

MK2 INHIBITORS AND USES THEREOF

CROSS-REFERENCE

[0001] This application claims the benefit of U. S. Provisional Application Serial No. 63/168,407 filed March 31, 2021 and U. S. Provisional Application Serial No. 63/318,118 filed March 9, 2022 which are hereby incorporated by reference in their entirety.

BACKGROUND OF THE INVENTION

[0002] Mitogen-activated protein kinases (MAPK) are a conserved family of enzymes that relay and propagate external stimuli, using phosphorylation cascades to generate a coordinated cellular response to the environment. The MAPK are proline-directed serine/threonine-specific protein kinases that regulate cellular activities, such as gene expression, mitosis, differentiation, and cell survival/apoptosis. To date, four distinct classes of mammalian MAPK have been identified: the extracellular signaling kinases (ERK1 and 2), the c-jun N-terminal kinase-1 (JNK1-3), the p38 MAPK (p38 α , β , γ , and δ), and ERK5. The MAPK are activated by the dual phosphorylation of Thr and Tyr residues within a TXY activation motif by coordinated dual-specificity MAPKK, where X is Glu, Pro, and Gly in ERK, JNK, and p38 MAPK, respectively. MAPK are 60-70% identical to each other, yet differ in their activation loop sequences and sizes. The activation loop is adjacent to the enzyme-active site, and its phosphorylation allows the enzyme to reposition active-site residues into the optimal orientation for substrate binding and catalysis. Downstream substrates of MAPK include mitogen-activated protein-kinase-activated protein (MAPKAP) kinases and transcription factors, the phosphorylation of which, either directly or indirectly, regulates gene expression at several points, including transcription, nuclear export, and mRNA stability and translation. The cellular consequences of MAPK activation include inflammation, apoptosis, differentiation, and proliferation.

[0003] Distinct genes encode four p38 MAPK in humans: p38 α , β , γ , and δ . Significant amino acid sequence homology is observed among the 4 isoforms, with 60 -75 overall sequence identity and > 90% identity within the kinase domains. Tissue- selective expression is observed, with p38 γ found predominantly in skeletal muscle, p38 δ in the testes, pancreas, and small intestine. In contrast, p38 α and β are more ubiquitously expressed.

[0004] p38 MAPK is the major isoform involved in the immune and inflammatory response. As such its function is critical for the production and activity of multiple proinflammatory cytokines, including TNF α , IL-1, IL-6, and IL-8, in cells such as macrophages, monocytes, synovial cells, and endothelial cells. p38 MAPK is also responsible for the induction of key inflammatory enzymes such as COX2 and iNOS, the major sources of eicosanoids and nitric oxide at sites of inflammation, respectively. Additionally, the p38 MAPK pathway regulates the expression of matrix metalloproteinases (MMP), including MMP2, MMP9, and MMP13.

[0005] The use of selective and potent inhibitors has facilitated the discovery of several families of p38 MAPK substrates, including transcription factors, MAPKAP kinases, and other enzymes. p38 MAPK can

directly phosphorylate several transcription factors, such as myocyte - specific enhancer binding factor 2C (MEF2C), CHOP, peroxisome proliferator- activated receptor (PPAR) α , PPAR γ co-activator 1 and p53. These transcription factors are involved in cellular functions such as apoptosis, gluconeogenesis, and synthesis of enzymes involved in fatty acid oxidation. p38 MAPK is also involved in the direct or indirect phosphorylation of enzyme substrates, such as cytosolic phospholipase A2, and the Cdc25 phosphatases, which are involved in the activation of cyclin-dependent protein kinase activity and cell-cycle regulation. Therefore in addition to its role in the inflammatory response, p38 MAPK has other functions associated with normal and abnormal cell growth and survival as well as cellular function and homeostasis. The MAPKAP kinases (MK2, MK-3, and PRAK) are selectively phosphorylated by p38 MAPK, while the phosphorylation of MSK1/2, MNK1/2, and RSKb is catalyzed by both p38 MAPK and ERK.

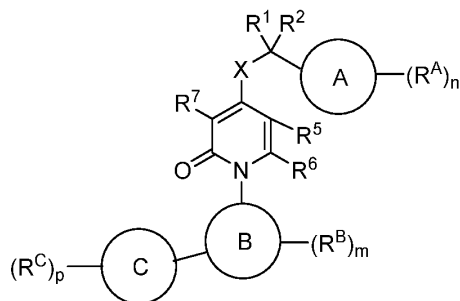
[0006] MK-2, MK-3, and PRAK, once phosphorylated and activated by p38 MAPK, share similar substrate specificities. All of these kinases can phosphorylate the small heat-shock protein Hsp27. Studies have shown that the PRAK- and MK3-deficient mice do not display any resistance to endotoxic shock or a decrease in lipopolysaccharide-(LPS)-induced cytokine production. In contrast, MK-2-deficient mice show a resistance to endotoxic shock and an impaired inflammatory response, as well as a significantly decreased production of cytokines such as TNF α , IFN γ and IL-6. Thus, the p38/MK2 axis is important for mediating pro-inflammatory responses.

[0007] The p38:MK2 complex is very stable with a K_d of 6 nM. The binding affinity of p38 for MK2 is driven by the C-terminal domain of MK2 containing several positively charged amino acid residues. Crystallographic studies of the p38:MK2 complex demonstrated that the C- terminal region of MK2 wraps around p38 α and binds to the negatively charged ED binding site. The tight binding of p38 to MK2 may give rise to conformational changes providing additional binding pockets for inhibitors that would specifically be dependent upon the p38:MK2 interaction. Taken together, these two studies suggests that selective p38/MK2 axis blockade is achievable with small molecule inhibitors. In comparison to traditional p38 MAPK inhibitors these p38/MK2 inhibitors should retain or enhance potency and exhibit improved safety features in animal models of disease or in human clinical settings.

[0008] The p38/MK2 role in the regulation of inflammatory cytokines (TNF α , IL-1 β , IL-6) and enzymes responsible for inflammation (COX-2, iNOS, and MMPs) makes it an attractive drug target. Several classical p38 MAPK inhibitors have progressed to testing in clinical trials. Some of these candidates have failed, for safety or other reasons, but several have reported clinical data in diseases such as rheumatoid arthritis, pain, Crohn's disease, acute coronary syndrome, multiple myeloma and chronic obstructive pulmonary disease. In addition to these diseases several IL-1 β mediated diseases could be impacted by a p38 inhibitor based upon the key role for the p38 MAPK pathway in the biosynthesis and activity of this cytokine. These diseases include the family of cryopyrin associated periodic disorders (CAPS), chronic gout, diabetes, Still's disease, Familial Mediterranean Fever among others.

SUMMARY OF THE INVENTION

[0009] Disclosed herein is a compound of Formula (II), or a pharmaceutically acceptable salt, solvate, N-oxide, or stereoisomer thereof:



Formula (II),

wherein:

Ring A is phenyl or heteroaryl;

each R^A is independently hydrogen, deuterium, halogen, -CN, -NO₂, -OH, -OR^a, -OC(=O)R^a, -OC(=O)OR^b, -OC(=O)NR^cR^d, -SH, -SR^a, -S(=O)R^a, -S(=O)₂R^a, -S(=O)₂NR^cR^d, -NR^cR^d, -NR^bC(=O)NR^cR^d, -NR^bC(=O)R^a, -NR^bC(=O)OR^b, -NR^bS(=O)₂R^a, -C(=O)R^a, -C(=O)OR^b, -C(=O)NR^cR^d, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein the alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is optionally and independently substituted with one or more R^{Aa};

or two R^A on the same atom are taken together to form an oxo;

each R^{Aa} is independently deuterium, halogen, -CN, -NO₂, -OH, -OR^a, -OC(=O)R^a, -OC(=O)OR^b, -OC(=O)NR^cR^d, -SH, -SR^a, -S(=O)R^a, -S(=O)₂R^a, -S(=O)₂NR^cR^d, -NR^cR^d, -NR^bC(=O)NR^cR^d, -NR^bC(=O)R^a, -NR^bC(=O)OR^b, -NR^bS(=O)₂R^a, -C(=O)R^a, -C(=O)C(=O)R^a, -C(=O)OR^b, -C(=O)NR^cR^d, -C(=O)C(=O)NR^cR^d, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

or two R^{Aa} on the same atom are taken together to form an oxo;

n is 0-4;

R¹ and R² are independently hydrogen, deuterium, halogen, -CN, -NO₂, -OH, -OR^a, -NR^cR^d, -C(=O)R^a, -C(=O)OR^b, -C(=O)NR^cR^d, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, or heterocycloalkyl;

or R^1 and R^2 are taken together to form an oxo:

or R¹ and R² are taken together to form a cycloalkyl or heterocycloalkyl; wherein the cycloalkyl and heterocycloalkyl is optionally substituted with deuterium, halogen, -CN, -OH, -OCH₃, -NH₂, -NHCH₃, -N(CH₃)₂, -C(=O)CH₃, -C(=O)OH, -C(=O)OCH₃, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, or C₁-C₆heteroalkyl;

X is $-\text{C}(\text{R}^3)_2$ -, $-\text{NR}^4$ -, $-\text{O}$ -, or $-\text{S}$ -;

each R^3 are independently hydrogen, deuterium, halogen, $-\text{CN}$, $-\text{NO}_2$, $-\text{OH}$, $-\text{OR}^a$, $-\text{NR}^c\text{R}^d$, $-\text{C}(=\text{O})\text{R}^a$, -

$\text{C}(=\text{O})\text{OR}^b$, $-\text{C}(=\text{O})\text{NR}^c\text{R}^d$, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_1 - C_6 deuteroalkyl, C_1 - C_6 hydroxyalkyl,

C_1 - C_6 aminoalkyl, C_1 - C_6 heteroalkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, cycloalkyl, or heterocycloalkyl;

or two R^3 are taken together to form an oxo;

R^4 is hydrogen, $-\text{C}(=\text{O})\text{R}^a$, $-\text{C}(=\text{O})\text{OR}^b$, $-\text{C}(=\text{O})\text{NR}^c\text{R}^d$, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_1 - C_6 deuteroalkyl,

C_1 - C_6 hydroxyalkyl, C_1 - C_6 aminoalkyl, C_1 - C_6 heteroalkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, cycloalkyl, or heterocycloalkyl;

R^5 is hydrogen, deuterium, halogen, $-\text{CN}$, $-\text{NO}_2$, $-\text{OH}$, $-\text{OR}^a$, $-\text{NR}^c\text{R}^d$, $-\text{C}(=\text{O})\text{R}^a$, $-\text{C}(=\text{O})\text{OR}^b$, $-\text{C}(=\text{O})\text{NR}^c\text{R}^d$,

C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_1 - C_6 deuteroalkyl, C_1 - C_6 hydroxyalkyl, C_1 - C_6 aminoalkyl, C_1 - C_6 heteroalkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, cycloalkyl, or heterocycloalkyl;

R^6 is hydrogen, deuterium, halogen, $-\text{CN}$, $-\text{NO}_2$, $-\text{OH}$, $-\text{OR}^a$, $-\text{NR}^c\text{R}^d$, $-\text{C}(=\text{O})\text{R}^a$, $-\text{C}(=\text{O})\text{OR}^b$, $-\text{C}(=\text{O})\text{NR}^c\text{R}^d$,

C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_1 - C_6 deuteroalkyl, C_1 - C_6 hydroxyalkyl, C_1 - C_6 aminoalkyl, C_1 - C_6 heteroalkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, cycloalkyl, or heterocycloalkyl;

R^7 is hydrogen, deuterium, halogen, $-\text{CN}$, $-\text{NO}_2$, $-\text{OH}$, $-\text{OR}^a$, $-\text{NR}^c\text{R}^d$, $-\text{C}(=\text{O})\text{R}^a$, $-\text{C}(=\text{O})\text{OR}^b$, $-\text{C}(=\text{O})\text{NR}^c\text{R}^d$,

C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_1 - C_6 deuteroalkyl, C_1 - C_6 hydroxyalkyl, C_1 - C_6 aminoalkyl, C_1 - C_6 heteroalkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, cycloalkyl, or heterocycloalkyl;

Ring B is heterocycloalkyl or heteroaryl;

each R^B is independently hydrogen, deuterium, halogen, $-\text{CN}$, $-\text{NO}_2$, $-\text{OH}$, $-\text{OR}^a$, $-\text{OC}(=\text{O})\text{R}^a$, $-\text{OC}(=\text{O})\text{OR}^b$,

$-\text{OC}(=\text{O})\text{NR}^c\text{R}^d$, $-\text{SH}$, $-\text{SR}^a$, $-\text{S}(=\text{O})\text{R}^a$, $-\text{S}(=\text{O})_2\text{R}^a$, $-\text{S}(=\text{O})_2\text{NR}^c\text{R}^d$, $-\text{NR}^c\text{R}^d$, $-\text{NR}^b\text{C}(=\text{O})\text{NR}^c\text{R}^d$, -

$\text{NR}^b\text{C}(=\text{O})\text{R}^a$, $-\text{NR}^b\text{C}(=\text{O})\text{OR}^b$, $-\text{NR}^b\text{S}(=\text{O})_2\text{R}^a$, $-\text{C}(=\text{O})\text{R}^a$, $-\text{C}(=\text{O})\text{OR}^b$, $-\text{C}(=\text{O})\text{NR}^c\text{R}^d$, C_1 - C_6 alkyl,

C_1 - C_6 haloalkyl, C_1 - C_6 deuteroalkyl, C_1 - C_6 hydroxyalkyl, C_1 - C_6 aminoalkyl, C_1 - C_6 heteroalkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein the alkyl, alkenyl,

alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is optionally and independently substituted with one or more R^{Ba} ;

or two R^B on the same atom are taken together to form an oxo;

each R^{Ba} is independently deuterium, halogen, $-\text{CN}$, $-\text{NO}_2$, $-\text{OH}$, $-\text{OR}^a$, $-\text{OC}(=\text{O})\text{R}^a$, $-\text{OC}(=\text{O})\text{OR}^b$, -

$\text{OC}(=\text{O})\text{NR}^c\text{R}^d$, $-\text{SH}$, $-\text{SR}^a$, $-\text{S}(=\text{O})\text{R}^a$, $-\text{S}(=\text{O})_2\text{R}^a$, $-\text{S}(=\text{O})_2\text{NR}^c\text{R}^d$, $-\text{NR}^c\text{R}^d$, $-\text{NR}^b\text{C}(=\text{O})\text{NR}^c\text{R}^d$, -

$\text{NR}^b\text{C}(=\text{O})\text{R}^a$, $-\text{NR}^b\text{C}(=\text{O})\text{OR}^b$, $-\text{NR}^b\text{S}(=\text{O})_2\text{R}^a$, $-\text{C}(=\text{O})\text{R}^a$, $-\text{C}(=\text{O})\text{C}(=\text{O})\text{R}^a$, $-\text{C}(=\text{O})\text{OR}^b$, $-\text{C}(=\text{O})\text{NR}^c\text{R}^d$, -

$\text{C}(=\text{O})\text{C}(=\text{O})\text{NR}^c\text{R}^d$, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_1 - C_6 deuteroalkyl, C_1 - C_6 hydroxyalkyl,

C_1 - C_6 aminoalkyl, C_1 - C_6 heteroalkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

or two R^{Ba} on the same atom are taken together to form an oxo;

m is 0-4;

Ring C is 5-membered heteroaryl;

each R^C is independently hydrogen, deuterium, halogen, $-\text{CN}$, $-\text{NO}_2$, $-\text{OH}$, $-\text{OR}^a$, $-\text{OC}(=\text{O})\text{R}^a$, $-\text{OC}(=\text{O})\text{OR}^b$,

$-\text{OC}(=\text{O})\text{NR}^c\text{R}^d$, $-\text{SH}$, $-\text{SR}^a$, $-\text{S}(=\text{O})\text{R}^a$, $-\text{S}(=\text{O})_2\text{R}^a$, $-\text{S}(=\text{O})_2\text{NR}^c\text{R}^d$, $-\text{S}(=\text{O})(=\text{NR}^b)\text{R}^a$, $-\text{SiR}^c\text{R}^d\text{OR}^b$, -

NR^cR^d , $-\text{NR}^b\text{C}(=\text{O})\text{NR}^c\text{R}^d$, $-\text{NR}^b\text{C}(=\text{O})\text{R}^a$, $-\text{NR}^b\text{C}(=\text{O})\text{OR}^b$, $-\text{NR}^b\text{S}(=\text{O})_2\text{R}^a$, $-\text{C}(=\text{O})\text{R}^a$, $-\text{C}(=\text{O})\text{OR}^b$, $-\text{C}(=\text{O})\text{NR}^c\text{R}^d$, $\text{C}_1\text{-C}_6\text{alkyl}$, $\text{C}_1\text{-C}_6\text{haloalkyl}$, $\text{C}_1\text{-C}_6\text{deuteroalkyl}$, $\text{C}_1\text{-C}_6\text{hydroxyalkyl}$, $\text{C}_1\text{-C}_6\text{aminoalkyl}$, $\text{C}_2\text{-C}_6\text{alkenyl}$, $\text{C}_2\text{-C}_6\text{alkynyl}$, cycloalkyl , heterocycloalkyl , aryl , heteroaryl , $(\text{C}_1\text{-C}_6\text{alkyl})\text{cycloalkyl}$, $(\text{C}_1\text{-C}_6\text{alkyl})\text{heterocycloalkyl}$, $(\text{C}_1\text{-C}_6\text{alkyl})\text{aryl}$, or $(\text{C}_1\text{-C}_6\text{alkyl})\text{heteroaryl}$; wherein the alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is optionally and independently substituted with one or more R^{Ca} ;

each R^{Ca} is independently deuterium, halogen, $-\text{CN}$, $-\text{NO}_2$, $-\text{OH}$, $-\text{OR}^a$, $-\text{OC}(=\text{O})\text{R}^a$, $-\text{OC}(=\text{O})\text{OR}^b$, $-\text{OC}(=\text{O})\text{NR}^c\text{R}^d$, $-\text{SH}$, $-\text{SR}^a$, $-\text{S}(=\text{O})\text{R}^a$, $-\text{S}(=\text{O})_2\text{R}^a$, $-\text{S}(=\text{O})_2\text{NR}^c\text{R}^d$, $-\text{NR}^c\text{R}^d$, $-\text{NR}^b\text{C}(=\text{O})\text{NR}^c\text{R}^d$, $-\text{NR}^b\text{C}(=\text{O})\text{R}^a$, $-\text{NR}^b\text{C}(=\text{O})\text{OR}^b$, $-\text{NR}^b\text{S}(=\text{O})_2\text{R}^a$, $-\text{C}(=\text{O})\text{R}^a$, $-\text{C}(=\text{O})\text{C}(=\text{O})\text{R}^a$, $-\text{C}(=\text{O})\text{OR}^b$, $-\text{C}(=\text{O})\text{NR}^c\text{R}^d$, $-\text{C}(=\text{O})\text{C}(=\text{O})\text{NR}^c\text{R}^d$, $\text{C}_1\text{-C}_6\text{alkyl}$, $\text{C}_1\text{-C}_6\text{haloalkyl}$, $\text{C}_1\text{-C}_6\text{deuteroalkyl}$, $\text{C}_1\text{-C}_6\text{hydroxyalkyl}$, $\text{C}_1\text{-C}_6\text{aminoalkyl}$, $\text{C}_1\text{-C}_6\text{heteroalkyl}$, $\text{C}_2\text{-C}_6\text{alkenyl}$, $\text{C}_2\text{-C}_6\text{alkynyl}$, cycloalkyl , heterocycloalkyl , aryl , or heteroaryl ;

or two R^{Ca} on the same atom are taken together to form an oxo;

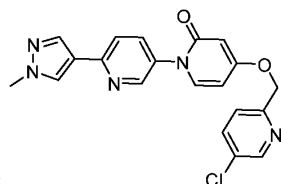
p is 0-4;

each R^a is independently $\text{C}_1\text{-C}_6\text{alkyl}$, $\text{C}_1\text{-C}_6\text{haloalkyl}$, $\text{C}_1\text{-C}_6\text{deuteroalkyl}$, $\text{C}_1\text{-C}_6\text{hydroxyalkyl}$, $\text{C}_1\text{-C}_6\text{aminoalkyl}$, $\text{C}_1\text{-C}_6\text{heteroalkyl}$, $\text{C}_2\text{-C}_6\text{alkenyl}$, $\text{C}_2\text{-C}_6\text{alkynyl}$, cycloalkyl , heterocycloalkyl , aryl , heteroaryl , $\text{C}_1\text{-C}_6\text{alkyl}(\text{cycloalkyl})$, $\text{C}_1\text{-C}_6\text{alkyl}(\text{heterocycloalkyl})$, $\text{C}_1\text{-C}_6\text{alkyl}(\text{aryl})$, or $\text{C}_1\text{-C}_6\text{alkyl}(\text{heteroaryl})$; wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more oxo, deuterium, halogen, $-\text{CN}$, $-\text{OH}$, $-\text{OCH}_3$, $-\text{S}(=\text{O})\text{CH}_3$, $-\text{S}(=\text{O})_2\text{CH}_3$, $-\text{S}(=\text{O})_2\text{NH}_2$, $-\text{S}(=\text{O})_2\text{NHCH}_3$, $-\text{S}(=\text{O})_2\text{N}(\text{CH}_3)_2$, $-\text{NH}_2$, $-\text{NHCH}_3$, $-\text{N}(\text{CH}_3)_2$, $-\text{C}(=\text{O})\text{CH}_3$, $-\text{C}(=\text{O})\text{OH}$, $-\text{C}(=\text{O})\text{OCH}_3$, $\text{C}_1\text{-C}_6\text{alkyl}$, $\text{C}_1\text{-C}_6\text{haloalkyl}$, $\text{C}_1\text{-C}_6\text{deuteroalkyl}$, $\text{C}_1\text{-C}_6\text{hydroxyalkyl}$, $\text{C}_1\text{-C}_6\text{aminoalkyl}$, or $\text{C}_1\text{-C}_6\text{heteroalkyl}$;

each R^b is independently hydrogen, $\text{C}_1\text{-C}_6\text{alkyl}$, $\text{C}_1\text{-C}_6\text{haloalkyl}$, $\text{C}_1\text{-C}_6\text{deuteroalkyl}$, $\text{C}_1\text{-C}_6\text{hydroxyalkyl}$, $\text{C}_1\text{-C}_6\text{aminoalkyl}$, $\text{C}_1\text{-C}_6\text{heteroalkyl}$, $\text{C}_2\text{-C}_6\text{alkenyl}$, $\text{C}_2\text{-C}_6\text{alkynyl}$, cycloalkyl , heterocycloalkyl , aryl , heteroaryl , $\text{C}_1\text{-C}_6\text{alkyl}(\text{cycloalkyl})$, $\text{C}_1\text{-C}_6\text{alkyl}(\text{heterocycloalkyl})$, $\text{C}_1\text{-C}_6\text{alkyl}(\text{aryl})$, or $\text{C}_1\text{-C}_6\text{alkyl}(\text{heteroaryl})$; wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more oxo, deuterium, halogen, $-\text{CN}$, $-\text{OH}$, $-\text{OCH}_3$, $-\text{S}(=\text{O})\text{CH}_3$, $-\text{S}(=\text{O})_2\text{CH}_3$, $-\text{S}(=\text{O})_2\text{NH}_2$, $-\text{S}(=\text{O})_2\text{NHCH}_3$, $-\text{S}(=\text{O})_2\text{N}(\text{CH}_3)_2$, $-\text{NH}_2$, $-\text{NHCH}_3$, $-\text{N}(\text{CH}_3)_2$, $-\text{C}(=\text{O})\text{CH}_3$, $-\text{C}(=\text{O})\text{OH}$, $-\text{C}(=\text{O})\text{OCH}_3$, $\text{C}_1\text{-C}_6\text{alkyl}$, $\text{C}_1\text{-C}_6\text{haloalkyl}$, $\text{C}_1\text{-C}_6\text{deuteroalkyl}$, $\text{C}_1\text{-C}_6\text{hydroxyalkyl}$, $\text{C}_1\text{-C}_6\text{aminoalkyl}$, or $\text{C}_1\text{-C}_6\text{heteroalkyl}$; and

