kinase Solution:

Material	Concentration of Stock Solution	Volume	2×Final Concentration	Final Concentration

HPK1	4878 nM	1μL	10 nM	5 nM
1× kinase reaction buffer solution		487μL		

Prepare 4×ATP mixture:

Material	ATP Km	Concentration of Stock Solution	Volume	4×Final Concentration	Final Concentration
ATP	1.669μM	1 mM (125×)	3μL	8μM	2μM
4×kinase reaction buffer solution			372μL		

Procedures:

Dilute the stock solution of the compound to be tested by 5 times with 100% DMSO, make a 4-fold equal dilution in a 96-well dilution plate, add 1 μL of the compound to 49 μL of kinase reaction buffer, and shake on a microplate shaker for 20 minutes. Transfer 2 μL of 2×HPK1 kinase solution to 384 reaction plate, add 1 μL of the test compound (prepared in step (1)) to the 384 reaction plate (Greiner, 784075), centrifuge for 1 minute (1000rpm/min), incubate at 25℃ for 10 minutes. Transfer 1 μL of the 4×ATP mixture to a 384 reaction plate, centrifuge for 1 minute (1000 rpm/min), and incubate at 25°C for 60 minutes. In the reaction system, the final concentration of DMSO was 0.5%. Transfer 4 μL of ADP-Glo to a 384 reaction plate, centrifuge for 1 minute (1000 rpm/min), and incubate at 25°C for 40 minutes. Transfer 8 μL detection solution to a 384 reaction plate, centrifuge for 1 minute (1000 rpm/min), and incubate at 25°C for 40 minutes. The fluorescence signal was read using a Biotek multi-function plate reader, and the IC50 (half inhibitory concentration) of the compound was obtained using a four-coefficient nonlinear fitting formula.

Compounds as shown in the Examples exhibited IC50 values in the following ranges: +++ = IC50 ≤ 50 nM,++ = 50 nM < IC50 ≤ 500 nM,+ = 500 nM < IC50 < 2000 nM.

Table 1 Inhibitory effects of compounds on HPK1 kinase activity

Compound	IC50	Compound	IC50
Compound 1	+++	Compound 123	+++
Compound 2	++	Compound 124	+++
Compound 3	+++	Compound 125	+++
Compound 4	+++	Compound 126	+++
Compound 5	++	Compound 127	+++
Compound 6	+++	Compound 128	+++
Compound 7	++	Compound 129	+++
Compound 8	+++	Compound 130	+++
Compound 9	+++	Compound 131	++
Compound 10	+++	Compound 132	+++
Compound 11	++	Compound 133	+++
Compound 12	+	Compound 134	+++
Compound 13	++	Compound 135	+++
Compound 14	++	Compound 136	+++
Compound 15	+	Compound 137	+++
Compound 16	+	Compound 138	+++
Compound 17	+	Compound 139	+++
Compound 19	+	Compound 140	+++
Compound 20	++	Compound 141	+++
Compound 21	++	Compound 142	+++
Compound 23	+++	Compound 143	+++
Compound 24	+++	Compound 144	+++
Compound 25	++	Compound 145	+++
Compound 26	+	Compound 146	+++

Compound 27	+++	Compound 147	+++
Compound 28	+++	Compound 148	+++
Compound 29	+++	Compound 149	+
Compound 32	++	Compound 150	+
Compound 33	+++	Compound 151	++
Compound 34	+++	Compound 152	++
Compound 42	+++	Compound 153	++
Compound 47	+	Compound 154	++
Compound 48	++	Compound 155	++
Compound 55	++	Compound 156	+++
Compound 58	++	Compound 157	+++
Compound 61	+++	Compound 158	++
Compound 72	++	Compound 159	+++
Compound 73	+++	Compound 160	+++
Compound 74	+++	Compound 161	+++
Compound 75	+	Compound 162	+++
Compound 76	+++	Compound 163	++
Compound 77	+++	Compound 164	++
Compound 78	++	Compound 165	++
Compound 79	+++	Compound 166	++
Compound 80	+++	Compound 167	++
Compound 81	+++	Compound 168	++
Compound 82	+++	Compound 169	++
Compound 83	+++	Compound 170	+++
Compound 84	++	Compound 171	++
Compound 85	+++	Compound 172	++
Compound 86	+++	Compound 173	++
Compound 87	+++	Compound 174	++
Compound 88	++	Compound 175	++
Compound 89	+++	Compound 176	+++
Compound 90	+++	Compound 177	+++
Compound 91	+++	Compound 178	++
Compound 92	+++	Compound 179	++
Compound 93	+++	Compound 180	+++
Compound 94	+++	Compound 181	++
Compound 95	++	Compound 182	++
Compound 96	++	Compound 183	+
Compound 97	++	Compound 184	++
Compound 98	+++	Compound 185	+
Compound 99	++	Compound 186	+
Compound 100	++	Compound 187	++
Compound 101	+++	Compound 188	++
Compound 102	++	Compound 189	++
Compound 103	+++	Compound 190	++
Compound 104	++	Compound 191	++
Compound 105	+++	Compound 193	+++
Compound 106	+++	Compound 194	+++
Compound 107	+++	Compound 195	++
Compound 108	++	Compound 196	++

Compound 109	+++	Compound 197	+++
Compound 110	++	Compound 198	+++
Compound 111	+++	Compound 199	+++
Compound 112	+++	Compound 200	+++
Compound 113	+++	Compound 201	+++
Compound 114	+++	Compound 202	+++
Compound 115	+++	Compound 203	+++
Compound 116	+++	Compound 204	+++
Compound 117	+++	Compound 205	+++
Compound 118	+++	Compound 206	++
Compound 119	+++	Compound 207	+
Compound 120	+++	Compound 208	+++
Compound 121	+++	Compound 209	++
Compound 122	+++	Compound 210	+++

The data in Table 1 show that the compounds of the examples of the present application have inhibitory effect on HPK1 kinase activity.

2. Measurement of IL-2 secretion of Jurkat cells by ELISA

Procedures:

Human Jurkat-E6-1 cells were incubated with various concentrations of test compounds for 30 minutes in a humidified incubator at 37°C and 5% CO2. Cells were transferred to cell culture plates pre-coated with anti-human CD3 antibody, then soluble anti-human CD28 antibody was added, and cells were stimulated for 24 hours at 37°C and 5% CO_2 in a humidified incubator. The cell culture medium was collected by centrifugation, and was then transferred to a 96-well transparent microtiter plate (Thermo) pre-coated with anti-human IL-2 antibody, incubated at room temperature for 2 hours, and gently shaken, washed with washing buffer for 4 times, and then followed the ELISA MAX Deluxe Set Human IL-2 (BioLegend) kit procedure, used a microplate reader (Molecular Device, i3X) to read the OD value. The best standard curve was selected by the microplate reader application software, and the corresponding concentration was calculated according to the OD value of the standard. Results are expressed as a percentage of the amount of IL-2 secreted from compound-treated/DMSO-treated cells.

Table 2 Effects of compounds on secretion of IL-2 from human Jurkat cells.

Compound	Percentage of the amount of IL-2 secreted from compound treated/DMSO-treated cells	Concentration of the Test Compound (μM)
Compound 1	277%	1.0
Compound 2	238%	3.0
Compound 3	211%	1.0
Compound 5	162%	1.0
Compound 6	185%	1.0
Compound 7	314%	1.0
Compound 8	306%	0.33
Compound 9	188%	3.0
Compound 11	296%	1.0
Compound 13	315%	3.0
Compound 14	255%	3.0
Compound 16	156%	1.0
Compound 20	329%	1.0
Compound 21	258%	3.0
Compound 23	379%	0.33
Compound 25	187%	1.0
Compound 27	302%	0.33
Compound 28	302%	1.0

Compound 29	291%	1.0
Compound 33	631%	1.0
Compound 34	284%	1.0
Compound 42	365%	3.0
Compound 58	233%	3.0
Compound 61	635%	3.0
Compound 73	926%	3.0
Compound 74	411%	3.0
Compound 76	561%	3.0
Compound 77	233%	1.0
Compound 79	361%	3.0
Compound 80	191%	3.0
Compound 81	679%	3.0
Compound 82	195%	3.0
Compound 83	252%	3.0
Compound 85	239%	3.0
Compound 86	334%	3.0
Compound 87	584%	3.0
Compound 88	550%	3.0
Compound 89	689%	3.0
Compound 90	667%	3.0
Compound 92	1101%	3.0
Compound 93	210%	3.0
Compound 94	414%	3.0
Compound 98	850%	3.0
Compound 99	237%	3.0
Compound 100	284%	3.0
Compound 103	716%	3.0
Compound 105	623%	3.0
Compound 106	833%	3.0
Compound 107	599%	3.0
Compound 108	312%	3.0
Compound 109	491%	3.0
Compound 111	522%	3.0
Compound 112	703%	3.0
Compound 113	368%	3.0
Compound 114	309%	3.0
Compound 115	542%	3.0
Compound 116	193%	1.0
Compound 117	566%	3.0
Compound 118	550%	3.0
Compound 119	531%	3.0
Compound 120	482%	3.0
Compound 121	459%	3.0
Compound 122	1008%	3.0
Compound 123	1117%	3.0
Compound 124	570%	3.0
Compound 125	216%	3.0
Compound 126	428%	3.0
Compound 127	758%	3.0
Compound 128	472%	3.0
Compound 129	807%	3.0
Compound 130	454%	3.0
Compound 133	800%	3.0
Compound 134	527%	3.0

Compound 135	964%	3.0
Compound 136	702%	3.0
Compound 137	291%	3.0
Compound 138	873%	3.0
Compound 139	315%	3.0
Compound 140	436%	3.0
Compound 141	390%	3.0
Compound 142	708%	3.0
Compound 143	786%	3.0
Compound 144	716%	3.0
Compound 145	776%	3.0
Compound 146	537%	3.0
Compound 147	616%	3.0
Compound 148	531%	1.0
Compound 151	230%	3.0
Compound 154	382%	1.0
Compound 155	435%	3.0
Compound 156	849%	3.0
Compound 157	935%	3.0
Compound 159	454%	3.0
Compound 160	354%	3.0
Compound 161	393%	3.0
Compound 162	586%	3.0
Compound 163	117%	3.0
Compound 164	159%	3.0
Compound 165	181%	1.0
Compound 170	279%	1.0
Compound 171	220%	3.0
Compound 177	481%	3.0
Compound 193	169%	3.0
Compound 198	280%	3.0
Compound 199	328%	1.0
Compound 200	286%	3.0
Compound 202	539%	1.0
Compound 204	260%	3.0
Compound 210	298%	1.0

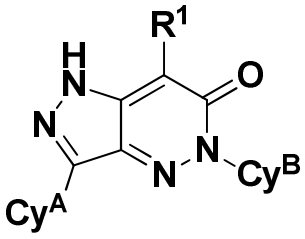
The data in Table 2 shows that, compared with Jurkat cells treated with DMSO as a blank control group, the compounds of the examples of the present application have a significant promoting effect on the secretion of cytokine IL-2 by Jurkat cells.

Unless otherwise defined, the terms used in this application are the meanings commonly understood by those skilled in the art.

The embodiments described in this application are only for exemplary purposes and are not intended to limit the protection scope of this application. Those skilled in the art can make various other substitutions, changes and improvements within the scope of this application. Therefore, this application is not limited to the above-described embodiments, but only by the claims.

Claims

1. A compound of formula (I) or a pharmaceutically acceptable salt, hydrate, solvate, active metabolite, polymorph, isotope labeled compound, isomer or prodrug thereof,



(I)

wherein, R^1 is selected from the group consisting of:

1) hydrogen, halogen, cyano, $-C(=O)NR^aR^b$, $-OR^a$ and $-NR^aR^b$;

2) C_{1-6} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{3-8} cycloalkyl and 3- to 8-membered aliphatic heterocyclyl, unsubstituted or optionally substituted with 1, 2, 3 or 4 substituents independently selected from R^{11};

R^a and R^b are each independently selected from the group consisting of:

1) hydrogen;

2) C_{1-6} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{3-6} monocyclic cycloalkyl, and 3- to 6-membered aliphatic monocyclic heterocyclyl, unsubstituted or optionally substituted with 1, 2, or 3 substituents independently selected from R^{11}; or

R^a and R^b attached to the same nitrogen atom, together with the nitrogen atom, form a 3-6 membered aliphatic monocyclic heterocyclyl, unsubstituted or optionally substituted with 1, 2 or 3 substituents independently selected from R^{11};

R^{11} is selected from the group consisting of fluorine, chlorine, cyano, C_{1-3} alkyl and hydroxyl;

Cy^A is selected from 6- to 10-membered aryl or 5- to 10-membered heteroaryl, unsubstituted or optionally substituted with 1, 2, 3, 4 or 5 substituents independently selected from R^{12};

R^{12} is selected from the group consisting of:

1) oxo, halogen, cyano, $-C(=O)R^{a2}$, $-C(=O)OR^{a2}$, $-C(=O)NR^{a2}R^{b2}$, $-C(=NR^{d2})NR^{a2}R^{b2}$, $-OR^{a2}$, $-OC(=O)R^{a2}$, $-OC(=O)OR^{c2}$, $-OC(=O)NR^{a2}R^{b2}$, $-SR^{a2}$, $-S(=O)R^{c2}$, $-S(=O)_2R^{c2}$, sulfonic acid group, $-S(=O)NR^{a2}R^{b2}$, $-S(=O)_2NR^{a2}R^{b2}$, $-S(=O)(=NR^{d2})R^{c2}$, $-NR^{a2}R^{b2}$, $-NR^{a2}C(=O)R^{b2}$, $-NR^{a2}C(=O)OR^{c2}$, $-NR^{e2}C(=O)NR^{a2}R^{b2}$, $-NR^{e2}C(=NR^{d2})NR^{a2}R^{b2}$, $-NR^{a2}S(=O)_2R^{c2}$, $-NR^{e2}S(=O)_2NR^{a2}R^{b2}$, nitro, $-PR^{c2}R^{f2}$, $-P(=O)R^{c2}R^{f2}$ and phosphonic acid group;

2) C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 6- to 10-membered aryl, 5- to 10-membered heteroaryl, C_{3-12} cycloalkyl and 3- to 12-membered aliphatic heterocyclyl, unsubstituted or optionally substituted with 1, 2, 3, 4, 5 or 6 substituents independently selected from R^{22};

3) the two R^{12} substituents attached to two adjacent ring-forming atoms on the aryl or heteroaryl group of Cy^A, respectively, together with the two said ring-forming atoms, form a C_{5-12} alicyclyl or a 5- to 12-membered aliphatic heterocyclyl, unsubstituted or optionally substituted by 1, 2, 3, 4, 5 or 6 substituents independently selected from R^{22};

R^{a2}, R^{b2} and R^{e2} are each independently selected from the group consisting of:

1) hydrogen;

2) C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, phenyl, 5-6 membered heteroaryl, C_{3-12} cycloalkyl and 3-12 membered aliphatic heterocyclyl, unsubstituted or optionally substituted with 1, 2, 3, 4, 5 or 6 substituents independently selected from R^{22};

or,

R^{a2} and R^{b2} attached to the same nitrogen atom, together with the nitrogen, form a 3-12 membered aliphatic heterocyclyl, unsubstituted or optionally substituted with 1, 2, 3, 4 or 5

substituents independently selected from R^{22};

R^{c2} and R^{f2} are each independently selected from the group consisting of C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, phenyl, 5-6 membered heteroaryl, C_{3-12} cycloalkyl and 3-12 membered aliphatic heterocyclyl, unsubstituted or optionally substituted with 1, 2, 3, 4 or 5 substituents independently selected from R^{22};

or,

R^{c2} and R^{f2} attached to the same phosphorous atom, together with the phosphorous, form a 3-12 membered aliphatic heterocyclyl, unsubstituted or optionally substituted with 1, 2, 3, 4 or 5 substituents independently selected from R^{22};

R^{d2} is selected from the group consisting of:

1) hydrogen, cyano, nitro and $-S(=O)_2R^G$;

2) C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, phenyl, 5-6 membered heteroaryl, C_{3-12} cycloalkyl and 3-12 membered aliphatic heterocyclyl, unsubstituted or optionally substituted with 1, 2, 3, 4 or 5 substituents independently selected from R^{22};

R^{22} is selected from the group consisting of:

1) oxo, halogen, cyano, $-C(=O)R^{a4}$, $-C(=O)OR^{a4}$, $-C(=O)NR^{a4}R^{b4}$, $-C(=NR^{d4})NR^{a4}R^{b4}$, $-OR^{a4}$, $-OC(=O)R^{a4}$, $-OC(=O)OR^{c4}$, $-OC(=O)NR^{a4}R^{b4}$, $-SR^{a4}$, $-S(=O)R^{c4}$, $-S(=O)_2R^{c4}$, sulphonic acid group, $-S(=O)NR^{a4}R^{b4}$, $-S(=O)_2NR^{a4}R^{b4}$, $-S(=O)(=NR^{d4})R^{c4}$, $-NR^{a4}R^{b4}$, $-NR^{a4}C(=O)R^{b4}$, $-NR^{a4}C(=O)OR^{c4}$, $-NR^{e4}C(=O)NR^{a4}R^{b4}$, $-NR^{e4}C(=NR^{d4})NR^{a4}R^{b4}$, $-NR^{a4}S(=O)_2R^{c4}$, $-NR^{e4}S(=O)_2NR^{a4}R^{b4}$, nitro, $-PR^{c4}R^{f4}$, $-P(=O)R^{c4}R^{f4}$, phosphonic acid group, and $=N-R^{d4}$;

2) C_{1-6} alkyl, C_{1-6} alkylene, C_{2-6} alkenyl, C_{2-6} alkynyl, phenyl, 5-6 membered heteroaryl, C_{3-10} cycloalkyl and 3-10 membered aliphatic heterocyclyl, unsubstituted or optionally substituted with 1, 2, 3, 4 or 5 substituents independently selected from R^{32};

R^{a4}, R^{b4} and R^{e4} are each independently selected from the group consisting of:

1) hydrogen;

2) C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, phenyl, 5-6 membered heteroaryl, C_{3-10} cycloalkyl and 3-10 membered aliphatic heterocyclyl, unsubstituted or optionally substituted with 1, 2, 3, 4 or 5 substituents independently selected from R^{32};

or,

R^{a4} and R^{b4} attached to the same nitrogen atom, together with the nitrogen, form a 3-10 membered aliphatic heterocyclyl, unsubstituted or optionally substituted with 1, 2, 3, 4 or 5 substituents independently selected from R^{32};

R^{c4} and R^{f4} are each independently selected from the group consisting of C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, phenyl, 5-6 membered heteroaryl, C_{3-10} cycloalkyl and 3-10 membered aliphatic heterocyclyl, unsubstituted or optionally substituted with 1, 2, 3, 4 or 5 substituents independently selected from R^{32};

or,

R^{c4} and R^{f4} attached to the same phosphorous atom, together with the phosphorous, form a 3-10 membered aliphatic heterocyclyl, unsubstituted or optionally substituted with 1, 2, 3, 4 or 5 substituents independently selected from R^{32};

R^{d4} is selected from the group consisting of:

1) hydrogen, cyano, nitro, and $-S(=O)_2R^G$;

2) C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, phenyl, 5-6 membered heteroaryl, C_{3-10} cycloalkyl and 3-10 membered aliphatic heterocyclyl, unsubstituted or optionally substituted with 1, 2, 3, 4 or 5 substituents independently selected from R^{32};

R^{32} is selected from the group consisting of:

1) oxo, halogen, cyano, $-C(=O)R^{a6}$, $-C(=O)OR^{a6}$, $-C(=O)NR^{a6}R^{b6}$, $-C(=NR^{d6})NR^{a6}R^{b6}$, $-OR^{a6}$, $-OC(=O)R^{a6}$, $-OC(=O)OR^{c6}$, $-OC(=O)NR^{a6}R^{b6}$, $-SR^{a6}$, $-S(=O)R^{c6}$, $-S(=O)_2R^{c6}$, sulphonic acid group, $-S(=O)NR^{a6}R^{b6}$, $-S(=O)_2NR^{a6}R^{b6}$, $-S(=O)(=NR^{d6})R^{c6}$, $-NR^{a6}R^{b6}$, $-NR^{a6}C(=O)R^{b6}$, $-NR^{a6}C(=O)OR^{c6}$, $-NR^{e6}C(=O)NR^{a6}R^{b6}$, $-NR^{e6}C(=NR^{d6})NR^{a6}R^{b6}$, $-NR^{a6}S(=O)_2R^{c6}$, $-$

$NR^{e6}S(=O)_2NR^{a6}R^{b6}$, nitro, $-PR^{c6}R^{f6}$, $-P(=O)R^{c6}R^{f6}$, phosphonic acid group, and $=N-R^{d6}$;

2) C_{1-4} alkyl, C_{1-4} alkylene, C_{2-4} alkenyl, C_{2-4} alkynyl, phenyl, 5-6 membered heteroaryl, C_{3-8} cycloalkyl, and 3-8 membered aliphatic heterocyclyl, unsubstituted or optionally substituted with 1, 2, 3 or 4 substituents independently selected from R^G;

R^{a6}, R^{b6} and R^{e6} are each independently selected from the group consisting of:

1) hydrogen;

2) C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, phenyl, 5-6 membered heteroaryl, C_{3-8} cycloalkyl, and 3-8 membered aliphatic heterocyclyl, unsubstituted or optionally substituted with 1, 2, 3 or 4 substituents independently selected from R^G;

or,

R^{a6} and R^{b6} attached to the same nitrogen atom, together with the nitrogen, form a 3-8 membered aliphatic heterocyclyl, unsubstituted or optionally substituted with 1, 2, 3 or 4 substituents independently selected from R^G;

R^{c6} and R^{f6} are each independently selected from the group consisting of C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, phenyl, 5-6 membered heteroaryl, C_{3-8} cycloalkyl, and 3-8 membered aliphatic heterocyclyl, unsubstituted or optionally substituted with 1, 2, 3 or 4 substituents independently selected from R^G;

or,

R^{c6} and R^{f6} attached to the same phosphorous atom, together with the phosphorous, form a 3-8 membered aliphatic heterocyclyl, unsubstituted or optionally substituted with 1, 2, 3 or 4 substituents independently selected from R^G;

R^{d6} is selected from the group consisting of:

1) hydrogen, cyano, nitro, and $-S(=O)_2R^G$;

2) C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, phenyl, 5-6 membered heteroaryl, C_{3-8} cycloalkyl, and 3-8 membered aliphatic heterocyclyl, unsubstituted or optionally substituted with 1, 2, 3 or 4 substituents independently selected from R^G;

Cy^B is selected from the group consisting of 6-10 membered aryl and 5-10 membered heteroaryl, unsubstituted or optionally substituted with 1, 2, 3, 4 or 5 substituents independently selected from R^{13};