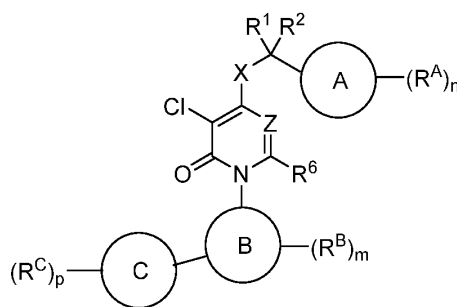
each R^c and R^d are independently hydrogen, $\text{C}_1\text{-C}_6\text{alkyl}$, $\text{C}_1\text{-C}_6\text{haloalkyl}$, $\text{C}_1\text{-C}_6\text{deuteroalkyl}$, $\text{C}_1\text{-C}_6\text{hydroxyalkyl}$, $\text{C}_1\text{-C}_6\text{aminoalkyl}$, $\text{C}_1\text{-C}_6\text{heteroalkyl}$, $\text{C}_2\text{-C}_6\text{alkenyl}$, $\text{C}_2\text{-C}_6\text{alkynyl}$, cycloalkyl , heterocycloalkyl , aryl , heteroaryl , $\text{C}_1\text{-C}_6\text{alkyl}(\text{cycloalkyl})$, $\text{C}_1\text{-C}_6\text{alkyl}(\text{heterocycloalkyl})$, $\text{C}_1\text{-C}_6\text{alkyl}(\text{aryl})$, or $\text{C}_1\text{-C}_6\text{alkyl}(\text{heteroaryl})$; wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more oxo, deuterium, halogen, $-\text{CN}$, $-\text{OH}$, $-\text{OCH}_3$, $-\text{S}(=\text{O})\text{CH}_3$, $-\text{S}(=\text{O})_2\text{CH}_3$, $-\text{S}(=\text{O})_2\text{NH}_2$, $-\text{S}(=\text{O})_2\text{NHCH}_3$, -

$S(=O)_2N(CH_3)_2$, $-NH_2$, $-NHCH_3$, $-N(CH_3)_2$, $-C(=O)CH_3$, $-C(=O)OH$, $-C(=O)OCH_3$, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_1 - C_6 deuteroalkyl, C_1 - C_6 hydroxyalkyl, C_1 - C_6 aminoalkyl, or C_1 - C_6 heteroalkyl; or R^c and R^d are taken together with the atom to which they are attached to form a heterocycloalkyl optionally substituted with one or more oxo, deuterium, halogen, $-CN$, $-OH$, $-OCH_3$, $-S(=O)CH_3$, $-S(=O)_2CH_3$, $-S(=O)_2NH_2$, $-S(=O)_2NHCH_3$, $-S(=O)_2N(CH_3)_2$, $-NH_2$, $-NHCH_3$, $-N(CH_3)_2$, $-C(=O)CH_3$, $-C(=O)OH$, $-C(=O)OCH_3$, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_1 - C_6 deuteroalkyl, C_1 - C_6 hydroxyalkyl, C_1 - C_6 aminoalkyl, or C_1 - C_6 heteroalkyl;



provided that the compound is not

[0010] Disclosed herein is a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, N-oxide, or stereoisomer thereof:



Formula (I),

wherein:

Ring A is phenyl or heteroaryl;

each R^A is independently hydrogen, deuterium, halogen, $-CN$, $-NO_2$, $-OH$, $-OR^a$, $-OC(=O)R^a$, $-OC(=O)OR^b$, $-OC(=O)NR^cR^d$, $-SH$, $-SR^a$, $-S(=O)R^a$, $-S(=O)_2R^a$, $-S(=O)_2NR^cR^d$, $-NR^cR^d$, $-NR^bC(=O)NR^cR^d$, $-NR^bC(=O)R^a$, $-NR^bC(=O)OR^b$, $-NR^bS(=O)_2R^a$, $-C(=O)R^a$, $-C(=O)OR^b$, $-C(=O)NR^cR^d$, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_1 - C_6 deuteroalkyl, C_1 - C_6 hydroxyalkyl, C_1 - C_6 aminoalkyl, C_1 - C_6 heteroalkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein the alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is optionally and independently substituted with one or more R^{Aa} ,

or two R^A on the same atom are taken together to form an oxo;

each R^{Aa} is independently deuterium, halogen, $-CN$, $-NO_2$, $-OH$, $-OR^a$, $-OC(=O)R^a$, $-OC(=O)OR^b$, $-OC(=O)NR^cR^d$, $-SH$, $-SR^a$, $-S(=O)R^a$, $-S(=O)_2R^a$, $-S(=O)_2NR^cR^d$, $-NR^cR^d$, $-NR^bC(=O)NR^cR^d$, $-NR^bC(=O)R^a$, $-NR^bC(=O)OR^b$, $-NR^bS(=O)_2R^a$, $-C(=O)R^a$, $-C(=O)C(=O)R^a$, $-C(=O)OR^b$, $-C(=O)NR^cR^d$, $-C(=O)C(=O)NR^cR^d$, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_1 - C_6 deuteroalkyl, C_1 - C_6 hydroxyalkyl,

C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

or two R^{Aa} on the same atom are taken together to form an oxo;

n is 0-4;

R¹ and R² are independently hydrogen, deuterium, halogen, -CN, -NO₂, -OH, -OR^a, -NR^cR^d, -C(=O)R^a, -C(=O)OR^b, -C(=O)NR^cR^d, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, or heterocycloalkyl;

or R¹ and R² are taken together to form an oxo;

or R¹ and R² are taken together to form a cycloalkyl or heterocycloalkyl; wherein the cycloalkyl and heterocycloalkyl is optionally substituted with deuterium, halogen, -CN, -OH, -OCH₃, -NH₂, -NHCH₃, -N(CH₃)₂, -C(=O)CH₃, -C(=O)OH, -C(=O)OCH₃, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, or C₁-C₆heteroalkyl;

X is -C(R³)₂-, -NR⁴-, -O-, or -S-;

each R³ are independently hydrogen, deuterium, halogen, -CN, -NO₂, -OH, -OR^a, -NR^cR^d, -C(=O)R^a, -C(=O)OR^b, -C(=O)NR^cR^d, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, or heterocycloalkyl;

or two R³ are taken together to form an oxo;

R⁴ is hydrogen, -C(=O)R^a, -C(=O)OR^b, -C(=O)NR^cR^d, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, or heterocycloalkyl;

Z is N or CR⁵;

R⁵ is hydrogen, deuterium, halogen, -CN, -NO₂, -OH, -OR^a, -NR^cR^d, -C(=O)R^a, -C(=O)OR^b, -C(=O)NR^cR^d, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, or heterocycloalkyl;

R⁶ is hydrogen, deuterium, halogen, -CN, -NO₂, -OH, -OR^a, -NR^cR^d, -C(=O)R^a, -C(=O)OR^b, -C(=O)NR^cR^d, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, or heterocycloalkyl;

Ring B is cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

each R^B is independently hydrogen, deuterium, halogen, -CN, -NO₂, -OH, -OR^a, -OC(=O)R^a, -OC(=O)OR^b, -OC(=O)NR^cR^d, -SH, -SR^a, -S(=O)R^a, -S(=O)₂R^a, -S(=O)₂NR^cR^d, -NR^cR^d, -NR^bC(=O)NR^cR^d, -NR^bC(=O)R^a, -NR^bC(=O)OR^b, -NR^bS(=O)₂R^a, -C(=O)R^a, -C(=O)OR^b, -C(=O)NR^cR^d, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein the alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is optionally and independently substituted with one or more R^{Ba};

or two R^B on the same atom are taken together to form an oxo;

each R^{Ba} is independently deuterium, halogen, -CN, -NO₂, -OH, -OR^a, -OC(=O)R^a, -OC(=O)OR^b, -OC(=O)NR^cR^d, -SH, -SR^a, -S(=O)R^a, -S(=O)₂R^a, -S(=O)₂NR^cR^d, -NR^cR^d, -NR^bC(=O)NR^cR^d, -NR^bC(=O)R^a, -NR^bC(=O)OR^b, -NR^bS(=O)₂R^a, -C(=O)R^a, -C(=O)C(=O)R^a, -C(=O)OR^b, -C(=O)NR^cR^d, -C(=O)C(=O)NR^cR^d, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

or two R^{Ba} on the same atom are taken together to form an oxo;

m is 0-4;

Ring C is heterocycloalkyl or heteroaryl;

each R^C is independently hydrogen, deuterium, halogen, -CN, -NO₂, -OH, -OR^a, -OC(=O)R^a, -OC(=O)OR^b, -OC(=O)NR^cR^d, -SH, -SR^a, -S(=O)R^a, -S(=O)₂R^a, -S(=O)₂NR^cR^d, -S(=O)(=NR^b)R^a, -SiR^cR^dOR^b, -NR^cR^d, -NR^bC(=O)NR^cR^d, -NR^bC(=O)R^a, -NR^bC(=O)OR^b, -NR^bS(=O)₂R^a, -C(=O)R^a, -C(=O)OR^b, -C(=O)NR^cR^d, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, (C₁-C₆alkyl)cycloalkyl, (C₁-C₆alkyl)heterocycloalkyl, (C₁-C₆alkyl)aryl, or (C₁-C₆alkyl)heteroaryl; wherein the alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is optionally and independently substituted with one or more R^{Ca} ;

or two R^C on the same atom are taken together to form an oxo;

each R^{Ca} is independently deuterium, halogen, -CN, -NO₂, -OH, -OR^a, -OC(=O)R^a, -OC(=O)OR^b, -OC(=O)NR^cR^d, -SH, -SR^a, -S(=O)R^a, -S(=O)₂R^a, -S(=O)₂NR^cR^d, -NR^cR^d, -NR^bC(=O)NR^cR^d, -NR^bC(=O)R^a, -NR^bC(=O)OR^b, -NR^bS(=O)₂R^a, -C(=O)R^a, -C(=O)OR^b, -C(=O)NR^cR^d, -C(=O)C(=O)NR^cR^d, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

or two R^{Ca} on the same atom are taken together to form an oxo;

p is 0-4;

each R^a is independently C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, C₁-C₆alkyl(cycloalkyl), C₁-C₆alkyl(heterocycloalkyl), C₁-C₆alkyl(aryl), or C₁-C₆alkyl(heteroaryl); wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more oxo, deuterium, halogen, -CN, -OH, -OCH₃, -S(=O)CH₃, -S(=O)₂CH₃, -S(=O)₂NH₂, -S(=O)₂NHCH₃, -S(=O)₂N(CH₃)₂, -NH₂, -NHCH₃, -N(CH₃)₂, -C(=O)CH₃, -C(=O)OH, -C(=O)OCH₃, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, or C₁-C₆heteroalkyl;

each R^b is independently hydrogen, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, C₁-C₆alkyl(cycloalkyl), C₁-C₆alkyl(heterocycloalkyl), C₁-C₆alkyl(aryl), or

C₁-C₆alkyl(heteroaryl); wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more oxo, deuterium, halogen, -CN, -OH, -OCH₃, -S(=O)CH₃, -S(=O)₂CH₃, -S(=O)₂NH₂, -S(=O)₂NHCH₃, -S(=O)₂N(CH₃)₂, -NH₂, -NHCH₃, -N(CH₃)₂, -C(=O)CH₃, -C(=O)OH, -C(=O)OCH₃, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, or C₁-C₆heteroalkyl; and

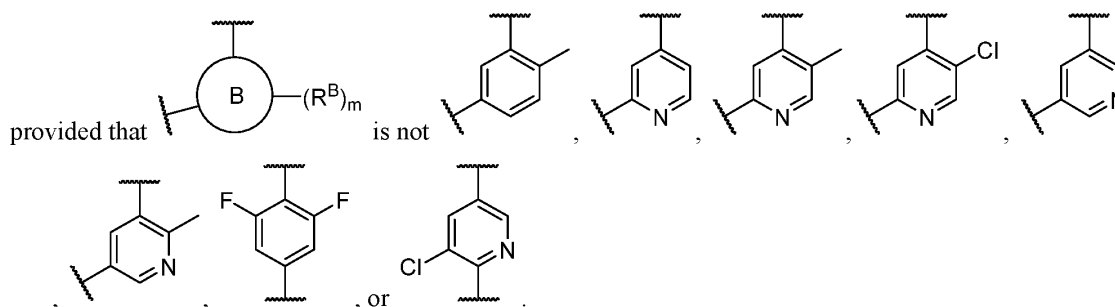
each R^c and R^d are independently hydrogen, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl,

C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, C₁-C₆alkyl(cycloalkyl), C₁-C₆alkyl(heterocycloalkyl),

C₁-C₆alkyl(aryl), or C₁-C₆alkyl(heteroaryl); wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more oxo, deuterium, halogen, -CN, -OH, -OCH₃, -S(=O)CH₃, -S(=O)₂CH₃, -S(=O)₂NH₂, -S(=O)₂NHCH₃, -S(=O)₂N(CH₃)₂, -NH₂, -NHCH₃, -N(CH₃)₂, -C(=O)CH₃, -C(=O)OH, -C(=O)OCH₃, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, or C₁-C₆heteroalkyl;

or R^c and R^d are taken together with the atom to which they are attached to form a heterocycloalkyl

optionally substituted with one or more oxo, deuterium, halogen, -CN, -OH, -OCH₃, -S(=O)CH₃, -S(=O)₂CH₃, -S(=O)₂NH₂, -S(=O)₂NHCH₃, -S(=O)₂N(CH₃)₂, -NH₂, -NHCH₃, -N(CH₃)₂, -C(=O)CH₃, -C(=O)OH, -C(=O)OCH₃, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, or C₁-C₆heteroalkyl;



[0011] Also disclosed herein is a pharmaceutical composition comprising a compound disclosed herein, or a pharmaceutically acceptable salt, solvate, N-oxide, or stereoisomer thereof, and a pharmaceutically acceptable carrier.

[0012] Also disclosed herein is a method for treating a condition comprising administering to a subject in need thereof a therapeutically effective amount of a compound disclosed herein, or a pharmaceutically acceptable salt, solvate, N-oxide, or stereoisomer thereof, wherein the condition is selected from the group consisting of an autoimmune disorder, a chronic inflammatory disorder, an acute inflammatory disorder, an auto-inflammatory disorder, a fibrotic disorder, a metabolic disorder, a neoplastic disorder, and a cardiovascular or a cerebrovascular disorder.

[0013] Also disclosed herein is a method of treating a p38 MAP kinase-mediated disease in a subject in need thereof comprising administering to the subject a therapeutically effective amount of a compound disclosed herein, or a pharmaceutically acceptable salt, solvate, N-oxide, or stereoisomer thereof.

[0014] Also disclosed herein is a method of treating a MK2-mediated disease in a subject in need thereof comprising administering to the subject a therapeutically effective amount of a compound disclosed herein, or a pharmaceutically acceptable salt, solvate, N-oxide, or stereoisomer thereof.

INCORPORATION BY REFERENCE

[0015] All publications, patents, and patent applications mentioned in this specification are herein incorporated by reference to the same extent as if each individual publication, patent, or patent application was specifically and individually indicated to be incorporated by reference.

DETAILED DESCRIPTION OF THE INVENTION

Definitions

[0016] In the following description, certain specific details are set forth in order to provide a thorough understanding of various embodiments. However, one skilled in the art will understand that the invention may be practiced without these details. In other instances, well-known structures have not been shown or described in detail to avoid unnecessarily obscuring descriptions of the embodiments. Unless the context requires otherwise, throughout the specification and claims which follow, the word “comprise” and variations thereof, such as, “comprises” and “comprising” are to be construed in an open, inclusive sense, that is, as “including, but not limited to.” Further, headings provided herein are for convenience only and do not interpret the scope or meaning of the claimed invention.

[0017] Reference throughout this specification to “some embodiments” or “an embodiment” means that a particular feature, structure or characteristic described in connection with the embodiment is included in at least one embodiment. Thus, the appearances of the phrases “in one embodiment” or “in an embodiment” in various places throughout this specification are not necessarily all referring to the same embodiment. Furthermore, the particular features, structures, or characteristics may be combined in any suitable manner in one or more embodiments. Also, as used in this specification and the appended claims, the singular forms “a,” “an,” and “the” include plural referents unless the content clearly dictates otherwise. It should also be noted that the term “or” is generally employed in its sense including “and/or” unless the content clearly dictates otherwise.

[0018] The terms below, as used herein, have the following meanings, unless indicated otherwise:

[0019] “oxo” refers to =O.

[0020] “Carboxyl” refers to -COOH.

[0021] “Alkyl” refers to a straight-chain, or branched-chain saturated hydrocarbon monoradical having from one to about ten carbon atoms, more preferably one to six carbon atoms. Examples include, but are not limited to methyl, ethyl, n-propyl, isopropyl, 2-methyl-1-propyl, 2-methyl-2-propyl, 2-methyl-1-butyl, 3-methyl-1-butyl, 2-methyl-3-butyl, 2,2-dimethyl-1-propyl, 2-methyl-1-pentyl, 3-methyl-1-pentyl, 4-methyl-1-pentyl, 2-methyl-2-pentyl, 3-methyl-2-pentyl, 4-methyl-2-pentyl, 2,2-dimethyl-1-butyl, 3,3-dimethyl-1-

butyl, 2-ethyl-1-butyl, n-butyl, isobutyl, sec-butyl, t-butyl, n-pentyl, isopentyl, neopentyl, tert-amyl and hexyl, and longer alkyl groups, such as heptyl, octyl and the like. Whenever it appears herein, a numerical range such as “C₁-C₆ alkyl” or “C₁₋₆alkyl”, means that the alkyl group may consist of 1 carbon atom, 2 carbon atoms, 3 carbon atoms, 4 carbon atoms, 5 carbon atoms or 6 carbon atoms, although the present definition also covers the occurrence of the term “alkyl” where no numerical range is designated. In some embodiments, the alkyl is a C₁₋₁₀alkyl. In some embodiments, the alkyl is a C₁₋₆alkyl. In some embodiments, the alkyl is a C₁₋₅alkyl. In some embodiments, the alkyl is a C₁₋₄alkyl. In some embodiments, the alkyl is a C₁₋₃alkyl. Unless stated otherwise specifically in the specification, an alkyl group may be optionally substituted, for example, with oxo, halogen, amino, nitrile, nitro, hydroxyl, haloalkyl, alkoxy, carboxyl, carboxylate, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, and the like. In some embodiments, the alkyl is optionally substituted with oxo, halogen, -CN, -COOH, -COOMe, -OH, -OMe, -NH₂, or -NO₂. In some embodiments, the alkyl is optionally substituted with halogen, -CN, -OH, or -OMe. In some embodiments, the alkyl is optionally substituted with halogen.

[0022] “Alkenyl” refers to a straight-chain, or branched-chain hydrocarbon monoradical having one or more carbon-carbon double-bonds and having from two to about ten carbon atoms, more preferably two to about six carbon atoms. The group may be in either the *cis* or *trans* conformation about the double bond(s), and should be understood to include both isomers. Examples include, but are not limited to ethenyl (-CH=CH₂), 1-propenyl (-CH₂CH=CH₂), isopropenyl [-C(CH₃)=CH₂], butenyl, 1,3-butadienyl and the like. Whenever it appears herein, a numerical range such as “C₂-C₆ alkenyl” or “C₂₋₆alkenyl”, means that the alkenyl group may consist of 2 carbon atoms, 3 carbon atoms, 4 carbon atoms, 5 carbon atoms or 6 carbon atoms, although the present definition also covers the occurrence of the term “alkenyl” where no numerical range is designated. Unless stated otherwise specifically in the specification, an alkenyl group may be optionally substituted, for example, with oxo, halogen, amino, nitrile, nitro, hydroxyl, haloalkyl, alkoxy, carboxyl, carboxylate, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, and the like. In some embodiments, the alkenyl is optionally substituted with oxo, halogen, -CN, -COOH, -COOMe, -OH, -OMe, -NH₂, or -NO₂. In some embodiments, the alkenyl is optionally substituted with halogen, -CN, -OH, or -OMe. In some embodiments, the alkenyl is optionally substituted with halogen.

[0023] “Alkynyl” refers to a straight-chain or branched-chain hydrocarbon monoradical having one or more carbon-carbon triple-bonds and having from two to about ten carbon atoms, more preferably from two to about six carbon atoms. Examples include, but are not limited to ethynyl, 2-propynyl, 2-butyne, 1,3-butadiynyl and the like. Whenever it appears herein, a numerical range such as “C₂-C₆ alkynyl” or “C₂₋₆alkynyl”, means that the alkynyl group may consist of 2 carbon atoms, 3 carbon atoms, 4 carbon atoms, 5 carbon atoms or 6 carbon atoms, although the present definition also covers the occurrence of the term “alkynyl” where no numerical range is designated. Unless stated otherwise specifically in the specification, an alkynyl group may be optionally substituted, for example, with oxo, halogen, amino, nitrile, nitro, hydroxyl, haloalkyl, alkoxy, carboxyl, carboxylate, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, and the like. In some embodiments, the alkynyl is optionally substituted with oxo, halogen, -CN, -COOH, COOMe,

-OH, -OMe, -NH₂, or -NO₂. In some embodiments, the alkynyl is optionally substituted with halogen, -CN, -OH, or -OMe. In some embodiments, the alkynyl is optionally substituted with halogen.

[0024] “Alkylene” refers to a straight or branched divalent hydrocarbon chain. Unless stated otherwise specifically in the specification, an alkylene group may be optionally substituted, for example, with oxo, halogen, amino, nitrile, nitro, hydroxyl, haloalkyl, alkoxy, carboxyl, carboxylate, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, and the like. In some embodiments, the alkylene is optionally substituted with oxo, halogen, -CN, -COOH, COOMe, -OH, -OMe, -NH₂, or -NO₂. In some embodiments, the alkylene is optionally substituted with halogen, -CN, -OH, or -OMe. In some embodiments, the alkylene is optionally substituted with halogen.

[0025] “Alkoxy” refers to a radical of the formula -OR_a where R_a is an alkyl radical as defined. Unless stated otherwise specifically in the specification, an alkoxy group may be optionally substituted, for example, with oxo, halogen, amino, nitrile, nitro, hydroxyl, haloalkyl, alkoxy, carboxyl, carboxylate, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, and the like. In some embodiments, the alkoxy is optionally substituted with halogen, -CN, -COOH, COOMe, -OH, -OMe, -NH₂, or -NO₂. In some embodiments, the alkoxy is optionally substituted with halogen, -CN, -OH, or -OMe. In some embodiments, the alkoxy is optionally substituted with halogen.

[0026] “Aryl” refers to a radical derived from a hydrocarbon ring system comprising 6 to 30 carbon atoms and at least one aromatic ring. The aryl radical may be a monocyclic, bicyclic, tricyclic or tetracyclic ring system, which may include fused (when fused with a cycloalkyl or heterocycloalkyl ring, the aryl is bonded through an aromatic ring atom) or bridged ring systems. In some embodiments, the aryl is a 6- to 10-membered aryl. In some embodiments, the aryl is a 6-membered aryl (phenyl). Aryl radicals include, but are not limited to, aryl radicals derived from the hydrocarbon ring systems of anthrylene, naphthylene, phenanthrylene, anthracene, azulene, benzene, chrysene, fluoranthene, fluorene, as-indacene, s-indacene, indane, indene, naphthalene, phenalene, phenanthrene, pleiadene, pyrene, and triphenylene. Unless stated otherwise specifically in the specification, an aryl may be optionally substituted, for example, with halogen, amino, nitrile, nitro, hydroxyl, alkyl, alkenyl, alkynyl, haloalkyl, alkoxy, carboxyl, carboxylate, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, and the like. In some embodiments, the aryl is optionally substituted with halogen, methyl, ethyl, -CN, -COOH, COOMe, -CF₃, -OH, -OMe, -NH₂, or -NO₂. In some embodiments, the aryl is optionally substituted with halogen, methyl, ethyl, -CN, -CF₃, -OH, or -OMe. In some embodiments, the aryl is optionally substituted with halogen.

[0027] “Cycloalkyl” refers to a partially or fully saturated, monocyclic or polycyclic carbocyclic ring, which may include fused (when fused with an aryl or a heteroaryl ring, the cycloalkyl is bonded through a non-aromatic ring atom) or bridged ring systems. In some embodiments, the cycloalkyl is fully saturated. Representative cycloalkyls include, but are not limited to, cycloalkyls having from three to fifteen carbon atoms (C₃-C₁₅ cycloalkyl or C₃-C₁₅ cycloalkenyl), from three to ten carbon atoms (C₃-C₁₀ cycloalkyl or C₃-C₁₀ cycloalkenyl), from three to eight carbon atoms (C₃-C₈ cycloalkyl or C₃-C₈ cycloalkenyl), from three to six carbon atoms (C₃-C₆ cycloalkyl or C₃-C₆ cycloalkenyl), from three to five carbon atoms (C₃-C₅

cycloalkyl or C₃-C₅ cycloalkenyl), or three to four carbon atoms (C₃-C₄ cycloalkyl or C₃-C₄ cycloalkenyl). In some embodiments, the cycloalkyl is a 3- to 10-membered cycloalkyl or a 3- to 10-membered cycloalkenyl. In some embodiments, the cycloalkyl is a 3- to 6-membered cycloalkyl or a 3- to 6-membered cycloalkenyl. In some embodiments, the cycloalkyl is a 5- to 6-membered cycloalkyl or a 5- to 6-membered cycloalkenyl. Monocyclic cycloalkyls include, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl. Polycyclic cycloalkyls include, for example, adamantyl, norbornyl, decalinyl, bicyclo[3.3.0]octane, bicyclo[4.3.0]nonane, cis-decalin, trans-decalin, bicyclo[2.1.1]hexane, bicyclo[2.2.1]heptane, bicyclo[2.2.2]octane, bicyclo[3.2.2]nonane, and bicyclo[3.3.2]decane, and 7,7-dimethyl-bicyclo[2.2.1]heptanyl. Partially saturated cycloalkyls include, for example cyclopentenyl, cyclohexenyl, cycloheptenyl, and cyclooctenyl. Unless stated otherwise specifically in the specification, a cycloalkyl is optionally substituted, for example, with oxo, halogen, amino, nitrile, nitro, hydroxyl, alkyl, alkenyl, alkynyl, haloalkyl, alkoxy, carboxyl, carboxylate, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, and the like. In some embodiments, a cycloalkyl is optionally substituted with oxo, halogen, methyl, ethyl, -CN, -COOH, COOMe, -CF₃, -OH, -OMe, -NH₂, or -NO₂. In some embodiments, a cycloalkyl is optionally substituted with oxo, halogen, methyl, ethyl, -CN, -CF₃, -OH, or -OMe. In some embodiments, the cycloalkyl is optionally substituted with halogen.

[0028] “Halo” or “halogen” refers to bromo, chloro, fluoro or iodo. In some embodiments, halogen is fluoro or chloro. In some embodiments, halogen is fluoro.

[0029] “Haloalkyl” refers to an alkyl radical, as defined above, that is substituted by one or more halo radicals, as defined above, *e.g.*, trifluoromethyl, difluoromethyl, fluoromethyl, trichloromethyl, 2,2,2-trifluoroethyl, 1,2-difluoroethyl, 3-bromo-2-fluoropropyl, 1,2-dibromoethyl, and the like.

[0030] “Hydroxyalkyl” refers to an alkyl radical, as defined above, that is substituted by one or more hydroxyls. In some embodiments, the alkyl is substituted with one hydroxyl. In some embodiments, the alkyl is substituted with one, two, or three hydroxyls. Hydroxyalkyl include, for example, hydroxymethyl, hydroxyethyl, hydroxypropyl, hydroxybutyl, or hydroxypentyl. In some embodiments, the hydroxyalkyl is hydroxymethyl.

[0031] “Aminoalkyl” refers to an alkyl radical, as defined above, that is substituted by one or more amines. In some embodiments, the alkyl is substituted with one amine. In some embodiments, the alkyl is substituted with one, two, or three amines. Aminoalkyl include, for example, aminomethyl, aminoethyl, aminopropyl, aminobutyl, or aminopentyl. In some embodiments, the aminoalkyl is aminomethyl.

[0032] “Deuteroalkyl” refers to an alkyl radical, as defined above, that is substituted by one or more deuteriums. In some embodiments, the alkyl is substituted with one deuterium. In some embodiments, the alkyl is substituted with one, two, or three deuteriums. In some embodiments, the alkyl is substituted with one, two, three, four, five, or six deuteriums. Deuteroalkyl include, for example, CD₃, CH₂D, CHD₂, CH₂CD₃, CD₂CD₃, CHDCD₃, CH₂CH₂D, or CH₂CHD₂. In some embodiments, the deuteroalkyl is CD₃.

[0033] “Heteroalkyl” refers to an alkyl group in which one or more skeletal atoms of the alkyl are selected from an atom other than carbon, *e.g.*, oxygen, nitrogen (*e.g.*, -NH-, -N(alkyl)-), sulfur, phosphorus,

or combinations thereof. A heteroalkyl is attached to the rest of the molecule at a carbon atom of the heteroalkyl. In one aspect, a heteroalkyl is a C₁-C₆ heteroalkyl wherein the heteroalkyl is comprised of 1 to 6 carbon atoms and one or more atoms other than carbon, e.g., oxygen, nitrogen (e.g. -NH-, -N(alkyl)-), sulfur, phosphorus, or combinations thereof wherein the heteroalkyl is attached to the rest of the molecule at a carbon atom of the heteroalkyl. Examples of such heteroalkyl are, for example, -CH₂OCH₃, -CH₂CH₂OCH₃, -CH₂CH₂OCH₂CH₂OCH₃, -CH(CH₃)OCH₃, -CH₂NHCH₃, -CH₂N(CH₃)₂, -CH₂CH₂NHCH₃, or -CH₂CH₂N(CH₃)₂. Unless stated otherwise specifically in the specification, a heteroalkyl is optionally substituted for example, with oxo, halogen, amino, nitrile, nitro, hydroxyl, alkyl, alkenyl, alkynyl, haloalkyl, alkoxy, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, and the like. In some embodiments, a heteroalkyl is optionally substituted with oxo, halogen, methyl, ethyl, -CN, -CF₃, -OH, -OMe, -NH₂, or -NO₂. In some embodiments, a heteroalkyl is optionally substituted with oxo, halogen, methyl, ethyl, -CN, -CF₃, -OH, or -OMe. In some embodiments, the heteroalkyl is optionally substituted with halogen.

[0034] “Heterocycloalkyl” refers to a 3- to 24-membered partially or fully saturated ring radical comprising 2 to 23 carbon atoms and from one to 8 heteroatoms selected from the group consisting of nitrogen, oxygen, phosphorous and sulfur. In some embodiments, the heterocycloalkyl is fully saturated. In some embodiments, the heterocycloalkyl comprises one to three heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur. In some embodiments, the heterocycloalkyl comprises one to three heteroatoms selected from the group consisting of nitrogen and oxygen. In some embodiments, the heterocycloalkyl comprises one to three nitrogens. In some embodiments, the heterocycloalkyl comprises one or two nitrogens. In some embodiments, the heterocycloalkyl comprises one nitrogen. In some embodiments, the heterocycloalkyl comprises one nitrogen and one oxygen. Unless stated otherwise specifically in the specification, the heterocycloalkyl radical may be a monocyclic, bicyclic, tricyclic or tetracyclic ring system, which may include fused (when fused with an aryl or a heteroaryl ring, the heterocycloalkyl is bonded through a non-aromatic ring atom) or bridged ring systems; and the nitrogen, carbon, or sulfur atoms in the heterocycloalkyl radical may be optionally oxidized; the nitrogen atom may be optionally quaternized. Representative heterocycloalkyls include, but are not limited to, heterocycloalkyls having from two to fifteen carbon atoms (C₂-C₁₅ heterocycloalkyl or C₂-C₁₅ heterocycloalkenyl), from two to ten carbon atoms (C₂-C₁₀ heterocycloalkyl or C₂-C₁₀ heterocycloalkenyl), from two to eight carbon atoms (C₂-C₈ heterocycloalkyl or C₂-C₈ heterocycloalkenyl), from two to seven carbon atoms (C₂-C₇ heterocycloalkyl or C₂-C₇ heterocycloalkenyl), from two to six carbon atoms (C₂-C₆ heterocycloalkyl or C₂-C₆ heterocycloalkenyl), from two to five carbon atoms (C₂-C₅ heterocycloalkyl or C₂-C₅ heterocycloalkenyl), or two to four carbon atoms (C₂-C₄ heterocycloalkyl or C₂-C₄ heterocycloalkenyl). Examples of such heterocycloalkyl radicals include, but are not limited to, aziridinyl, azetidiny, oxetanyl, dioxolanyl, thienyl[1,3]dithianyl, decahydroisoquinolyl, imidazoliny, imidazolidiny, isothiazolidiny, isoxazolidiny, morpholiny, octahydroindolyl, octahydroisindolyl, 2-oxopiperazinyl, 2-oxopiperidinyl, 2-oxopyrrolidinyl, oxazolidiny, piperidinyl, piperazinyl, 4-piperidonyl, pyrrolidinyl, pyrazolidiny, quinuclidiny, thiazolidiny, tetrahydrofuryl, trithianyl, tetrahydropyrany, thiomorpholiny, thiamorpholiny,

1-oxo-thiomorpholinyl, 1,1-dioxo-thiomorpholinyl, 1,3-dihydroisobenzofuran-1-yl, 3-oxo-1,3-dihydroisobenzofuran-1-yl, methyl-2-oxo-1,3-dioxol-4-yl, and 2-oxo-1,3-dioxol-4-yl. The term heterocycloalkyl also includes all ring forms of the carbohydrates, including but not limited to the monosaccharides, the disaccharides and the oligosaccharides. Unless otherwise noted, heterocycloalkyls have from 2 to 10 carbons in the ring. It is understood that when referring to the number of carbon atoms in a heterocycloalkyl, the number of carbon atoms in the heterocycloalkyl is not the same as the total number of atoms (including the heteroatoms) that make up the heterocycloalkyl (i.e. skeletal atoms of the heterocycloalkyl ring). In some embodiments, the heterocycloalkyl is a 3- to 8-membered heterocycloalkyl. In some embodiments, the heterocycloalkyl is a 3- to 7-membered heterocycloalkyl. In some embodiments, the heterocycloalkyl is a 3- to 6-membered heterocycloalkyl. In some embodiments, the heterocycloalkyl is a 4- to 6-membered heterocycloalkyl. In some embodiments, the heterocycloalkyl is a 5- to 6-membered heterocycloalkyl. In some embodiments, the heterocycloalkyl is a 3- to 8-membered heterocycloalkenyl. In some embodiments, the heterocycloalkyl is a 3- to 7-membered heterocycloalkenyl. In some embodiments, the heterocycloalkyl is a 3- to 6-membered heterocycloalkenyl. In some embodiments, the heterocycloalkyl is a 4- to 6-membered heterocycloalkenyl. In some embodiments, the heterocycloalkyl is a 5- to 6-membered heterocycloalkenyl. Unless stated otherwise specifically in the specification, a heterocycloalkyl may be optionally substituted as described below, for example, with oxo, halogen, amino, nitrile, nitro, hydroxyl, alkyl, alkenyl, alkynyl, haloalkyl, alkoxy, carboxyl, carboxylate, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, and the like. In some embodiments, the heterocycloalkyl is optionally substituted with oxo, halogen, methyl, ethyl, -CN, -COOH, COOMe, -CF₃, -OH, -OMe, -NH₂, or -NO₂. In some embodiments, the heterocycloalkyl is optionally substituted with halogen, methyl, ethyl, -CN, -CF₃, -OH, or -OMe. In some embodiments, the heterocycloalkyl is optionally substituted with halogen.

[0035] “Heteroaryl” refers to a 5- to 14-membered ring system radical comprising one to thirteen carbon atoms, one to six heteroatoms selected from the group consisting of nitrogen, oxygen, phosphorous, and sulfur, and at least one aromatic ring. In some embodiments, the heteroaryl comprises one to three heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur. In some embodiments, the heteroaryl comprises one to three heteroatoms selected from the group consisting of nitrogen and oxygen. In some embodiments, the heteroaryl comprises one to three nitrogens. In some embodiments, the heteroaryl comprises one or two nitrogens. In some embodiments, the heteroaryl comprises one nitrogen. The heteroaryl radical may be a monocyclic, bicyclic, tricyclic or tetracyclic ring system, which may include fused (when fused with a cycloalkyl or heterocycloalkyl ring, the heteroaryl is bonded through an aromatic ring atom) or bridged ring systems; and the nitrogen, carbon or sulfur atoms in the heteroaryl radical may be optionally oxidized; the nitrogen atom may be optionally quaternized. In some embodiments, the heteroaryl is a 5- to 10-membered heteroaryl. In some embodiments, the heteroaryl is a 5- to 6-membered heteroaryl. In some embodiments, the heteroaryl is a 6-membered heteroaryl. In some embodiments, the heteroaryl is a 5-membered heteroaryl. Examples include, but are not limited to, azepinyl, acridinyl, benzimidazolyl, benzothiazolyl, benzindolyl, benzodioxolyl, benzofuranyl, benzooxazolyl, benzothiazolyl,

benzothiadiazolyl, benzo[b][1,4]dioxepinyl, 1,4-benzodioxanyl, benzonaphthofuranyl, benzoxazolyl, benzodioxolyl, benzodioxinyl, benzopyranyl, benzopyranonyl, benzofuranyl, benzofuranonyl, benzothieryl (benzothiophenyl), benzotriazolyl, benzo[4,6]imidazo[1,2-a]pyridinyl, carbazolyl, cinnolinyl, dibenzofuranyl, dibenzothiophenyl, furanyl, furanonyl, isothiazolyl, imidazolyl, indazolyl, indolyl, indazolyl, isoindolyl, indolinyl, isoindolinyl, isoquinolyl, indoliziny, isoxazolyl, naphthyridinyl, oxadiazolyl, 2-oxoazepinyl, oxazolyl, oxiranyl, 1-oxidopyridinyl, 1-oxidopyrimidinyl, 1-oxidopyrazinyl, 1-oxidopyridazinyl, 1-phenyl-1H-pyrrolyl, phenazinyl, phenothiazinyl, phenoxazinyl, phthalazinyl, pteridinyl, purinyl, pyrrolyl, pyrazolyl, pyridinyl, pyrazinyl, pyrimidinyl, pyridazinyl, quinazolinyl, quinoxalinyl, quinolinyl, quinuclidinyl, isoquinolinyl, tetrahydroquinolinyl, thiazolyl, thiadiazolyl, triazolyl, tetrazolyl, triazinyl, and thiophenyl (i.e., thienyl). Unless stated otherwise specifically in the specification, a heteroaryl may be optionally substituted, for example, with halogen, amino, nitrile, nitro, hydroxyl, alkyl, alkenyl, alkynyl, haloalkyl, alkoxy, carboxyl, carboxylate, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, and the like. In some embodiments, the heteroaryl is optionally substituted with halogen, methyl, ethyl, -CN, -COOH, COOMe, -CF₃, -OH, -OMe, -NH₂, or -NO₂. In some embodiments, the heteroaryl is optionally substituted with halogen, methyl, ethyl, -CN, -CF₃, -OH, or -OMe. In some embodiments, the heteroaryl is optionally substituted with halogen.

[0036] The term “optional” or “optionally” means that the subsequently described event or circumstance may or may not occur, and that the description includes instances where said event or circumstance occurs and instances in which it does not. For example, “optionally substituted alkyl” means either “alkyl” or “substituted alkyl” as defined above. Further, an optionally substituted group may be un-substituted (e.g., -CH₂CH₃), fully substituted (e.g., -CF₂CF₃), mono-substituted (e.g., -CH₂CH₂F) or substituted at a level anywhere in-between fully substituted and mono-substituted (e.g., -CH₂CHF₂, -CH₂CF₃, -CF₂CH₃, -CFHCHF₂, etc.). It will be understood by those skilled in the art with respect to any group containing one or more substituents that such groups are not intended to introduce any substitution or substitution patterns (e.g., substituted alkyl includes optionally substituted cycloalkyl groups, which in turn are defined as including optionally substituted alkyl groups, potentially ad infinitum) that are sterically impractical and/or synthetically non-feasible. Thus, any substituents described should generally be understood as having a maximum molecular weight of about 1,000 daltons, and more typically, up to about 500 daltons.

[0037] An “effective amount” or “therapeutically effective amount” refers to an amount of a compound administered to a mammalian subject, either as a single dose or as part of a series of doses, which is effective to produce a desired therapeutic effect.

[0038] “Treatment” of an individual (e.g. a mammal, such as a human) or a cell is any type of intervention used in an attempt to alter the natural course of the individual or cell. In some embodiments, treatment includes administration of a pharmaceutical composition, subsequent to the initiation of a pathologic event or contact with an etiologic agent and includes stabilization of the condition (e.g., condition does not worsen) or alleviation of the condition.

[0039] “Synergy” or “synergize” refers to an effect of a combination that is greater than additive of the effects of each component alone at the same doses.

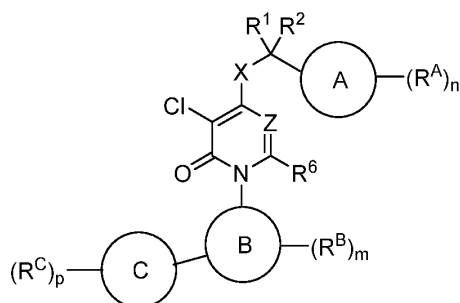
[0040] As used herein, a “disease or disorder associated with MK2” or, alternatively, “an MK2-mediated disease or disorder” means any disease or other deleterious condition in which MK2, or a mutant thereof, is known or suspected to play a role.

As used herein, a “disease or disorder associated with p38 MAP kinase” or, alternatively, “an p38 MAP kinase-mediated disease or disorder” means any disease or other deleterious condition in which p38 MAP kinase, or a mutant thereof, is known or suspected to play a role.

Compounds

[0041] Described herein are compounds of Formula (I)-(VIII), or a pharmaceutically acceptable salt, solvate, N-oxide, or stereoisomer thereof useful in the treatment of autoimmune disorders, chronic inflammatory disorders, acute inflammatory disorders, auto-inflammatory disorders, fibrotic disorders, metabolic disorders, neoplastic disorders, or cardiovascular or cerebrovascular disorders.

[0042] Disclosed herein is a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, N-oxide, or stereoisomer thereof:



Formula (I),

wherein:

Ring A is phenyl or heteroaryl;

each R^A is independently hydrogen, deuterium, halogen, -CN, -NO₂, -OH, -OR^a, -OC(=O)R^a, -OC(=O)OR^b, -OC(=O)NR^cR^d, -SH, -SR^a, -S(=O)R^a, -S(=O)₂R^a, -S(=O)₂NR^cR^d, -NR^cR^d, -NR^bC(=O)NR^cR^d, -NR^bC(=O)R^a, -NR^bC(=O)OR^b, -NR^bS(=O)₂R^a, -C(=O)R^a, -C(=O)OR^b, -C(=O)NR^cR^d, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein the alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is optionally and independently substituted with one or more R^{Aa} ;

or two R^A on the same atom are taken together to form an oxo;

each R^{Aa} is independently deuterium, halogen, -CN, -NO₂, -OH, -OR^a, -OC(=O)R^a, -OC(=O)OR^b, -OC(=O)NR^cR^d, -SH, -SR^a, -S(=O)R^a, -S(=O)₂R^a, -S(=O)₂NR^cR^d, -NR^cR^d, -NR^bC(=O)NR^cR^d, -NR^bC(=O)R^a, -NR^bC(=O)OR^b, -NR^bS(=O)₂R^a, -C(=O)R^a, -C(=O)C(=O)R^a, -C(=O)OR^b, -C(=O)NR^cR^d, -

$C(=O)C(=O)NR^cR^d$, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_1 - C_6 deuteroalkyl, C_1 - C_6 hydroxyalkyl, C_1 - C_6 aminoalkyl, C_1 - C_6 heteroalkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

or two R^{Aa} on the same atom are taken together to form an oxo;

n is 0-4;

R^1 and R^2 are independently hydrogen, deuterium, halogen, -CN, -NO₂, -OH, -OR^a, -NR^cR^d, -C(=O)R^a, -C(=O)OR^b, -C(=O)NR^cR^d, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_1 - C_6 deuteroalkyl, C_1 - C_6 hydroxyalkyl, C_1 - C_6 aminoalkyl, C_1 - C_6 heteroalkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, cycloalkyl, or heterocycloalkyl;

or R^1 and R^2 are taken together to form an oxo;

or R^1 and R^2 are taken together to form a cycloalkyl or heterocycloalkyl; wherein the cycloalkyl and heterocycloalkyl is optionally substituted with deuterium, halogen, -CN, -OH, -OCH₃, -NH₂, -NHCH₃, -N(CH₃)₂, -C(=O)CH₃, -C(=O)OH, -C(=O)OCH₃, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_1 - C_6 deuteroalkyl, C_1 - C_6 hydroxyalkyl, C_1 - C_6 aminoalkyl, or C_1 - C_6 heteroalkyl;

X is -C(R³)₂-, -NR⁴-, -O-, or -S-;

each R^3 are independently hydrogen, deuterium, halogen, -CN, -NO₂, -OH, -OR^a, -NR^cR^d, -C(=O)R^a, -C(=O)OR^b, -C(=O)NR^cR^d, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_1 - C_6 deuteroalkyl, C_1 - C_6 hydroxyalkyl, C_1 - C_6 aminoalkyl, C_1 - C_6 heteroalkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, cycloalkyl, or heterocycloalkyl;

or two R^3 are taken together to form an oxo;

R^4 is hydrogen, -C(=O)R^a, -C(=O)OR^b, -C(=O)NR^cR^d, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_1 - C_6 deuteroalkyl, C_1 - C_6 hydroxyalkyl, C_1 - C_6 aminoalkyl, C_1 - C_6 heteroalkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, cycloalkyl, or heterocycloalkyl;

Z is N or CR⁵;

R^5 is hydrogen, deuterium, halogen, -CN, -NO₂, -OH, -OR^a, -NR^cR^d, -C(=O)R^a, -C(=O)OR^b, -C(=O)NR^cR^d, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_1 - C_6 deuteroalkyl, C_1 - C_6 hydroxyalkyl, C_1 - C_6 aminoalkyl, C_1 - C_6 heteroalkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, cycloalkyl, or heterocycloalkyl;

R^6 is hydrogen, deuterium, halogen, -CN, -NO₂, -OH, -OR^a, -NR^cR^d, -C(=O)R^a, -C(=O)OR^b, -C(=O)NR^cR^d, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_1 - C_6 deuteroalkyl, C_1 - C_6 hydroxyalkyl, C_1 - C_6 aminoalkyl, C_1 - C_6 heteroalkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, cycloalkyl, or heterocycloalkyl;

Ring B is cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

each R^B is independently hydrogen, deuterium, halogen, -CN, -NO₂, -OH, -OR^a, -OC(=O)R^a, -OC(=O)OR^b, -OC(=O)NR^cR^d, -SH, -SR^a, -S(=O)R^a, -S(=O)₂R^a, -S(=O)₂NR^cR^d, -NR^cR^d, -NR^bC(=O)NR^cR^d, -NR^bC(=O)R^a, -NR^bC(=O)OR^b, -NR^bS(=O)₂R^a, -C(=O)R^a, -C(=O)OR^b, -C(=O)NR^cR^d, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_1 - C_6 deuteroalkyl, C_1 - C_6 hydroxyalkyl, C_1 - C_6 aminoalkyl, C_1 - C_6 heteroalkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein the alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is optionally and independently substituted with one or more R^{Ba} ;

or two R^B on the same atom are taken together to form an oxo;

each R^{Ba} is independently deuterium, halogen, -CN, -NO₂, -OH, -OR^a, -OC(=O)R^a, -OC(=O)OR^b, -OC(=O)NR^cR^d, -SH, -SR^a, -S(=O)R^a, -S(=O)₂R^a, -S(=O)₂NR^cR^d, -NR^cR^d, -NR^bC(=O)NR^cR^d, -NR^bC(=O)R^a, -NR^bC(=O)OR^b, -NR^bS(=O)₂R^a, -C(=O)R^a, -C(=O)C(=O)R^a, -C(=O)OR^b, -C(=O)NR^cR^d, -C(=O)C(=O)NR^cR^d, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

or two R^{Ba} on the same atom are taken together to form an oxo;

m is 0-4;

Ring C is heterocycloalkyl or heteroaryl;

each R^C is independently hydrogen, deuterium, halogen, -CN, -NO₂, -OH, -OR^a, -OC(=O)R^a, -OC(=O)OR^b, -OC(=O)NR^cR^d, -SH, -SR^a, -S(=O)R^a, -S(=O)₂R^a, -S(=O)₂NR^cR^d, -S(=O)(=NR^b)R^a, -SiR^cR^dOR^b, -NR^cR^d, -NR^bC(=O)NR^cR^d, -NR^bC(=O)R^a, -NR^bC(=O)OR^b, -NR^bS(=O)₂R^a, -C(=O)R^a, -C(=O)OR^b, -C(=O)NR^cR^d, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, (C₁-C₆alkyl)cycloalkyl, (C₁-C₆alkyl)heterocycloalkyl, (C₁-C₆alkyl)aryl, or (C₁-C₆alkyl)heteroaryl; wherein the alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is optionally and independently substituted with one or more R^{Ca} ;

or two R^C on the same atom are taken together to form an oxo;

each R^{Ca} is independently deuterium, halogen, -CN, -NO₂, -OH, -OR^a, -OC(=O)R^a, -OC(=O)OR^b, -OC(=O)NR^cR^d, -SH, -SR^a, -S(=O)R^a, -S(=O)₂R^a, -S(=O)₂NR^cR^d, -NR^cR^d, -NR^bC(=O)NR^cR^d, -NR^bC(=O)R^a, -NR^bC(=O)OR^b, -NR^bS(=O)₂R^a, -C(=O)R^a, -C(=O)C(=O)R^a, -C(=O)OR^b, -C(=O)NR^cR^d, -C(=O)C(=O)NR^cR^d, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

or two R^{Ca} on the same atom are taken together to form an oxo;

p is 0-4;

each R^a is independently C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, C₁-C₆alkyl(cycloalkyl), C₁-C₆alkyl(heterocycloalkyl), C₁-C₆alkyl(aryl), or C₁-C₆alkyl(heteroaryl); wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more oxo, deuterium, halogen, -CN, -OH, -OCH₃, -S(=O)CH₃, -S(=O)₂CH₃, -S(=O)₂NH₂, -S(=O)₂NHCH₃, -S(=O)₂N(CH₃)₂, -NH₂, -NHCH₃, -N(CH₃)₂, -C(=O)CH₃, -C(=O)OH, -C(=O)OCH₃, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, or C₁-C₆heteroalkyl;

each R^b is independently hydrogen, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, C₁-C₆alkyl(cycloalkyl), C₁-C₆alkyl(heterocycloalkyl), C₁-C₆alkyl(aryl), or