R^{13} is selected from the group consisting of:

1) oxo, halogen, cyano, $-C(=O)R^{a3}$, $-C(=O)OR^{a3}$, $-C(=O)NR^{a3}R^{b3}$, $-C(=NR^{d3})NR^{a3}R^{b3}$, $-OR^{a3}$, $-OC(=O)R^{a3}$, $-OC(=O)OR^{c3}$, $-OC(=O)NR^{a3}R^{b3}$, $-SR^{a3}$, $-S(=O)R^{c3}$, $-S(=O)_2R^{c3}$, sulphonic acid group, $-S(=O)NR^{a3}R^{b3}$, $-S(=O)_2NR^{a3}R^{b3}$, $-S(=O)(=NR^{d3})R^{c3}$, $-NR^{a3}R^{b3}$, $-NR^{a3}C(=O)R^{b3}$, $-NR^{a3}C(=O)OR^{c3}$, $-NR^{e3}C(=O)NR^{a3}R^{b3}$, $-NR^{e3}C(=NR^{d3})NR^{a3}R^{b3}$, $-NR^{a3}S(=O)_2R^{c3}$, $-NR^{e3}S(=O)_2NR^{a3}R^{b3}$, nitro, $-PR^{c3}R^{f3}$, $-P(=O)R^{c3}R^{f3}$, and phosphonic acid group ;

2) C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 6-10 membered aryl, 5-10 membered heteroaryl, C_{3-12} cycloalkyl, and 3-12 membered aliphatic heterocyclyl, unsubstituted or optionally substituted with 1, 2, 3, 4, 5 or 6 substituents independently selected from R^{23};

3) two R^{13} substituents attached to two adjacent ring-forming atoms of the aryl or heteroaryl of Cy^B respectively, together with the two said ring-forming atoms, form a C_{5-12} aliphatic cyclyl or a 5-12 membered aliphatic heterocyclyl, unsubstituted or optionally substituted with 1, 2, 3, 4 or 5 substituents independently selected from R^{23};

R^{a3}, R^{b3} and R^{e3} are each independently selected from the group consisting of:

1) hydrogen;

2) C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, phenyl, 5-6 membered heteroaryl, C_{3-12} cycloalkyl, and 3-12 membered aliphatic heterocyclyl, unsubstituted or optionally substituted with 1, 2, 3, 4, 5 or 6 substituents independently selected from R^{23};

or,

R^{a3} and R^{b3} attached to the same nitrogen atom, together with the nitrogen, form a 3-12

membered aliphatic heterocyclyl, unsubstituted or optionally substituted with 1, 2, 3, 4 or 5 substituents independently selected from R^{23};

R^{c3} and R^{f3} are each independently selected from the group consisting of C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, phenyl, 5-6 membered heteroaryl, C_{3-12} cycloalkyl, and 3-12 membered aliphatic heterocyclyl, unsubstituted or optionally substituted with 1, 2, 3, 4 or 5 substituents independently selected from R^{23};

or,

R^{c3} and R^{f3} attached to the same phosphorous atom, together with the phosphorous atom, form a 3-12 membered aliphatic heterocyclyl, unsubstituted or optionally substituted with 1, 2, 3, 4 or 5 substituents independently selected from R^{23};

R^{d3} is selected from the group consisting of:

1) hydrogen, cyano, nitro, and $S(=O)_2R^G$;

2) C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, phenyl, 5-6 membered heteroaryl, C_{3-12} cycloalkyl, and 3-12 membered aliphatic heterocyclyl, unsubstituted or optionally substituted with 1, 2, 3, 4 or 5 substituents independently selected from R^{23};

R^{23} is selected from the group consisting of:

1) oxo, halogen, cyano, $-C(=O)R^{a5}$, $-C(=O)OR^{a5}$, $-C(=O)NR^{a5}R^{b5}$, $-C(=NR^{d5})NR^{a5}R^{b5}$, $-OR^{a5}$, $-OC(=O)R^{a5}$, $-OC(=O)OR^{c5}$, $-OC(=O)NR^{a5}R^{b5}$, $-SR^{a5}$, $-S(=O)R^{c5}$, $-S(=O)_2R^{c5}$, sulphonic acid group, $-S(=O)NR^{a5}R^{b5}$, $-S(=O)_2NR^{a5}R^{b5}$, $-S(=O)(=NR^{d5})R^{c5}$, $-NR^{a5}R^{b5}$, $-NR^{a5}C(=O)R^{b5}$, $-NR^{a5}C(=O)OR^{c5}$, $-NR^{e5}C(=O)NR^{a5}R^{b5}$, $-NR^{e5}C(=NR^{d5})NR^{a5}R^{b5}$, $-NR^{a5}S(=O)_2R^{c5}$, $-NR^{e5}S(=O)_2NR^{a5}R^{b5}$, nitro, $-PR^{c5}R^{f5}$, $-P(=O)R^{c5}R^{f5}$, phosphonic acid group, and $=N-R^{d5}$;

2) C_{1-6} alkyl, C_{1-6} alkylene, C_{2-6} alkenyl, C_{2-6} alkynyl, phenyl, 5-6 membered heteroaryl, C_{3-10} cycloalkyl, and 3-10 membered aliphatic heterocyclyl, unsubstituted or optionally substituted with 1, 2, 3, 4 or 5 substituents independently selected from R^{33};

R^{a5}, R^{b5} and R^{e5} are each independently selected from the group consisting of:

1) hydrogen;

2) C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, phenyl, 5-6 membered heteroaryl, C_{3-10} cycloalkyl, and 3-10 membered aliphatic heterocyclyl, unsubstituted or optionally substituted with 1, 2, 3, 4 or 5 substituents independently selected from R^{33};

or,

R^{a5} and R^{b5} attached to the same nitrogen atom, together with the nitrogen atom, form a 3-10 membered aliphatic heterocyclyl, unsubstituted or optionally substituted with 1, 2, 3, 4 or 5 substituents independently selected from R^{33};

R^{c5} and R^{f5} are each independently selected from the group consisting of C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, phenyl, 5-6 membered heteroaryl, C_{3-10} cycloalkyl, and 3-10 membered aliphatic heterocyclyl, unsubstituted or optionally substituted with 1, 2, 3, 4 or 5 substituents independently selected from R^{33};

or,

R^{c5} and R^{f5} attached to the same phosphorous atom, together with the phosphorous atom, form a 3-10 membered aliphatic heterocyclyl, unsubstituted or optionally substituted with 1, 2, 3, 4 or 5 substituents independently selected from R^{33};

R^{d5} is selected from the group consisting of:

1) hydrogen, cyano, nitro, and $-S(=O)_2R^G$;

2) C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, phenyl, 5-6 membered heteroaryl, C_{3-10} cycloalkyl, and 3-10 membered aliphatic heterocyclyl, unsubstituted or optionally substituted with 1, 2, 3, 4 or 5 substituents independently selected from R^{33};

R^{33} is selected from the group consisting of:

1) oxo, halogen, cyano, $-C(=O)R^{a7}$, $-C(=O)OR^{a7}$, $-C(=O)NR^{a7}R^{b7}$, $-C(=NR^{d7})NR^{a7}R^{b7}$, $-OR^{a7}$, $-OC(=O)R^{a7}$, $-OC(=O)OR^{c7}$, $-OC(=O)NR^{a7}R^{b7}$, $-SR^{a7}$, $-S(=O)R^{c7}$, $-S(=O)_2R^{c7}$, sulphonic acid group, $-S(=O)NR^{a7}R^{b7}$, $-S(=O)_2NR^{a7}R^{b7}$, $-S(=O)(=NR^{d7})R^{c7}$, $-NR^{a7}R^{b7}$, $-NR^{a7}C(=O)R^{b7}$, -

$NR^{a7}C(=O)OR^{c7}$, $-NR^{e7}C(=O)NR^{a7}R^{b7}$, $-NR^{e7}C(=NR^{d7})NR^{a7}R^{b7}$, $-NR^{a7}S(=O)_2R^{c7}$, $-NR^{e7}S(=O)_2NR^{a7}R^{b7}$, nitro, $-PR^{c7}R^{f7}$, $-P(=O)R^{c7}R^{f7}$, phosphonic acid group, and $=N-R^{d7}$;

2) C_{1-4} alkyl, C_{1-4} alkylene, C_{2-4} alkenyl, C_{2-4} alkynyl, phenyl, 5-6 membered heteroaryl, C_{3-8} cycloalkyl, and 3-8 membered aliphatic heterocyclyl, unsubstituted or optionally substituted with 1, 2, 3 or 4 substituents independently selected from R^G;

R^{a7}, R^{b7} and R^{e7} are each independently selected from the group consisting of:

1) hydrogen;

2) C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, phenyl, 5-6 membered heteroaryl, C_{3-8} cycloalkyl, and 3-8 membered aliphatic heterocyclyl, unsubstituted or optionally substituted with 1, 2, 3 or 4 substituents independently selected from R^G;

or,

R^{a7} and R^{b7} attached to the same nitrogen atom, together with the nitrogen atom, form a 3-8 membered aliphatic heterocyclyl, unsubstituted or optionally substituted with 1, 2, 3 or 4 substituents independently selected from R^G;

R^{c7} and R^{f7} are each independently selected from the group consisting of C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, phenyl, 5-6 membered heteroaryl, C_{3-8} cycloalkyl, and 3-8 membered aliphatic heterocyclyl, unsubstituted or optionally substituted with 1, 2, 3 or 4 substituents independently selected from R^G;

or,

R^{c7} and R^{f7} attached to the same phosphorous atom, together with the phosphorous atom, form a 3-8 membered aliphatic heterocyclyl, unsubstituted or optionally substituted with 1, 2, 3 or 4 substituents independently selected from R^G;

R^{d7} is selected from the group consisting of:

1) hydrogen, cyano, nitro, and $-S(=O)_2R^G$;

2) C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, phenyl, 5-6 membered heteroaryl, C_{3-8} cycloalkyl, and 3-8 membered aliphatic heterocyclyl, unsubstituted or optionally substituted with 1, 2, 3 or 4 substituents independently selected from R^G;

R^G is selected from the group consisting of:

1) halogen, oxo, cyano, carboxyl, hydroxyl, C_{1-4} alkoxy, amino, C_{1-4} alkylamino, nitro, C_{1-4} alkylthio, sulphonic acid group, C_{1-4} alkyl sulfinyl, C_{1-4} alkyl sulfonyl, C_{1-4} alkylaminosulfinyl, and C_{1-4} alkylaminosulfonyl;

2) C_{1-4} alkyl, C_{1-4} alkylene, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{3-6} cycloalkyl and 3-8 membered aliphatic heterocyclyl, unsubstituted or optionally substituted with 1, 2, 3 or 4 substituents independently selected from the group consisting of oxo, halogen, hydroxyl, hydroxymethyl, carboxyl, cyano, C_{1-3} alkoxy, amino, C_{1-4} alkylamino, nitro, and sulphonic acid group.

2. The compound according to claim 1, wherein,

R^1 is selected from the group consisting of hydrogen, fluorine, cyano, methyl, ethyl, 1-propyl, isopropyl, cyclopropyl, methoxy, ethoxy and cyclopropyloxy;

Cy^A is selected from the group consisting of phenyl, naphthyl and 5-10 membered heteroaryl, unsubstituted or optionally substituted with 1, 2, 3 or 4 substituents independently selected from R^{12}; wherein 5-10 membered heteroaryl contains at least two ring-forming carbon atoms and 1, 2, or 3 ring-forming heteroatoms independently selected from the group consisting of N, O and S;

R^{12} is selected from the group consisting of:

1) oxo, halogen, cyano, $-C(=O)R^{a2}$, $-C(=O)OR^{a2}$, $-C(=O)NR^{a2}R^{b2}$, $-C(=NR^{d2})NR^{a2}R^{b2}$, $-OR^{a2}$, $-NR^{a2}R^{b2}$, $-NR^{a2}C(=O)R^{b2}$, $-NR^{a2}C(=O)OR^{c2}$, $-NR^{e2}C(=O)NR^{a2}R^{b2}$, $-NR^{e2}C(=NR^{d2})NR^{a2}R^{b2}$, $-NR^{a2}S(=O)_2R^{c2}$ and $-NR^{e2}S(=O)_2NR^{a2}R^{b2}$;

2) C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 6-10 membered aryl, 5-10 membered heteroaryl, C_{3-10} cycloalkyl, 3-10 membered aliphatic heterocyclyl, unsubstituted or optionally substituted with

1, 2, 3 or 4 substituents independently selected from R^{22};

3) two R^{12}, together with two adjacent ring-forming atoms of the aryl or heteroaryl in Cy^A to which they are attached respectively, form a C_{4-8} aliphatic cyclyl or 4-8 membered aliphatic heterocyclyl, unsubstituted or optionally substituted with 1, 2 or 3 substituens independently selected from R^{22};

R^{a2}, R^{b2} and R^{e2} are each independently selected from the group consisting of:

1) hydrogen;

2) C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, phenyl, 5-6 membered heteroaryl, C_{3-6} cycloalkyl and 3-6 membered aliphatic heterocyclyl, unsubstituted or optionally substituted with 1, 2 or 3 subsituents independently selected from R^{22};

or,

R^{a2} and R^{b2}, togehter with the same N atom to which they are attached, form a 3-8 membered aliphatic heterocyclyl, unsubstituted or optionally substituted with 1, 2 or 3 substituents independently selected from R^{22};

R^{c2} is selected from the group consisting of C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, phenyl, 5-6 membered heteroaryl, C_{3-6} cycloalkyl and 3-6 membered aliphatic heterocyclyl, unsubstituted or optionally substituted with 1, 2 or 3 substituents independently selected from R^{22};

R^{d2} is selected from the group consisting of:

1) hydrogen, cyano, nitro, and $-S(=O)_2R^G$;

2) C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, phenyl, 5-6 membered heteroaryl, C_{3-6} cycloalkyl, and 3-6 membered aliphatic heterocyclyl, unsubstituted or optionally substituted with 1, 2 or 3 substituents independently selected from R^{22};

R^{22} is selected from the group consisting of:

1) oxo, halogen, cyano, carboxyl, $-C(=O)R^{a4}$, $-C(=O)OR^{a4}$, $-C(=O)NR^{a4}R^{b4}$, $-C(=NR^{d4})NR^{a4}R^{b4}$, $-OR^{a4}$, $-S(=O)_2R^{c4}$, sulphonic acid group, $-S(=O)_2NR^{a4}R^{b4}$, $-S(=O)(=NR^{d4})R^{c4}$, $-NR^{a4}R^{b4}$, $-NR^{a4}C(=O)R^{b4}$, $-NR^{e4}C(=O)NR^{a4}R^{b4}$, $-NR^{e4}C(=NR^{d4})NR^{a4}R^{b4}$, $-NR^{a4}S(=O)_2R^{c4}$, $-NR^{e4}S(=O)_2NR^{a4}R^{b4}$ and $=N-R^{d4}$;

2) C_{1-4} alkyl, C_{1-4} alkylene, phenyl, 5-6 membered heteroaryl, C_{3-7} cycloalkyl and 3-7 membered aliphatic heterocyclyl, unsubstituted or optionally substituted with 1, 2 or 3 substituents independently selected from R^{32};

R^{a4}, R^{b4} and R^{e4} are each independently selected from the group consisting of:

1) hydrogen;

2) C_{1-4} alkyl, phenyl, 5-6 membered heteraryl, C_{3-6} cycloalkyl, and 3-6 membered aliphatic heterocyclyl, unsubstituted or optionally substituted with 1, 2 or 3 substituents independently selected from R^{32};

or,

R^{a4} and R^{b4}, together with the same N atom to which they are attached, form a 3-6 membered aliphatic heterocyclyl, unsubstituted or optionally substituted with 1, 2 or 3 substituents independently selected from R^{32};

R^{c4} is selected from the group consisting of C_{1-4} alkyl, phenyl, 5-6 membered heteroaryl, C_{3-6} cycloalkyl, and 3-6 membered aliphatic heterocyclyl, unsubstituted or optionally substituted with 1, 2 or 3 substituents independently selected from R^{32};

R^{d4} is selected from the group consisting of:

1) hydrogen, cyano, nitro, and $-S(=O)_2R^G$;

2) C_{1-4} alkyl, phenyl, 5-6 membered heteroaryl, C_{3-6} cycloalkyl, and 3-6 membered aliphatic heterocyclyl, unsubstituted or optionally substituted with 1, 2 or 3 substituents independently selected from R^{32};

R^{32} is selected from the group consisting of:

1) oxo, halogen, cyano, $-C(=O)R^{a6}$, $-C(=O)OR^{a6}$, $C(=O)NR^{a6}R^{b6}$, $-C(=NR^{d6})NR^{a6}R^{b6}$, $-OR^{a6}$, $-S(=O)_2R^{c6}$, $-S(=O)_2NR^{a6}R^{b6}$, $-S(=O)(=NR^{d6})R^{c6}$, $-NR^{a6}R^{b6}$, $-NR^{a6}C(=O)R^{b6}$, -

$NR^{e6}C(=O)NR^{a6}R^{b6}$, $-NR^{e6}C(=NR^{d6})NR^{a6}R^{b6}$, $-NR^{a6}S(=O)_2R^{c6}$, $-NR^{e6}S(=O)_2NR^{a6}R^{b6}$, and $=N-R^{d6}$;

2) C_{1-4} alkyl, C_{1-4} alkylene, phenyl, 5-6 membered heteroaryl, C_{3-6} cycloalkyl, and 3-6 membered aliphatic heterocyclyl, unsubstituted or optionally substituted with 1, 2, 3 or 4 substituents independently selected from R^G;

R^{a6}, R^{b6} and R^{e6} are each independently selected from the group consisting of:

1) hydrogen;

2) C_{1-4} alkyl, phenyl, 5-6 membered heteroaryl, C_{3-6} cycloalkyl, and 3-6 membered aliphatic heterocyclyl, unsubstituted or optionally substituted with 1, 2, or 3 substituents independently selected from R^G;

or,

R^{a6} and R^{b6} attached to the same nitrogen atom, together with the nitrogen, form a 3-6 membered aliphatic heterocyclyl, unsubstituted or optionally substituted with 1, 2, or 3 substituents independently selected from R^G;

R^{c6} is independently selected from the group consisting of C_{1-4} alkyl, phenyl, 5-6 membered heteroaryl, C_{3-6} cycloalkyl and 3-6 membered aliphatic heterocyclyl, unsubstituted or optionally substituted with 1, 2, or 3 substituents independently selected from R^G;

R^{d6} is selected from the group consisting of:

1) hydrogen, cyano, nitro, and $-S(=O)_2R^G$;

2) C_{1-4} alkyl, phenyl, 5-6 membered heteroaryl, C_{3-6} cycloalkyl, and 3-6 membered aliphatic heterocyclyl, unsubstituted or optionally substituted with 1, 2 or 3 substituents independently selected from R^G;

Cy^B is selected from the group consisting of phenyl, naphthyl and 5-10 membered heteroaryl, unsubstituted or optionally substituted with 1, 2, 3 or 4 substituents independently selected from R^{12}; wherein the 5-10 membered heteroaryl contains at least one ring-forming carbon atom and 1, 2, or 3 ring-forming heteroatoms independently selected from the group consisting of N, O and S;

R^{13} is selected from the group consisting of:

1) oxo, halogen, cyano, $-C(=O)R^{a3}$, $-C(=O)OR^{a3}$, $-C(=O)NR^{a3}R^{b3}$, $-C(=NR^{d3})NR^{a3}R^{b3}$, $-OR^{a3}$, $-NR^{a3}R^{b3}$, $-NR^{a3}C(=O)R^{b3}$, $-NR^{e3}C(=O)NR^{a3}R^{b3}$, $-NR^{e3}C(=NR^{d3})NR^{a3}R^{b3}$, $-NR^{a3}S(=O)_2R^{c3}$ and $-NR^{e3}S(=O)_2NR^{a3}R^{b3}$;

2) C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 6-10 membered aryl, 5-10 membered heteroaryl, C_{3-10} cycloalkyl, and 3-10 membered aliphatic heterocyclyl;

3) two R^{13}, together with two adjacent ring-forming atoms of the aryl or heteroaryl of Cy^B to which they are attached respectively, form a C_{4-8} aliphatic cyclyl or 4-8 membered aliphatic heterocyclyl, unsubstituted or optionally substituted with 1, 2 or 3 substituents independently selected from R^{23};

R^{a3}, R^{b3} and R^{e3} are each independently selected from the group consisting of:

1) hydrogen;

2) C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, phenyl, 5-6 membered heteroaryl, C_{3-6} cycloalkyl and 3-6 membered aliphatic heterocyclyl, unsubstituted or optionally substituted with 1, 2 or 3 substituents independently selected from R^{23};

or,

R^{a3} and R^{b3} together with the same N atom to which they are attached form a 3-8 membered aliphatic heterocyclyl, unsubstituted or optionally substituted with 1, 2 or 3 substituents independently selected from R^{23};

R^{c3} is selected from the group consisting of C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, phenyl, 5-6 membered heteroaryl, C_{3-6} cycloalkyl and 3-6 membered aliphatic heterocyclyl, unsubstituted or optionally substituted with 1, 2 or 3 substituents independently selected from R^{23};

R^{d3} is selected from the group consisting of:

1) hydrogen, cyano, nitro and $-S(=O)_2R^G$;

2) C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, phenyl, 5-6 membered heteroaryl, C_{3-6} cycloalkyl and 3-6 membered aliphatic heterocyclyl, unsubstituted or optionally substituted with 1, 2 or 3 substituents independently selected from R^{23};

R^{23} is selected from the group consisting of:

1) oxo, halogen, cyano, carboxyl, $-C(=O)R^{a5}$, $-C(=O)OR^{a5}$, $-C(=O)NR^{a5}R^{b5}$, $-C(=NR^{d5})NR^{a5}R^{b5}$, $-OR^{a5}$, $-S(=O)_2R^{c5}$, sulphonic acid group, $-S(=O)_2NR^{a5}R^{b5}$, $-S(=O)(=NR^{d5})R^{c5}$, $-NR^{a5}R^{b5}$, $-NR^{a5}C(=O)R^{b5}$, $-NR^{e5}C(=O)NR^{a5}R^{b5}$, $-NR^{e5}C(=NR^{d5})NR^{a5}R^{b5}$, $-NR^{a5}S(=O)_2R^{c5}$, $-NR^{e5}S(=O)_2NR^{a5}R^{b5}$ and $=N-R^{d5}$;

2) C_{1-6} alkyl, C_{1-6} alkylene, phenyl, 5-6 membered heteroaryl, C_{3-7} cycloalkyl and 3-7 membered aliphatic heterocyclyl, unsubstituted or optionally substituted with 1, 2 or 3 substituens independently selected from R^{33};