C₁-C₆alkyl(heteroaryl); wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more oxo, deuterium, halogen, -CN, -OH, -OCH₃, -S(=O)CH₃, -S(=O)₂CH₃, -S(=O)₂NH₂, -S(=O)₂NHCH₃, -S(=O)₂N(CH₃)₂, -NH₂, -NHCH₃, -N(CH₃)₂, -C(=O)CH₃, -C(=O)OH, -C(=O)OCH₃, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, or C₁-C₆heteroalkyl; and

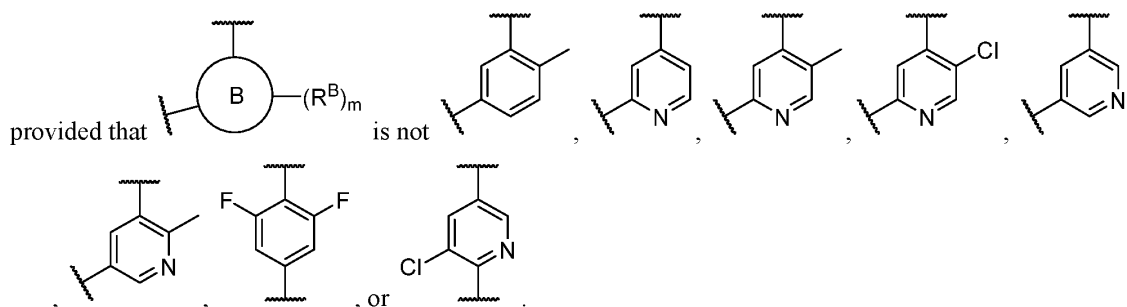
each R^c and R^d are independently hydrogen, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl,

C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, C₁-C₆alkyl(cycloalkyl), C₁-C₆alkyl(heterocycloalkyl),

C₁-C₆alkyl(aryl), or C₁-C₆alkyl(heteroaryl); wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more oxo, deuterium, halogen, -CN, -OH, -OCH₃, -S(=O)CH₃, -S(=O)₂CH₃, -S(=O)₂NH₂, -S(=O)₂NHCH₃, -S(=O)₂N(CH₃)₂, -NH₂, -NHCH₃, -N(CH₃)₂, -C(=O)CH₃, -C(=O)OH, -C(=O)OCH₃, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, or C₁-C₆heteroalkyl;

or R^c and R^d are taken together with the atom to which they are attached to form a heterocycloalkyl

optionally substituted with one or more oxo, deuterium, halogen, -CN, -OH, -OCH₃, -S(=O)CH₃, -S(=O)₂CH₃, -S(=O)₂NH₂, -S(=O)₂NHCH₃, -S(=O)₂N(CH₃)₂, -NH₂, -NHCH₃, -N(CH₃)₂, -C(=O)CH₃, -C(=O)OH, -C(=O)OCH₃, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, or C₁-C₆heteroalkyl;



[0043] In some embodiments of a compound of Formula (I), Ring A is heteroaryl. In some embodiments of a compound of Formula (I), Ring A is pyridyl. In some embodiments of a compound of Formula (I), Ring A is phenyl.

[0044] In some embodiments of a compound of Formula (I), each R^A is independently deuterium, halogen, -CN, -OH, -OR^a, -NR^cR^d, C₁-C₆alkyl, C₁-C₆haloalkyl, or C₁-C₆deuteroalkyl. In some embodiments of a compound of Formula (I), each R^A is independently halogen or C₁-C₆alkyl. In some embodiments of a compound of Formula (I), each R^A is independently halogen.

[0045] In some embodiments of a compound of Formula (I), n is 1 or 2. In some embodiments of a compound of Formula (I), n is 1-3. In some embodiments of a compound of Formula (I), n is 2. In some embodiments of a compound of Formula (I), n is 1.

[0046] In some embodiments of a compound of Formula (I), R¹ and R² are independently hydrogen, deuterium, halogen, C₁-C₆alkyl, C₁-C₆haloalkyl, or C₁-C₆deuteroalkyl. In some embodiments of a compound

of Formula (I), R^1 and R^2 are independently hydrogen, deuterium, halogen, or C_1 - C_6 alkyl. In some embodiments of a compound of Formula (I), R^1 and R^2 are hydrogen or deuterium. In some embodiments of a compound of Formula (I), R^1 and R^2 are hydrogen.

[0047] In some embodiments of a compound of Formula (I), X is -O-. In some embodiments of a compound of Formula (I), Z is N. In some embodiments of a compound of Formula (I), Z is CR^5 .

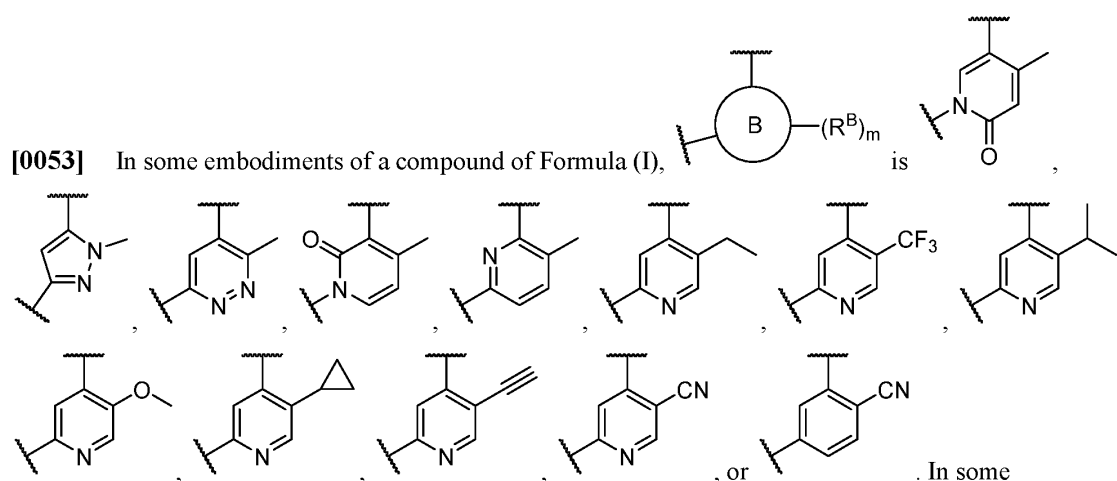
[0048] In some embodiments of a compound of Formula (I), R^5 is hydrogen, deuterium, halogen, -CN, -OH, -OR^a, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_1 - C_6 deuteroalkyl, C_1 - C_6 hydroxyalkyl, C_1 - C_6 aminoalkyl, C_1 - C_6 heteroalkyl, C_2 - C_6 alkynyl, or cycloalkyl. In some embodiments of a compound of Formula (I), R^5 is hydrogen, deuterium, halogen, -CN, or C_1 - C_6 alkyl.

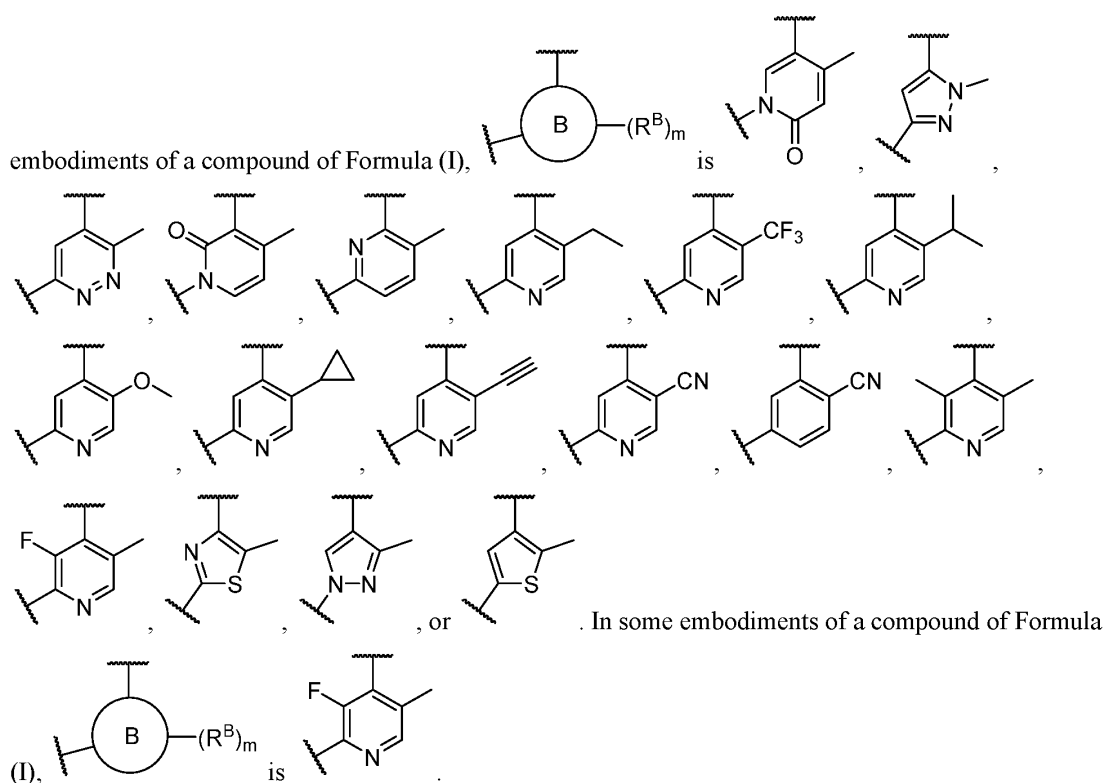
[0049] In some embodiments of a compound of Formula (I), R^6 is hydrogen, deuterium, halogen, -CN, -OH, -OR^a, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_1 - C_6 deuteroalkyl, C_1 - C_6 hydroxyalkyl, C_1 - C_6 aminoalkyl, C_1 - C_6 heteroalkyl, C_2 - C_6 alkynyl, or cycloalkyl. In some embodiments of a compound of Formula (I), R^6 is hydrogen, deuterium, halogen, -CN, or C_1 - C_6 alkyl.

[0050] In some embodiments of a compound of Formula (I), Ring B is phenyl. In some embodiments of a compound of Formula (I), Ring B is a 5-membered heteroaryl. In some embodiments of a compound of Formula (I), Ring B is 6-membered heteroaryl. In some embodiments of a compound of Formula (I), Ring B is pyridinyl. In some embodiments of a compound of Formula (I), Ring B is pyridinone.

[0051] In some embodiments of a compound of Formula (I), each R^B is independently deuterium, halogen, -CN, -OH, -OR^a, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_1 - C_6 deuteroalkyl, C_2 - C_6 alkynyl, or cycloalkyl. In some embodiments of a compound of Formula (I), each R^B is independently deuterium, -CN, -OH, -OR^a, C_2 - C_6 alkyl, C_1 - C_6 haloalkyl, C_1 - C_6 deuteroalkyl, C_2 - C_6 alkynyl, or cycloalkyl. In some embodiments of a compound of Formula (I), each R^B is independently halogen or C_1 - C_6 alkyl.

[0052] In some embodiments of a compound of Formula (I), m is 1 or 2. In some embodiments of a compound of Formula (I), m is 1-4. In some embodiments of a compound of Formula (I), m is 2-4. In some embodiments of a compound of Formula (I), m is 1. In some embodiments of a compound of Formula (I), m is 2.





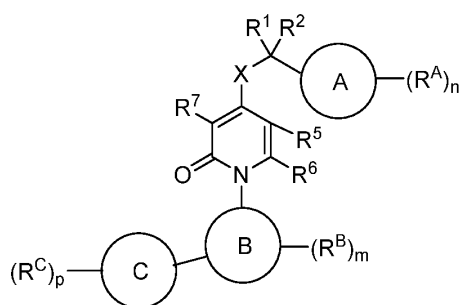
[0054] In some embodiments of a compound of Formula (I), Ring C is a 5- or 6-membered heteroaryl. In some embodiments of a compound of Formula (I), Ring C is a pyrimidinyl.

[0055] In some embodiments of a compound of Formula (I), Ring C is thiazolyl, pyrazolyl, imidazolyl, oxazolyl, thiadiazole, or triazolyl. In some embodiments of a compound of Formula (I), Ring C is thiazolyl. In some embodiments of a compound of Formula (I), Ring C is pyrazolyl. In some embodiments of a compound of Formula (I), Ring C is imidazolyl. In some embodiments of a compound of Formula (I), Ring C is thiadiazole. In some embodiments of a compound of Formula (I), Ring C is triazolyl.

[0056] In some embodiments of a compound of Formula (I), each R^C is independently hydrogen, deuterium, halogen, -CN, -OH, -OR^a, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, or C₁-C₆heteroalkyl. In some embodiments of a compound of Formula (I), each R^C is independently C₁-C₆hydroxyalkyl.

[0057] In some embodiments of a compound of Formula (I), p is 1 or 2. In some embodiments of a compound of Formula (I), p is 1. In some embodiments of a compound of Formula (I), p 2.

[0058] Also disclosed herein is a compound of Formula (II), or a pharmaceutically acceptable salt, solvate, N-oxide, or stereoisomer thereof:



Formula (II),

wherein:

Ring A is phenyl or heteroaryl;

each R^A is independently hydrogen, deuterium, halogen, -CN, -NO₂, -OH, -OR^a, -OC(=O)R^a, -OC(=O)OR^b, -OC(=O)NR^cR^d, -SH, -SR^a, -S(=O)R^a, -S(=O)₂R^a, -S(=O)₂NR^cR^d, -NR^cR^d, -NR^bC(=O)NR^cR^d, -NR^bC(=O)R^a, -NR^bC(=O)OR^b, -NR^bS(=O)₂R^a, -C(=O)R^a, -C(=O)OR^b, -C(=O)NR^cR^d, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein the alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is optionally and independently substituted with one or more R^{Aa};

or two R^A on the same atom are taken together to form an oxo;

each R^{Aa} is independently deuterium, halogen, -CN, -NO₂, -OH, -OR^a, -OC(=O)R^a, -OC(=O)OR^b, -OC(=O)NR^cR^d, -SH, -SR^a, -S(=O)R^a, -S(=O)₂R^a, -S(=O)₂NR^cR^d, -NR^cR^d, -NR^bC(=O)NR^cR^d, -NR^bC(=O)R^a, -NR^bC(=O)OR^b, -NR^bS(=O)₂R^a, -C(=O)R^a, -C(=O)C(=O)R^a, -C(=O)OR^b, -C(=O)NR^cR^d, -C(=O)C(=O)NR^cR^d, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

or two R^{Aa} on the same atom are taken together to form an oxo;

n is 0-4;

R¹ and R² are independently hydrogen, deuterium, halogen, -CN, -NO₂, -OH, -OR^a, -NR^cR^d, -C(=O)R^a, -C(=O)OR^b, -C(=O)NR^cR^d, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, or heterocycloalkyl;

or R¹ and R² are taken together to form an oxo;

or R¹ and R² are taken together to form a cycloalkyl or heterocycloalkyl; wherein the cycloalkyl and heterocycloalkyl is optionally substituted with deuterium, halogen, -CN, -OH, -OCH₃, -NH₂, -NHCH₃, -N(CH₃)₂, -C(=O)CH₃, -C(=O)OH, -C(=O)OCH₃, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, or C₁-C₆heteroalkyl;

X is -C(R³)₂-, -NR⁴-, -O-, or -S-;

each R^3 are independently hydrogen, deuterium, halogen, -CN, -NO₂, -OH, -OR^a, -NR^cR^d, -C(=O)R^a, -C(=O)OR^b, -C(=O)NR^cR^d, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, or heterocycloalkyl; or two R^3 are taken together to form an oxo;

R^4 is hydrogen, -C(=O)R^a, -C(=O)OR^b, -C(=O)NR^cR^d, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, or heterocycloalkyl;

R^5 is hydrogen, deuterium, halogen, -CN, -NO₂, -OH, -OR^a, -NR^cR^d, -C(=O)R^a, -C(=O)OR^b, -C(=O)NR^cR^d, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, or heterocycloalkyl;

R^6 is hydrogen, deuterium, halogen, -CN, -NO₂, -OH, -OR^a, -NR^cR^d, -C(=O)R^a, -C(=O)OR^b, -C(=O)NR^cR^d, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, or heterocycloalkyl;

R^7 is hydrogen, deuterium, halogen, -CN, -NO₂, -OH, -OR^a, -NR^cR^d, -C(=O)R^a, -C(=O)OR^b, -C(=O)NR^cR^d, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, or heterocycloalkyl;

Ring B is heterocycloalkyl or heteroaryl;

each R^B is independently hydrogen, deuterium, halogen, -CN, -NO₂, -OH, -OR^a, -OC(=O)R^a, -OC(=O)OR^b, -OC(=O)NR^cR^d, -SH, -SR^a, -S(=O)R^a, -S(=O)₂R^a, -S(=O)₂NR^cR^d, -NR^cR^d, -NR^bC(=O)NR^cR^d, -NR^bC(=O)R^a, -NR^bC(=O)OR^b, -NR^bS(=O)₂R^a, -C(=O)R^a, -C(=O)OR^b, -C(=O)NR^cR^d, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein the alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is optionally and independently substituted with one or more R^{Ba} ;

or two R^B on the same atom are taken together to form an oxo;

each R^{Ba} is independently deuterium, halogen, -CN, -NO₂, -OH, -OR^a, -OC(=O)R^a, -OC(=O)OR^b, -OC(=O)NR^cR^d, -SH, -SR^a, -S(=O)R^a, -S(=O)₂R^a, -S(=O)₂NR^cR^d, -NR^cR^d, -NR^bC(=O)NR^cR^d, -NR^bC(=O)R^a, -NR^bC(=O)OR^b, -NR^bS(=O)₂R^a, -C(=O)R^a, -C(=O)C(=O)R^a, -C(=O)OR^b, -C(=O)NR^cR^d, -C(=O)C(=O)NR^cR^d, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

or two R^{Ba} on the same atom are taken together to form an oxo;

m is 0-4;

Ring C is 5-membered heteroaryl;

each R^C is independently hydrogen, deuterium, halogen, -CN, -NO₂, -OH, -OR^a, -OC(=O)R^a, -OC(=O)OR^b, -OC(=O)NR^cR^d, -SH, -SR^a, -S(=O)R^a, -S(=O)₂R^a, -S(=O)₂NR^cR^d, -S(=O)(=NR^b)R^a, -SiR^cR^dOR^b, -NR^cR^d, -NR^bC(=O)NR^cR^d, -NR^bC(=O)R^a, -NR^bC(=O)OR^b, -NR^bS(=O)₂R^a, -C(=O)R^a, -C(=O)OR^b, -

C(=O)NR^cR^d, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, (C₁-C₆alkyl)cycloalkyl, (C₁-C₆alkyl)heterocycloalkyl, (C₁-C₆alkyl)aryl, or (C₁-C₆alkyl)heteroaryl; wherein the alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is optionally and independently substituted with one or more R^{Ca};

each R^{Ca} is independently deuterium, halogen, -CN, -NO₂, -OH, -OR^a, -OC(=O)R^a, -OC(=O)OR^b, -OC(=O)NR^cR^d, -SH, -SR^a, -S(=O)R^a, -S(=O)₂R^a, -S(=O)₂NR^cR^d, -NR^cR^d, -NR^bC(=O)NR^cR^d, -NR^bC(=O)R^a, -NR^bC(=O)OR^b, -NR^bS(=O)₂R^a, -C(=O)R^a, -C(=O)C(=O)R^a, -C(=O)OR^b, -C(=O)NR^cR^d, -C(=O)C(=O)NR^cR^d, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

or two R^{Ca} on the same atom are taken together to form an oxo;

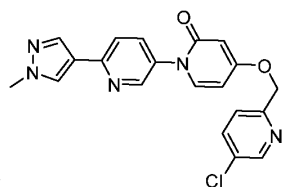
p is 0-4;

each R^a is independently C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, C₁-C₆alkyl(cycloalkyl), C₁-C₆alkyl(heterocycloalkyl), C₁-C₆alkyl(aryl), or C₁-C₆alkyl(heteroaryl); wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more oxo, deuterium, halogen, -CN, -OH, -OCH₃, -S(=O)CH₃, -S(=O)₂CH₃, -S(=O)₂NH₂, -S(=O)₂NHCH₃, -S(=O)₂N(CH₃)₂, -NH₂, -NHCH₃, -N(CH₃)₂, -C(=O)CH₃, -C(=O)OH, -C(=O)OCH₃, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, or C₁-C₆heteroalkyl;

each R^b is independently hydrogen, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, C₁-C₆alkyl(cycloalkyl), C₁-C₆alkyl(heterocycloalkyl), C₁-C₆alkyl(aryl), or C₁-C₆alkyl(heteroaryl); wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more oxo, deuterium, halogen, -CN, -OH, -OCH₃, -S(=O)CH₃, -S(=O)₂CH₃, -S(=O)₂NH₂, -S(=O)₂NHCH₃, -S(=O)₂N(CH₃)₂, -NH₂, -NHCH₃, -N(CH₃)₂, -C(=O)CH₃, -C(=O)OH, -C(=O)OCH₃, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, or C₁-C₆heteroalkyl; and

each R^c and R^d are independently hydrogen, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, C₁-C₆alkyl(cycloalkyl), C₁-C₆alkyl(heterocycloalkyl), C₁-C₆alkyl(aryl), or C₁-C₆alkyl(heteroaryl); wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more oxo, deuterium, halogen, -CN, -OH, -OCH₃, -S(=O)CH₃, -S(=O)₂CH₃, -S(=O)₂NH₂, -S(=O)₂NHCH₃, -S(=O)₂N(CH₃)₂, -NH₂, -NHCH₃, -N(CH₃)₂, -C(=O)CH₃, -C(=O)OH, -C(=O)OCH₃, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, or C₁-C₆heteroalkyl;

or R^c and R^d are taken together with the atom to which they are attached to form a heterocycloalkyl optionally substituted with one or more oxo, deuterium, halogen, -CN, -OH, -OCH₃, -S(=O)CH₃, -S(=O)₂CH₃, -S(=O)₂NH₂, -S(=O)₂NHCH₃, -S(=O)₂N(CH₃)₂, -NH₂, -NHCH₃, -N(CH₃)₂, -C(=O)CH₃, -C(=O)OH, -C(=O)OCH₃, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, or C₁-C₆heteroalkyl;



provided that the compound is not

[0059] In some embodiments of a compound of Formula (II), Ring A is heteroaryl. In some embodiments of a compound of Formula (II), Ring A is pyridyl. In some embodiments of a compound of Formula (II), Ring A is phenyl.

[0060] In some embodiments of a compound of Formula (II), each R^A is independently deuterium, halogen, -CN, -OH, -OR^a, -NR^cR^d, C₁-C₆alkyl, C₁-C₆haloalkyl, or C₁-C₆deuteroalkyl. In some embodiments of a compound of Formula (II), each R^A is independently halogen or C₁-C₆alkyl. In some embodiments of a compound of Formula (II), each R^A is independently halogen.

[0061] In some embodiments of a compound of Formula (II), n is 1 or 2. In some embodiments of a compound of Formula (II), n is 1-3. In some embodiments of a compound of Formula (II), n is 2. In some embodiments of a compound of Formula (II), n is 1.

[0062] In some embodiments of a compound of Formula (II), R¹ and R² are independently hydrogen, deuterium, halogen, C₁-C₆alkyl, C₁-C₆haloalkyl, or C₁-C₆deuteroalkyl. In some embodiments of a compound of Formula (II), R¹ and R² are independently hydrogen, deuterium, halogen, or C₁-C₆alkyl. In some embodiments of a compound of Formula (II), R¹ and R² are independently hydrogen or deuterium. In some embodiments of a compound of Formula (II), R¹ and R² are hydrogen.