R^{a5}, R^{b5} and R^{e5} are each independently selected from the group consisting of:

1) hydrogen;

2) C_{1-4} alkyl, phenyl, 5-6 membered heteroaryl, C_{3-6} cycloalkyl and 3-6 membered aliphatic heterocyclyl, unsubstituted or optionally substituted with 1, 2 or 3 substituents independently selected from R^{33};

or,

R^{a5} and R^{b5} together with the same N atom to which they are linked form a 3-6 membered aliphatic heterocyclyl, unsubstituted or optionally substituted with 1, 2 or 3 substitents independently selected from R^{33};

R^{c5} is selected from the group consisting of C_{1-4} alkyl, phenyl, 5-6 membered heteroaryl, C_{3-6} cycloalkyl and 3-6 membered aliphatic heterocyclyl, unsubstituted or optionally substituted with 1, 2 or 3 substituents independently selected from R^{33};

R^{d5} is selected from the group consisting of:

1) hydrogen, cyano, nitro and $-S(=O)_2R^G$;

2) C_{1-4} alkyl, phenyl, 5-6 membered heteroaryl, C_{3-6} cycloalkyl and 3-6 membered aliphatic heterocyclyl, unsubstituted or optionally substituted with 1, 2 or 3 substituents independently selected from R^{33};

R^{33} is selected from the group consisting of:

1) oxo, halogen, cyano, $-C(=O)R^{a7}$, $-C(=O)OR^{a7}$, $-C(=O)NR^{a7}R^{b7}$, $-C(=NR^{d7})NR^{a7}R^{b7}$, $-OR^{a7}$, $-S(=O)_2R^{c7}$, $-S(=O)_2NR^{a7}R^{b7}$, $-S(=O)(=NR^{d7})R^{c7}$, $-NR^{a7}R^{b7}$, $-NR^{a7}C(=O)R^{b7}$, $-NR^{e7}C(=O)NR^{a7}R^{b7}$, $-NR^{e7}C(=NR^{d7})NR^{a7}R^{b7}$, $-NR^{a7}S(=O)_2R^{c7}$, $-NR^{e7}S(=O)_2NR^{a7}R^{b7}$ and $=N-R^{d7}$;

2) C_{1-4} alkyl, C_{1-4} alkylene, phenyl, 5-6 membered heteroaryl, C_{3-6} cycloalkyl and 3-6 membered aliphatic heterocyclyl, unsubstituted or optionally substituted with 1, 2 or 3 substituents independently selected from R^G;

R^{a7}, R^{b7} and R^{e7} are each independently selected from the group consisting of:

1) hydrogen;

2) C_{1-4} alkyl, phenyl, 5-6 membered heteroaryl, C_{3-6} cycloalkyl and 3-6 membered aliphatic heterocyclyl, unsubstituted or optionally substituted with 1, 2 or 3 substituents independently selected from R^G;

or,

R^{a7} and R^{b7} together with the same N atom to which they are attahced form a 3-6 membered aliphatic heterocyclyl, unsubstituted or optionally substituted with 1, 2 or 3 substituents independently selected from R^G;

R^{c7} is selected from the group consisting of C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, phenyl, 5-6 membered heteroaryl, C_{3-6} cycloalkyl and 3-6 membered aliphatic heterocyclyl, unsubstituted or optionally substituted with 1, 2 or 3 substituents independently selected from R^G;

R^{d7} is selected from the group consisting of:

1) hydrogen, cyano, nitro and $-S(=O)_2R^G$;

2) C_{1-4} alkyl, phenyl, 5-6 membered heteroaryl, C_{3-6} cycloalkyl and 3-6 membered aliphatic heterocyclyl, unsubstituted or optionally substituted with 1, 2 or 3 substituents independently selected from R^G;

R^G is selected from the group consisting of:

1) halogen, oxo, cyano, carboxyl, hydroxyl, C_{1-4} alkoxy, amino, C_{1-4} alkylamino, sulfonic acid group, C_{1-4} alkylsulfonyl and C_{1-4} alkylaminosulfonyl;

2) C_{1-4} alkyl, C_{1-4} alkylene, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{3-6} cycloalkyl and 3-8 membered aliphatic heterocyclyl, unsubstituted or optionally substituted with 1, 2, or 3 substituents independently selected from the group consisting of oxo, halogen, hydroxyl, hydroxymethyl, carboxyl, cyano, C_{1-3} alkoxy, amino, and C_{1-3} alkylamino;

or a pharmaceutically acceptable salt, hydrate, solvate, active metabolite, polymorph, isotope labeled compound, isomer or prodrug thereof.

3. The compound according to claim 2, wherein,

R^1 is selected from the group consisting of hydrogen, fluorine, cyano, methyl and methoxy;

Cy^A is selected from phenyl and 5 or 6 membered heteroaryl, unsubstituted or optionally substituted with 1 or 2, or 3 substituents independently selected from R^{12}; wherein 5 or 6 membered heteroaryl contains 1 or 2 heteroatom(s) independently selected from the group consisting of N and S;

Cy^B is selected from phenyl and 5 or 6 membered heteroaryl, unsubstituted or optionally substituted with 1, 2, 3 or 4 substituents independently selected from R^{13}; wherein the 5 or 6 membered heteroaryl contains 1, 2, or 3 ring-forming heteroatoms independently selected from the group consisting of N and S;

R^{12} is selected from the group consisting of:

1) oxo, halogen, cyano, $-C(=O)R^{a2}$, $-C(=O)NR^{a2}R^{b2}$, $-C(=NR^{d2})NR^{a2}R^{b2}$, $-OR^{a2}$, $-NR^{a2}R^{b2}$, $-NR^{a2}C(=O)R^{b2}$, $-NR^{a2}C(=O)OR^{c2}$, $-NR^{e2}C(=O)NR^{a2}R^{b2}$, $-NR^{e2}C(=NR^{d2})NR^{a2}R^{b2}$, $-NR^{a2}S(=O)_2R^{c2}$, and $-NR^{e2}S(=O)_2NR^{a2}R^{b2}$;

2) C_{1-6} alkyl, phenyl, 5-6 membered heteroaryl, C_{3-10} cycloalkyl and 3-10 membered aliphatic heterocyclyl, unsubstituted or optionally substituted with 1, 2, 3 or 4 substituents independently selected from R^{22};

3) two R^{12}, together with two adjacent ring-forming atoms of the aryl or heteroaryl of Cy^A to which they are connected respectively, form a C_5, C_6, C_7 aliphatic monocyclyl or 5-, 6-, 7-membered aliphatic monoheterocyclyl, unsubstituted or optionally substituted with 1, 2 or 3 substituens independently selected from R^{22};

R^{13} is selected from the group consisting of:

1) oxo, halogen, cyano, $-C(=O)R^{a3}$, $-C(=O)NR^{a3}R^{b3}$, $-C(=NR^{d3})NR^{a3}R^{b3}$, $-OR^{a3}$, $-NR^{a3}R^{b3}$, $-NR^{a3}C(=O)R^{b3}$, $-NR^{e3}C(=O)NR^{a3}R^{b3}$, $-NR^{e3}C(=NR^{d3})NR^{a3}R^{b3}$, $-NR^{a3}S(=O)_2R^{c3}$, and $-NR^{e3}S(=O)_2NR^{a3}R^{b3}$;

2) C_{1-6} alkyl, phenyl, 5-6 membered heteroaryl, C_{3-10} cycloalkyl and 3-10 membered aliphatic heterocyclyl, unsubstituted or optionally substituted with 1, 2, 3 or 4 substituents independently selected from R^{23};

3) two R^{13}, together with two adjacent ring-forming atoms of the aryl or heteroaryl of Cy^B to which they are connected respectively, form a C_5, C_6, C_7 aliphatic monocyclyl or 5-, 6-, 7-membered aliphatic monoheterocyclyl, unsubstituted or optionally substituted with 1, 2 or 3 substituens independently selected from R^{23};

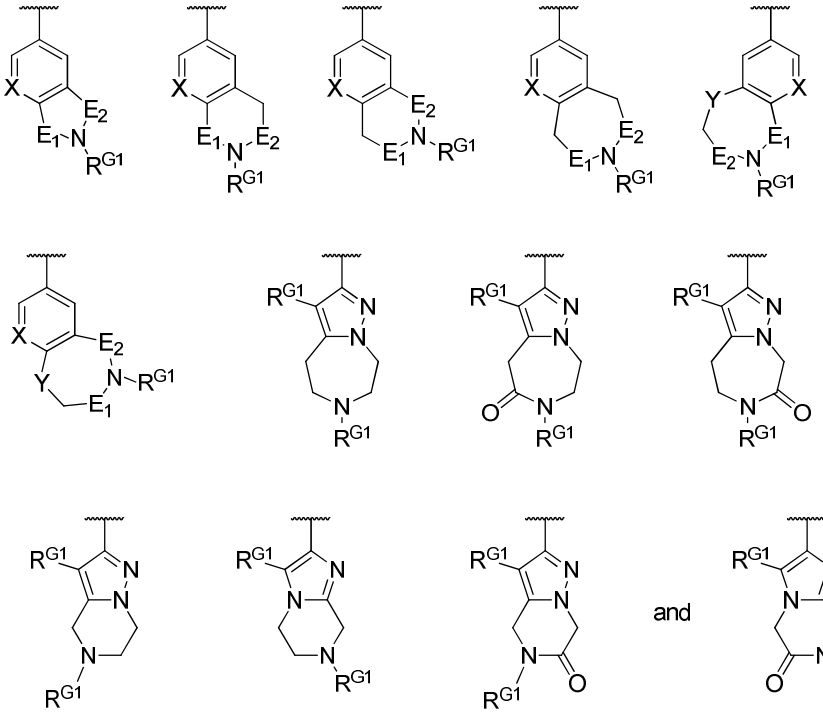
or a pharmaceutically acceptable salt, hydrate, solvate, active metabolite, polymorph, isotope labeled compound, isomer or prodrug thereof.

4. The compound according to claim 2, wherein,

R^1 is selected from the group consisting of hydrogen, fluorine, cyano, methyl and methoxy;

Cy^A is selected from the group consisting of:

1) the following structures, wherein the "〰" at the end of the chemical bond in each structure means that the structures is connected to the rest of formula (I) through the bond:



and

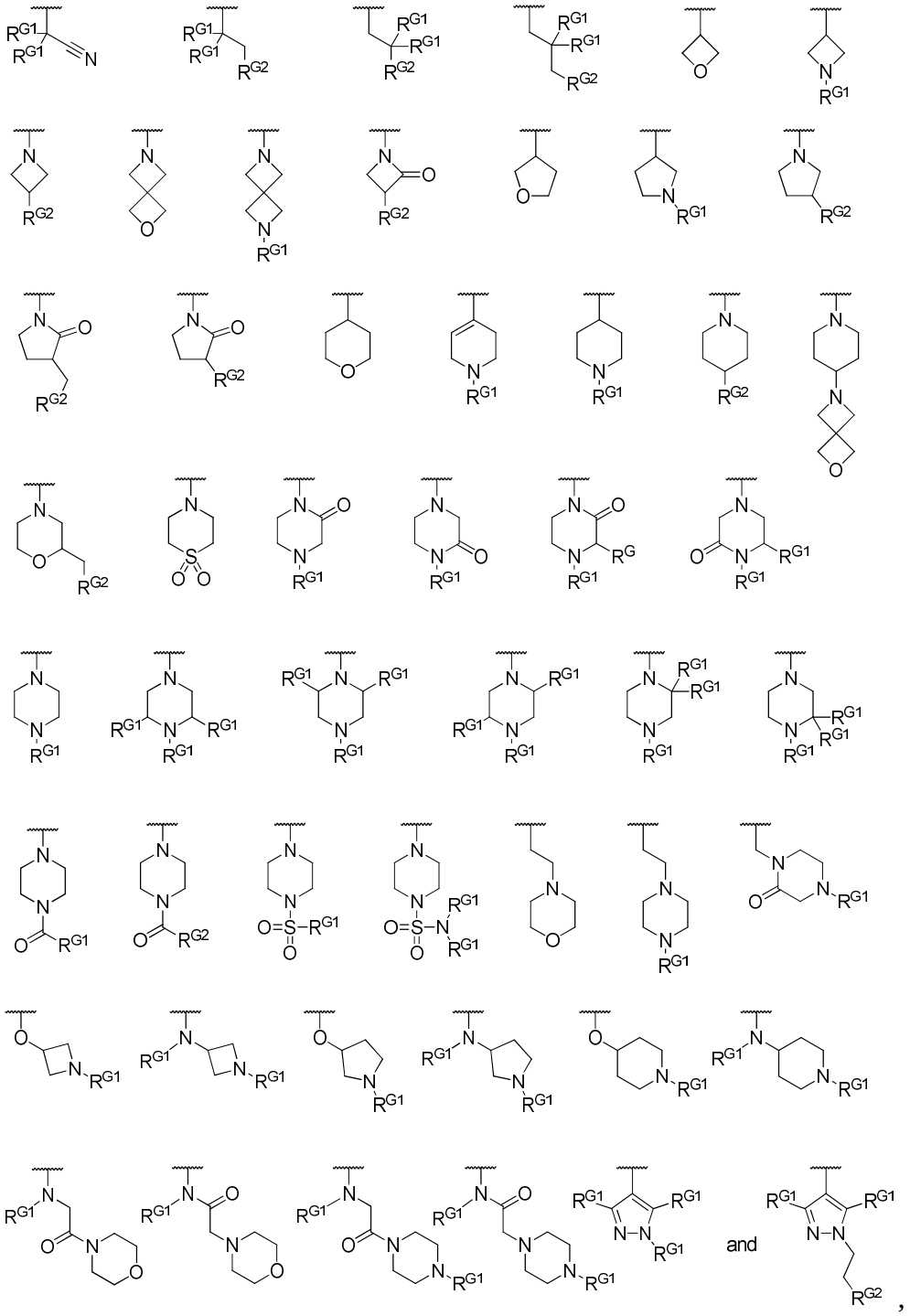
;

2) phenyl, pyridyl, pyrimidyl, pyrazolyl, imidazolyl, thiazolyl, isothiazolyl, oxazolyl, or isoxazolyl, unsubstituted or optionally substituted with 1, 2 or 3 substituents independently selected from R^{12}; wherein,

(a) each R^{12} is independently selected from the group consisting of fluorine and chlorine; non-hydrogen R^{G1}, and OR^{G1};

or,

(b) Cy^A contains one R^{12}, and the R^{12} is selected from one of the following structures, wherein the "〰" at the end of the chemical bond in each structure means that the structure is connected to the rest of formula (I) through the bond:



or,

Cy^A contains two or three R^{12}, wherein one of R^{12} is selected from the group consisting of the above structures and the others of $R^{12}$are each independently selected from the group consisting of fluorine, chlorine, non-hydrogen R^{G1}, and $-OR^{G1}$;

wherein

X is selected from the group consisting of CH and N;

Y is selected from the group consisting of $-CH_2-$, NH and O;

E_1 and E_2 are each independently selected from the group consisting of $-CH_2-$ and carbonyl, provided that E_1 and E_2 are not carbonyl simultaneously;

R^{G2} is selected from the group consisting of hydrogen, $-OR^{G1}$ and $-N(R^{G1})_2$;

each R^{G1} is independently selected from the group consisting of:

1) hydrogen, methyl, ethyl, isopropyl, cyclopropyl, 3-oxetanyl and 3-methyl-3-azetidinyl;

2) two R^{G1} attached to the same atom, together with said atom, form a C_{3-6} monocyclyl or 3-6 membered aliphatic monoheterocyclyl;

3) two R^{G1} attached to two different ring-forming atoms of the same monocycle are connected to form a ring structure together with part of the ring-forming atoms of said monocycle, wherein the two connected R^{G1} form a C2, C3 or C4 alkylene;

Cy^B is phenyl, pyridyl, pyrimidyl, pyridazinyl, pyrazolyl, imidazolyl, thiazolyl, isothiazolyl, thienyl, optionally substituted with 1, 2 or 3 substituents independently selected from R^{13};

R^{13} is selected from the group consisting of:

1) oxo, halogen, cyano, $-C(=O)R^{a3}$, $-C(=O)NR^{a3}R^{b3}$, $-C(=NR^{d3})NR^{a3}R^{b3}$, $-OR^{a3}$, $-NR^{a3}R^{b3}$, $-NR^{a3}C(=O)R^{b3}$, $-NR^{e3}C(=O)NR^{a3}R^{b3}$, $-NR^{e3}C(=NR^{d3})NR^{a3}R^{b3}$, $-NR^{a3}S(=O)_2R^{c3}$, and $-NR^{e3}S(=O)_2NR^{a3}R^{b3}$;

2) C_{1-6} alkyl, phenyl, 5-6 membered heteroaryl, C_{3-6} monocyclic cycloalkyl and 3-6 membered aliphatic monoheterocyclyl, unsubstituted or optionally substituted with 1, 2, 3 or 4 substituents independently selected from R^{23};

3) two R^{13}, together with two adjacent ring-forming atoms of the aryl or heteroaryl of Cy^B to which they are connected respectively, form a C_5, C_6, C_7 aliphatic monocyclyl or 5-, 6-, 7-membered aliphatic monocyclic heterocyclyl, unsubstituted or optionally substituted with 1, 2 or 3 substituens independently selected from R^{23};

or a pharmaceutically acceptable salt, hydrate, solvate, active metabolite, polymorph, isotope labeled compound, isomer or prodrug thereof.

5. The compound according to claim 1, wherein,

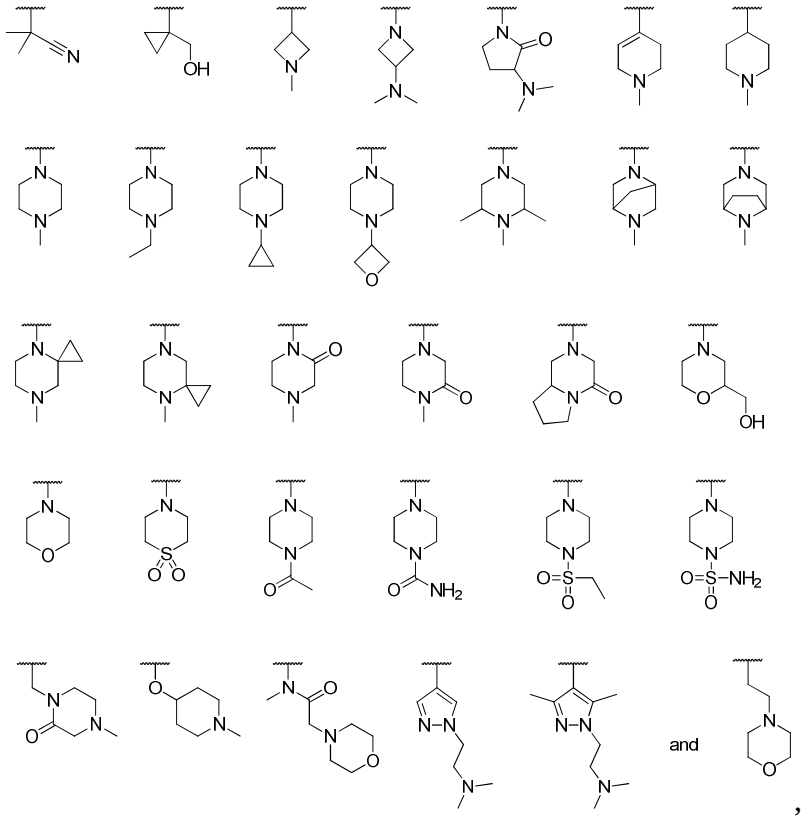
R^1 is selected from the group consisting of hydrogen, fluorine, cyano, methyl and methoxy;

Cy^A is phenyl, pyridyl, pyrimidyl, pyrazolyl, imidazolyl, thiazolyl or isothiazolyl, unsubstituted or optionally substituted with 1, 2 or 3 substituents independently selected from R^{12}, wherein

1) each R^{12} is independently selected from the group consisting of: fluorine, chlorine; non-hydrogen R^{G1}, and OR^{G1};

or,

2) Cy^A contains one R^{12}, and the R^{12} is selected from one of the following strucutres:



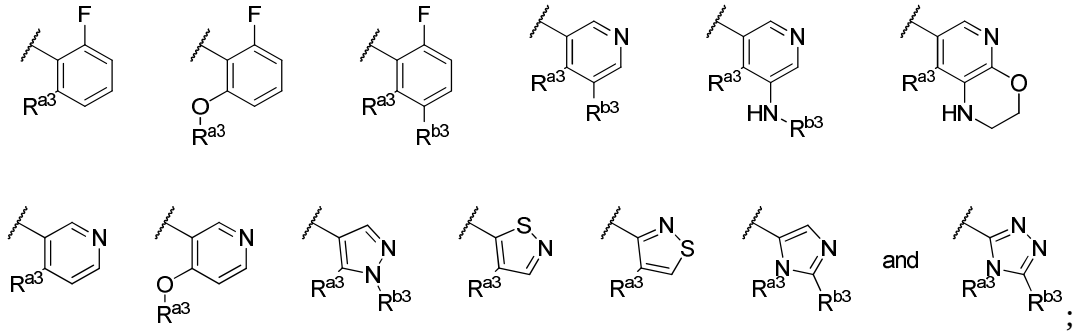
or,

Cy^A contains two or three R^{12}, wherein one of R^{12} is selected from the group consisting of the above structures and others of R^{12} are each independently selected from the group consisting of fluorine, chlorine, non-hydrogen R^{G1}, and $-OR^{G1}$;

each R^{G1} is independently selected from the group consisting of:

1) hydrogen,
2) methyl, ethyl, isopropyl, cyclopropyl, 3-oxetanyl and 3-methyl-3-azetidinyl; optionally substituted with hydroxyl, C_{1-6} alkoxy or amino;

Cy^B is selected from one of the following structures:

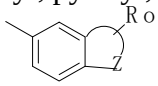


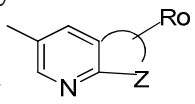
R^{a3} and R^{b3} are each independently selected from the group consisting of hydrogen, C_{1-6} alkyl and C_{1-6} cycloalkyl, or, two R^{a3} and R^{b3} attached to two adjacent ring-forming atoms respectively, together with said two ring-forming atoms form unsubstituted 5-6 membered aliphatic cyclyl or unsubstituted 5-6 membered aliphatic heterocyclyl;

or a pharmaceutically acceptable salt, hydrate, solvate, active metabolite, polymorph, isotope labeled compound, isomer or prodrug thereof.