[0063] In some embodiments of a compound of Formula (II), X is -O-.

[0064] In some embodiments of a compound of Formula (II), R⁵ is hydrogen, deuterium, halogen, -CN, -OH, -OR^a, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkynyl, or cycloalkyl. In some embodiments of a compound of Formula (II), R⁵ is hydrogen, deuterium, halogen, -CN, or C₁-C₆alkyl.

[0065] In some embodiments of a compound of Formula (II), R⁶ is hydrogen, deuterium, halogen, -CN, -OH, -OR^a, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkynyl, or cycloalkyl. In some embodiments of a compound of Formula (II), R⁶ is hydrogen, deuterium, halogen, -CN, or C₁-C₆alkyl.

[0066] In some embodiments of a compound of Formula (II), R⁷ is hydrogen, deuterium, halogen, -CN, -OH, -OR^a, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl,

C₁-C₆heteroalkyl, C₂-C₆alkynyl, or cycloalkyl. In some embodiments of a compound of Formula (II), R⁷ is hydrogen, deuterium, halogen, -CN, or C₁-C₆alkyl.

[0067] In some embodiments of a compound of Formula (II), Ring B is a 6-membered heteroaryl. In some embodiments of a compound of Formula (II), Ring B is pyridinyl.

[0068] In some embodiments of a compound of Formula (II), each R^B is independently hydrogen, deuterium, halogen, -CN, -OH, -OR^a, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkynyl, or cycloalkyl. In some embodiments of a compound of Formula (II), each R^B is independently halogen or C₁-C₆alkyl. In some embodiments of a compound of Formula (II), each R^B is independently C₁-C₆alkyl.

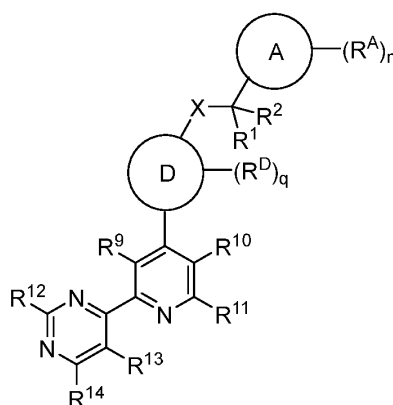
[0069] In some embodiments of a compound of Formula (II), m is 1 or 2. In some embodiments of a compound of Formula (II), m is 1-4. In some embodiments of a compound of Formula (II), m is 2-4. In some embodiments of a compound of Formula (II), m is 1. In some embodiments of a compound of Formula (II), m is 2.

[0070] In some embodiments of a compound of Formula (II), Ring C is thiazolyl, pyrazolyl, imidazolyl, oxazolyl, thiadiazole, or triazolyl. In some embodiments of a compound of Formula (II), Ring C is thiazolyl. In some embodiments of a compound of Formula (II), Ring C is pyrazolyl. In some embodiments of a compound of Formula (II), Ring C is imidazolyl. In some embodiments of a compound of Formula (II), Ring C is thiadiazole. In some embodiments of a compound of Formula (II), Ring C is triazolyl.

[0071] In some embodiments of a compound of Formula (II), each R^C is independently hydrogen, deuterium, halogen, -CN, -OH, -OR^a, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, or C₁-C₆heteroalkyl. In some embodiments of a compound of Formula (II), each R^C is independently C₁-C₆hydroxyalkyl.

[0072] In some embodiments of a compound of Formula (II), p is 1 or 2. In some embodiments of a compound of Formula (II), p is 1-3. In some embodiments of a compound of Formula (II), p is 1. In some embodiments of a compound of Formula (II), p is 2.

[0073] Also disclosed herein is a compound of Formula (III), or a pharmaceutically acceptable salt, solvate, N-oxide, or stereoisomer thereof:



Formula (III),

wherein:

Ring A is phenyl or heteroaryl;

each R^A is independently hydrogen, deuterium, halogen, -CN, -NO₂, -OH, -OR^a, -OC(=O)R^a, -OC(=O)OR^b, -OC(=O)NR^cR^d, -SH, -SR^a, -S(=O)R^a, -S(=O)₂R^a, -S(=O)₂NR^cR^d, -NR^cR^d, -NR^bC(=O)NR^cR^d, -NR^bC(=O)R^a, -NR^bC(=O)OR^b, -NR^bS(=O)₂R^a, -C(=O)R^a, -C(=O)OR^b, -C(=O)NR^cR^d, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein the alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is optionally and independently substituted with one or more R^{Aa};

or two R^A on the same atom are taken together to form an oxo;

each R^{Aa} is independently deuterium, halogen, -CN, -NO₂, -OH, -OR^a, -OC(=O)R^a, -OC(=O)OR^b, -OC(=O)NR^cR^d, -SH, -SR^a, -S(=O)R^a, -S(=O)₂R^a, -S(=O)₂NR^cR^d, -NR^cR^d, -NR^bC(=O)NR^cR^d, -NR^bC(=O)R^a, -NR^bC(=O)OR^b, -NR^bS(=O)₂R^a, -C(=O)R^a, -C(=O)C(=O)R^a, -C(=O)OR^b, -C(=O)NR^cR^d, -C(=O)C(=O)NR^cR^d, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

or two R^{Aa} on the same atom are taken together to form an oxo;

n is 0-4;

R¹ and R² are independently hydrogen, deuterium, halogen, -CN, -NO₂, -OH, -OR^a, -NR^cR^d, -C(=O)R^a, -C(=O)OR^b, -C(=O)NR^cR^d, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, or heterocycloalkyl;

or R¹ and R² are taken together to form an oxo;

or R¹ and R² are taken together to form a cycloalkyl or heterocycloalkyl; wherein the cycloalkyl and heterocycloalkyl is optionally substituted with deuterium, halogen, -CN, -OH, -OCH₃, -NH₂, -NHCH₃, -N(CH₃)₂, -C(=O)CH₃, -C(=O)OH, -C(=O)OCH₃, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, or C₁-C₆heteroalkyl;

X is -C(R³)₂-, -NR⁴-, -O-, or -S-;

each R³ are independently hydrogen, deuterium, halogen, -CN, -NO₂, -OH, -OR^a, -NR^cR^d, -C(=O)R^a, -C(=O)OR^b, -C(=O)NR^cR^d, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, or heterocycloalkyl;

or two R³ are taken together to form an oxo;

R⁴ is hydrogen, -C(=O)R^a, -C(=O)OR^b, -C(=O)NR^cR^d, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, or heterocycloalkyl;

Ring D is cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

each R^D is independently hydrogen, deuterium, halogen, -CN, -NO₂, -OH, -OR^a, -OC(=O)R^a, -OC(=O)OR^b, -OC(=O)NR^cR^d, -SH, -SR^a, -S(=O)R^a, -S(=O)₂R^a, -S(=O)₂NR^cR^d, -NR^cR^d, -NR^bC(=O)NR^cR^d, -

NR^bC(=O)R^a, -NR^bC(=O)OR^b, -NR^bS(=O)₂R^a, -C(=O)R^a, -C(=O)OR^b, -C(=O)NR^cR^d, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein the alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is optionally and independently substituted with one or more R^{Da}.

or two R^D on the same atom are taken together to form an oxo;

each R^{Da} is independently deuterium, halogen, -CN, -NO₂, -OH, -OR^a, -OC(=O)R^a, -OC(=O)OR^b, -OC(=O)NR^cR^d, -SH, -SR^a, -S(=O)R^a, -S(=O)₂R^a, -S(=O)₂NR^cR^d, -NR^cR^d, -NR^bC(=O)NR^cR^d, -NR^bC(=O)R^a, -NR^bC(=O)OR^b, -NR^bS(=O)₂R^a, -C(=O)R^a, -C(=O)C(=O)R^a, -C(=O)OR^b, -C(=O)NR^cR^d, -C(=O)C(=O)NR^cR^d, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

or two R^{Da} on the same atom are taken together to form an oxo;

q is 0-6;

R⁹ is hydrogen, deuterium, halogen, -CN, -NO₂, -OH, -OR^a, -NR^cR^d, -C(=O)R^a, -C(=O)OR^b, -C(=O)NR^cR^d, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, or heterocycloalkyl;

R^{10} is hydrogen, deuterium, halogen, -CN, -NO₂, -OH, -OR^a, -NR^dR^d, -C(=O)R^a, -C(=O)OR^b, -C(=O)NR^cR^d, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, or heterocycloalkyl;

R¹¹ is hydrogen, deuterium, halogen, -CN, -NO₂, -OH, -OR^a, -NR^cR^d, -C(=O)R^a, -C(=O)OR^b, -C(=O)NR^cR^d, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, or heterocycloalkyl;

R¹² is hydrogen, deuterium, halogen, -CN, -NO₂, -OH, -OR^a, -OC(=O)R^a, -OC(=O)OR^b, -OC(=O)NR^cR^d, -SH, -SR^a, -S(=O)R^a, -S(=O)₂R^a, -S(=O)₂NR^cR^d, -S(=O)(=NR^b)R^a, -SiR^cR^dOR^b, -NR^cR^d, -NR^bC(=O)NR^cR^d, -NR^bC(=O)R^a, -NR^bC(=O)OR^b, -NR^bS(=O)₂R^a, -C(=O)R^a, -C(=O)OR^b, -C(=O)NR^cR^d, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, (C₁-C₆alkyl)cycloalkyl, (C₁-C₆alkyl)heterocycloalkyl, (C₁-C₆alkyl)aryl, or (C₁-C₆alkyl)heteroaryl; wherein the alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is optionally and independently substituted with one or more R^{12a}.

each R^{12a} is independently deuterium, halogen, -CN, -NO₂, -OH, -OR^a, -OC(=O)R^a, -OC(=O)OR^b, -OC(=O)NR^cR^d, -SH, -SR^a, -S(=O)R^a, -S(=O)₂R^a, -S(=O)₂NR^cR^d, -NR^cR^d, -NR^bC(=O)NR^cR^d, -NR^bC(=O)R^a, -NR^bC(=O)OR^b, -NR^bS(=O)₂R^a, -C(=O)R^a, -C(=O)C(=O)R^a, -C(=O)OR^b, -C(=O)NR^cR^d, -C(=O)C(=O)NR^cR^d, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

or two R^{12a} on the same atom are taken together to form an oxo;

R¹³ is hydrogen, deuterium, halogen, -CN, -NO₂, -OH, -OR^a, -NR^cR^d, -C(=O)R^a, -C(=O)OR^b, -C(=O)NR^cR^d, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, or heterocycloalkyl;

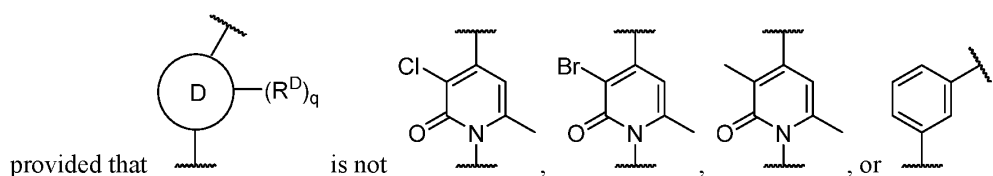
R¹⁴ is hydrogen, deuterium, halogen, -CN, -NO₂, -OH, -OR^a, -NR^cR^d, -C(=O)R^a, -C(=O)OR^b, -C(=O)NR^cR^d, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, or heterocycloalkyl;

each R^a is independently C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, C₁-C₆alkyl(cycloalkyl), C₁-C₆alkyl(heterocycloalkyl), C₁-C₆alkyl(aryl), or C₁-C₆alkyl(heteroaryl); wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more oxo, deuterium, halogen, -CN, -OH, -OCH₃, -S(=O)CH₃, -S(=O)₂CH₃, -S(=O)₂NH₂, -S(=O)₂NHCH₃, -S(=O)₂N(CH₃)₂, -NH₂, -NHCH₃, -N(CH₃)₂, -C(=O)CH₃, -C(=O)OH, -C(=O)OCH₃, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, or C₁-C₆heteroalkyl;

each R^b is independently hydrogen, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, C₁-C₆alkyl(cycloalkyl), C₁-C₆alkyl(heterocycloalkyl), C₁-C₆alkyl(aryl), or C₁-C₆alkyl(heteroaryl); wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more oxo, deuterium, halogen, -CN, -OH, -OCH₃, -S(=O)CH₃, -S(=O)₂CH₃, -S(=O)₂NH₂, -S(=O)₂NHCH₃, -S(=O)₂N(CH₃)₂, -NH₂, -NHCH₃, -N(CH₃)₂, -C(=O)CH₃, -C(=O)OH, -C(=O)OCH₃, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, or C₁-C₆heteroalkyl; and

each R^c and R^d are independently hydrogen, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, C₁-C₆alkyl(cycloalkyl), C₁-C₆alkyl(heterocycloalkyl), C₁-C₆alkyl(aryl), or C₁-C₆alkyl(heteroaryl); wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more oxo, deuterium, halogen, -CN, -OH, -OCH₃, -S(=O)CH₃, -S(=O)₂CH₃, -S(=O)₂NH₂, -S(=O)₂NHCH₃, -S(=O)₂N(CH₃)₂, -NH₂, -NHCH₃, -N(CH₃)₂, -C(=O)CH₃, -C(=O)OH, -C(=O)OCH₃, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, or C₁-C₆heteroalkyl;

or R^c and R^d are taken together with the atom to which they are attached to form a heterocycloalkyl optionally substituted with one or more oxo, deuterium, halogen, -CN, -OH, -OCH₃, -S(=O)CH₃, -S(=O)₂CH₃, -S(=O)₂NH₂, -S(=O)₂NHCH₃, -S(=O)₂N(CH₃)₂, -NH₂, -NHCH₃, -N(CH₃)₂, -C(=O)CH₃, -C(=O)OH, -C(=O)OCH₃, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, or C₁-C₆heteroalkyl;



[0074] In some embodiments of a compound of Formula (III), Ring A is heteroaryl. In some embodiments of a compound of Formula (III), Ring A is pyridyl. In some embodiments of a compound of Formula (III), Ring A is phenyl.

[0075] In some embodiments of a compound of Formula (III), each R^A is independently deuterium, halogen, -CN, -OH, -OR^a, -NR^dR^d, C₁-C₆alkyl, C₁-C₆haloalkyl, or C₁-C₆deuteroalkyl. In some embodiments of a compound of Formula (III), each R^A is independently halogen or C₁-C₆alkyl. In some embodiments of a compound of Formula (III), each R^A is independently halogen.

[0076] In some embodiments of a compound of Formula (III), n is 1 or 2. In some embodiments of a compound of Formula (III), n is 1-3. In some embodiments of a compound of Formula (III), n is 2. In some embodiments of a compound of Formula (III), n is 1.

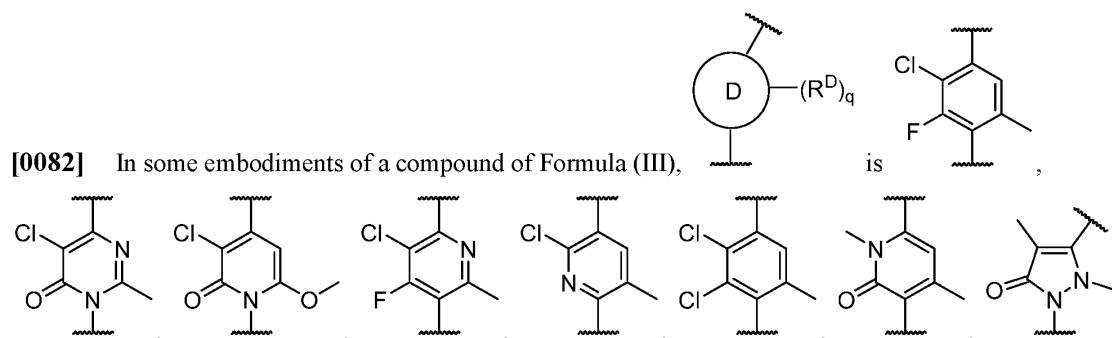
[0077] In some embodiments of a compound of Formula (III), R¹ and R² are independently hydrogen, deuterium, halogen, C₁-C₆alkyl, C₁-C₆haloalkyl, or C₁-C₆deuteroalkyl. In some embodiments of a compound of Formula (III), R¹ and R² are independently hydrogen, deuterium, halogen, or C₁-C₆alkyl. In some embodiments of a compound of Formula (III), R¹ and R² are hydrogen.

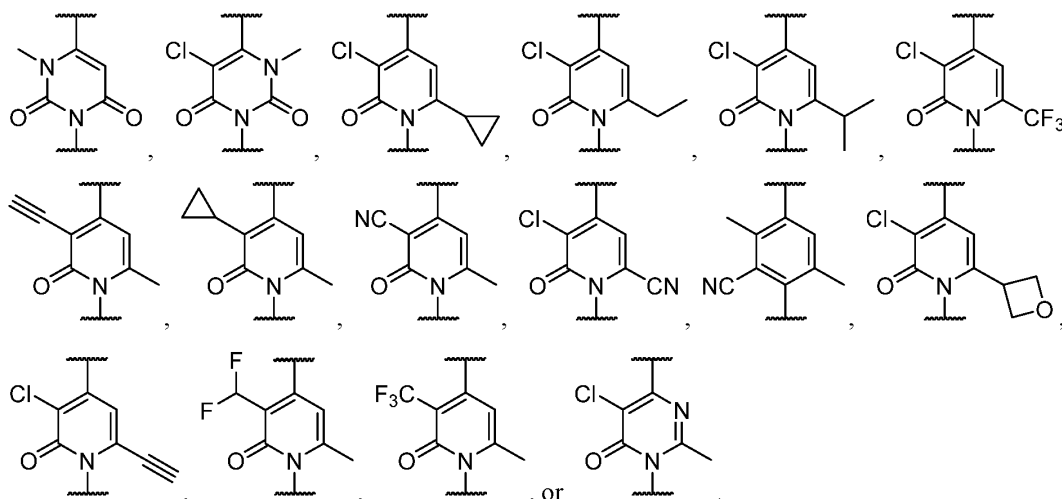
[0078] In some embodiments of a compound of Formula (III), X is -O-.

[0079] In some embodiments of a compound of Formula (III), Ring D is phenyl. In some embodiments of a compound of Formula (III), Ring D is pyridinyl.

[0080] In some embodiments of a compound of Formula (III), each R^D is independently hydrogen, deuterium, halogen, -CN, -OH, -OR^a, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkynyl, cycloalkyl, or heterocycloalkyl; or two R^D on the same atom are taken together to form an oxo. In some embodiments of a compound of Formula (III), each R^D is independently hydrogen, deuterium, halogen, -CN, -OR^a, C₁-C₆alkyl, C₂-C₆alkynyl, cycloalkyl, or heterocycloalkyl; or two R^D on the same atom are taken together to form an oxo.

[0081] In some embodiments of a compound of Formula (III), q is 1-4. In some embodiments of a compound of Formula (III), q is 1-3. In some embodiments of a compound of Formula (III), q is 2-4.





[0083] In some embodiments of a compound of Formula (III), R^9 is hydrogen, deuterium, halogen, C_1 - C_6 alkyl, or C_1 - C_6 haloalkyl.

[0084] In some embodiments of a compound of Formula (III), R^{10} is hydrogen, deuterium, halogen, C_1 - C_6 alkyl, or C_1 - C_6 haloalkyl.

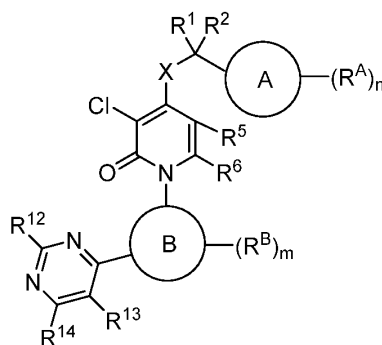
[0085] In some embodiments of a compound of Formula (III), R^{11} is hydrogen, deuterium, halogen, C_1 - C_6 alkyl, or C_1 - C_6 haloalkyl.

[0086] In some embodiments of a compound of Formula (III), R^{12} is hydrogen, deuterium, halogen, -CN, -OH, -OR^a, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_1 - C_6 deuteroalkyl, C_1 - C_6 hydroxyalkyl, C_1 - C_6 aminoalkyl, or C_1 - C_6 heteroalkyl. In some embodiments of a compound of Formula (III), R^{12} is C_1 - C_6 hydroxyalkyl.

[0087] In some embodiments of a compound of Formula (III), R^{13} is hydrogen, deuterium, halogen, or C_1 - C_6 alkyl.

[0088] In some embodiments of a compound of Formula (III), R^{14} is hydrogen, deuterium, halogen, or C_1 - C_6 alkyl.

[0089] A compound of Formula (IV), or a pharmaceutically acceptable salt, solvate, N-oxide, or stereoisomer thereof:



Formula (IV),

wherein:

Ring A is phenyl or heteroaryl;

each R^A is independently hydrogen, deuterium, halogen, -CN, -NO₂, -OH, -OR^a, -OC(=O)R^a, -OC(=O)OR^b, -OC(=O)NR^cR^d, -SH, -SR^a, -S(=O)R^a, -S(=O)₂R^a, -S(=O)₂NR^cR^d, -NR^cR^d, -NR^bC(=O)NR^cR^d, -NR^bC(=O)R^a, -NR^bC(=O)OR^b, -NR^bS(=O)₂R^a, -C(=O)R^a, -C(=O)OR^b, -C(=O)NR^cR^d, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein the alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is optionally and independently substituted with one or more R^{Aa};

or two R^A on the same atom are taken together to form an oxo;

each R^{Aa} is independently deuterium, halogen, -CN, -NO₂, -OH, -OR^a, -OC(=O)R^a, -OC(=O)OR^b, -OC(=O)NR^cR^d, -SH, -SR^a, -S(=O)R^a, -S(=O)₂R^a, -S(=O)₂NR^cR^d, -NR^cR^d, -NR^bC(=O)NR^cR^d, -NR^bC(=O)R^a, -NR^bC(=O)OR^b, -NR^bS(=O)₂R^a, -C(=O)R^a, -C(=O)C(=O)R^a, -C(=O)OR^b, -C(=O)NR^cR^d, -C(=O)C(=O)NR^cR^d, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

or two R^{Aa} on the same atom are taken together to form an oxo;

n is 0-4;

R¹ and R² are independently hydrogen, deuterium, halogen, -CN, -NO₂, -OH, -OR^a, -NR^cR^d, -C(=O)R^a, -C(=O)OR^b, -C(=O)NR^cR^d, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, or heterocycloalkyl;

or R¹ and R² are taken together to form an oxo;

or R¹ and R² are taken together to form a cycloalkyl or heterocycloalkyl; wherein the cycloalkyl and heterocycloalkyl is optionally substituted with deuterium, halogen, -CN, -OH, -OCH₃, -NH₂, -NHCH₃, -N(CH₃)₂, -C(=O)CH₃, -C(=O)OH, -C(=O)OCH₃, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, or C₁-C₆heteroalkyl;

X is -C(R³)₂-, -NR⁴-, -O-, or -S-;

each R³ are independently hydrogen, deuterium, halogen, -CN, -NO₂, -OH, -OR^a, -NR^cR^d, -C(=O)R^a, -C(=O)OR^b, -C(=O)NR^cR^d, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, or heterocycloalkyl;

or two R³ are taken together to form an oxo;

R⁴ is hydrogen, -C(=O)R^a, -C(=O)OR^b, -C(=O)NR^cR^d, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, or heterocycloalkyl;

R⁵ is hydrogen, deuterium, halogen, -CN, -NO₂, -OH, -OR^a, -NR^cR^d, -C(=O)R^a, -C(=O)OR^b, -C(=O)NR^cR^d, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, or heterocycloalkyl;

R^6 is hydrogen, deuterium, halogen, -CN, -NO₂, -OH, -OR^a, -NR^cR^d, -C(=O)R^a, -C(=O)OR^b, -C(=O)NR^cR^d, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, or heterocycloalkyl;

Ring B is cycloalkyl, heterocycloalkyl, alkyl, or heteroaryl;

each R^B is independently hydrogen, deuterium, halogen, -CN, -NO₂, -OH, -OR^a, -OC(=O)R^a, -OC(=O)OR^b, -OC(=O)NR^cR^d, -SH, -SR^a, -S(=O)R^a, -S(=O)₂R^a, -S(=O)₂NR^cR^d, -NR^cR^d, -NR^bC(=O)NR^cR^d, -NR^bC(=O)R^a, -NR^bC(=O)OR^b, -NR^bS(=O)₂R^a, -C(=O)R^a, -C(=O)OR^b, -C(=O)NR^cR^d, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein the alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is optionally and independently substituted with one or more R^{Ba};

or two R^B on the same atom are taken together to form an oxo;

each R^{Ba} is independently deuterium, halogen, -CN, -NO₂, -OH, -OR^a, -OC(=O)R^a, -OC(=O)OR^b, -OC(=O)NR^cR^d, -SH, -SR^a, -S(=O)R^a, -S(=O)₂R^a, -S(=O)₂NR^cR^d, -NR^cR^d, -NR^bC(=O)NR^cR^d, -NR^bC(=O)R^a, -NR^bC(=O)OR^b, -NR^bS(=O)₂R^a, -C(=O)R^a, -C(=O)C(=O)R^a, -C(=O)OR^b, -C(=O)NR^cR^d, -C(=O)C(=O)NR^cR^d, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

or two R^{Ba} on the same atom are taken together to form an oxo;

m is 0-4;

R¹², R¹³, and R¹⁴ are defined in (a), (b), or (c) as follow:

(a)

R¹² is deuterium, halogen, -CN, -NO₂, -OH, -OR^a, -OC(=O)R^a, -OC(=O)OR^b, -OC(=O)NR^cR^d, -SH, -SR^a, -S(=O)R^a, -S(=O)₂R^a, -S(=O)₂NR^cR^d, -S(=O)(=NR^b)R^a, -SiR^cR^dOR^b, -NR^cR^d, -NR^bC(=O)NR^cR^d, -NR^bC(=O)R^a, -NR^bC(=O)OR^b, -NR^bS(=O)₂R^a, -C(=O)R^a, -C(=O)OR^b, -C(=O)NR^cR^d, C₁-C₆haloalkyl, C₁-C₆dihydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆hydroxyheteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, (C₁-C₆alkyl)cycloalkyl, (C₁-C₆alkyl)heterocycloalkyl, (C₁-C₆alkyl)aryl, or (C₁-C₆alkyl)heteroaryl; wherein the alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is optionally and independently substituted with one or more R^{12a};

each R^{12a} is independently deuterium, halogen, -CN, -NO₂, -OH, -OR^a, -OC(=O)R^a, -OC(=O)OR^b, -OC(=O)NR^cR^d, -SH, -SR^a, -S(=O)R^a, -S(=O)₂R^a, -S(=O)₂NR^cR^d, -NR^cR^d, -NR^bC(=O)NR^cR^d, -NR^bC(=O)R^a, -NR^bC(=O)OR^b, -NR^bS(=O)₂R^a, -C(=O)R^a, -C(=O)C(=O)R^a, -C(=O)OR^b, -C(=O)NR^cR^d, -C(=O)C(=O)NR^cR^d, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

or two R^{12a} on the same atom are taken together to form an oxo;

R¹³ is hydrogen, deuterium, halogen, -CN, -NO₂, -OH, -OR^a, -NR^cR^d, -C(=O)R^a, -C(=O)OR^b, -C(=O)NR^cR^d, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, or heterocycloalkyl;

R¹⁴ is hydrogen, deuterium, halogen, -CN, -NO₂, -OH, -OR^a, -NR^cR^d, -C(=O)R^a, -C(=O)OR^b, -C(=O)NR^cR^d, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, or heterocycloalkyl;

or

(b)

R¹² is hydrogen, deuterium, halogen, -CN, -NO₂, -OH, -OR^a, -NR^cR^d, -C(=O)R^a, -C(=O)OR^b, -C(=O)NR^cR^d, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, or heterocycloalkyl;

R¹³ is deuterium, halogen, -CN, -NO₂, -OH, -OR^a, -NR^cR^d, -C(=O)R^a, -C(=O)OR^b, -C(=O)NR^cR^d, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, or heterocycloalkyl;

R¹⁴ is hydrogen, deuterium, halogen, -CN, -NO₂, -OH, -OR^a, -NR^cR^d, -C(=O)R^a, -C(=O)OR^b, -C(=O)NR^cR^d, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, or heterocycloalkyl;

or

(c)

R¹² is hydrogen, deuterium, halogen, -CN, -NO₂, -OH, -OR^a, -NR^cR^d, -C(=O)R^a, -C(=O)OR^b, -C(=O)NR^cR^d, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, or heterocycloalkyl;

R¹³ is hydrogen, deuterium, halogen, -CN, -NO₂, -OH, -OR^a, -NR^cR^d, -C(=O)R^a, -C(=O)OR^b, -C(=O)NR^cR^d, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, or heterocycloalkyl;

R¹⁴ is deuterium, halogen, -CN, -NO₂, -OH, -OR^a, -NR^cR^d, -C(=O)R^a, -C(=O)OR^b, -C(=O)NR^cR^d, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, or heterocycloalkyl;

each R^a is independently C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl,

C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, C₁-C₆alkyl(cycloalkyl), C₁-C₆alkyl(heterocycloalkyl), C₁-C₆alkyl(aryl), or

C₁-C₆alkyl(heteroaryl); wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and

heteroaryl is independently optionally substituted with one or more oxo, deuterium, halogen, -CN, -OH,

-OCH₃, -S(=O)CH₃, -S(=O)₂CH₃, -S(=O)₂NH₂, -S(=O)₂NHCH₃, -S(=O)₂N(CH₃)₂, -NH₂, -NHCH₃, -

N(CH₃)₂, -C(=O)CH₃, -C(=O)OH, -C(=O)OCH₃, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl,

C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, or C₁-C₆heteroalkyl;

each R^b is independently hydrogen, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, C₁-C₆alkyl(cycloalkyl), C₁-C₆alkyl(heterocycloalkyl), C₁-C₆alkyl(aryl), or C₁-C₆alkyl(heteroaryl); wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more oxo, deuterium, halogen, -CN, -OH, -OCH₃, -S(=O)CH₃, -S(=O)₂CH₃, -S(=O)₂NH₂, -S(=O)₂NHCH₃, -S(=O)₂N(CH₃)₂, -NH₂, -NHCH₃, -N(CH₃)₂, -C(=O)CH₃, -C(=O)OH, -C(=O)OCH₃, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, or C₁-C₆heteroalkyl; and

each R^c and R^d are independently hydrogen, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, C₁-C₆alkyl(cycloalkyl), C₁-C₆alkyl(heterocycloalkyl), C₁-C₆alkyl(aryl), or C₁-C₆alkyl(heteroaryl); wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more oxo, deuterium, halogen, -CN, -OH, -OCH₃, -S(=O)CH₃, -S(=O)₂CH₃, -S(=O)₂NH₂, -S(=O)₂NHCH₃, -S(=O)₂N(CH₃)₂, -NH₂, -NHCH₃, -N(CH₃)₂, -C(=O)CH₃, -C(=O)OH, -C(=O)OCH₃, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, or C₁-C₆heteroalkyl;

or R^c and R^d are taken together with the atom to which they are attached to form a heterocycloalkyl optionally substituted with one or more oxo, deuterium, halogen, -CN, -OH, -OCH₃, -S(=O)CH₃, -S(=O)₂CH₃, -S(=O)₂NH₂, -S(=O)₂NHCH₃, -S(=O)₂N(CH₃)₂, -NH₂, -NHCH₃, -N(CH₃)₂, -C(=O)CH₃, -C(=O)OH, -C(=O)OCH₃, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, or C₁-C₆heteroalkyl.

[0090] In some embodiments of a compound of Formula (IV), Ring A is heteroaryl. In some embodiments of a compound of Formula (IV), Ring A is pyridyl. In some embodiments of a compound of Formula (IV), Ring A is phenyl.

[0091] In some embodiments of a compound of Formula (IV), each R^A is independently deuterium, halogen, -CN, -OH, -OR^a, -NR^cR^d, C₁-C₆alkyl, C₁-C₆haloalkyl, or C₁-C₆deuteroalkyl. In some embodiments of a compound of Formula (IV), each R^A is independently halogen or C₁-C₆alkyl. In some embodiments of a compound of Formula (IV), each R^A is independently halogen.

[0092] In some embodiments of a compound of Formula (IV), n is 1 or 2. In some embodiments of a compound of Formula (IV), n is 1-3. In some embodiments of a compound of Formula (IV), n is 2. In some embodiments of a compound of Formula (IV), n is 1.

[0093] In some embodiments of a compound of Formula (IV), R¹ and R² are independently hydrogen, deuterium, halogen, C₁-C₆alkyl, C₁-C₆haloalkyl, or C₁-C₆deuteroalkyl. In some embodiments of a compound of Formula (IV), R¹ and R² are independently hydrogen, deuterium, halogen, or C₁-C₆alkyl. In some embodiments of a compound of Formula (IV), R¹ and R² are hydrogen.

[0094] In some embodiments of a compound of Formula (IV), X is -O-.

[0095] In some embodiments of a compound of Formula (IV), R^5 is hydrogen, deuterium, halogen, -CN, -OH, -OR^a, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkynyl, or cycloalkyl. In some embodiments of a compound of Formula (IV), R^5 is hydrogen, deuterium, halogen, -CN, or C₁-C₆alkyl.

[0096] In some embodiments of a compound of Formula (IV), R^6 is hydrogen, deuterium, halogen, -CN, -OH, -OR^a, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkynyl, or cycloalkyl. In some embodiments of a compound of Formula (IV), R^6 is hydrogen, deuterium, halogen, -CN, or C₁-C₆alkyl.

[0097] In some embodiments of a compound of Formula (IV), Ring B is a 6-membered heteroaryl. In some embodiments of a compound of Formula (IV), Ring B is pyridinyl.

[0098] In some embodiments of a compound of Formula (IV), each R^B is independently hydrogen, deuterium, halogen, -CN, -OH, -OR^a, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkynyl, or cycloalkyl. In some embodiments of a compound of Formula (IV), each R^B is independently hydrogen, deuterium, halogen, -CN, -OR^a, C₁-C₆alkyl, C₂-C₆alkynyl, or cycloalkyl. In some embodiments of a compound of Formula (IV), each R^B is independently C₁-C₆alkyl.

[0099] In some embodiments of a compound of Formula (IV), m is 1 or 2. In some embodiments of a compound of Formula (IV), m is 1-4. In some embodiments of a compound of Formula (IV), m is 2-4. In some embodiments of a compound of Formula (IV), m is 1. In some embodiments of a compound of Formula (IV), m is 2.

[00100] In some embodiments of a compound of Formula (IV):

R^{12} is deuterium, halogen, -CN, -OH, -OR^a, -S(=O)₂NR^cR^d, -S(=O)(=NR^b)R^a, -SiR^cR^dOR^b, -NR^bS(=O)₂R^a, C₁-C₆haloalkyl, C₁-C₆dihydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆hydroxyheteroalkyl, C₂-C₆alkynyl, cycloalkyl, heterocycloalkyl, (C₁-C₆alkyl)cycloalkyl, or (C₁-C₆alkyl)heterocycloalkyl; wherein the alkyl, alkynyl, cycloalkyl, and heterocycloalkyl is optionally and independently substituted with one or more R^{12a} ;

each R^{12a} is independently deuterium, halogen, -CN, -OH, -OR^a, -NR^cR^d, C₁-C₆alkyl, C₁-C₆haloalkyl,

C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, or C₁-C₆heteroalkyl; or two R^{12a} on the same atom are taken together to form an oxo;

R^{13} is hydrogen, deuterium, halogen, or C₁-C₆alkyl; and

R^{14} is hydrogen, deuterium, halogen, or C₁-C₆alkyl.

[00101] In some embodiments of a compound of Formula (IV):

R^{12} is -S(=O)(=NR^b)R^a, -SiR^cR^dOR^b, -NR^bS(=O)₂R^a, C₁-C₆haloalkyl, C₁-C₆dihydroxyalkyl,

C₁-C₆aminoalkyl, C₁-C₆hydroxyheteroalkyl, C₂-C₆alkynyl, cycloalkyl, heterocycloalkyl, or (C₁-C₆alkyl)cycloalkyl; wherein the alkyl, alkynyl, cycloalkyl, and heterocycloalkyl is optionally and independently substituted with one or more R^{12a} ;

each R^{12a} is independently -OH, -NR^cR^d, or C₁-C₆haloalkyl;

R¹³ is hydrogen; and

R¹⁴ is hydrogen.

[00102] In some embodiments of a compound of Formula (IV):

R¹² is C₁-C₆hydroxyalkyl;

R¹³ is deuterium, halogen, -CN, -OH, -OR^a, -NR^cR^d, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkynyl, cycloalkyl, or heterocycloalkyl; and

R¹⁴ is hydrogen, deuterium, halogen, or C₁-C₆alkyl.

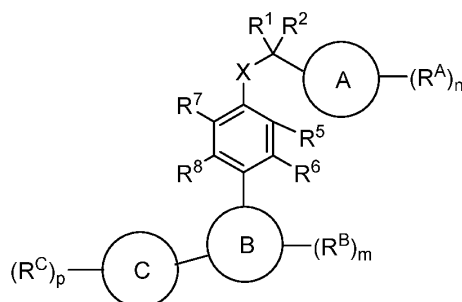
[00103] In some embodiments of a compound of Formula (IV):

R¹² is C₁-C₆hydroxyalkyl;

R¹³ is hydrogen, deuterium, halogen, or C₁-C₆alkyl; and

R¹⁴ is deuterium, halogen, -CN, -OH, -OR^a, -NR^cR^d, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkynyl, cycloalkyl, or heterocycloalkyl.

[00104] Also disclosed herein is a compound of Formula (V), or a pharmaceutically acceptable salt, solvate, N-oxide, or stereoisomer thereof:



Formula (V),

wherein:

Ring A is phenyl or heteroaryl;

each R^A is independently hydrogen, deuterium, halogen, -CN, -NO₂, -OH, -OR^a, -OC(=O)R^a, -OC(=O)OR^b, -OC(=O)NR^cR^d, -SH, -SR^a, -S(=O)R^a, -S(=O)₂R^a, -S(=O)₂NR^cR^d, -NR^cR^d, -NR^bC(=O)NR^cR^d, -NR^bC(=O)R^a, -NR^bC(=O)OR^b, -NR^bS(=O)₂R^a, -C(=O)R^a, -C(=O)OR^b, -C(=O)NR^cR^d, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein the alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is optionally and independently substituted with one or more R^{Aa};

or two R^A on the same atom are taken together to form an oxo;

each R^{Aa} is independently deuterium, halogen, -CN, -NO₂, -OH, -OR^a, -OC(=O)R^a, -OC(=O)OR^b, -OC(=O)NR^cR^d, -SH, -SR^a, -S(=O)R^a, -S(=O)₂R^a, -S(=O)₂NR^cR^d, -NR^cR^d, -NR^bC(=O)NR^cR^d, -NR^bC(=O)R^a, -NR^bC(=O)OR^b, -NR^bS(=O)₂R^a, -C(=O)R^a, -C(=O)C(=O)R^a, -C(=O)OR^b, -C(=O)NR^cR^d, -C(=O)C(=O)NR^cR^d, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl,

C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

or two R^{Aa} on the same atom are taken together to form an oxo;

n is 0-4;

R¹ and R² are independently hydrogen, deuterium, halogen, -CN, -NO₂, -OH, -OR^a, -NR^cR^d, -C(=O)R^a, -C(=O)OR^b, -C(=O)NR^cR^d, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, or heterocycloalkyl;

or R¹ and R² are taken together to form an oxo;

or R¹ and R² are taken together to form a cycloalkyl or heterocycloalkyl; wherein the cycloalkyl and heterocycloalkyl is optionally substituted with deuterium, halogen, -CN, -OH, -OCH₃, -NH₂, -NHCH₃, -N(CH₃)₂, -C(=O)CH₃, -C(=O)OH, -C(=O)OCH₃, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, or C₁-C₆heteroalkyl;

X is -C(R³)₂-, -NR⁴-, -O-, or -S-;

each R³ are independently hydrogen, deuterium, halogen, -CN, -NO₂, -OH, -OR^a, -NR^cR^d, -C(=O)R^a, -C(=O)OR^b, -C(=O)NR^cR^d, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, or heterocycloalkyl;

or two R³ are taken together to form an oxo;

R⁴ is hydrogen, -C(=O)R^a, -C(=O)OR^b, -C(=O)NR^cR^d, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, or heterocycloalkyl;

R⁵ is hydrogen, deuterium, halogen, -CN, -NO₂, -OH, -OR^a, -NR^cR^d, -C(=O)R^a, -C(=O)OR^b, -C(=O)NR^cR^d, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, or heterocycloalkyl;

R⁶ is hydrogen, deuterium, halogen, -CN, -NO₂, -OH, -OR^a, -NR^cR^d, -C(=O)R^a, -C(=O)OR^b, -C(=O)NR^cR^d, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, or heterocycloalkyl;

R⁷ is hydrogen, deuterium, halogen, -CN, -NO₂, -OH, -OR^a, -NR^cR^d, -C(=O)R^a, -C(=O)OR^b, -C(=O)NR^cR^d, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, or heterocycloalkyl;

R⁸ is hydrogen, deuterium, halogen, -CN, -NO₂, -OH, -OR^a, -NR^cR^d, -C(=O)R^a, -C(=O)OR^b, -C(=O)NR^cR^d, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, or heterocycloalkyl;

Ring B is pyridinone, pyrimidinone, pyrazinone, or pyridazinone;

each R^B is independently hydrogen, deuterium, halogen, -CN, -NO₂, -OH, -OR^a, -OC(=O)R^a, -OC(=O)OR^b, -OC(=O)NR^cR^d, -SH, -SR^a, -S(=O)R^a, -S(=O)₂R^a, -S(=O)₂NR^cR^d, -NR^cR^d, -NR^bC(=O)NR^cR^d, -NR^bC(=O)R^a, -NR^bC(=O)OR^b, -NR^bS(=O)₂R^a, -C(=O)R^a, -C(=O)OR^b, -C(=O)NR^cR^d, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-

C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein the alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is optionally and independently substituted with one or more R^{Ba};

or two R^B on the same atom are taken together to form an oxo;

each R^{Ba} is independently deuterium, halogen, -CN, -NO₂, -OH, -OR^a, -OC(=O)R^a, -OC(=O)OR^b, -OC(=O)NR^cR^d, -SH, -SR^a, -S(=O)R^a, -S(=O)₂R^a, -S(=O)₂NR^cR^d, -NR^cR^d, -NR^bC(=O)NR^cR^d, -NR^bC(=O)R^a, -NR^bC(=O)OR^b, -NR^bS(=O)₂R^a, -C(=O)R^a, -C(=O)C(=O)R^a, -C(=O)OR^b, -C(=O)NR^cR^d, -C(=O)C(=O)NR^cR^d, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

or two R^{Ba} on the same atom are taken together to form an oxo;

m is 0-4;

Ring C is heterocycloalkyl or heteroaryl;

each R^C is independently hydrogen, deuterium, halogen, -CN, -NO₂, -OH, -OR^a, -OC(=O)R^a, -OC(=O)OR^b, -OC(=O)NR^cR^d, -SH, -SR^a, -S(=O)R^a, -S(=O)₂R^a, -S(=O)₂NR^cR^d, -S(=O)(=NR^b)R^a, -SiR^cR^dOR^b, -NR^cR^d, -NR^bC(=O)NR^cR^d, -NR^bC(=O)R^a, -NR^bC(=O)OR^b, -NR^bS(=O)₂R^a, -C(=O)R^a, -C(=O)OR^b, -C(=O)NR^cR^d, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, (C₁-C₆alkyl)cycloalkyl, (C₁-C₆alkyl)heterocycloalkyl, (C₁-C₆alkyl)aryl, or (C₁-C₆alkyl)heteroaryl; wherein the alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is optionally and independently substituted with one or more R^{Ca};

or two R^C on the same atom are taken together to form an oxo;

each R^{Ca} is independently deuterium, halogen, -CN, -NO₂, -OH, -OR^a, -OC(=O)R^a, -OC(=O)OR^b, -OC(=O)NR^cR^d, -SH, -SR^a, -S(=O)R^a, -S(=O)₂R^a, -S(=O)₂NR^cR^d, -NR^cR^d, -NR^bC(=O)NR^cR^d, -NR^bC(=O)R^a, -NR^bC(=O)OR^b, -NR^bS(=O)₂R^a, -C(=O)R^a, -C(=O)C(=O)R^a, -C(=O)OR^b, -C(=O)NR^cR^d, -C(=O)C(=O)NR^cR^d, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

or two R^{Ca} on the same atom are taken together to form an oxo;

p is 0-4;

each R^a is independently C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, C₁-C₆alkyl(cycloalkyl), C₁-C₆alkyl(heterocycloalkyl), C₁-C₆alkyl(aryl), or C₁-C₆alkyl(heteroaryl); wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more oxo, deuterium, halogen, -CN, -OH, -OCH₃, -S(=O)CH₃, -S(=O)₂CH₃, -S(=O)₂NH₂, -S(=O)₂NHCH₃, -S(=O)₂N(CH₃)₂, -NH₂, -NHCH₃, -

$N(CH_3)_2$, $-C(=O)CH_3$, $-C(=O)OH$, $-C(=O)OCH_3$, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_1 - C_6 deuteroalkyl, C_1 - C_6 hydroxyalkyl, C_1 - C_6 aminoalkyl, or C_1 - C_6 heteroalkyl;

each R^b is independently hydrogen, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_1 - C_6 deuteroalkyl, C_1 - C_6 hydroxyalkyl, C_1 - C_6 aminoalkyl, C_1 - C_6 heteroalkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, C_1 - C_6 alkyl(cycloalkyl), C_1 - C_6 alkyl(heterocycloalkyl), C_1 - C_6 alkyl(aryl), or C_1 - C_6 alkyl(heteroaryl); wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more oxo, deuterium, halogen, $-CN$, $-OH$, $-OCH_3$, $-S(=O)CH_3$, $-S(=O)_2CH_3$, $-S(=O)_2NH_2$, $-S(=O)_2NHCH_3$, $-S(=O)_2N(CH_3)_2$, $-NH_2$, $-NHCH_3$, $-N(CH_3)_2$, $-C(=O)CH_3$, $-C(=O)OH$, $-C(=O)OCH_3$, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_1 - C_6 deuteroalkyl, C_1 - C_6 hydroxyalkyl, C_1 - C_6 aminoalkyl, or C_1 - C_6 heteroalkyl; and

each R^c and R^d are independently hydrogen, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_1 - C_6 deuteroalkyl, C_1 - C_6 hydroxyalkyl, C_1 - C_6 aminoalkyl, C_1 - C_6 heteroalkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, C_1 - C_6 alkyl(cycloalkyl), C_1 - C_6 alkyl(heterocycloalkyl), C_1 - C_6 alkyl(aryl), or C_1 - C_6 alkyl(heteroaryl); wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more oxo, deuterium, halogen, $-CN$, $-OH$, $-OCH_3$, $-S(=O)CH_3$, $-S(=O)_2CH_3$, $-S(=O)_2NH_2$, $-S(=O)_2NHCH_3$, $-S(=O)_2N(CH_3)_2$, $-NH_2$, $-NHCH_3$, $-N(CH_3)_2$, $-C(=O)CH_3$, $-C(=O)OH$, $-C(=O)OCH_3$, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_1 - C_6 deuteroalkyl, C_1 - C_6 hydroxyalkyl, C_1 - C_6 aminoalkyl, or C_1 - C_6 heteroalkyl;

or R^c and R^d are taken together with the atom to which they are attached to form a heterocycloalkyl optionally substituted with one or more oxo, deuterium, halogen, $-CN$, $-OH$, $-OCH_3$, $-S(=O)CH_3$, $-S(=O)_2CH_3$, $-S(=O)_2NH_2$, $-S(=O)_2NHCH_3$, $-S(=O)_2N(CH_3)_2$, $-NH_2$, $-NHCH_3$, $-N(CH_3)_2$, $-C(=O)CH_3$, $-C(=O)OH$, $-C(=O)OCH_3$, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_1 - C_6 deuteroalkyl, C_1 - C_6 hydroxyalkyl, C_1 - C_6 aminoalkyl, or C_1 - C_6 heteroalkyl.

[00105] In some embodiments of a compound of Formula (V), Ring A is heteroaryl.

[00106] In some embodiments of a compound of Formula (V), Ring A is pyridyl.

[00107] In some embodiments of a compound of Formula (V), Ring A is phenyl.

[00108] In some embodiments of a compound of Formula (V), each R^A is independently deuterium, halogen, $-CN$, $-OH$, $-OR^a$, $-NR^cR^d$, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, or C_1 - C_6 deuteroalkyl. In some embodiments of a compound of Formula (V), each R^A is independently halogen or C_1 - C_6 alkyl. In some embodiments of a compound of Formula (V), each R^A is independently halogen.

[00109] In some embodiments of a compound of Formula (V), n is 1 or 2. In some embodiments of a compound of Formula (V), n is 1-3. In some embodiments of a compound of Formula (V), n is 2. In some embodiments of a compound of Formula (V), n is 1.