6. The compound according to claim 1, wherein,

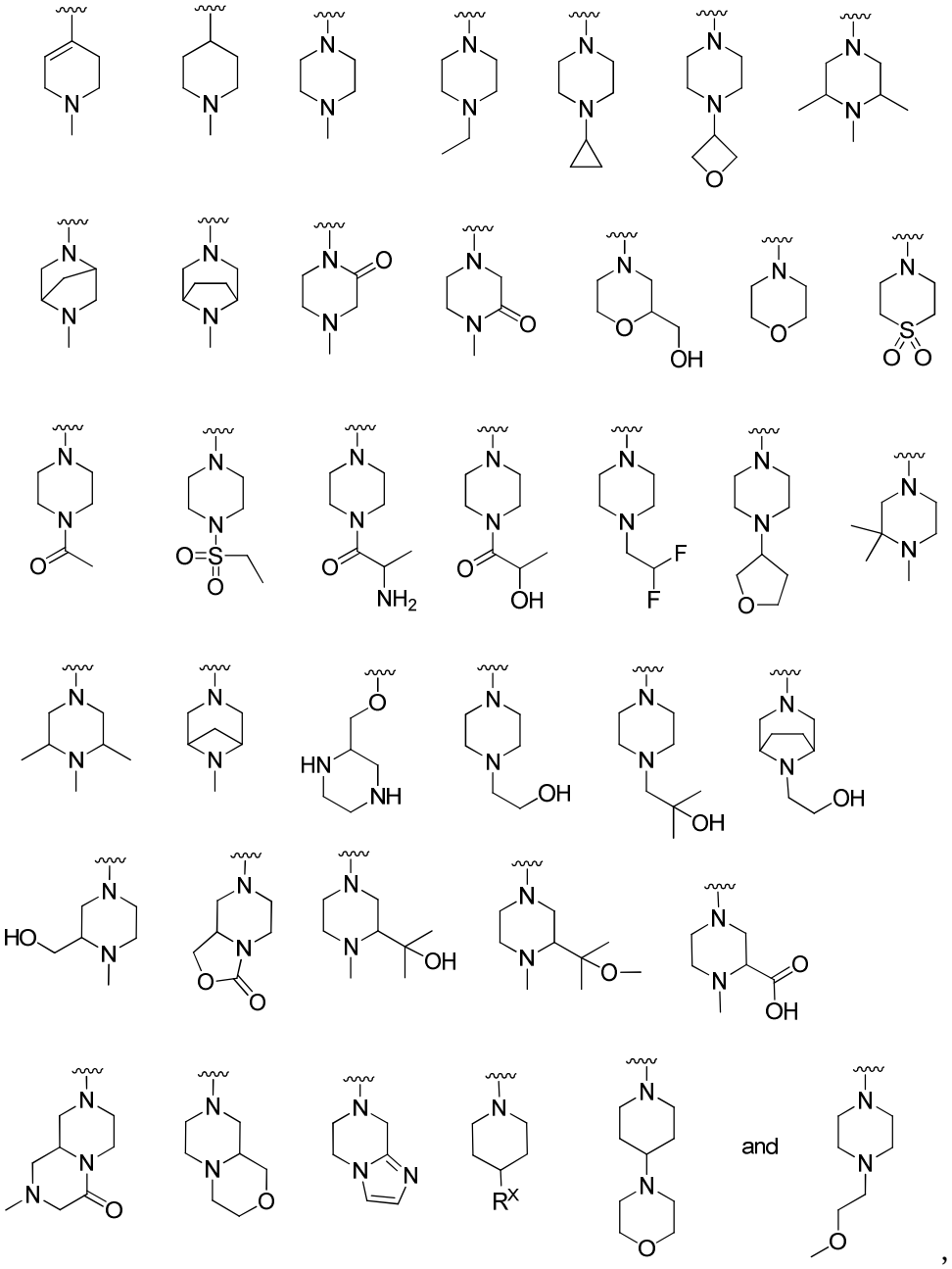
R^1 is selected from the group consisting of hydrogen, fluorine, cyano, methyl and methoxy;

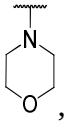
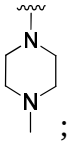
Cy^A is phenyl, pyridyl, pyrimidyl, pyrazolyl, imidazolyl, thiazolyl, isothiazolyl or a bicyclyl represented by 

where a phenyl is fused with a 5-7 membered saturated aliphatic heterocyclyl, or a bicyclyl represented by 

where a pyridyl is fused with a 5-7 membered saturated aliphatic heterocyclyl; wherein Z represents 1-3 heteroatoms selected from the group consisting of nitrogen and oxygen; when Z=N, N is optionally linked to Ry; Ro is selected from the group consisting of oxo, F, amino, and optionally substituted C_{1-3} alkyl; wherein said aliphatic heterocyclyl may be fused with another 5-6 membered nitrogen-containing saturated aliphatic heterocyclyl to form a fused ring; said phenyl, pyridyl, pyrimidyl, pyrazolyl, imidazolyl, thiazolyl, and isothiazolyl is unsubstituted or optionally substituted with 1, 2 or 3 substituents independently selected from R^{12}, wherein,

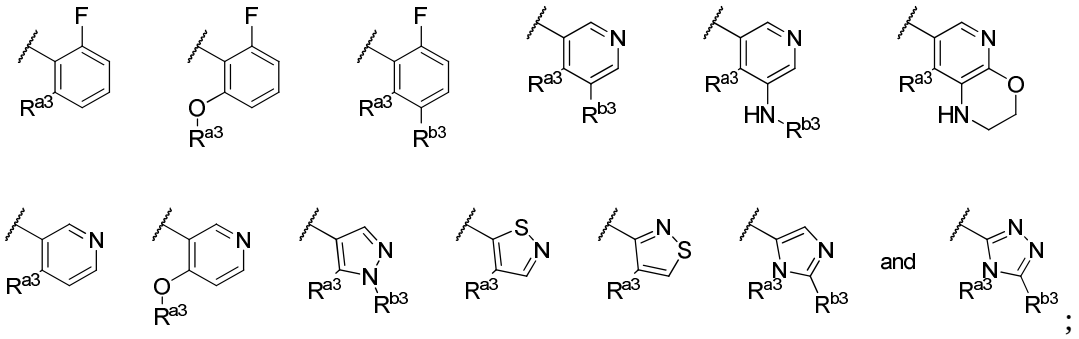
1) when Cy^A contains one R^{12}, the R^{12} is selected from one of the followings:



wherein R^x is selected from the group consisting of -OH, C_{1-6} alkyl, C1-6 alkoxy, $-NH_2$, C_{1-6} alkylamino,  , and  ;

2) when Cy^A contains more than one R^{12}, the others of R^{12} are each independently selected from the group consisting of fluorine, C_{1-6} alkyl, C_{1-6} alkoxy, and (C_{1-6} alkylamino)methyl;

Cy^B is selected from one of the following structures:



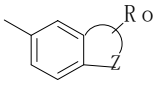
;

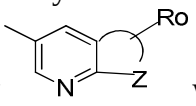
R^{a3} and R^{b3} are each independently selected from the group consisting of hydrogen, C_{1-6} alkyl and C_{3-6} cycloalkyl, or R^{a3} and R^{b3} together with N atom to which they are attached form a 4-6 membered saturated aliphatic heterocyclyl; said C_{1-6} alkyl, C_{3-6} cycloalkyl, and 4-6 membered saturated aliphatic heterocyclyl is unsubstituted or optionally substituted with substituent(s) selected from the group consisting of fluorine, hydroxyl, C_{1-6} alkyl, and fluoro-substituted C_{1-6} alkyl;

R^y is selected from the group consisting of H, C_{1-6} alkyl, C_{1-6} alkyl substituted with a substituent selected from the group consisting of hydroxyl and halogen, C_{3-6} cycloalkyl, nitrogen-containing 4-6 membered saturated aliphatic heterocyclyl, oxygen-containing 5-6 membered saturated aliphatic heterocyclyl, and -C(=O)Rs; Rs is selected from C_{1-6} alkyl optionally substituted with substituents selected from the group consisting of hydroxyl, amino, and nitrogen-containing aliphatic heterocyclyl;

or a pharmaceutically acceptable salt, hydrate, solvate, active metabolite, polymorph, isotope labeled compound, isomer or prodrug thereof.

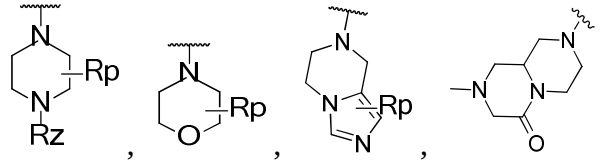
7. The compound according to any of claims 1-6, wherein,

Cy^A is phenyl, pyridyl, pyrimidyl, thiazolyl or a bicyclyl represented by 

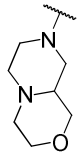
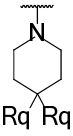
where a phenyl is fused with a 5-7 membered saturated aliphatic heterocyclyl, or a bicyclyl represented by 

where a pyridyl is fused with a 5-7 membered saturated aliphatic heterocyclyl, wherein Z represents 1-3 heteroatoms selected from the group consisting of nitrogen and oxygen; when Z=N, N is optionally linked to Ry; Ro is selected from the group consisting of oxo, F, amino, optionally substituted C1-3 alkyl; wherein said saturated aliphatic heterocyclyl may be fused with another 5-6 membered nitrogen-containing saturated aliphatic heterocyclyl form a fused ring, wherein,

R^y is selected from the group consisting of H, C_{1-6} alkyl, C_{1-6} alkyl substituted with the substituent consisting of hydroxyl and halogen, C_{3-6} cycloalkyl, 4-6 membered N-containing saturated aliphatic heterocyclyl, 5-6 membered O-containing saturated aliphatic heterocyclyl, and -C(=O)Rs, Rs is selected from C_{1-6} alkyl optionally substituted with the group consisting of hydroxyl, amino, and N-containing aliphatic heterocyclyl;

when Cy^A is selected from the group consisting of phenyl, pyridyl, pyrimidyl, and thiazolyl, R^{12} is selected from the group consisting of 

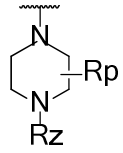
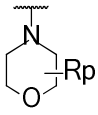
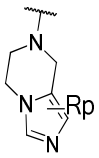
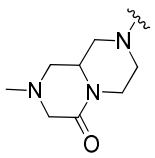
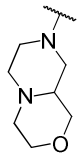
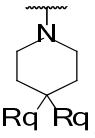
,


, and  , wherein Rz is selected from the group consisting of hydrogen, optionally substituted C_{1-6} alkyl, 4-6 membered O-containing aliphatic heterocyclyl, and $-S(=O)_2-C_{1-6}$ alkyl; Rp, single or multiple substituent(s), are each optionally selected from the group consisting of hydrogen, and optionally substituted C_{1-6} alkyl; Rq is selected from the group consisting of hydroxyl, amino, optionally substituted C_{1-3} alkyl, spiro heterocyclyl composed of two 4-5 membered nitrogen- and/or oxygen-containing rings, and 5-6 membered aliphatic heterocyclyl containing one or two heteroatoms selected from the group consisting of nitrogen and oxygen, said aliphatic heterocyclyl is optionally substituted with F, and C_{1-3} alkyl;

or a pharmaceutically acceptable salt, hydrate, solvate, active metabolite, polymorph, isotope labeled compound, isomer or prodrug thereof.

8. The compound according to claim 7, wherein,

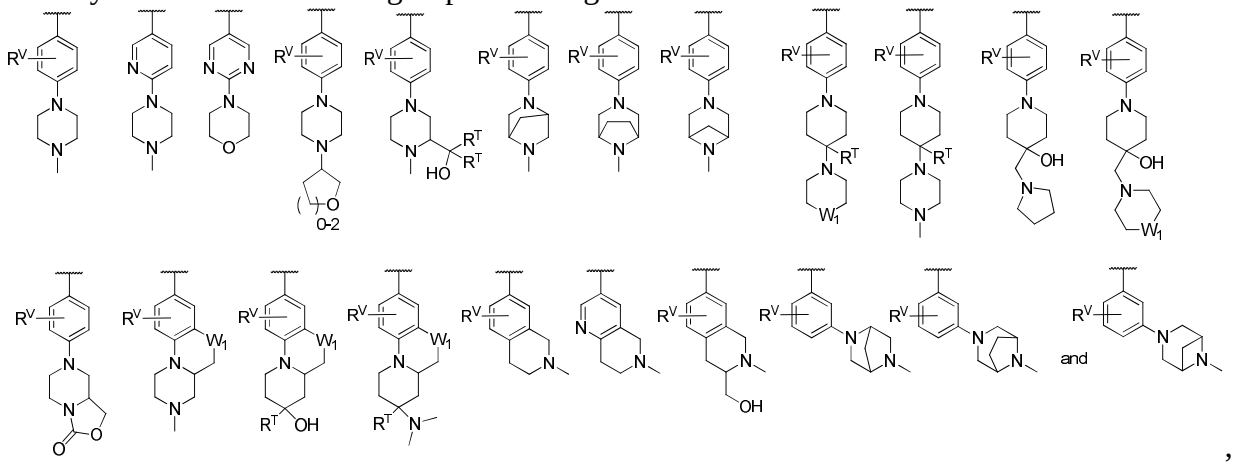
Cy^A is selected from phenyl,

R^{12} is selected from the group consisting of  ,  ,  ,  ,  , and  , wherein Rz is selected from the group consisting of hydrogen, optionally substituted C_{1-6} alkyl, 4-6 membered O-containing aliphatic heterocyclyl, and $-S(=O)_2-C_{1-6}$ alkyl; Rp, single or multiple substituent(s), are each optionally selected from the group consisting of hydrogen, and optionally substituted C_{1-6} alkyl; Rq is selected from the group consisting of hydroxyl, amino, optionally substituted C_{1-3} alkyl, spiro heterocyclyl composed of two 4-5 membered nitrogen and/or oxygen containing rings, and 5-6 membered aliphatic heterocyclyl containing one or two heteroatoms selected from the group consisting of nitrogen and oxygen, said aliphatic heterocyclyl is optionally substituted with F, and C_{1-3} alkyl;

or a pharmaceutically acceptable salt, hydrate, solvate, active metabolite, polymorph, isotope labeled compound, isomer or prodrug thereof.

9. The compound according to any of claims 1-8, wherein,

Cy^A is selected from the group consisting of:



wherein, W_1 is selected from CH_2 or oxygen;

R^T is selected from hydrogen or methyl;

R^V is selected from fluorine or methyl, the number of R^V is 0, 1 or 2;

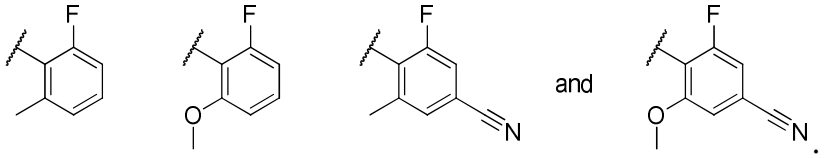
or a pharmaceutically acceptable salt, hydrate, solvate, active metabolite, polymorph, isotope labeled compound, isomer or prodrug thereof.

10. The compound according to any of claims 1-9, wherein,

Cy^B is selected from phenyl optionally substituted with a group selected from the group consisting of H, F, -CN, optionally substituted C_{1-3} alkyl, optionally substituted C_{1-3} alkoxy, optionally substituted C_{3-6} cycloalkoxy and $C(=O)NR^{a3}R^{b3}$, wherein R^{a3} and R^{b3} are each independently selected from the group consisting of hydrogen, C_{1-6} alkyl and optionally substituted C_{3-6} cycloalkyl, or R^{a3} and R^{b3} together with the N atom to which whihch they attached form an optionally substituted 4-5 membered alicyclic heterocyclyl;

or a pharmaceutically acceptable salt, hydrate, solvate, active metabolite, polymorph, isotope labeled compound, isomer or prodrug thereof.

11. The compound according to any of claims 1-10, wherein, Cy^B is selected from the group consisting of:



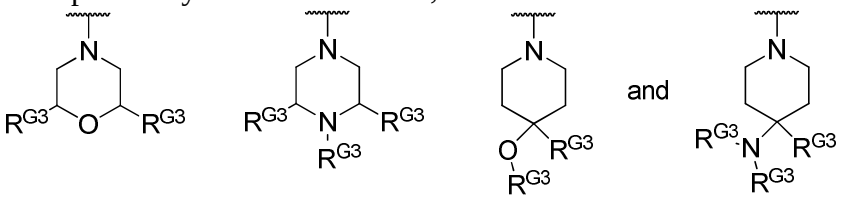
12. The compound according to claim 1, wherein,

R^1 is H;

Cy^A is selected from the group consisting of:

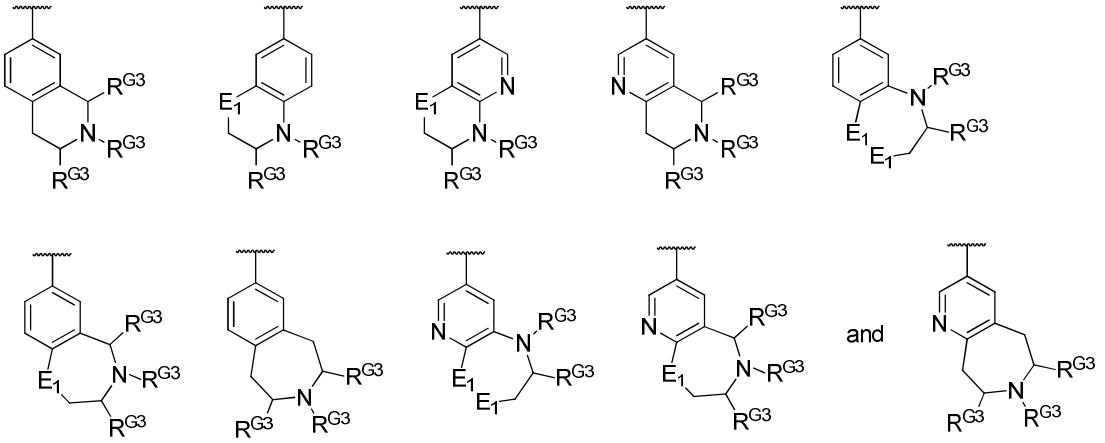
1) phenyl, pyridyl, and pyrimidyl, unsubstituted or optionally substituted with 1, 2 or 3 substituents independently selected from R^{12}; each R^{12} is independently selected from the group consisting of fluorine, chlorine, non-hydrogen R^{G1}, and OR^{G1};

2) phenyl, pyridyl, and pyrimidyl, optionally substituted with 1, 2 or 3 substituents independently selected from R^{12}; one of R^{12} is selected from the group consisting of:



and other R^{12} are each independently selected from the group consisting of: fluorine, chlorine; non-hydrogen R^{G1}, and OR^{G1};

3) the following structure:



wherein the phenyl or pyridyl is unsubstituted or optionally substituted with 1 or 2 substituents independently selected from R^{12};

Cy^B is selected from



wherein

R^{a3} is selected from the group consisting of methyl, ethyl, difluoromethyl, trifluoromethyl, isopropyl and cyclopropyl; preferably selected from methyl, or ethyl;

E^1 is independently selected from the group consisting of -CH_2- and oxygen;

R^{G3} is selected from the group consisting of hydrogen, oxo, methyl, ethyl, isopropyl, cyclopropyl, 3-oxetanyl and 3-methyl-3-azetidinyl;

R^{13} is selected from the group consisting of hydrogen, fluorine, cyano and -C(=O)-N(R^{G3})$_2$; preferably selected from the group consisting of hydrogen and cyano;

each R^{G3} is independently selected from the group consisting of:

1) hydrogen, methyl, ethyl, isopropyl, cyclopropyl, oxetanyl, oxacyclopentyl, azetidinyl, and azacyclopentyl;

2) two R^{G3} connected to the same atom, together with said atom, form a C_{3-6} monocyclyl or a 3-6 membered aliphatic monoheterocyclyl;

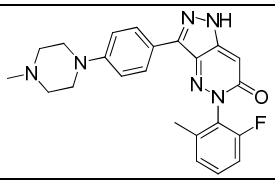
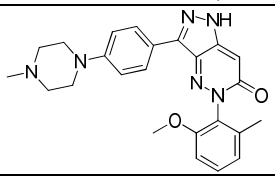
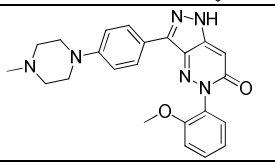
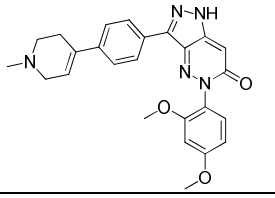
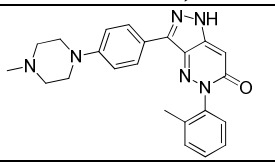
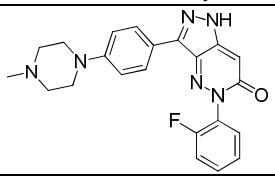
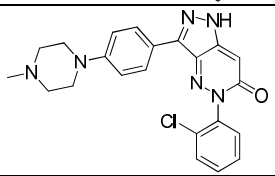
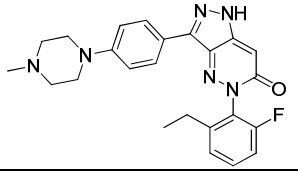
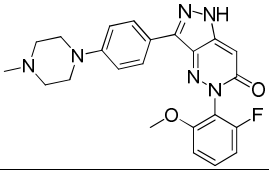
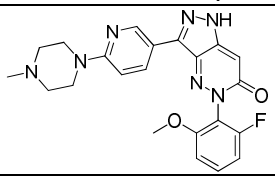
3) two R^{G3} respectively connected to two different ring-forming atoms on the same single ring are connected to form a ring structure together with part of the ring-forming atoms of said single ring, and the two connected R^{G3} form a C_2, C_3 or C_4 alkylene, or a 2-, 3- or 4-membered oxaalkylene, or a 2-, 3- or 4-membered azaalkylene;

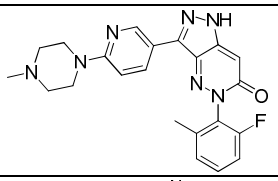
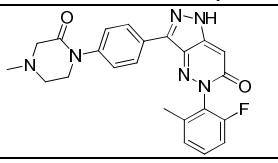
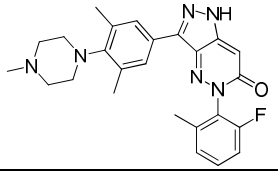
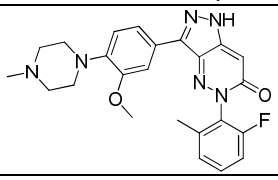
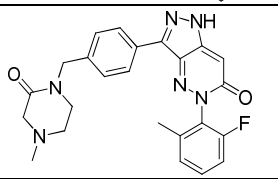
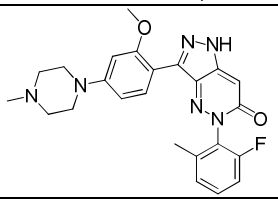
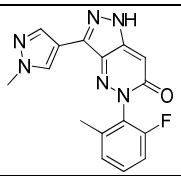
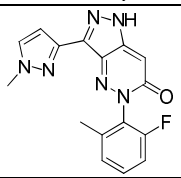
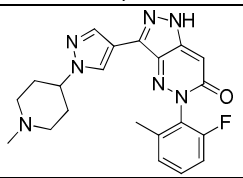
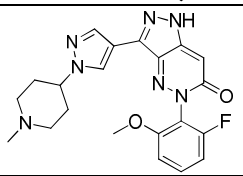
and, when R^{G3} is not hydrogen, R^{G3} is unsubstituted or independently substituted with 1, 2 or 3 substituents optionally selected from the group consisting of oxo, fluorine, hydroxyl, methoxy, amino, methylamino, dimethylamino, methyl, ethyl, and cyano;

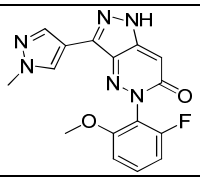
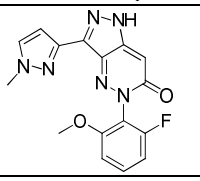
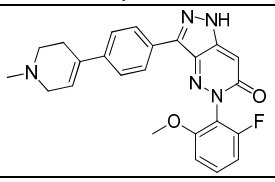
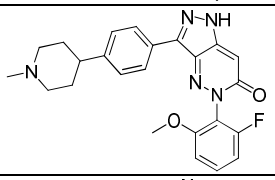
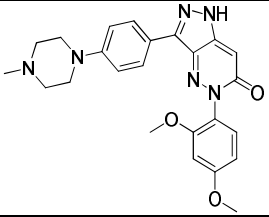
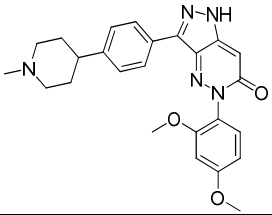
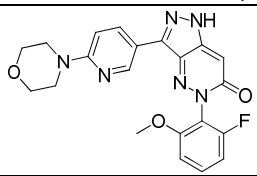
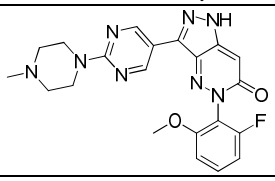
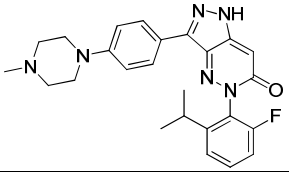
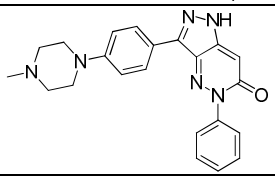
or a pharmaceutically acceptable salt, hydrate, solvate, active metabolite, polymorph, isotope labeled compound, isomer or prodrug thereof.