[00110] In some embodiments of a compound of Formula (V), R^1 and R^2 are independently hydrogen, deuterium, halogen, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, or C_1 - C_6 deuteroalkyl. In some embodiments of a compound of Formula (V), R^1 and R^2 are independently hydrogen, deuterium, halogen, or C_1 - C_6 alkyl. In some embodiments of a compound of Formula (V), R^1 and R^2 are hydrogen.

[00111] In some embodiments of a compound of Formula (V), X is -O-.

[00112] In some embodiments of a compound of Formula (V), R⁵ is hydrogen, deuterium, halogen, -CN, -OH, -OR^a, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkynyl, or cycloalkyl. In some embodiments of a compound of Formula (V), R⁵ is hydrogen, deuterium, halogen, -CN, or C₁-C₆alkyl.

[00113] In some embodiments of a compound of Formula (V), R⁶ is hydrogen, deuterium, halogen, -CN, -OH, -OR^a, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkynyl, or cycloalkyl. In some embodiments of a compound of Formula (V), R⁶ is hydrogen, deuterium, halogen, -CN, or C₁-C₆alkyl.

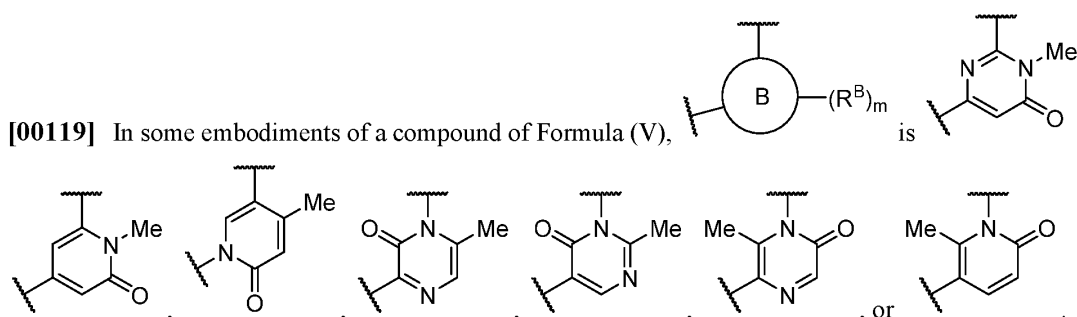
[00114] In some embodiments of a compound of Formula (V), R⁷ is hydrogen, deuterium, halogen, -CN, -OH, -OR^a, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkynyl, or cycloalkyl. In some embodiments of a compound of Formula (V), R⁷ is hydrogen, deuterium, halogen, -CN, or C₁-C₆alkyl.

[00115] In some embodiments of a compound of Formula (V), R⁸ is hydrogen, deuterium, halogen, -CN, -OH, -OR^a, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkynyl, or cycloalkyl. In some embodiments of a compound of Formula (V), R⁸ is hydrogen, deuterium, halogen, -CN, or C₁-C₆alkyl.

[00116] In some embodiments of a compound of Formula (V), Ring B is pyridinone. In some embodiments of a compound of Formula (V), Ring B is pyrimidinone. In some embodiments of a compound of Formula (V), Ring B is pyrazinone. In some embodiments of a compound of Formula (V), Ring B is pyridazinone.

[00117] In some embodiments of a compound of Formula (V), each R^B is independently hydrogen, deuterium, halogen, -CN, -OH, -OR^a, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkynyl, or cycloalkyl. In some embodiments of a compound of Formula (V), each R^B is independently C₁-C₆alkyl.

[00118] In some embodiments of a compound of Formula (IV), m is 1 or 2. In some embodiments of a compound of Formula (IV), m is 1-4. In some embodiments of a compound of Formula (IV), m is 2-4. In some embodiments of a compound of Formula (IV), m is 1. In some embodiments of a compound of Formula (IV), m is 2.

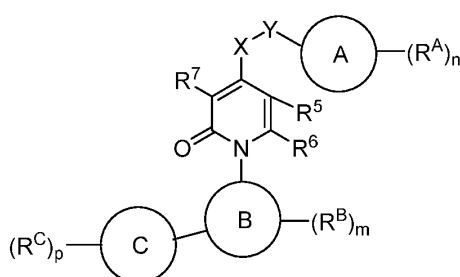


[00120] In some embodiments of a compound of Formula (V), Ring C is a 5- or 6-membered heteroaryl. In some embodiments of a compound of Formula (V), Ring C is a pyrimidinyl.

[00121] In some embodiments of a compound of Formula (V), each R^C is independently hydrogen, deuterium, halogen, -CN, -OH, -OR^a, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, or C₁-C₆heteroalkyl. In some embodiments of a compound of Formula (V), each R^C is independently C₁-C₆hydroxyalkyl.

[00122] In some embodiments of a compound of Formula (V), p is 1 or 2. In some embodiments of a compound of Formula (V), p is 1-3. In some embodiments of a compound of Formula (V), p is 1. In some embodiments of a compound of Formula (V), p is 2.

[00123] Also disclosed herein is a compound of Formula (VI), or a pharmaceutically acceptable salt, solvate, N-oxide, or stereoisomer thereof:



Formula (VI),

wherein:

Ring A is phenyl or heteroaryl;

each R^A is independently hydrogen, deuterium, halogen, -CN, -NO₂, -OH, -OR^a, -OC(=O)R^a, -OC(=O)OR^b, -OC(=O)NR^cR^d, -SH, -SR^a, -S(=O)R^a, -S(=O)₂R^a, -S(=O)₂NR^cR^d, -NR^cR^d, -NR^bC(=O)NR^cR^d, -NR^bC(=O)R^a, -NR^bC(=O)OR^b, -NR^bS(=O)₂R^a, -C(=O)R^a, -C(=O)OR^b, -C(=O)NR^cR^d, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein the alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is optionally and independently substituted with one or more R^{Aa};

or two R^A on the same atom are taken together to form an oxo;

each R^{Aa} is independently deuterium, halogen, -CN, -NO₂, -OH, -OR^a, -OC(=O)R^a, -OC(=O)OR^b, -OC(=O)NR^cR^d, -SH, -SR^a, -S(=O)R^a, -S(=O)₂R^a, -S(=O)₂NR^cR^d, -NR^cR^d, -NR^bC(=O)NR^cR^d, -NR^bC(=O)R^a, -NR^bC(=O)OR^b, -NR^bS(=O)₂R^a, -C(=O)R^a, -C(=O)C(=O)R^a, -C(=O)OR^b, -C(=O)NR^cR^d, -C(=O)C(=O)NR^cR^d, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

or two R^{Aa} on the same atom are taken together to form an oxo;

n is 0-4;

X and Y are defined in (a) or (b) as follow:

(a)

X is $-C(R^3)_2-$, $-NR^4-$, $-O-$, or $-S-$;

Y is $-CR^1R^2-$;

R^1 halogen, $-CN$, $-NO_2$, $-OH$, $-OR^a$, $-NR^cR^d$, $-C(=O)R^a$, $-C(=O)OR^b$, $-C(=O)NR^cR^d$, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_1 - C_6 deuteroalkyl, C_1 - C_6 hydroxyalkyl, C_1 - C_6 aminoalkyl, C_1 - C_6 heteroalkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, cycloalkyl, or heterocycloalkyl;

R^2 is hydrogen, deuterium, halogen, $-CN$, $-NO_2$, $-OH$, $-OR^a$, $-NR^cR^d$, $-C(=O)R^a$, $-C(=O)OR^b$, $-C(=O)NR^cR^d$, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_1 - C_6 deuteroalkyl, C_1 - C_6 hydroxyalkyl, C_1 - C_6 aminoalkyl, C_1 - C_6 heteroalkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, cycloalkyl, or heterocycloalkyl;

or R^1 and R^2 are taken together to form an oxo;

or R^1 and R^2 are taken together to form a cycloalkyl or heterocycloalkyl; wherein the cycloalkyl and heterocycloalkyl is optionally substituted with deuterium, halogen, $-CN$, $-OH$, $-OCH_3$, $-NH_2$, $-NHCH_3$, $-N(CH_3)_2$, $-C(=O)CH_3$, $-C(=O)OH$, $-C(=O)OCH_3$, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_1 - C_6 deuteroalkyl, C_1 - C_6 hydroxyalkyl, C_1 - C_6 aminoalkyl, or C_1 - C_6 heteroalkyl;

each R^3 are independently hydrogen, deuterium, halogen, $-CN$, $-NO_2$, $-OH$, $-OR^a$, $-NR^cR^d$, $-C(=O)R^a$, $-C(=O)OR^b$, $-C(=O)NR^cR^d$, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_1 - C_6 deuteroalkyl, C_1 - C_6 hydroxyalkyl, C_1 - C_6 aminoalkyl, C_1 - C_6 heteroalkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, cycloalkyl, or heterocycloalkyl;

or two R^3 are taken together to form an oxo; and

R^4 is hydrogen, $-C(=O)R^a$, $-C(=O)OR^b$, $-C(=O)NR^cR^d$, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_1 - C_6 deuteroalkyl, C_1 - C_6 hydroxyalkyl, C_1 - C_6 aminoalkyl, C_1 - C_6 heteroalkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, cycloalkyl, or heterocycloalkyl;

or

(b)

X is $-C(R^3)_2-$, $-NR^4-$, or $-S-$;

Y is $-CR^1R^2-$, $-NR^4-$, $-O-$, or $-S-$;

R^1 and R^2 are independently hydrogen, deuterium, halogen, $-CN$, $-NO_2$, $-OH$, $-OR^a$, $-NR^cR^d$, $-C(=O)R^a$, $-C(=O)OR^b$, $-C(=O)NR^cR^d$, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_1 - C_6 deuteroalkyl, C_1 - C_6 hydroxyalkyl, C_1 - C_6 aminoalkyl, C_1 - C_6 heteroalkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, cycloalkyl, or heterocycloalkyl;

or R^1 and R^2 are taken together to form an oxo;

or R^1 and R^2 are taken together to form a cycloalkyl or heterocycloalkyl; wherein the cycloalkyl and heterocycloalkyl is optionally substituted with deuterium, halogen, $-CN$, $-OH$, $-OCH_3$, $-NH_2$, $-NHCH_3$, $-N(CH_3)_2$, $-C(=O)CH_3$, $-C(=O)OH$, $-C(=O)OCH_3$, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_1 - C_6 deuteroalkyl, C_1 - C_6 hydroxyalkyl, C_1 - C_6 aminoalkyl, or C_1 - C_6 heteroalkyl;

each R^3 are independently hydrogen, deuterium, halogen, $-CN$, $-NO_2$, $-OH$, $-OR^a$, $-NR^cR^d$, $-C(=O)R^a$, $-C(=O)OR^b$, $-C(=O)NR^cR^d$, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_1 - C_6 deuteroalkyl, C_1 - C_6 hydroxyalkyl, C_1 - C_6 aminoalkyl, C_1 - C_6 heteroalkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, cycloalkyl, or heterocycloalkyl;

or two R^3 are taken together to form an oxo; and

R^4 is hydrogen, $-C(=O)R^a$, $-C(=O)OR^b$, $-C(=O)NR^cR^d$, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_1 - C_6 deuteroalkyl, C_1 - C_6 hydroxyalkyl, C_1 - C_6 aminoalkyl, C_1 - C_6 heteroalkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, cycloalkyl, or heterocycloalkyl;

R^5 is hydrogen, deuterium, halogen, $-CN$, $-NO_2$, $-OH$, $-OR^a$, $-NR^cR^d$, $-C(=O)R^a$, $-C(=O)OR^b$, $-C(=O)NR^cR^d$, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_1 - C_6 deuteroalkyl, C_1 - C_6 hydroxyalkyl, C_1 - C_6 aminoalkyl, C_1 - C_6 heteroalkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, cycloalkyl, or heterocycloalkyl;

R^6 is hydrogen, deuterium, halogen, $-CN$, $-NO_2$, $-OH$, $-OR^a$, $-NR^cR^d$, $-C(=O)R^a$, $-C(=O)OR^b$, $-C(=O)NR^cR^d$, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_1 - C_6 deuteroalkyl, C_1 - C_6 hydroxyalkyl, C_1 - C_6 aminoalkyl, C_1 - C_6 heteroalkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, cycloalkyl, or heterocycloalkyl;

R^7 is hydrogen, deuterium, halogen, $-CN$, $-NO_2$, $-OH$, $-OR^a$, $-NR^cR^d$, $-C(=O)R^a$, $-C(=O)OR^b$, $-C(=O)NR^cR^d$, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_1 - C_6 deuteroalkyl, C_1 - C_6 hydroxyalkyl, C_1 - C_6 aminoalkyl, C_1 - C_6 heteroalkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, cycloalkyl, or heterocycloalkyl;

Ring B is heterocycloalkyl or heteroaryl;

each R^B is independently hydrogen, deuterium, halogen, $-CN$, $-NO_2$, $-OH$, $-OR^a$, $-OC(=O)R^a$, $-OC(=O)OR^b$, $-OC(=O)NR^cR^d$, $-SH$, $-SR^a$, $-S(=O)R^a$, $-S(=O)_2R^a$, $-S(=O)_2NR^cR^d$, $-NR^cR^d$, $-NR^bC(=O)NR^cR^d$, $-NR^bC(=O)R^a$, $-NR^bC(=O)OR^b$, $-NR^bS(=O)_2R^a$, $-C(=O)R^a$, $-C(=O)OR^b$, $-C(=O)NR^cR^d$, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_1 - C_6 deuteroalkyl, C_1 - C_6 hydroxyalkyl, C_1 - C_6 aminoalkyl, C_1 - C_6 heteroalkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein the alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is optionally and independently substituted with one or more R^{Ba} ;

or two R^B on the same atom are taken together to form an oxo;

each R^{Ba} is independently deuterium, halogen, $-CN$, $-NO_2$, $-OH$, $-OR^a$, $-OC(=O)R^a$, $-OC(=O)OR^b$, $-OC(=O)NR^cR^d$, $-SH$, $-SR^a$, $-S(=O)R^a$, $-S(=O)_2R^a$, $-S(=O)_2NR^cR^d$, $-NR^cR^d$, $-NR^bC(=O)NR^cR^d$, $-NR^bC(=O)R^a$, $-NR^bC(=O)OR^b$, $-NR^bS(=O)_2R^a$, $-C(=O)R^a$, $-C(=O)C(=O)R^a$, $-C(=O)OR^b$, $-C(=O)NR^cR^d$, $-C(=O)C(=O)NR^cR^d$, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_1 - C_6 deuteroalkyl, C_1 - C_6 hydroxyalkyl, C_1 - C_6 aminoalkyl, C_1 - C_6 heteroalkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

or two R^{Ba} on the same atom are taken together to form an oxo;

m is 0-4;

Ring C is heterocycloalkyl or heteroaryl;

each R^C is independently hydrogen, deuterium, halogen, $-CN$, $-NO_2$, $-OH$, $-OR^a$, $-OC(=O)R^a$, $-OC(=O)OR^b$, $-OC(=O)NR^cR^d$, $-SH$, $-SR^a$, $-S(=O)R^a$, $-S(=O)_2R^a$, $-S(=O)_2NR^cR^d$, $-S(=O)(=NR^b)R^a$, $-SiR^cR^dOR^b$, $-NR^cR^d$, $-NR^bC(=O)NR^cR^d$, $-NR^bC(=O)R^a$, $-NR^bC(=O)OR^b$, $-NR^bS(=O)_2R^a$, $-C(=O)R^a$, $-C(=O)OR^b$, $-C(=O)NR^cR^d$, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_1 - C_6 deuteroalkyl, C_1 - C_6 hydroxyalkyl, C_1 - C_6 aminoalkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, $(C_1$ - C_6 alkyl)cycloalkyl, $(C_1$ - C_6 alkyl)heterocycloalkyl, $(C_1$ - C_6 alkyl)aryl, or $(C_1$ - C_6 alkyl)heteroaryl; wherein the alkyl, alkenyl,

alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is optionally and independently substituted with one or more R^{Ca};

or two R^C on the same atom are taken together to form an oxo;

each R^{Ca} is independently deuterium, halogen, -CN, -NO₂, -OH, -OR^a, -OC(=O)R^a, -OC(=O)OR^b, -OC(=O)NR^cR^d, -SH, -SR^a, -S(=O)R^a, -S(=O)₂R^a, -S(=O)₂NR^cR^d, -NR^cR^d, -NR^bC(=O)NR^cR^d, -NR^bC(=O)R^a, -NR^bC(=O)OR^b, -NR^bS(=O)₂R^a, -C(=O)R^a, -C(=O)C(=O)R^a, -C(=O)OR^b, -C(=O)NR^cR^d, -C(=O)C(=O)NR^cR^d, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

or two R^{Ca} on the same atom are taken together to form an oxo;

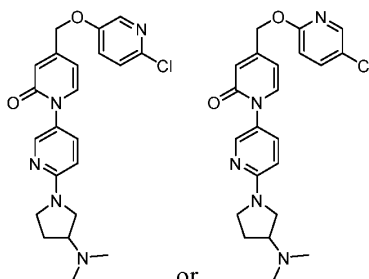
p is 0-4;

each R^a is independently C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, C₁-C₆alkyl(cycloalkyl), C₁-C₆alkyl(heterocycloalkyl), C₁-C₆alkyl(aryl), or C₁-C₆alkyl(heteroaryl); wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more oxo, deuterium, halogen, -CN, -OH, -OCH₃, -S(=O)CH₃, -S(=O)₂CH₃, -S(=O)₂NH₂, -S(=O)₂NHCH₃, -S(=O)₂N(CH₃)₂, -NH₂, -NHCH₃, -N(CH₃)₂, -C(=O)CH₃, -C(=O)OH, -C(=O)OCH₃, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, or C₁-C₆heteroalkyl;

each R^b is independently hydrogen, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, C₁-C₆alkyl(cycloalkyl), C₁-C₆alkyl(heterocycloalkyl), C₁-C₆alkyl(aryl), or C₁-C₆alkyl(heteroaryl); wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more oxo, deuterium, halogen, -CN, -OH, -OCH₃, -S(=O)CH₃, -S(=O)₂CH₃, -S(=O)₂NH₂, -S(=O)₂NHCH₃, -S(=O)₂N(CH₃)₂, -NH₂, -NHCH₃, -N(CH₃)₂, -C(=O)CH₃, -C(=O)OH, -C(=O)OCH₃, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, or C₁-C₆heteroalkyl; and

each R^c and R^d are independently hydrogen, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, C₁-C₆alkyl(cycloalkyl), C₁-C₆alkyl(heterocycloalkyl), C₁-C₆alkyl(aryl), or C₁-C₆alkyl(heteroaryl); wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more oxo, deuterium, halogen, -CN, -OH, -OCH₃, -S(=O)CH₃, -S(=O)₂CH₃, -S(=O)₂NH₂, -S(=O)₂NHCH₃, -S(=O)₂N(CH₃)₂, -NH₂, -NHCH₃, -N(CH₃)₂, -C(=O)CH₃, -C(=O)OH, -C(=O)OCH₃, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, or C₁-C₆heteroalkyl; or R^c and R^d are taken together with the atom to which they are attached to form a heterocycloalkyl optionally substituted with one or more oxo, deuterium, halogen, -CN, -OH, -OCH₃, -S(=O)CH₃, -

$S(=O)_2CH_3$, $-S(=O)_2NH_2$, $-S(=O)_2NHCH_3$, $-S(=O)_2N(CH_3)_2$, $-NH_2$, $-NHCH_3$, $-N(CH_3)_2$, $-C(=O)CH_3$, $-C(=O)OH$, $-C(=O)OCH_3$, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_1 - C_6 deuteroalkyl, C_1 - C_6 hydroxyalkyl, C_1 - C_6 aminoalkyl, or C_1 - C_6 heteroalkyl;



provided that the compound is not:

or

[00124] In some embodiments of a compound of Formula (VI), Ring A is heteroaryl. In some embodiments of a compound of Formula (VI), Ring A is pyridyl. In some embodiments of a compound of Formula (VI), Ring A is phenyl.

[00125] In some embodiments of a compound of Formula (VI), each R^A is independently deuterium, halogen, $-CN$, $-OH$, $-OR^a$, $-NR^cR^d$, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, or C_1 - C_6 deuteroalkyl. In some embodiments of a compound of Formula (VI), each R^A is independently halogen or C_1 - C_6 alkyl. In some embodiments of a compound of Formula (VI), each R^A is independently halogen.

[00126] In some embodiments of a compound of Formula (VI), n is 1 or 2. In some embodiments of a compound of Formula (VI), n is 1-3. In some embodiments of a compound of Formula (VI), n is 2. In some embodiments of a compound of Formula (VI), n is 1.

[00127] In some embodiments of a compound of Formula (VI):

X is $-C(R^3)_2$ -, $-NR^4$ -, $-O$ -, or $-S$ -;

Y is $-CR^1R^2$ -;

R^1 halogen, $-CN$, $-NO_2$, $-OH$, $-OR^a$, $-NR^cR^d$, $-C(=O)R^a$, $-C(=O)OR^b$, $-C(=O)NR^cR^d$, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_1 - C_6 deuteroalkyl, C_1 - C_6 hydroxyalkyl, C_1 - C_6 aminoalkyl, C_1 - C_6 heteroalkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, cycloalkyl, or heterocycloalkyl;

R^2 is hydrogen, deuterium, halogen, $-CN$, $-NO_2$, $-OH$, $-OR^a$, $-NR^cR^d$, $-C(=O)R^a$, $-C(=O)OR^b$, $-C(=O)NR^cR^d$, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_1 - C_6 deuteroalkyl, C_1 - C_6 hydroxyalkyl, C_1 - C_6 aminoalkyl, C_1 - C_6 heteroalkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, cycloalkyl, or heterocycloalkyl;

or R^1 and R^2 are taken together to form an oxo;

or R^1 and R^2 are taken together to form a cycloalkyl or heterocycloalkyl; wherein the cycloalkyl and heterocycloalkyl is optionally substituted with deuterium, halogen, $-CN$, $-OH$, $-OCH_3$, $-NH_2$, $-NHCH_3$, $-N(CH_3)_2$, $-C(=O)CH_3$, $-C(=O)OH$, $-C(=O)OCH_3$, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_1 - C_6 deuteroalkyl, C_1 - C_6 hydroxyalkyl, C_1 - C_6 aminoalkyl, or C_1 - C_6 heteroalkyl;

each R^3 are independently hydrogen, deuterium, halogen, $-CN$, $-NO_2$, $-OH$, $-OR^a$, $-NR^cR^d$, $-C(=O)R^a$, $-C(=O)OR^b$, $-C(=O)NR^cR^d$, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_1 - C_6 deuteroalkyl, C_1 - C_6 hydroxyalkyl, C_1 - C_6 aminoalkyl, C_1 - C_6 heteroalkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, cycloalkyl, or heterocycloalkyl;

or two R³ are taken together to form an oxo; and

R⁴ is hydrogen, -C(=O)R^a, -C(=O)OR^b, -C(=O)NR^cR^d, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, or heterocycloalkyl.

[00128] In some embodiments of a compound of Formula (VI):

X is -C(R³)₂-, -NR⁴-, -O-, or -S-;

Y is -CR¹R²-;

R¹ halogen, C₁-C₆alkyl, C₁-C₆haloalkyl, or C₁-C₆deuteroalkyl;

R² is hydrogen, deuterium, halogen, or C₁-C₆alkyl;

or R¹ and R² are taken together to form a cycloalkyl or heterocycloalkyl;

each R³ are independently hydrogen, deuterium, halogen, C₁-C₆alkyl, C₁-C₆haloalkyl, or C₁-C₆deuteroalkyl;

R⁴ is hydrogen or C₁-C₆alkyl.

[00129] In some embodiments of a compound of Formula (VI):

X is -C(R³)₂-, -NR⁴-, or -S-;

Y is -CR¹R²-, -NR⁴-, -O-, or -S-;

R¹ and R² are independently hydrogen, deuterium, halogen, -CN, -NO₂, -OH, -OR^a, -NR^cR^d, -C(=O)R^a, -C(=O)OR^b, -C(=O)NR^cR^d, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, or heterocycloalkyl;

or R¹ and R² are taken together to form an oxo;

or R¹ and R² are taken together to form a cycloalkyl or heterocycloalkyl; wherein the cycloalkyl and heterocycloalkyl is optionally substituted with deuterium, halogen, -CN, -OH, -OCH₃, -NH₂, -NHCH₃, -N(CH₃)₂, -C(=O)CH₃, -C(=O)OH, -C(=O)OCH₃, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, or C₁-C₆heteroalkyl;

each R³ are independently hydrogen, deuterium, halogen, -CN, -NO₂, -OH, -OR^a, -NR^cR^d, -C(=O)R^a, -C(=O)OR^b, -C(=O)NR^cR^d, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, or heterocycloalkyl;

or two R³ are taken together to form an oxo; and

R⁴ is hydrogen, -C(=O)R^a, -C(=O)OR^b, -C(=O)NR^cR^d, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, or heterocycloalkyl.