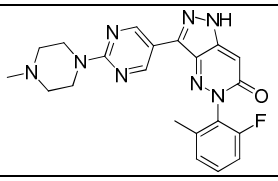
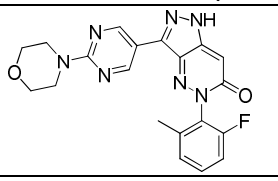
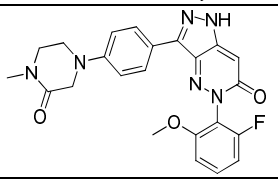
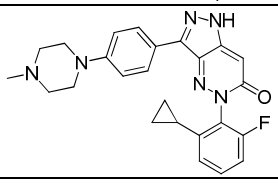
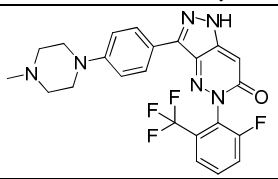
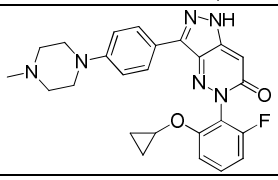
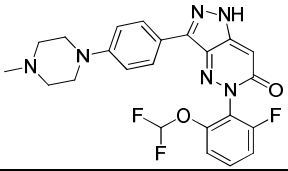
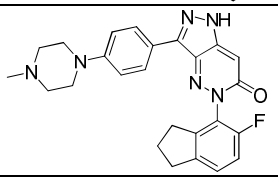
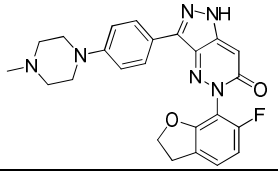
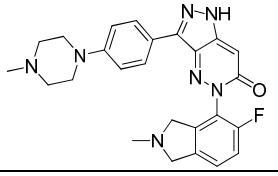
13. The compound according to any of claims 1-12, wherein, when Cy^A is phenyl, and R^{12} is heterocyclyl, R^{12} is attached to para- or meta- position of the phenyl; or a pharmaceutically acceptable salt, hydrate, solvate, active metabolite, polymorph, isotope labeled compound, isomer or prodrug thereof.

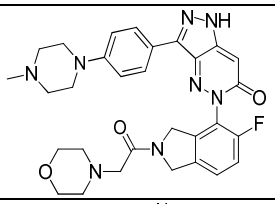
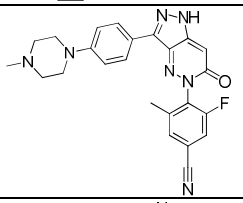
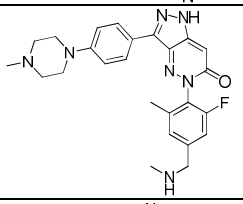
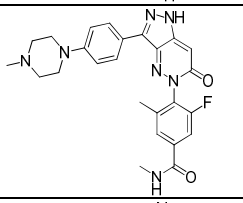
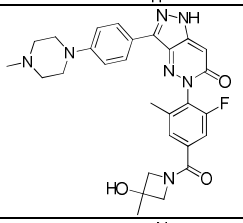
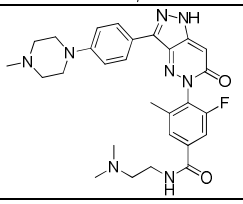
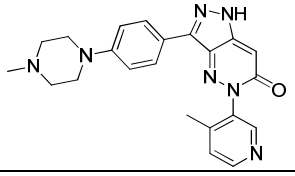
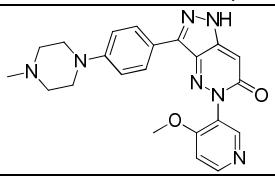
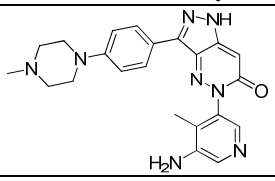
14. The compound according to claim 1, wherein the compound is selected from:

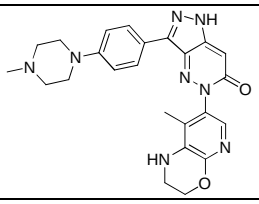
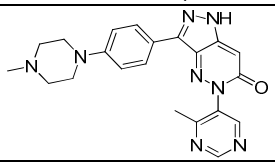
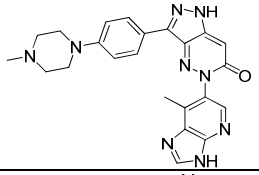
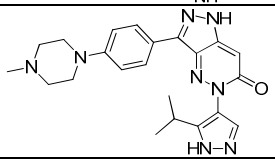
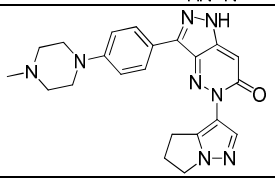
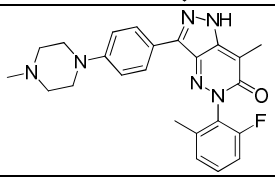
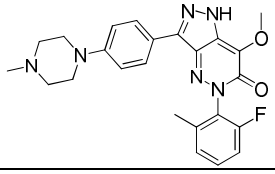
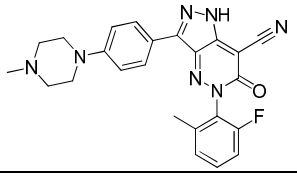
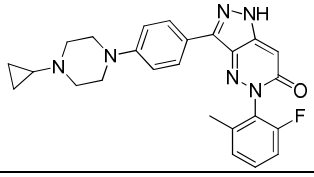
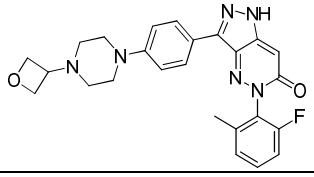
Compound	Structural Formula	Name of Compound
Compound 1		5-(2-fluoro-6-methylphenyl)-3-(4-(4-methylpiperazin-1-yl)phenyl)-*1H*-pyrazolo[4,3-c]pyridazin-6(*5H*)-one
Compound 2		5-(2-methoxy-6-methylphenyl)-3-(4-(4-methylpiperazin-1-yl)phenyl)-*1H*-pyrazolo[4,3-c]pyridazin-6(*5H*)-one
Compound 3		5-(2-methoxyphenyl)-3-(4-(4-methylpiperazin-1-yl)phenyl)-*1H*-pyrazolo[4,3-c]pyridazin-6(*5H*)-one
Compound 4		5-(2,4-dimethoxyphenyl)-3-(4-(1-methyl-1,2,3,6-tetrahydropyridin-4-yl)phenyl)-*1H*-pyrazolo[4,3-c]pyridazin-6(*5H*)-one
Compound 5		5-(2-methylphenyl)-3-(4-(4-methylpiperazin-1-yl)phenyl)-*1H*-pyrazolo[4,3-c]pyridazin-6(*5H*)-one
Compound 6		5-(2-fluorophenyl)-3-(4-(4-methylpiperazin-1-yl)phenyl)-*1H*-pyrazolo[4,3-c]pyridazin-6(*5H*)-one
Compound 7		5-(2-chlorophenyl)-3-(4-(4-methylpiperazin-1-yl)phenyl)-*1H*-pyrazolo[4,3-c]pyridazin-6(*5H*)-one
Compound 8		5-(2-ethyl-6-fluorophenyl)-3-(4-(4-methylpiperazin-1-yl)phenyl)-*1H*-pyrazolo[4,3-c]pyridazin-6(*5H*)-one
Compound 9		5-(2-fluoro-6-methoxyphenyl)-3-(4-(4-methylpiperazin-1-yl)phenyl)-*1H*-pyrazolo[4,3-c]pyridazin-6(*5H*)-one
Compound 10		5-(2-fluoro-6-methoxyphenyl)-3-(6-(4-methylpiperazin-1-yl)pyrid-3-yl)-*1H*-pyrazolo[4,3-c]pyridazin-6(*5H*)-one

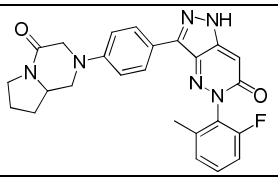
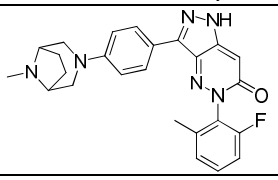
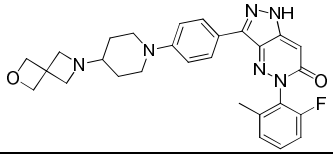
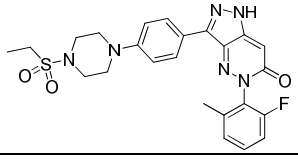
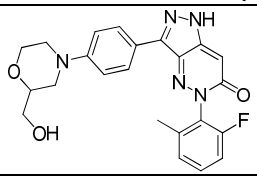
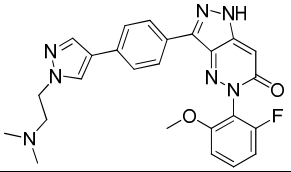
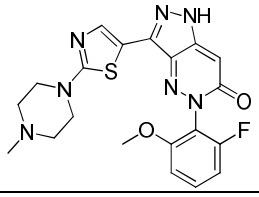
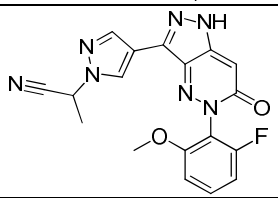
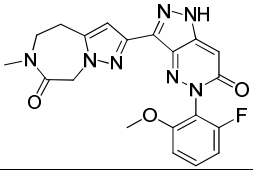
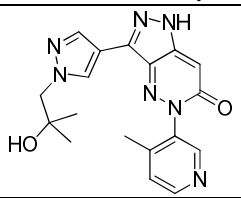
Compound 11		5-(2-fluoro-6-methylphenyl)-3-(6-(4-methylpiperazin-1-yl)pyrid-3-yl)-*1H*-pyrazolo[4,3-c]pyridazin-6(*5H*)-one
Compound 12		5-(2-fluoro-6-methylphenyl)-3-(4-(4-methyl-2-oxopiperazin-1-yl)phenyl)-*1H*-pyrazolo[4,3-c]pyridazin-6(*5H*)-one
Compound 13		3-(3,5-dimethyl-4-(4-methylpiperazin-1-yl)phenyl)-5-(2-fluoro-6-methylphenyl)-*1H*-pyrazolo[4,3-c]pyridazin-6(*5H*)-one
Compound 14		5-(2-fluoro-6-methylphenyl)-3-(3-methoxy-4-(4-methylpiperazin-1-yl)phenyl)-*1H*-pyrazolo[4,3-c]pyridazin-6(*5H*)-one
Compound 15		5-(2-fluoro-6-methylphenyl)-3-(4-((4-methyl-2-oxo-piperazin-1-yl)methyl)phenyl)-*1H*-pyrazolo[4,3-c]pyridazin-6(*5H*)-one
Compound 16		5-(2-fluoro-6-methylphenyl)-3-(2-methoxy-4-(4-methylpiperazin-1-yl)phenyl)-*1H*-pyrazolo[4,3-c]pyridazin-6(*5H*)-one
Compound 17		5-(2-fluoro-6-methylphenyl)-3-(1-methyl-*1H*-pyrazol-4-yl)-*1H*-pyrazolo[4,3-c]pyridazin-6(*5H*)-one
Compound 18		5-(2-fluoro-6-methylphenyl)-3-(1-methyl-*1H*-pyrazol-3-yl)-*1H*-pyrazolo[4,3-c]pyridazin-6(*5H*)-one
Compound 19		5-(2-fluoro-6-methylphenyl)-3-(1-(1-methylpiperidin-4-yl)-*1H*-pyrazol-4-yl)-*1H*-pyrazolo[4,3-c]pyridazin-6(*5H*)-one
Compound 20		5-(2-fluoro-6-methoxyphenyl)-3-(1-(1-methylpiperidin-4-yl)-*1H*-pyrazol-4-yl)-*1H*-pyrazolo[4,3-c]pyridazin-6(*5H*)-one

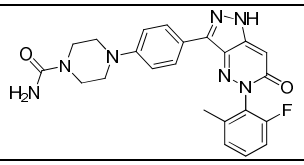
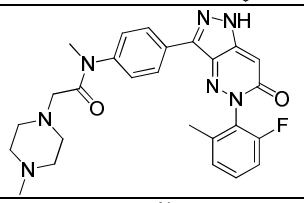
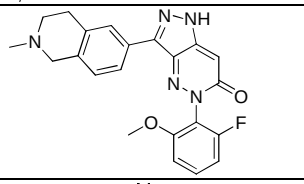
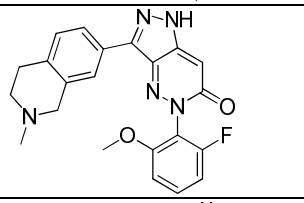
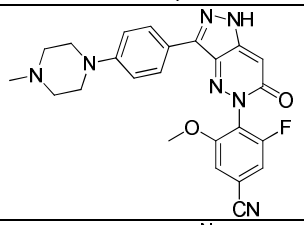
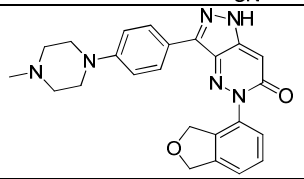
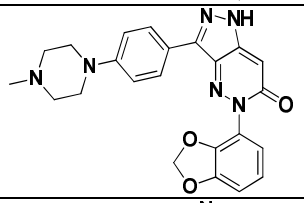
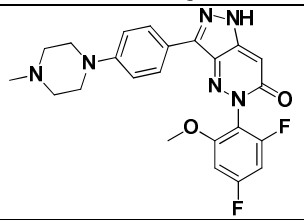
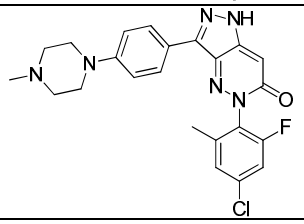
Compound 21		5-(2-fluoro-6-methoxyphenyl)-3-(1-methyl-*1H*-pyrazol-4-yl)-*1H*-pyrazolo[4,3-c]pyridazin-6(*5H*)-one
Compound 22		5-(2-fluoro-6-methoxyphenyl)-3-(1-methyl-*1H*-pyrazol-3-yl)-*1H*-pyrazolo[4,3-c]pyridazin-6(*5H*)-one
Compound 23		5-(2-fluoro-6-methoxyphenyl)-3-(4-(1-methyl-1,2,3,6-tetrahydropyridin-4-yl)phenyl)-*1H*-pyrazolo[4,3-c]pyridazin-6(*5H*)-one
Compound 24		5-(2-fluoro-6-methoxyphenyl)-3-(4-(1-methylpiperidin-4-yl)phenyl)-*1H*-pyrazolo[4,3-c]pyridazin-6(*5H*)-one
Compound 25		5-(2,4-dimethoxyphenyl)-3-(4-(4-methylpiperazin-1-yl)phenyl)-*1H*-pyrazolo[4,3-c]pyridazin-6(*5H*)-one
Compound 26		5-(2,4-dimethoxyphenyl)-3-(4-(1-methylpiperidin-4-yl)phenyl)-*1H*-pyrazolo[4,3-c]pyridazin-6(*5H*)-one
Compound 27		5-(2-fluoro-6-methoxyphenyl)-3-(6-morpholinopyrid-3-yl)-*1H*-pyrazolo[4,3-c]pyridazin-6(*5H*)-one
Compound 28		5-(2-fluoro-6-methoxyphenyl)-3-(2-(4-methylpiperazin-1-yl)pyrimidin-5-yl)-*1H*-pyrazolo[4,3-c]pyridazin-6(*5H*)-one
Compound 29		5-(2-fluoro-6-isopropylphenyl)-3-(4-(4-methylpiperazin-1-yl)phenyl)-*1H*-pyrazolo[4,3-c]pyridazin-6(*5H*)-one
Compound 30		3-(4-(4-methylpiperazin-1-yl)phenyl)-5-phenyl-*1H*-pyrazolo[4,3-c]pyridazin-6(*5H*)-one

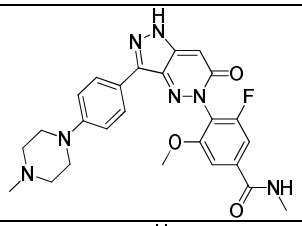
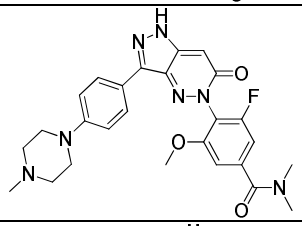
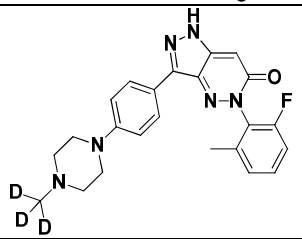
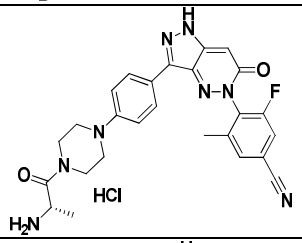
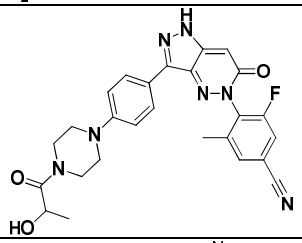
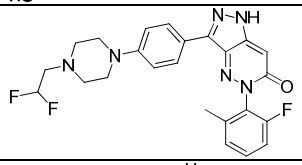
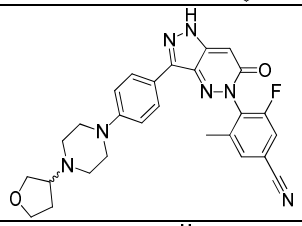
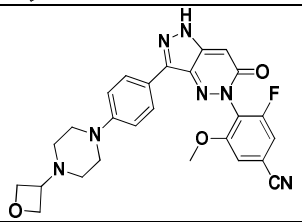
Compound 31		5-(2-fluoro-6-methylphenyl)-3-(2-(4-methylpiperazin-1-yl)pyrimidin-5-yl)-*1H*-pyrazolo[4,3-c]pyridazin-6(*5H*)-one
Compound 32		5-(2-fluoro-6-methylphenyl)-3-(2-morpholinyl pyrimidin-5-yl)-*1H*-pyrazolo[4,3-c]pyridazin-6(*5H*)-one
Compound 33		5-(2-fluoro-6-methoxyphenyl)-3-(4-(4-methyl-3-oxopiperazin-1-yl)phenyl)-*1H*-pyrazolo[4,3-c]pyridazin-6(*5H*)-one
Compound 34		5-(2-cyclopropyl-6-fluorophenyl)-3-(4-(4-methylpiperazin-1-yl)phenyl)-*1H*-pyrazolo[4,3-c]pyridazin-6(*5H*)-one
Compound 35		5-(2-fluoro-6-(trifluoromethyl)phenyl)-3-(4-(4-methylpiperazin-1-yl)phenyl)-*1H*-pyrazolo[4,3-c]pyridazin-6(*5H*)-one
Compound 36		5-(2-cyclopropoxy-6-fluorophenyl)-3-(4-(4-methylpiperazin-1-yl)phenyl)-*1H*-pyrazolo[4,3-c]pyridazin-6(*5H*)-one
Compound 37		5-(2-(difluoromethoxy)-6-fluorophenyl)-3-(4-(4-methylpiperazin-1-yl)phenyl)-*1H*-pyrazolo[4,3-c]pyridazin-6(*5H*)-one
Compound 38		5-(5-fluoro-2,3-dihydro-*1H*-indan-4-yl)-3-(4-(4-methylpiperazin-1-yl)phenyl)-*1H*-pyrazolo[4,3-c]pyridazin-6(*5H*)-one
Compound 39		5-(6-fluoro-2,3-dihydrobenzofuran-7-yl)-3-(4-(4-methylpiperazin-1-yl)phenyl)-*1H*-pyrazolo[4,3-c]pyridazin-6(*5H*)-one
Compound 40		5-(5-fluoro-2-methylisoindolin-4-yl)-3-(4-(4-methylpiperazin-1-yl)phenyl)-*1H*-pyrazolo[4,3-c]pyridazin-6(*5H*)-one

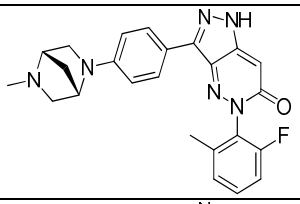
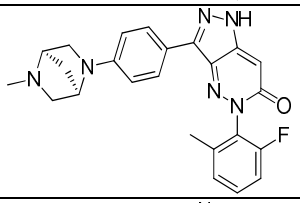
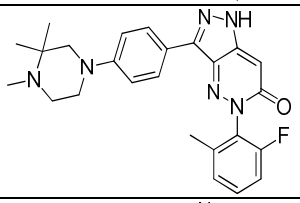
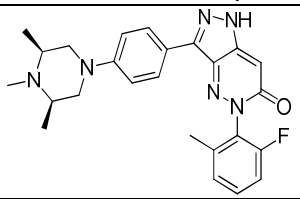
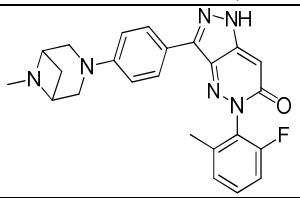
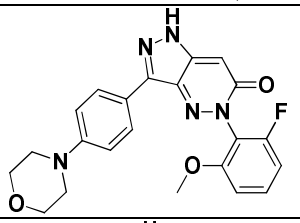
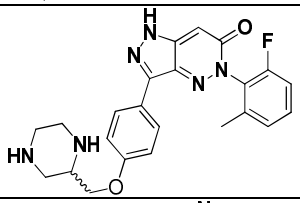
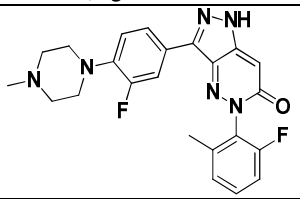
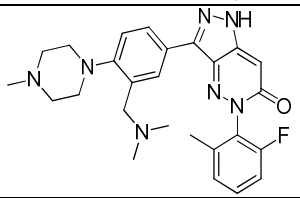
Compound 41		5-(5-fluoro-2-(2-morpholinoacetyl)isoindolin-4-yl)-3-(4-(4-methylpiperazin-1-yl)phenyl)-*1H*-pyrazolo[4,3-c]pyridazin-6(*5H*)-one
Compound 42		3-fluoro-5-methyl-4-(3-(4-(4-methylpiperazin-1-yl)phenyl)-6-oxo-*1H*-pyrazolo[4,3-c]pyridazin-5(*6H*)-yl)benzonitrile
Compound 43		5-(2-fluoro-6-methyl-4-((methylamino)methyl)phenyl)-3-(4-(4-methylpiperazin-1-yl)phenyl)-1*H*-pyrazolo[4,3-c]pyridazin-6(5*H*)-one
Compound 44		3-fluoro-*N*,5-dimethyl-4-(3-(4-(4-methylpiperazin-1-yl)phenyl)-6-oxo-*1H*-pyrazolo[4,3-c]pyridazin-5(*6H*)-yl)benzamide
Compound 45		5-(2-fluoro-4-(3-hydroxyl-3-methylazetidine-1-carbonyl)-6-methylphenyl)-3-(4-(4-methylpiperazin-1-yl)phenyl)-*1H*-pyrazolo[4,3-c]pyridazin-6(*5H*)-one
Compound 46		*N*-(2-(dimethylamino)ethyl)-3-fluoro-5-methyl-4-(3-(4-(4-methylpiperazin-1-yl)phenyl)-6-oxo-*1H*-pyrazolo[4,3-c]pyridazin-5(*6H*)-yl)benzamide
Compound 47		3-(4-(4-methylpiperazin-1-yl)phenyl)-5-(4-methylpyrid-3-yl)-*1H*-pyrazolo[4,3-c]pyridazin-6(*5H*)-one
Compound 48		5-(4-methoxypyrid-3-yl)-3-(4-(4-methylpiperazin-1-yl)phenyl)-*1H*-pyrazolo[4,3-c]pyridazin-6(*5H*)-one
Compound 49		5-(5-amino-4-methylpyrid-3-yl)-3-(4-(4-methylpiperazin-1-yl)phenyl)-*1H*-pyrazolo[4,3-c]pyridazin-6(*5H*)-one

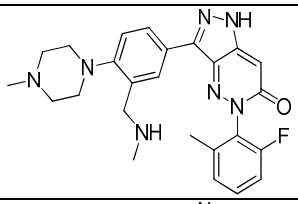
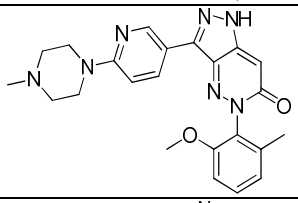
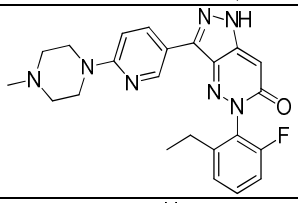
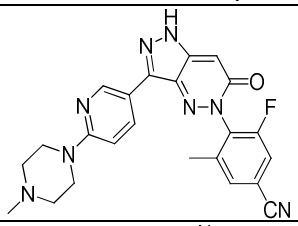
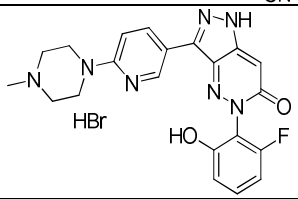
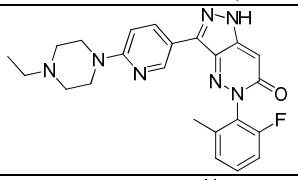
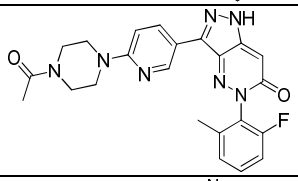
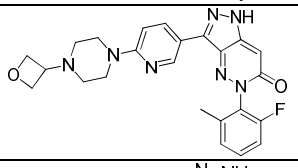
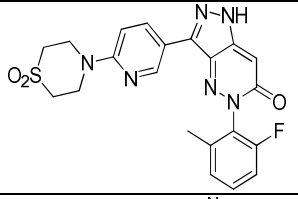
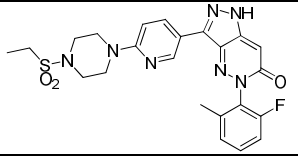
Compound 50		5-(8-methyl-2,3-dihydro-*1H*-pyrido[2,3-b][1,4]oxazin-7-yl)-3-(4-(4-methylpiperazin-1-yl)phenyl)-*1H*-pyrazolo[4,3-c]pyridazin-6(*5H*)-one
Compound 51		3-(4-(4-methylpiperazin-1-yl)phenyl)-5-(4-methylpyrimidin-5-yl)-*1H*-pyrazolo[4,3-c]pyridazin-6(*5H*)-one
Compound 52		5-(7-methyl-3*H*-imidazolo[4,5-b]pyrid-6-yl)-3-(4-(4-methylpiperazin-1-yl)phenyl)-*1H*-pyrazolo[4,3-c]pyridazin-6(*5H*)-one
Compound 53		5-(5-isopropyl-*1H*-pyrazol-4-yl)-3-(4-(4-methylpiperazin-1-yl)phenyl)-*1H*-pyrazolo[4,3-c]pyridazin-6(*5H*)-one
Compound 54		5-(5,6-dihydro-4*H*-pyrrolo[1,2-b]pyrazol-3-yl)-3-(4-(4-methylpiperazin-1-yl)phenyl)-*1H*-pyrazolo[4,3-c]pyridazin-6(*5H*)-one
Compound 55		5-(2-fluoro-6-methylphenyl)-7-methyl-3-(4-(4-methylpiperazin-1-yl)phenyl)-*1H*-pyrazolo[4,3-c]pyridazin-6(*5H*)-one
Compound 56		5-(2-fluoro-6-methylphenyl)-7-methoxy-3-(4-(4-methylpiperazin-1-yl)phenyl)-*1H*-pyrazolo[4,3-c]pyridazin-6(*5H*)-one
Compound 57		5-(2-fluoro-6-methylphenyl)-3-(4-(4-methylpiperazin-1-yl)phenyl)-6-oxo-5,6-dihydro-*1H*-pyrazolo[4,3-c]pyridazin-7-carbonitrile
Compound 58		3-(4-(4-cyclopropylpiperazin-1-yl)phenyl)-5-(2-fluoro-6-methylphenyl)-*1H*-pyrazolo[4,3-c]pyridazin-6(*5H*)-one
Compound 59		5-(2-fluoro-6-methylphenyl)-3-(4-(4-(oxetan-3-yl)piperazin-1-yl)phenyl)-*1H*-pyrazolo[4,3-c]pyridazin-6(*5H*)-one

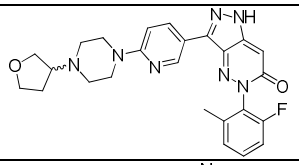
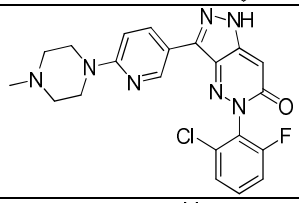
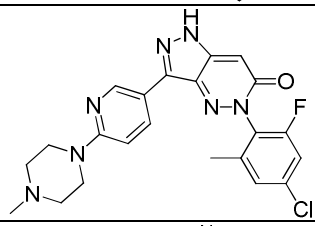
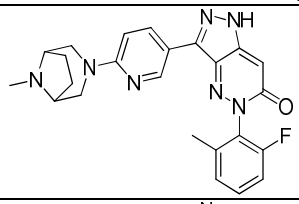
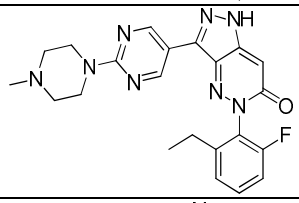
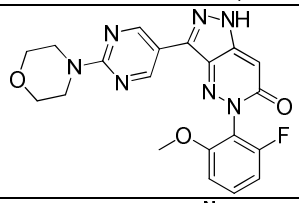
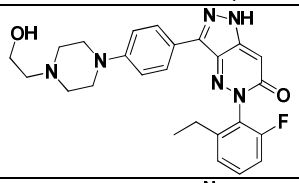
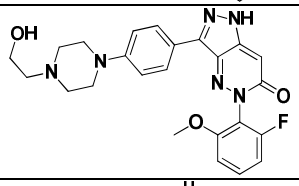
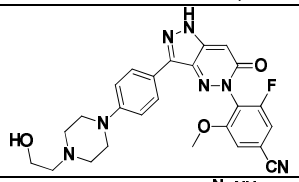
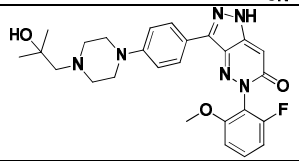
Compound 60		5-(2-fluoro-6-methylphenyl)-3-(4-(4-oxohexahydropyrrolo[1,2-a]pyrazin-2(*1H*)-yl)phenyl)-*1H*-pyrazolo[4,3-c]pyridazin-6(*5H*)-one
Compound 61		5-(2-fluoro-6-methylphenyl)-3-(4-(8-methyl-3,8-diazabicyclo[3.2.1]octan-3-yl)phenyl)-*1H*-pyrazolo[4,3-c]pyridazin-6(*5H*)-one
Compound 62		3-(4-(4-(2-oxa-6-azaspiro[3.3]heptan-6-yl)piperidin-1-yl)phenyl)-5-(2-fluoro-6-methylphenyl)-*1H*-pyrazolo[4,3-c]pyridazin-6(*5H*)-one
Compound 63		3-(4-(4-(ethylsulfonyl)piperazin-1-yl)phenyl)-5-(2-fluoro-6-methylphenyl)-*1H*-pyrazolo[4,3-c]pyridazin-6(*5H*)-one
Compound 64		5-(2-fluoro-6-methylphenyl)-3-(4-(2-(hydroxymethyl)morpholino)phenyl)-*1H*-pyrazolo[4,3-c]pyridazin-6(*5H*)-one
Compound 65		3-(4-(1-(2-(dimethylamino)ethyl)-*1H*-pyrazol-4-yl)phenyl)-5-(2-fluoro-6-methoxyphenyl)-*1H*-pyrazolo[4,3-c]pyridazin-6(*5H*)-one
Compound 66		5-(2-fluoro-6-methoxyphenyl)-3-(2-(4-methylpiperazin-1-yl)thiazol-5-yl)-*1H*-pyrazolo[4,3-c]pyridazin-6(*5H*)-one
Compound 67		2-(4-(5-(2-fluoro-6-methoxyphenyl)-6-oxo-5,6-dihydro-*1H*-pyrazolo[4,3-c]pyridazin-3-yl)-*1H*-pyrazol-1-yl)propionitrile
Compound 68		2-(5-(2-fluoro-6-methoxyphenyl)-6-oxo-5,6-dihydro-*1H*-pyrazolo[4,3-c]pyridazin-3-yl)-6-methyl-5,6-dihydro-4*H*-pyrazolo[1,5-d][1,4]diazepin-7(*8H*)-one
Compound 69		3-(1-(2-hydroxyl-2-methylpropyl)-*1H*-pyrazol-4-yl)-5-(4-methylpyrid-3-yl)-*1H*-pyrazolo[4,3-c]pyridazin-6(*5H*)-one

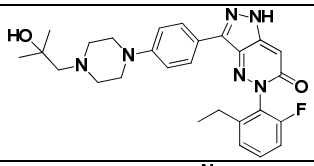
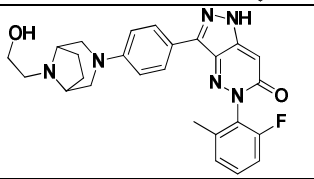
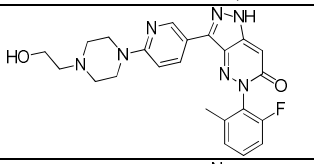
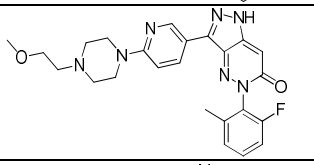
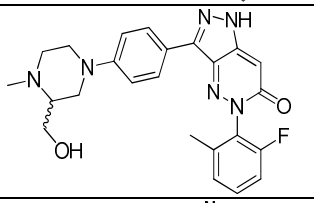
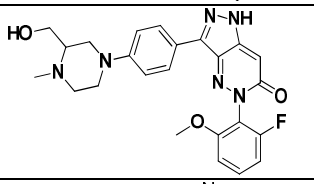
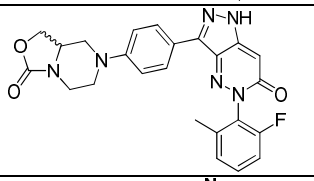
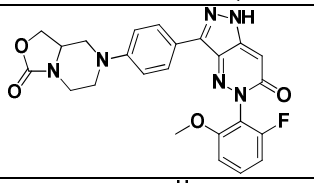
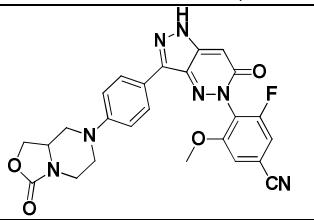
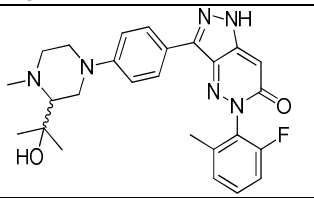
Compound 70		4-(4-(5-(2-fluoro-6-methylphenyl)-6-oxo-5,6-dihydro-*1H*-pyrazolo[4,3-c]pyridazin-3-yl)phenyl)piperazinyl-1-carbonamide
Compound 71		*N*-(4-(5-(2-fluoro-6-methylphenyl)-6-oxo-5,6-dihydro-*1H*-pyrazolo[4,3-c]pyridazin-3-yl)phenyl)-*N*-methyl-2-(4-methylpiperazin-1-yl)acetamide
Compound 72		5-(2-fluoro-6-methoxyphenyl)-3-(2-methyl-1,2,3,4-tetrahydroisoquinolin-6-yl)-1H-pyrazolo[4,3-c]pyridazin-6(5H)-one
Compound 73		5-(2-fluoro-6-methoxyphenyl)-3-(2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-1H-pyrazolo[4,3-c]pyridazin-6(5H)-one
Compound 74		3-fluoro-5-methoxy-4-(3-(4-(4-methylpiperazin-1-yl)phenyl)-6-oxo-1H-pyrazolo[4,3-c]pyridazin-5(6H)-yl)benzonitrile
Compound 75		5-(1,3-dihydroisobenzofuran-4-yl)-3-(4-(4-methylpiperazin-1-yl)phenyl)-1H-pyrazolo[4,3-c]pyridazin-6(5H)-one
Compound 76		5-(benzo[d][1,3]dioxacyclopent-4-yl)-3-(4-(4-methylpiperazin-1-yl)phenyl)-1H-pyrazolo[4,3-c]pyridazin-6(5H)-one
Compound 77		5-(2,4-difluoro-6-methoxyphenyl)-3-(4-(4-methylpiperazin-1-yl)phenyl)-1H-pyrazolo[4,3-c]pyridazin-6(5H)-one
Compound 78		5-(4-chloro-2-fluoro-6-methylphenyl)-3-(4-(4-methylpiperazin-1-yl)phenyl)-1H-pyrazolo[4,3-c]pyridazin-6(5H)-one

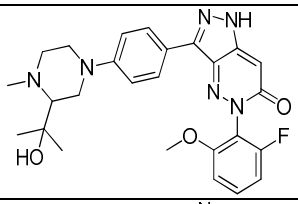
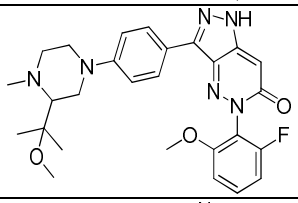
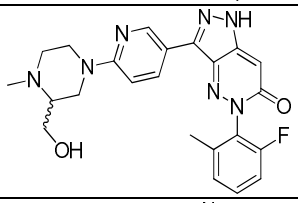
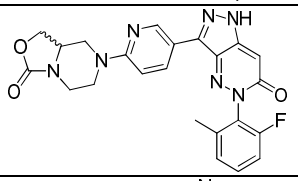
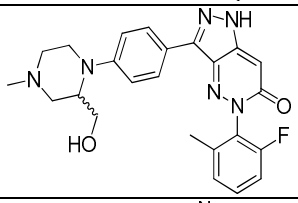
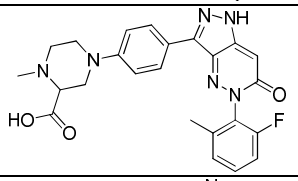
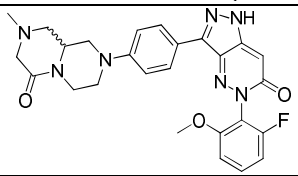
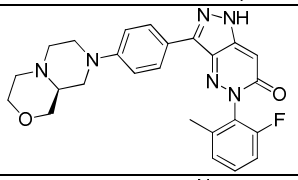
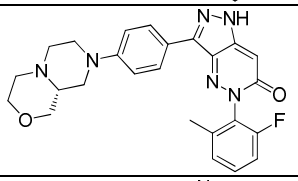
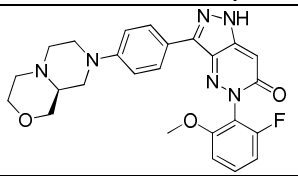
Compound 79		3-fluoro-5-methoxy-*N*-methyl-4-(3-(4-(4-methylpiperazin-1-yl)phenyl)-6-oxo-1H-pyrazolo[4,3-c]pyridazin-5(6H)-yl)benzamide
Compound 80		3-fluoro-5-methoxy-*N*,*N*-dimethyl-4-(3-(4-(4-methylpiperazin-1-yl)phenyl)-6-oxo-1H-pyrazolo[4,3-c]pyridazin-5(6H)-yl)benzamide
Compound 81		5-(2-fluoro-6-(methyl-d_3)phenyl)-3-(4-(4-methylpiperazin-1-yl)phenyl)-1H-pyrazolo[4,3-c]pyridazin-6(5H)-one
Compound 82		(*S*)-4-(3-(4-(4-(2-aminopropionyl)piperazin-1-yl)phenyl)-6-oxo-1H-pyrazolo[4,3-c]pyridazin-5(6H)-yl)-3-fluoro-5-methylbenzonitrile hydrochloride
Compound 83		4-(3-(4-(4-(2-hydroxylpropionyl)piperazin-1-yl)phenyl)-6-oxo-1H-pyrazolo[4,3-c]pyridazin-5(6H)-yl)-3-fluoro-5-methylbenzonitrile
Compound 84		3-(4-(4-(2,2-difluoroethyl)piperazin-1-yl)phenyl)-5-(2-fluoro-6-methylphenyl)-1H-pyrazolo[4,3-c]pyridazin-6(5H)-one
Compound 85		3-fluoro-5-methyl-4-(6-oxa-3-(4-(4-(tetrahydrofuran-3-yl)piperazin-1-yl)phenyl)-1H-pyrazolo[4,3-c]pyridazin-5(6H)-yl)benzonitrile
Compound 86		5-(2-fluoro-6-methoxyphenyl)-3-(4-(4-(oxetan-3-yl)piperazin-1-yl)phenyl)-*1H*-pyrazolo[4,3-c]pyridazin-6(*5H*)-one

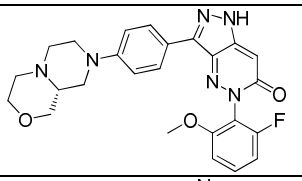
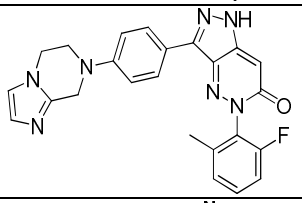
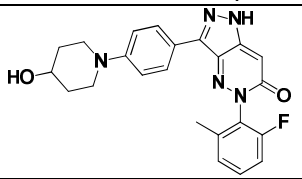
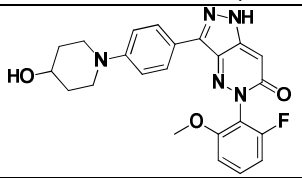
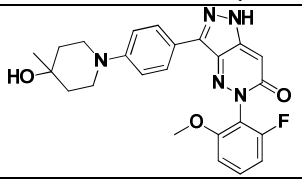
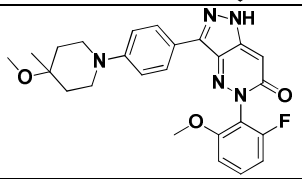
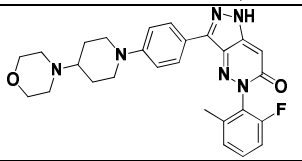
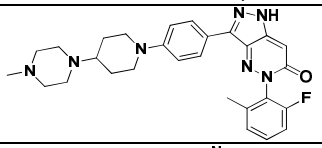
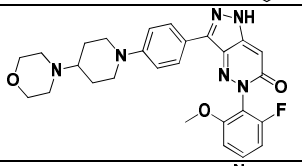
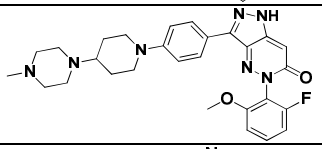
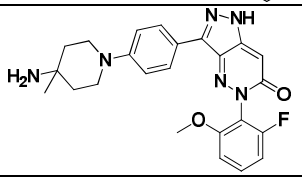
Compound 87		5-(2-fluoro-6-methylphenyl)-3-(4-((1*S*,4*S*)-5-methyl-2,5-diazabicyclo[2.2.1]heptan-2-yl)phenyl)-1H-pyrazolo[4,3-c]pyridazin-6(5H)-one
Compound 88		5-(2-fluoro-6-methylphenyl)-3-(4-((1*R*,4*R*)-5-methyl-2,5-diazabicyclo[2.2.1]heptan-2-yl)phenyl)-1H-pyrazolo[4,3-c]pyridazin-6(5H)-one
Compound 89		5-(2-fluoro-6-methylphenyl)-3-(4-(3,3,4-trimethylpiperazin-1-yl)phenyl)-1H-pyrazolo[4,3-c]pyridazin-6(5H)-one
Compound 90		5-(2-fluoro-6-methylphenyl)-3-(4-((3*S*,5*R*)-3,4,5-trimethylpiperazin-1-yl)phenyl)-1H-pyrazolo[4,3-c]pyridazin-6(5H)-one
Compound 91		5-(2-fluoro-6-methylphenyl)-3-(4-(6-methyl-3,6-diazabicyclo[3.1.1]heptan-3-yl)phenyl)-1H-pyrazolo[4,3-c]pyridazin-6(5H)-one
Compound 92		5-(2-fluoro-6-methoxyphenyl)-3-(4-morpholinophenyl)-1H-pyrazolo[4,3-c]pyridazin-6(5H)-one
Compound 93		5-(2-fluoro-6-methylphenyl)-3-(4-(piperazin-2-ylmethoxy)phenyl)-1H-pyrazolo[4,3-c]pyridazin-6(5H)-one
Compound 94		3-(3-fluoro-4-(4-methylpiperazin-1-yl)phenyl)-5-(2-fluoro-6-methylphenyl)-1H-pyrazolo[4,3-c]pyridazin-6(5H)-one
Compound 95		3-(3-((dimethylamino)methyl)-4-(4-methylpiperazin-1-yl)phenyl)-5-(2-fluoro-6-methylphenyl)-1H-pyrazolo[4,3-c]pyridazin-6(5H)-one

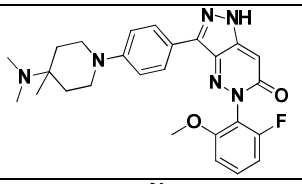
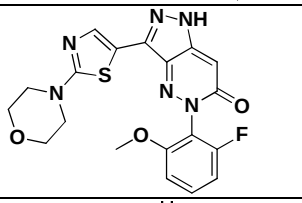
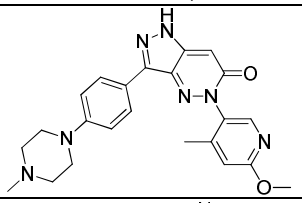
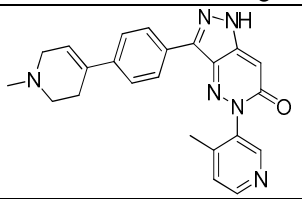
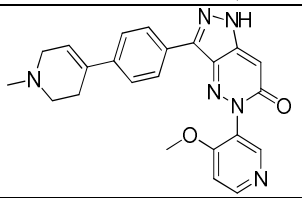
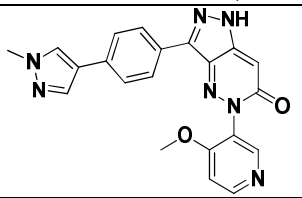
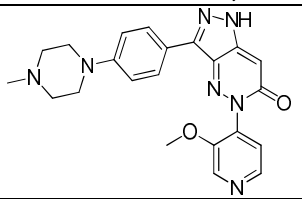
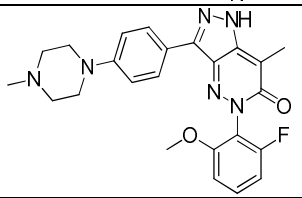
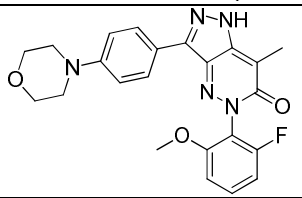
Compound 96		3-(3-((methylamino)methyl)-4-(4-methylpiperazin-1-yl)phenyl)-5-(2-fluoro-6-methylphenyl)-1H-pyrazolo[4,3-c]pyridazin-6(5H)-one
Compound 97		5-(2-methoxy-6-methylphenyl)-3-(6-(4-methylpiperazin-1-yl)pyrid-3-yl)-1H-pyrazolo[4,3-c]pyridazin-6(5H)-one
Compound 98		5-(2-ethyl-6-fluorophenyl)-3-(6-(4-methylpiperazin-1-yl)pyrid-3-yl)-1H-pyrazolo[4,3-c]pyridazin-6(5H)-one
Compound 99		3-fluoro-5-methyl-4-(3-(6-(4-methylpiperazin-1-yl)pyrid-3-yl)-6-oxo-1H-pyrazolo[4,3-c]pyridazin-5(6H)-yl)benzonitrile
Compound 100		5-(2-fluoro-6-hydroxylphenyl)-3-(6-(4-methylpiperazin-1-yl)pyrid-3-yl)-1H-pyrazolo[4,3-c]pyridazin-6(5H)-one hydrobromide
Compound 101		3-(6-(4-ethylpiperazin-1-yl)pyrid-3-yl)-5-(2-fluoro-6-methylphenyl)-1H-pyrazolo[4,3-c]pyridazin-6(5H)-one
Compound 102		3-(6-(4-acetylpiperazin-1-yl)pyrid-3-yl)-5-(2-fluoro-6-methylphenyl)-1H-pyrazolo[4,3-c]pyridazin-6(5H)-one
Compound 103		5-(2-fluoro-6-methylphenyl)-3-(6-(4-(oxetan-3-yl))piperazin-1-yl)pyrid-3-yl)-1H-pyrazolo[4,3-c]pyridazin-6(5H)-one
Compound 104		3-(6-(1,1-dioxidothiomorpholino)pyrid-3-yl)-5-(2-fluoro-6-methylphenyl)-1H-pyrazolo[4,3-c]pyridazin-6(5H)-one
Compound 105		3-(6-(4-(ethylsulfonyl)piperazin-1-yl)pyrid-3-yl)-5-(2-fluoro-6-methylphenyl)-1H-pyrazolo[4,3-c]pyridazin-6(5H)-one

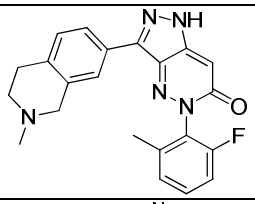
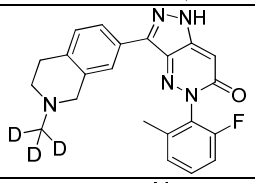
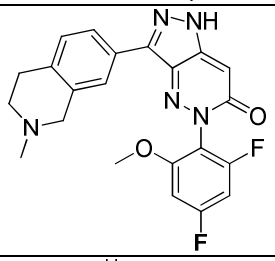
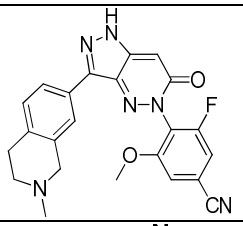
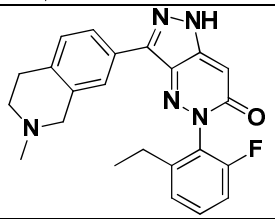
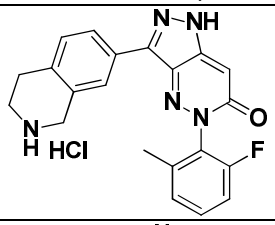
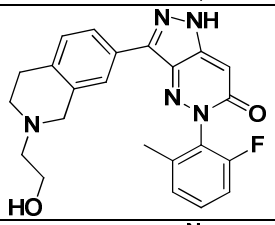
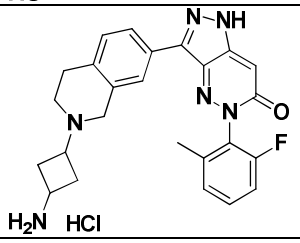
Compound 106		5-(2-fluoro-6-methylphenyl)-3-(6-(4-(tetrahydrofuran-3-yl)piperazin-1-yl)pyrid-3-yl)-1H-pyrazolo[4,3-c] pyridazin-6(5H)-one
Compound 107		5-(2-chloro-6-fluorophenyl)-3-(6-(4-methylpiperazin-1-yl)pyrid-3-yl)-1H-pyrazolo[4,3-c]pyridazin-6(5H)-one
Compound 108		5-(4-chloro-2-fluoro-6-methylphenyl)-3-(4-(4-methylpiperazin-1-yl)pyrid-3-yl)-1H-pyrazolo[4,3-c]pyridazin-6(5H)-one
Compound 109		5-(2-fluoro-6-methylphenyl)-3-(6-(8-methyl-3,8-diazabicyclo[3.2.1]octan-3-yl)pyrid-3-yl)-1H-pyrazolo[4,3-c]pyridazin-6(5H)-one
Compound 110		5-(2-ethyl-6-fluorophenyl)-3-(2-(4-methylpiperazin-1-yl)pyrimidin-5-yl)-1H-pyrazolo[4,3-c]pyridazin-6(5H)-one
Compound 111		5-(2-fluoro-6-methoxyphenyl)-3-(2-morpholinyl-pyrimidin-5-yl)-1H-pyrazolo[4,3-c]pyridazin-6(5H)-one
Compound 112		5-(2-ethyl-6-fluorophenyl)-3-(4-(4-(2-hydroxyethyl)piperazin-1-yl)phenyl)-1H-pyrazolo[4,3-c]pyridazin-6(5H)-one
Compound 113		5-(2-fluoro-6-methoxyphenyl)-3-(4-(4-(2-hydroxyethyl)piperazin-1-yl)phenyl)-1H-pyrazolo[4,3-c]pyridazin-6(5H)–one
Compound 114		3-fluoro-4-(3-(4-(4-(2-hydroxyethyl)piperazin-1-yl)phenyl)-6-oxo-1H-pyrazolo[4,3-c]pyridazin-5(6H)-yl)-5-methoxybenzonitrile
Compound 115		5-(2-fluoro-6-methoxyphenyl)-3-(4-(4-(2-hydroxyl-2-methylpropyl)piperazin-1-yl)phenyl)-1H-pyrazolo[4,3-c]pyridazin-6(5H)-one

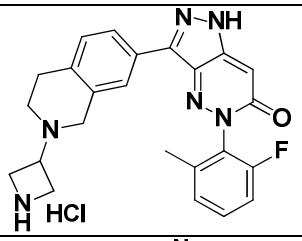
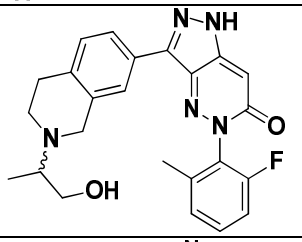
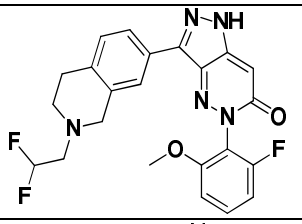
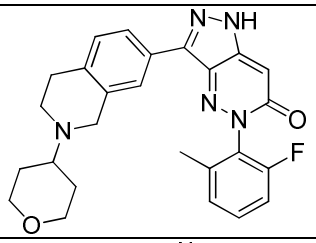
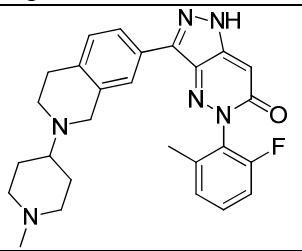
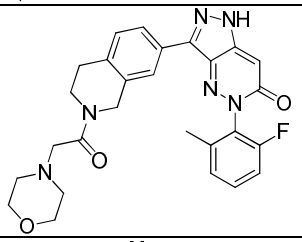
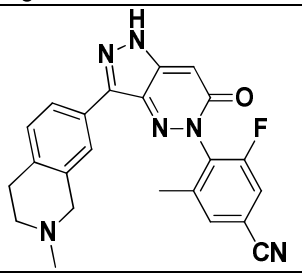
Compound 116		5-(2-ethyl-6-fluorophenyl)-3-(4-(4-(2-hydroxyl-2-methylpropyl)piperazin-1-yl)phenyl)-1H-pyrazolo[4,3-c]pyridazin-6(5H)-one
Compound 117		5-(2-fluoro-6-methylphenyl)-3-(4-(8-(2-hydroxyethyl)-3,8-diazabicyclo[3.2.1]octan-3-yl)phenyl)-1H-pyrazolo[4,3-c]pyridazin-6(5H)-one
Compound 118		5-(2-fluoro-6-methylphenyl)-3-(6-(4-(2-hydroxyethyl)piperazin-1-yl)pyrid-3-yl)-1H-pyrazolo[4,3-c]pyridazin-6(5H)-one
Compound 119		5-(2-fluoro-6-methylphenyl)-3-(6-(4-(2-methoxyethyl)piperazin-1-yl)pyrid-3-yl)-1H-pyrazolo[4,3-c]pyridazin-6(5H)-one
Compound 120		5-(2-fluoro-6-methylphenyl)-3-(4-(3-(hydroxymethyl)-4-methylpiperazin-1-yl)phenyl)-1H-pyrazolo[4,3-c]pyridazin-6(5H)-one
Compound 121		5-(2-fluoro-6-methoxyphenyl)-3-(4-(3-(hydroxymethyl)-4-methylpiperazin-1-yl)phenyl)-1H-pyrazolo[4,3-c]pyridazin-6(5H)-one
Compound 122		7-(4-(5-(2-fluoro-6-methylphenyl)-6-oxo-5,6-dihydro-1H-pyrazolo[4,3-c]pyridazin-3-yl)phenyl)tetrahydro-1H-oxazolo[3,4-a]pyrazin-3(5H)-one
Compound 123		7-(4-(5-(2-fluoro-6-methoxyphenyl)-6-oxo-5,6-dihydro-1H-pyrazolo[4,3-c]pyridazin-3-yl)phenyl)tetrahydro-1H-oxazolo[3,4-a]pyrazin-3(5H)-one
Compound 124		3-fluoro-5-methoxy-4-(6-oxo-3-(4-(3-oxotetrahydro-1H-oxazolo[3,4-a]pyrazin-7(3H)-yl)phenyl)-1H-pyrazolo[4,3-c]pyridazin-5(6H)-yl)benzonitrile
Compound 125		5-(2-fluoro-6-methylphenyl)-3-(4-(3-(2-hydroxylprop-2-yl)-4-methylpiperazin-1-yl)phenyl)-1H-pyrazolo[4,3-c]pyridazin-6(5H)-one

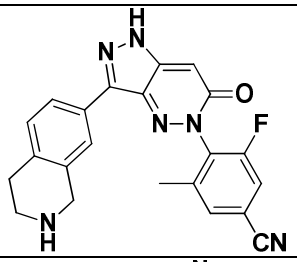
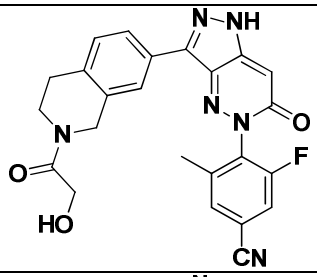
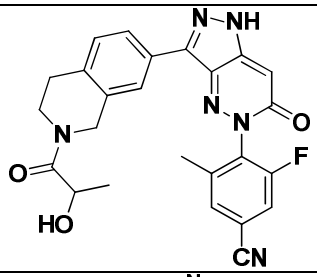
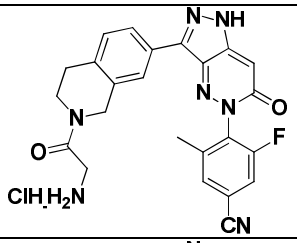
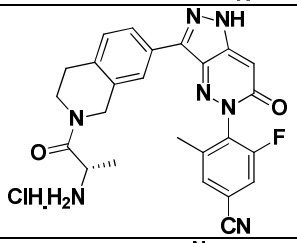
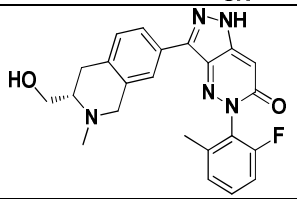
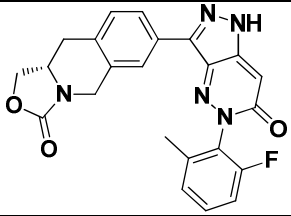
Compound 126		5-(2-fluoro-6-methoxyphenyl)-3-(4-(3-(2-hydroxylprop-2-yl)-4-methylpiperazin-1-yl)phenyl)-1H-pyrazolo[4,3-c]pyridazin-6(5H)-one
Compound 127		5-(2-fluoro-6-methoxyphenyl)-3-(4-(3-(2-methoxyprop-2-yl)-4-methylpiperazin-1-yl)phenyl)-1H-pyrazolo[4,3-c]pyridazin-6(5H)-one
Compound 128		5-(2-fluoro-6-methylphenyl)-3-(6-(3-(hydroxymethyl)-4-methylpiperazin-1-yl)pyrid-3-yl)-1H-pyrazolo[4,3-c]pyridazin-6(5H)-one
Compound 129		7-(5-(5-(2-fluoro-6-methylphenyl)-6-oxo-5,6-dihydro-1H-pyrazolo[4,3-c]pyridazin-3-yl)pyridin-2-yl)tetrahydro-1H-oxazolo[3,4-a]pyrazin-3(5H)-
Compound 130		5-(2-fluoro-6-methylphenyl)-3-(4-(2-(hydroxymethyl)-4-methylpiperazin-1-yl)phenyl)-1H-pyrazolo[4,3-c]pyridazin-6(5H)-one
Compound 131		4-(4-(5-(2-fluoro-6-methylphenyl)-6-oxo-5,6-dihydro-1H-pyrazolo[4,3-c]pyridazin-3-yl)phenyl)-1-methylpiperazin-2-carboxylic acid
Compound 132		8-(4-(5-(2-fluoro-6-methoxyphenyl)-6-oxo-5,6-dihydro-1H-pyrazolo[4,3-c]pyridazin-3-yl)phenyl)-2-methylhexahydro-1H-pyrazino[1,2-a]pyrazin-4(6H)-one
Compound 133		(S)-5-(2-fluoro-6-methylphenyl)-3-(4-(hexahydropyrazino[2,1-c][1,4]oxazin-8(1H)-yl)phenyl)-1H-pyrazolo[4,3-c]pyridazin-6(5H)-one
Compound 134		(R)-5-(2-fluoro-6-methylphenyl)-3-(4-(hexahydropyrazino[2,1-c][1,4]oxazin-8(1H)-yl)phenyl)-1H-pyrazolo[4,3-c]pyridazin-6(5H)-one
Compound 135		(S)-5-(2-fluoro-6-methoxyphenyl)-3-(4-(hexahydropyrazino[2,1-c][1,4]oxazin-8(1H)-yl)phenyl)-1H-pyrazolo[4,3-c]pyridazin-6(5H)-one

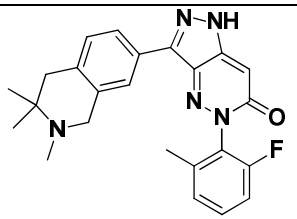
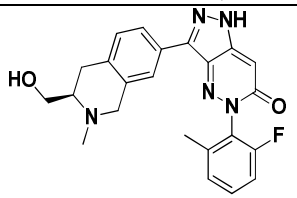
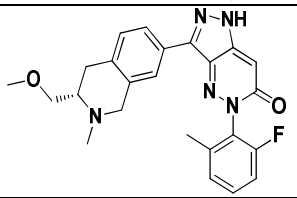
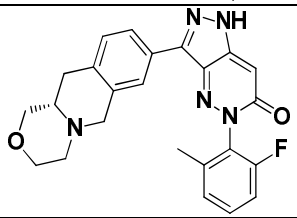
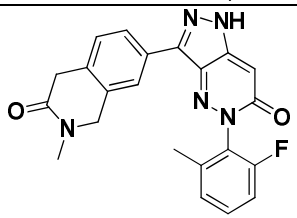
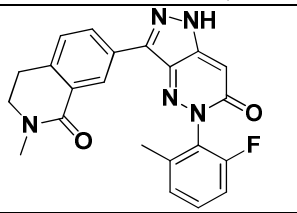
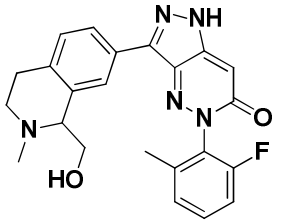
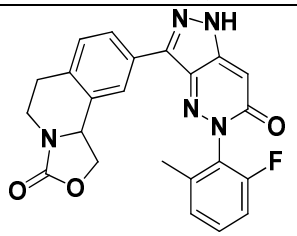
Compound 136		(R)-5-(2-fluoro-6-methoxyphenyl)-3-(4-(hexahydropyrazino[2,1-c][1,4]oxazin-8(1H)-yl)phenyl)-1H-pyrazolo[4,3-c]pyridazin-6(5H)-one
Compound 137		3-(4-(5,6-dihydroimidazolo[1,2-a]pyrazin-7(8H)-yl)phenyl)-5-(2-fluoro-6-methylphenyl)-1H-pyrazolo[4,3-c]pyridazin-6(5H)-one
Compound 138		5-(2-fluoro-6-methylphenyl)-3-(4-(4-hydroxylpiperidin-1-yl)phenyl)-1H-pyrazolo[4,3-c]pyridazin-6(5H)-one
Compound 139		5-(2-fluoro-6-methoxyphenyl)-3-(4-(4-hydroxylpiperidin-1-yl)phenyl)-1H-pyrazolo[4,3-c]pyridazin-6(5H)-one
Compound 140		5-(2-fluoro-6-methoxyphenyl)-3-(4-(4-hydroxyl-4-methylpiperidin-1-yl)phenyl)-1H-pyrazolo[4,3-c]pyridazin-6(5H)-one
Compound 141		5-(2-fluoro-6-methoxyphenyl)-3-(4-(4-methoxy-4-methylpiperidin-1-yl)phenyl)-1H-pyrazolo[4,3-c]pyridazin-6(5H)-one
Compound 142		5-(2-fluoro-6-methylphenyl)-3-(4-(4-morpholinopiperidin-1-yl)phenyl)-1H-pyrazolo[4,3-c]pyridazin-6(5H)-
Compound 143		5-(2-fluoro-6-methylphenyl)-3-(4-(4-(4-methylpiperazin-1-yl)piperidin-1-yl)phenyl)-1H-pyrazolo[4,3-c]pyridazin-6(5H)-one
Compound 144		5-(2-fluoro-6-methoxyphenyl)-3-(4-(4-morpholinopiperidin-1-yl)phenyl)-1H-pyrazolo[4,3-c]pyridazin-6(5H)-one
Compound 145		5-(2-fluoro-6-methoxyphenyl)-3-(4-(4-(4-methylpiperazin-1-yl)piperidin-1-yl)phenyl)-1H-pyrazolo[4,3-c]pyridazin-6(5H)-one
Compound 146		3-(4-(4-amino-4-methylpiperidin-1-yl)phenyl)-5-(2-fluoro-6-methoxyphenyl)-1H-pyrazolo[4,3-c]pyridazin-6(5H)-one

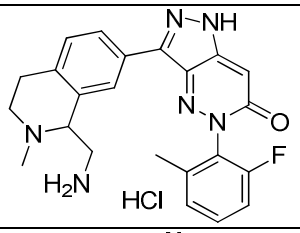
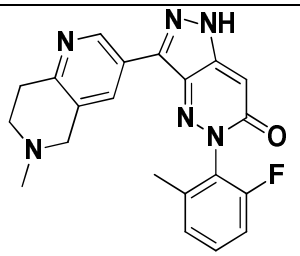
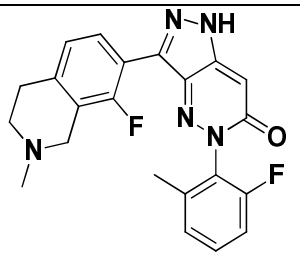
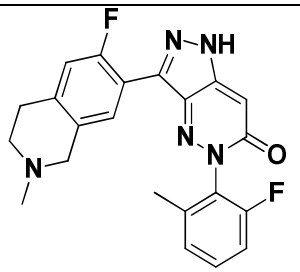
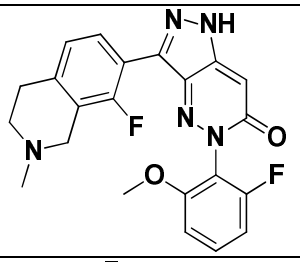
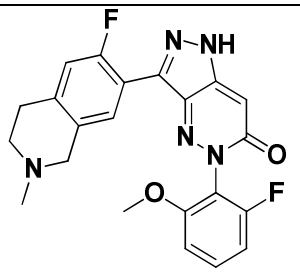
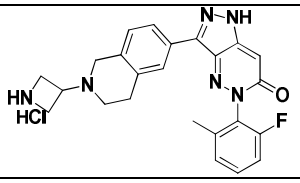
Compound 147		3-(4-(4-(dimethylamino)-4-methylpiperidin-1-yl)phenyl)-5-(2-fluoro-6-methoxyphenyl)-1H-pyrazolo[4,3-c]pyridazin-6(5H)-one
Compound 148		5-(2-fluoro-6-methoxyphenyl)-3-(2-morpholinothiazol-5-yl)-1H-pyrazolo[4,3-c]pyridazin-6(5H)-one
Compound 149		5-(6-methoxy-4-methylpyrid-3-yl)-3-(4-(4-methylpiperazin-1-yl)phenyl)-1H-pyrazolo[4,3-c]pyridazin-6(5H)-one
Compound 150		3-(4-(1-methyl-1,2,3,6-tetrahydropyridin-4-yl)phenyl)-5-(4-methylpyrid-3-yl)-1H-pyrazolo[4,3-c]pyridazin-6(5H)-one
Compound 151		5-(4-methoxypyrid-3-yl)-3-(4-(1-methyl-1,2,3,6-tetrahydropyridin-4-yl)phenyl)-1H-pyrazolo[4,3-c]pyridazin-6(5H)-one
Compound 152		5-(4-methoxypyrid-3-yl)-3-(4-(1-methyl-1H-pyrazol-4-yl)phenyl)-1H-pyrazolo[4,3-c]pyridazin-6(5H)-one
Compound 153		5-(3-methoxypyrid-4-yl)-3-(4-(4-methylpiperazin-1-yl)phenyl)-1H-pyrazolo[4,3-c]pyridazin-6(5H)-one
Compound 154		5-(2-fluoro-6-methoxyphenyl)-7-methyl-3-(4-(4-methylpiperazin-1-yl)phenyl)-1H-pyrazolo[4,3-c]pyridazin-6(5H)-one
Compound 155		5-(2-fluoro-6-methoxyphenyl)-7-methyl-3-(4-morpholinophenyl)-1H-pyrazolo[4,3-c]pyridazin-6(5H)-one

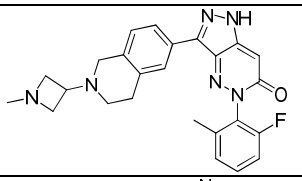
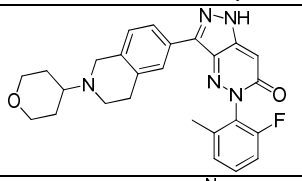
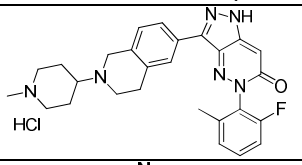
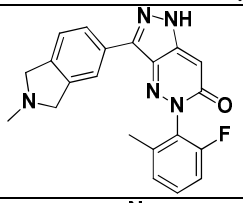
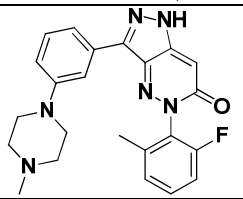
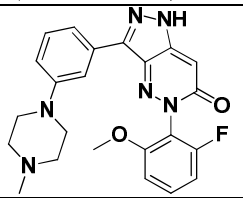
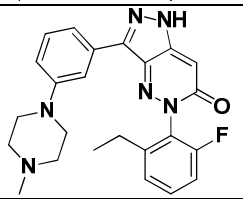
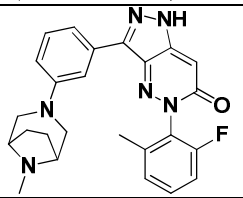
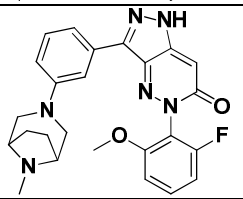
Compound 156		5-(2-fluoro-6-methylphenyl)-3-(2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-1H-pyrazolo[4,3-c]pyridazin-6(5H)-one
Compound 157		5-(2-fluoro-6-methylphenyl)-3-(2-(methyl-d_3) -1,2,3,4-tetrahydroisoquinolin-7-yl)-1H-pyrazolo[4,3-c]pyridazin-6(5H)-one
Compound 158		5-(2,4-difluoro-6-methoxyphenyl)-3-(2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-1H-pyrazolo[4,3-c]pyridazin-6(5H)-one
Compound 159		3-fluoro-5-methoxy-4-(3-(2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-6-oxo-1H-pyrazolo[4,3-c]pyridazin-5(6H)-yl)benzonitrile
Compound 160		5-(2-ethyl-6-fluorophenyl)-3-(2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-1H-pyrazolo[4,3-c]pyridazin-6(5H)-one
Compound 161		5-(2-fluoro-6-methylphenyl)-3-(1,2,3,4-tetrahydroisoquinolin-7-yl)-1H-pyrazolo[4,3-c]pyridazin-6(5H)-one hydrochloride
Compound 162		5-(2-fluoro-6-methylphenyl)-3-(2-(2-hydroxyethyl)-1,2,3,4-tetrahydroisoquinolin-7-yl)-1H-pyrazolo[4,3-c]pyridazin-6(5H)-one
Compound 163		3-(2-(3-aminocyclobutyl)-1,2,3,4-tetrahydroisoquinolin-7-yl)-5-(2-fluoro-6-methylphenyl)-1H-pyrazolo[4,3-c]pyridazin-6(5H)-one hydrochloride

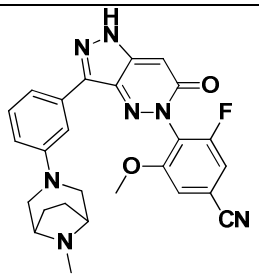
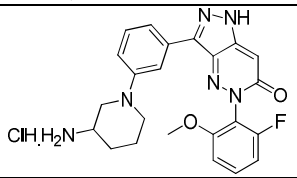
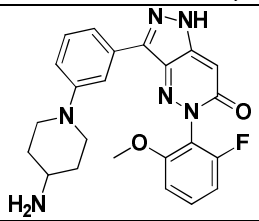
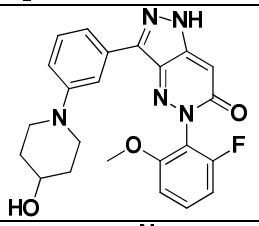
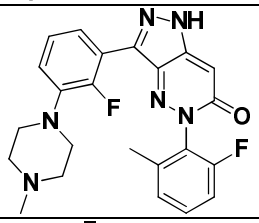
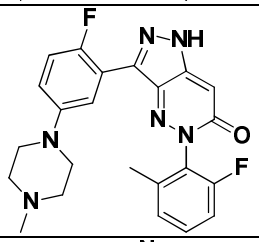
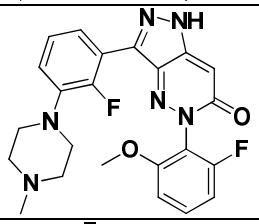
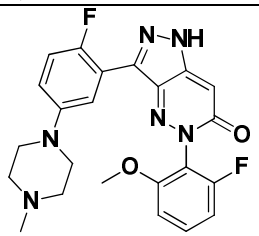
Compound 164		3-(2-(azetidin-3-yl)-1,2,3,4-tetrahydroisoquinolin-7-yl)-5-(2-fluoro-6-methylphenyl)-1H-pyrazolo[4,3-c]pyridazin-6(5H)-one hydrochloride
Compound 165		5-(2-fluoro-6-methylphenyl)-3-(2-(1-hydroxylprop-2-yl)-1,2,3,4-tetrahydroisoquinolin-7-yl)-1H-pyrazolo[4,3-c]pyridazin-6(5H)-one
Compound 166		3-(2-(2,2-difluoroethyl)-1,2,3,4-tetrahydroisoquinolin-7-yl)-5-(2-fluoro-6-methoxyphenyl)-1H-pyrazolo[4,3-c]pyridazin-6(5H)-one
Compound 167		5-(2-fluoro-6-methylphenyl)-3-(2-(tetrahydro-2H-pyran-4-yl)-1,2,3,4-tetrahydroisoquinolin-7-yl)-1H-pyrazolo[4,3-c]pyridazin-6(5H)-one
Compound 168		5-(2-fluoro-6-methylphenyl)-3-(2-(1-methylpiperidin-4-yl)-1,2,3,4-tetrahydroisoquinolin-7-yl)-1H-pyrazolo[4,3-c]pyridazin-6(5H)-one
Compound 169		5-(2-fluoro-6-methylphenyl)-3-(2-(2-morpholinoacetyl)-1,2,3,4-tetrahydroisoquinolin-7-yl)-1H-pyrazolo[4,3-c]pyridazin-6(5H)-one
Compound 170		3-fluoro-5-methyl-4-(3-(2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-6-oxo-1H-pyrazolo[4,3-c]pyridazin-5(6H)-yl)benzonitrile

Compound 171		3-fluoro-5-methyl-4-(3-(1,2,3,4-tetrahydroisoquinolin-7-yl)-6-oxo-1H-pyrazolo[4,3-c]pyridazin-5(6H)-yl)benzonitrile
Compound 172		3-fluoro-4-(3-(2-(2-hydroxylacetyl)-1,2,3,4-tetrahydroisoquinolin-7-yl)-6-oxo-1H-pyrazolo[4,3-c]pyridazin-5(6H)-yl)-5-methylbenzonitrile
Compound 173		3-fluoro-4-(3-(2-(2-hydroxylpropionyl)-1,2,3,4-tetrahydroisoquinolin-7-yl)-6-oxo-1H-pyrazolo[4,3-c]pyridazin-5(6H)-yl)-5-methylbenzonitrile
Compound 174		3-fluoro-4-(3-(2-(2-aminoacetyl)-1,2,3,4-tetrahydroisoquinolin-7-yl)-6-oxo-1H-pyrazolo[4,3-c]pyridazin-5(6H)-yl)-5-methylbenzonitrile
Compound 175		(*S*)-3-fluoro-4-(3-(2-(2-aminopropionyl)-1,2,3,4-tetrahydroisoquinolin-7-yl)-6-oxo-1H-pyrazolo[4,3-c]pyridazin-5(6H)-yl)-5-methylbenzonitrile hydrochloride
Compound 176		(S)-5-(2-fluoro-6-methylphenyl)-3-(3-(hydroxymethyl)-2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-1H-pyrazolo[4,3-c]pyridazin-6(5H)-one
Compound 177		(S)-7-(5-(2-fluoro-6-methylphenyl)-6-oxa-5,6-dihydro-1H-pyrazolo[4,3-c]pyridazin-3-yl)-10,10a-dihydro-1H-oxazolo[3,4-b]isoquinolin-3(5H)-one

Compound 178		5-(2-fluoro-6-methylphenyl)-3-(2,3,3-trimethyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-1H-pyrazolo[4,3-c]pyridazin-6(5H)-one
Compound 179		(R)-5-(2-fluoro-6-methylphenyl)-3-(3-(hydroxymethyl)-2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-1H-pyrazolo[4,3-c]pyridazin-6(5H)-one
Compound 180		(S)-5-(2-fluoro-6-methylphenyl)-3-(3-(methoxymethyl)-2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-1H-pyrazolo[4,3-c]pyridazin-6(5H)-one
Compound 181		(S)-5-(2-fluoro-6-methylphenyl)-3-(1,3,4,6,11,11a-hexahydro-[1,4]oxazino[4,3-b]isoquinolin-8-yl)-1H-pyrazolo[4,3-c]pyridazin-6(5H)-one
Compound 182		7-(5-(2-fluoro-6-methylphenyl)-6-oxa-5,6-dihydro-1H-pyrazolo[4,3-c]pyridazin-3-yl)-2-methyl-1,2-dihydroisoquinolin-3(4H)-one
Compound 183		7-(5-(2-fluoro-6-methylphenyl)-6-oxa-5,6-dihydro-1H-pyrazolo[4,3-c]pyridazin-3-yl)-2-methyl-3,4-dihydroisoquinolin-1(2H)-one
Compound 184		5-(2-fluoro-6-methylphenyl)-3-(1-(hydroxymethyl)-2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-1H-pyrazolo[4,3-c] pyridazin-6(5H)-one
Compound 185		9-(5-(2-fluoro-6-methylphenyl)-6-oxa-5,6-dihydro-1H-pyrazolo[4,3-c]pyridazin-3-yl)-5,6-dihydro-1H-oxazolo[4,3-a]isoquinolin-3(10bH)-one

Compound 186		3-(1-(aminomethyl)-2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-5-(2-fluoro-6-methylphenyl)-1H-pyrazolo[4,3-c]pyridazin-6(5H)-one hydrochloride
Compound 187		5-(2-fluoro-6-methylphenyl)-3-(6-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-3-yl)-1H-pyrazolo[4,3-c]pyridazin-6(5H)-one
Compound 188		3-(8-fluoro-2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-5-(2-fluoro-6-methylphenyl)-1H-pyrazolo[4,3-c]pyridazin-6(5H)-one
Compound 189		3-(6-fluoro-2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-5-(2-fluoro-6-methylphenyl)-1H-pyrazolo[4,3-c]pyridazin-6(5H)-one
Compound 190		3-(8-fluoro-2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-5-(2-fluoro-6-methoxyphenyl)-1H-pyrazolo[4,3-c]pyridazin-6(5H)-one
Compound 191		3-(6-fluoro-2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-5-(2-fluoro-6-methoxyphenyl)-1H-pyrazolo[4,3-c]pyridazin-6(5H)-one
Compound 193		3-(2-(azetidin-3-yl)-1,2,3,4-tetrahydroisoquinolin-6-yl)-5-(2-fluoro-6-methylphenyl)-1H-pyrazolo[4,3-c] pyridazin-6(5H)-one hydrochloride

Compound 194		5-(2-fluoro-6-methylphenyl)-3-(2-(1-methylazetidin-3-yl)-1,2,3,4-tetrahydroisoquinolin-6-yl)-1H-pyrazolo[4,3-c]pyridazin-6(5H)-one
Compound 195		5-(2-fluoro-6-methylphenyl)-3-(2-(tetrahydro-2H-pyran-4-yl)-1,2,3,4-tetrahydroisoquinolin-6-yl)-1H-pyrazolo[4,3-c]pyridazin-6(5H)-one
Compound 196		5-(2-fluoro-6-methylphenyl)-3-(2-(1-methylpiperidin-4-yl)-1,2,3,4-tetrahydroisoquinolin-6-yl)-1H-pyrazolo[4,3-c]pyridazin-6(5H)-one hydrochloride
Compound 197		5-(2-fluoro-6-methylphenyl)-3-(2-methylisoindolin-5-yl)-1H-pyrazolo[4,3-c]pyridazin-6(5H)-one
Compound 198		5-(2-fluoro-6-methylphenyl)-3-(3-(4-methylpiperazin-1-yl)phenyl)-1H-pyrazolo[4,3-c]pyridazin-6(5H)-one
Compound 199		5-(2-fluoro-6-methoxyphenyl)-3-(3-(4-methylpiperazin-1-yl)phenyl)-1H-pyrazolo[4,3-c]pyridazin-6(5H)-one
Compound 200		5-(2-ethyl-6-fluorophenyl)-3-(3-(4-methylpiperazin-1-yl)phenyl)-1H-pyrazolo[4,3-c]pyridazin-6(5H)-one
Compound 201		5-(2-fluoro-6-methylphenyl)-3-(3-(8-methyl-3,8-diazabicyclo[3.2.1]octan-3-yl)phenyl)-1H-pyrazolo[4,3-c]pyridazin-6(5H)-one
Compound 202		5-(2-fluoro-6-methoxyphenyl)-3-(3-(8-methyl-3,8-diazabicyclo[3.2.1]octan-3-yl)phenyl)-1H-pyrazolo[4,3-c]pyridazin-6(5H)-one

Compound 203		3-fluoro-5-methoxy-4-(3-(3-(8-methyl-3,8-diazabicyclo[3.2.1]octan-3-yl)phenyl)-6-oxo-1H-pyrazolo[4,3-c]pyridazin-5(6H)-yl)benzonitrile
Compound 204		3-(3-(3-aminopiperidin-1-yl)phenyl)-5-(2-fluoro-6-methoxyphenyl)-1H-pyrazolo[4,3-c]pyridazin-6(5H)-one hydrochloride
Compound 205		3-(3-(4-aminopiperidin-1-yl)phenyl)-5-(2-fluoro-6-methoxyphenyl)-1H-pyrazolo[4,3-c]pyridazin-6(5H)-one
Compound 206		3-(3-(4-hydroxylpiperidin-1-yl)phenyl)-5-(2-fluoro-6-methoxyphenyl)-1H-pyrazolo[4,3-c]pyridazin-6(5H)-one
Compound 207		3-(2-fluoro-3-(4-methylpiperazin-1-yl)phenyl)-5-(2-fluoro-6-methylphenyl)-1H-pyrazolo[4,3-c]pyridazin-6(5H)-one
Compound 208		3-(2-fluoro-5-(4-methylpiperazin-1-yl)phenyl)-5-(2-fluoro-6-methylphenyl)-1H-pyrazolo[4,3-c]pyridazin-6(5H)-one
Compound 209		3-(2-fluoro-3-(4-methoxypiperazin-1-yl)phenyl)-5-(2-fluoro-6-methylphenyl)-1H-pyrazolo[4,3-c]pyridazin-6(5H)-one
Compound 210		3-(2-fluoro-5-(4-methoxypiperazin-1-yl)phenyl)-5-(2-fluoro-6-methylphenyl)-1H-pyrazolo[4,3-c]pyridazin-6(5H)-one

15. A pharmaceutical composition comprising the compound or a pharmaceutically

acceptable salt, hydrate, solvate, active metabolite, polymorph, isotope labeled compound, isomer or prodrug thereof according to any of claims 1-14 and a pharmaceutically acceptable carrier.

16. Use of the compound or a pharmaceutically acceptable salt, hydrate, solvate, active metabolite, polymorph, isotope labeled compound, isomer or prodrug thereof, or a pharmaceutical composition thereof according to any of claims 1-14, or the pharmaceutical composition of claim 15 in the preparation of a medicament for the prevention or treatment of a disease mediated with HPK1.

17. Use of the compound or a pharmaceutically acceptable salt, hydrate, solvate, active metabolite, polymorph, isotope labeled compound, isomer or prodrug thereof, or a pharmaceutical composition thereof according to any of claims 1-14, or the pharmaceutical composition of claim 15 in the preparation of a medicament for the prevention or treatment of benign or malignant tumors, myelodysplastic syndromes and diseases caused by viruses.

18. The use according to claim 17, wherein the benign or malignant tumor is selected from the group consisting of leukemia, lymphoma, multiple myeloma, lung cancer, hepatocellular carcinoma, cholangiocarcinoma, gallbladder cancer, gastric cancer, colorectal cancer, intestinal leiomyosarcoma, breast cancer, ovarian cancer, cervical cancer, endometrial cancer, vaginal cancer, malignant teratoma, pancreatic cancer, pancreatic ductal adenocarcinoma, nasopharyngeal cancer, oral cancer, laryngeal cancer, esophageal squamous cell carcinoma, thyroid cancer, kidney cancer, bladder cancer, malignant brain tumor, rhabdomyosarcoma, osteosarcoma, chondrosarcoma, osteofibrosarcoma, malignant thymoma, malignant peripheral nerve sheath tumor, prostate cancer, testicular cancer, penile cancer and other malignant tumors, as well as benign and malignant tumors of the skin.

19. The use according to claim 17, wherein the virus is selected from the group consisting of hepatitis virus, human immunodeficiency virus, human papillomavirus, herpes simplex virus, measles virus, norovirus, Boca virus, Coxsackie virus, Ebola virus, enterovirus, lymphocytic meningitis virus, influenza virus, SARS virus and COVID-19 virus.