[00130] In some embodiments of a compound of Formula (VI):

X is -C(R³)₂-;

Y is -CR¹R²-, -NR⁴-, -O-, or -S-;

R¹ and R² are independently hydrogen, deuterium, halogen, -OH, C₁-C₆alkyl, C₁-C₆haloalkyl, or C₁-C₆deuteroalkyl;

or R¹ and R² are taken together to form an oxo;

or R¹ and R² are taken together to form a cycloalkyl or heterocycloalkyl;
each R³ are independently hydrogen, deuterium, halogen, -OH, C₁-C₆alkyl, C₁-C₆haloalkyl, or
C₁-C₆deuteroalkyl;
or two R³ are taken together to form an oxo; and
R⁴ is hydrogen or C₁-C₆alkyl.

[00131] In some embodiments of a compound of Formula (VI):

X is -NR⁴- or -S-;

Y is -CR¹R²-;

R¹ and R² are independently hydrogen, deuterium, halogen, C₁-C₆alkyl, C₁-C₆haloalkyl, or
C₁-C₆deuteroalkyl;

or R¹ and R² are taken together to form an oxo;

or R¹ and R² are taken together to form a cycloalkyl or heterocycloalkyl; and

R⁴ is hydrogen or C₁-C₆alkyl.

[00132] In some embodiments of a compound of Formula (VI), R⁵ is hydrogen, deuterium, halogen, -CN, -OH, -OR^a, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkynyl, or cycloalkyl. In some embodiments of a compound of Formula (VI), R⁵ is hydrogen, deuterium, halogen, -CN, or C₁-C₆alkyl.

[00133] In some embodiments of a compound of Formula (VI), R⁶ is hydrogen, deuterium, halogen, -CN, -OH, -OR^a, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkynyl, or cycloalkyl. In some embodiments of a compound of Formula (VI), R⁶ is hydrogen, deuterium, halogen, -CN, or C₁-C₆alkyl.

[00134] In some embodiments of a compound of Formula (VI), R⁷ is hydrogen, deuterium, halogen, -CN, -OH, -OR^a, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkynyl, or cycloalkyl. In some embodiments of a compound of Formula (VI), R⁷ is hydrogen, deuterium, halogen, -CN, or C₁-C₆alkyl.

[00135] In some embodiments of a compound of Formula (VI), Ring B is a 6-membered heteroaryl. In some embodiments of a compound of Formula (VI), Ring B is pyridinyl.

[00136] In some embodiments of a compound of Formula (VI), each R^B is independently hydrogen, deuterium, halogen, -CN, -OH, -OR^a, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkynyl, or cycloalkyl. In some embodiments of a compound of Formula (VI), each R^B is independently C₁-C₆alkyl.

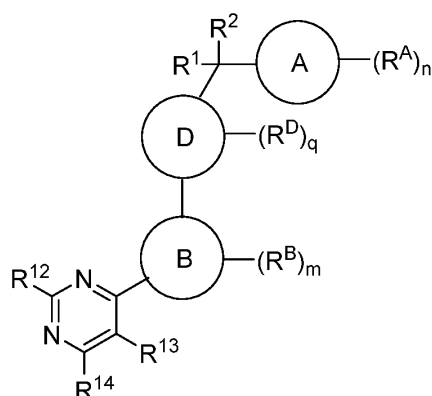
[00137] In some embodiments of a compound of Formula (VI), m is 1 or 2. In some embodiments of a compound of Formula (VI), m is 1-4. In some embodiments of a compound of Formula (VI), m is 2-4. In some embodiments of a compound of Formula (VI), m is 1. In some embodiments of a compound of Formula (VI), m is 2.

[00138] In some embodiments of a compound of Formula (VI), Ring C is a 5- or 6-membered heteroaryl. In some embodiments of a compound of Formula (VI), Ring C is a pyrimidinyl.

[00139] In some embodiments of a compound of Formula (VI), each R^C is independently hydrogen, deuterium, halogen, -CN, -OH, -OR^a, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, or C₁-C₆heteroalkyl. In some embodiments of a compound of Formula (VI), each R^C is independently C₁-C₆hydroxyalkyl.

[00140] In some embodiments of a compound of Formula (VI), p is 1 or 2. In some embodiments of a compound of Formula (VI), p is 1-3. In some embodiments of a compound of Formula (VI), p is 1. In some embodiments of a compound of Formula (VI), p is 2.

[00141] Also disclosed herein is a compound of Formula (VII), or a pharmaceutically acceptable salt, solvate, N-oxide, or stereoisomer thereof:



Formula (VII),

wherein:

Ring A is phenyl or heteroaryl;

each R^A is independently hydrogen, deuterium, halogen, -CN, -NO₂, -OH, -OR^a, -OC(=O)R^a, -OC(=O)OR^b, -OC(=O)NR^cR^d, -SH, -SR^a, -S(=O)R^a, -S(=O)₂R^a, -S(=O)₂NR^cR^d, -NR^cR^d, -NR^bC(=O)NR^cR^d, -NR^bC(=O)R^a, -NR^bC(=O)OR^b, -NR^bS(=O)₂R^a, -C(=O)R^a, -C(=O)OR^b, -C(=O)NR^cR^d, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein the alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is optionally and independently substituted with one or more R^{Aa} ;

or two R^A on the same atom are taken together to form an oxo;

each R^{Aa} is independently deuterium, halogen, -CN, -NO₂, -OH, -OR^a, -OC(=O)R^a, -OC(=O)OR^b, -OC(=O)NR^cR^d, -SH, -SR^a, -S(=O)R^a, -S(=O)₂R^a, -S(=O)₂NR^cR^d, -NR^cR^d, -NR^bC(=O)NR^cR^d, -NR^bC(=O)R^a, -NR^bC(=O)OR^b, -NR^bS(=O)₂R^a, -C(=O)R^a, -C(=O)C(=O)R^a, -C(=O)OR^b, -C(=O)NR^cR^d, -C(=O)C(=O)NR^cR^d, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

or two R^{Aa} on the same atom are taken together to form an oxo;

n is 0-4;

R^1 and R^2 are independently hydrogen, deuterium, halogen, -CN, -NO₂, -OH, -OR^a, -NR^cR^d, -C(=O)R^a, -C(=O)OR^b, -C(=O)NR^cR^d, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, or heterocycloalkyl;

or R^1 and R^2 are taken together to form an oxo;

or R^1 and R^2 are taken together to form a cycloalkyl or heterocycloalkyl; wherein the cycloalkyl and heterocycloalkyl is optionally substituted with deuterium, halogen, -CN, -OH, -OCH₃, -NH₂, -NHCH₃, -N(CH₃)₂, -C(=O)CH₃, -C(=O)OH, -C(=O)OCH₃, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, or C₁-C₆heteroalkyl;

Ring B is pyridinyl;

each R^B is independently hydrogen, deuterium, halogen, -CN, -NO₂, -OH, -OR^a, -OC(=O)R^a, -OC(=O)OR^b, -OC(=O)NR^cR^d, -SH, -SR^a, -S(=O)R^a, -S(=O)₂R^a, -S(=O)₂NR^cR^d, -NR^cR^d, -NR^bC(=O)NR^cR^d, -NR^bC(=O)R^a, -NR^bC(=O)OR^b, -NR^bS(=O)₂R^a, -C(=O)R^a, -C(=O)OR^b, -C(=O)NR^cR^d, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein the alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is optionally and independently substituted with one or more R^{Ba} ;

each R^{Ba} is independently deuterium, halogen, -CN, -NO₂, -OH, -OR^a, -OC(=O)R^a, -OC(=O)OR^b, -OC(=O)NR^cR^d, -SH, -SR^a, -S(=O)R^a, -S(=O)₂R^a, -S(=O)₂NR^cR^d, -NR^cR^d, -NR^bC(=O)NR^cR^d, -NR^bC(=O)R^a, -NR^bC(=O)OR^b, -NR^bS(=O)₂R^a, -C(=O)R^a, -C(=O)C(=O)R^a, -C(=O)OR^b, -C(=O)NR^cR^d, -C(=O)C(=O)NR^cR^d, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

or two R^{Ba} on the same atom are taken together to form an oxo;

m is 0-3;

Ring D is a bicyclic ring;

each R^D is independently hydrogen, deuterium, halogen, -CN, -NO₂, -OH, -OR^a, -OC(=O)R^a, -OC(=O)OR^b, -OC(=O)NR^cR^d, -SH, -SR^a, -S(=O)R^a, -S(=O)₂R^a, -S(=O)₂NR^cR^d, -NR^cR^d, -NR^bC(=O)NR^cR^d, -NR^bC(=O)R^a, -NR^bC(=O)OR^b, -NR^bS(=O)₂R^a, -C(=O)R^a, -C(=O)OR^b, -C(=O)NR^cR^d, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein the alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is optionally and independently substituted with one or more R^{Da} ;

or two R^D on the same atom are taken together to form an oxo;

each R^{Da} is independently deuterium, halogen, -CN, -NO₂, -OH, -OR^a, -OC(=O)R^a, -OC(=O)OR^b, -OC(=O)NR^cR^d, -SH, -SR^a, -S(=O)R^a, -S(=O)₂R^a, -S(=O)₂NR^cR^d, -NR^cR^d, -NR^bC(=O)NR^cR^d, -NR^bC(=O)R^a, -NR^bC(=O)OR^b, -NR^bS(=O)₂R^a, -C(=O)R^a, -C(=O)C(=O)R^a, -C(=O)OR^b, -C(=O)NR^cR^d, -C(=O)C(=O)NR^cR^d, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl,

C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

or two R^{Da} on the same atom are taken together to form an oxo;

q is 0-6;

R¹² is hydrogen, deuterium, halogen, -CN, -NO₂, -OH, -OR^a, -OC(=O)R^a, -OC(=O)OR^b, -OC(=O)NR^cR^d, -SH, -SR^a, -S(=O)R^a, -S(=O)₂R^a, -S(=O)₂NR^cR^d, -S(=O)(=NR^b)R^a, -SiR^cR^dOR^b, -NR^cR^d, -NR^bC(=O)NR^cR^d, -NR^bC(=O)R^a, -NR^bC(=O)OR^b, -NR^bS(=O)₂R^a, -C(=O)R^a, -C(=O)OR^b, -C(=O)NR^cR^d, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, (C₁-C₆alkyl)cycloalkyl, (C₁-C₆alkyl)heterocycloalkyl, (C₁-C₆alkyl)aryl, or (C₁-C₆alkyl)heteroaryl; wherein the alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is optionally and independently substituted with one or more R^{12a};

each R^{12a} is independently deuterium, halogen, -CN, -NO₂, -OH, -OR^a, -OC(=O)R^a, -OC(=O)OR^b, -OC(=O)NR^cR^d, -SH, -SR^a, -S(=O)R^a, -S(=O)₂R^a, -S(=O)₂NR^cR^d, -NR^cR^d, -NR^bC(=O)NR^cR^d, -NR^bC(=O)R^a, -NR^bC(=O)OR^b, -NR^bS(=O)₂R^a, -C(=O)R^a, -C(=O)C(=O)R^a, -C(=O)OR^b, -C(=O)NR^cR^d, -C(=O)C(=O)NR^cR^d, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

or two R^{12a} on the same atom are taken together to form an oxo;

R¹³ is hydrogen, deuterium, halogen, -CN, -NO₂, -OH, -OR^a, -NR^cR^d, -C(=O)R^a, -C(=O)OR^b, -C(=O)NR^cR^d, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, or heterocycloalkyl;

R¹⁴ is hydrogen, deuterium, halogen, -CN, -NO₂, -OH, -OR^a, -NR^cR^d, -C(=O)R^a, -C(=O)OR^b, -C(=O)NR^cR^d, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, or heterocycloalkyl;

each R^a is independently C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, C₁-C₆alkyl(cycloalkyl), C₁-C₆alkyl(heterocycloalkyl), C₁-C₆alkyl(aryl), or C₁-C₆alkyl(heteroaryl); wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more oxo, deuterium, halogen, -CN, -OH, -OCH₃, -S(=O)CH₃, -S(=O)₂CH₃, -S(=O)₂NH₂, -S(=O)₂NHCH₃, -S(=O)₂N(CH₃)₂, -NH₂, -NHCH₃, -N(CH₃)₂, -C(=O)CH₃, -C(=O)OH, -C(=O)OCH₃, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, or C₁-C₆heteroalkyl;

each R^b is independently hydrogen, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, C₁-C₆alkyl(cycloalkyl), C₁-C₆alkyl(heterocycloalkyl), C₁-C₆alkyl(aryl), or C₁-C₆alkyl(heteroaryl); wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and

heteroaryl is independently optionally substituted with one or more oxo, deuterium, halogen, -CN, -OH, -OCH₃, -S(=O)CH₃, -S(=O)₂CH₃, -S(=O)₂NH₂, -S(=O)₂NHCH₃, -S(=O)₂N(CH₃)₂, -NH₂, -NHCH₃, -N(CH₃)₂, -C(=O)CH₃, -C(=O)OH, -C(=O)OCH₃, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, or C₁-C₆heteroalkyl; and

each R^c and R^d are independently hydrogen, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl,

C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, C₁-C₆alkyl(cycloalkyl), C₁-C₆alkyl(heterocycloalkyl),

C₁-C₆alkyl(aryl), or C₁-C₆alkyl(heteroaryl); wherein each alkyl, alkenyl, alkynyl, cycloalkyl,

heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more oxo, deuterium, halogen, -CN, -OH, -OCH₃, -S(=O)CH₃, -S(=O)₂CH₃, -S(=O)₂NH₂, -S(=O)₂NHCH₃, -S(=O)₂N(CH₃)₂, -NH₂, -NHCH₃, -N(CH₃)₂, -C(=O)CH₃, -C(=O)OH, -C(=O)OCH₃, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, or C₁-C₆heteroalkyl;

or R^c and R^d are taken together with the atom to which they are attached to form a heterocycloalkyl

optionally substituted with one or more oxo, deuterium, halogen, -CN, -OH, -OCH₃, -S(=O)CH₃, -S(=O)₂CH₃, -S(=O)₂NH₂, -S(=O)₂NHCH₃, -S(=O)₂N(CH₃)₂, -NH₂, -NHCH₃, -N(CH₃)₂, -C(=O)CH₃, -C(=O)OH, -C(=O)OCH₃, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, or C₁-C₆heteroalkyl.

[00142] In some embodiments of a compound of Formula (VII), Ring A is heteroaryl. In some embodiments of a compound of Formula (VII), Ring A is pyridyl. In some embodiments of a compound of Formula (VII), Ring A is phenyl.

[00143] In some embodiments of a compound of Formula (VII), each R^A is independently deuterium, halogen, -CN, -OH, -OR^a, -NR^cR^d, C₁-C₆alkyl, C₁-C₆haloalkyl, or C₁-C₆deuteroalkyl. In some embodiments of a compound of Formula (I), each R^A is independently halogen or C₁-C₆alkyl. In some embodiments of a compound of Formula (VII), each R^A is independently halogen.

[00144] In some embodiments of a compound of Formula (VII), n is 1 or 2. In some embodiments of a compound of Formula (VII), n is 1-3. In some embodiments of a compound of Formula (VII), n is 2. In some embodiments of a compound of Formula (VII), n is 1.

[00145] In some embodiments of a compound of Formula (VII), R¹ and R² are independently hydrogen, deuterium, halogen, C₁-C₆alkyl, C₁-C₆haloalkyl, or C₁-C₆deuteroalkyl. In some embodiments of a compound of Formula (VII), R¹ and R² are independently hydrogen, deuterium, halogen, or C₁-C₆alkyl. In some embodiments of a compound of Formula (VII), R¹ and R² are hydrogen.

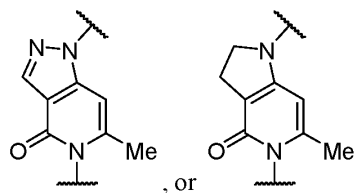
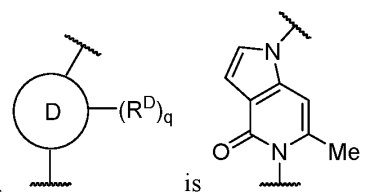
[00146] In some embodiments of a compound of Formula (VII), Ring D is a 6- to 12-membered bicyclic ring optionally comprising 1-4 heteroatoms selected from the group consisting of O, S, N, P, or B. In some embodiments of a compound of Formula (VII), Ring D is a 6- to 12-membered bicyclic ring optionally comprising 1-4 heteroatoms selected from the group consisting of O, S, or N. In some embodiments of a compound of Formula (VII), Ring D is a 6- to 12-membered bicyclic ring optionally comprising 1-4 heteroatoms selected from the group consisting of O and N. In some embodiments of a compound of

Formula (VII), Ring D is a 6- to 12-membered bicyclic ring optionally comprising 1-4 heteroatoms selected from the group consisting of O and N. In some embodiments of a compound of Formula (VII), Ring D is a 6- to 12-membered bicyclic ring comprising 1-3 heteroatoms selected from the group consisting of O and N. In some embodiments of a compound of Formula (VII), Ring D is a 6- to 10-membered bicyclic ring comprising 1-3 heteroatoms that are N.

[00147] In some embodiments of a compound of Formula (VII), each R^D is independently hydrogen, deuterium, halogen, -CN, -OH, -OR^a, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkynyl, or cycloalkyl; or two R^D on the same atom are taken together to form an oxo. In some embodiments of a compound of Formula (VII), each R^D is independently hydrogen, deuterium, halogen, -CN, -OR^a, C₁-C₆alkyl, C₁-C₆haloalkyl, C₂-C₆alkynyl, or cycloalkyl; or two R^D on the same atom are taken together to form an oxo.

[00148] In some embodiments of a compound of Formula (VII), q is 1-4. In some embodiments of a compound of Formula (VII), q is 1-3. In some embodiments of a compound of Formula (VII), q is 2-4.

[00149] In some embodiments of a compound of Formula (VII),



[00150] In some embodiments of a compound of Formula (VII), each R^B is independently deuterium, halogen, -CN, -OH, -OR^a, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₂-C₆alkynyl, or cycloalkyl. In some embodiments of a compound of Formula (VII), each R^B is independently deuterium, -CN, -OH, -OR^a, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₂-C₆alkynyl, or cycloalkyl. In some embodiments of a compound of Formula (VII), each R^B is independently C₁-C₆alkyl.

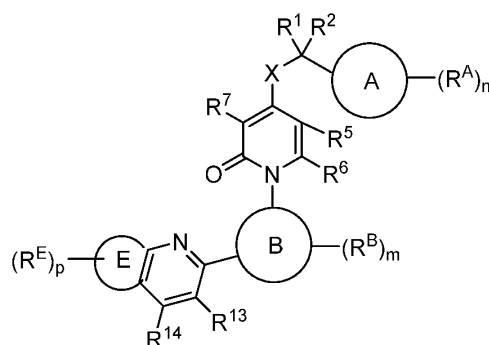
[00151] In some embodiments of a compound of Formula (VII), m is 1 or 2. In some embodiments of a compound of Formula (VII), m is 1. In some embodiments of a compound of Formula (VII), m is 2.

[00152] In some embodiments of a compound of Formula (VII), R^{12} is hydrogen, deuterium, halogen, -CN, -OH, -OR^a, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, or C₁-C₆heteroalkyl. In some embodiments of a compound of Formula (VII), R^{12} is C₁-C₆hydroxyalkyl.

[00153] In some embodiments of a compound of Formula (VII), R^{13} is hydrogen, deuterium, halogen, or C₁-C₆alkyl.

[00154] In some embodiments of a compound of Formula (VII), R^{14} is hydrogen, deuterium, halogen, or C₁-C₆alkyl.

[00155] Also disclosed herein is a compound of Formula (VIII), or a pharmaceutically acceptable salt, solvate, N-oxide, or stereoisomer thereof:



Formula (VIII),

wherein:

Ring A is phenyl or heteroaryl;

each R^A is independently hydrogen, deuterium, halogen, -CN, -NO₂, -OH, -OR^a, -OC(=O)R^a, -OC(=O)OR^b, -OC(=O)NR^cR^d, -SH, -SR^a, -S(=O)R^a, -S(=O)₂R^a, -S(=O)₂NR^cR^d, -NR^cR^d, -NR^bC(=O)NR^cR^d, -NR^bC(=O)R^a, -NR^bC(=O)OR^b, -NR^bS(=O)₂R^a, -C(=O)R^a, -C(=O)OR^b, -C(=O)NR^cR^d, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein the alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is optionally and independently substituted with one or more R^{Aa};

or two R^A on the same atom are taken together to form an oxo;

each R^{Aa} is independently deuterium, halogen, -CN, -NO₂, -OH, -OR^a, -OC(=O)R^a, -OC(=O)OR^b, -OC(=O)NR^cR^d, -SH, -SR^a, -S(=O)R^a, -S(=O)₂R^a, -S(=O)₂NR^cR^d, -NR^cR^d, -NR^bC(=O)NR^cR^d, -NR^bC(=O)R^a, -NR^bC(=O)OR^b, -NR^bS(=O)₂R^a, -C(=O)R^a, -C(=O)C(=O)R^a, -C(=O)OR^b, -C(=O)NR^cR^d, -C(=O)C(=O)NR^cR^d, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

or two R^{Aa} on the same atom are taken together to form an oxo;

n is 0-4;

R¹ and R² are independently hydrogen, deuterium, halogen, -CN, -NO₂, -OH, -OR^a, -NR^cR^d, -C(=O)R^a, -C(=O)OR^b, -C(=O)NR^cR^d, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, or heterocycloalkyl;

or R¹ and R² are taken together to form an oxo;

or R¹ and R² are taken together to form a cycloalkyl or heterocycloalkyl; wherein the cycloalkyl and heterocycloalkyl is optionally substituted with deuterium, halogen, -CN, -OH, -OCH₃, -NH₂, -NHCH₃, -N(CH₃)₂, -C(=O)CH₃, -C(=O)OH, -C(=O)OCH₃, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, or C₁-C₆heteroalkyl;

X is $-\text{C}(\text{R}^3)_2-$, $-\text{NR}^4-$, $-\text{O}-$, or $-\text{S}-$;

each R³ are independently hydrogen, deuterium, halogen, -CN, -NO₂, -OH, -OR^a, -NR^cR^d, -C(=O)R^a, -

C(=O)OR^b, -C(=O)NR^cR^d, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl,

C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, or heterocycloalkyl;

or two R^3 are taken together to form an oxo;

R⁴ is hydrogen, -C(=O)R^a, -C(=O)OR^b, -C(=O)NR^cR^d, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl,

C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, or

heterocycloalkyl;

R^5 is hydrogen, deuterium, halogen, $-CN$, $-NO_2$, $-OH$, $-OR^a$, $-NR^cR^d$, $-C(=O)R^a$, $-C(=O)OR^b$, $-C(=O)NR^cR^d$,

C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl,

C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, or heterocycloalkyl;

R^6 is hydrogen, deuterium, halogen, -CN, -NO₂, -OH, -OR^a, -NR^cR^d, -C(=O)R^a, -C(=O)OR^b, -C(=O)NR^cR^d,

C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl,

C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, or heterocycloalkyl;

R^7 is hydrogen, deuterium, halogen, -CN, -NO₂, -OH, -OR^a, -NR^cR^d, -C(=O)R^a, -C(=O)OR^b, -C(=O)NR^cR^d.

C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl,

C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, or heterocycloalkyl;

Ring B is cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

each R^B is independently hydrogen, deuterium, halogen, -CN, -NO₂, -OH, -OR^a, -OC(=O)R^a, -OC(=O)OR^b,

-OC(=O)NR^cR^d, -SH, -SR^a, -S(=O)R^a, -S(=O)₂R^a, -S(=O)₂NR^cR^d, -NR^cR^d, -NR^bC(=O)NR^cR^d, -

$$\text{NR}^b\text{C}(=\text{O})\text{R}^a, -\text{NR}^b\text{C}(=\text{O})\text{OR}^b, -\text{NR}^b\text{S}(=\text{O})_2\text{R}^a, -\text{C}(=\text{O})\text{R}^a, -\text{C}(=\text{O})\text{OR}^b, -\text{C}(=\text{O})\text{NR}^c\text{R}^d, \text{C}_1\text{-C}_6\text{alkyl},$$

C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-

C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein the alkyl, alkenyl,

alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is optionally and independently substituted

with one or more R^{Ba}.

or two R^B on the same atom are taken together to form an oxo;

each R^{Ba} is independently deuterium, halogen, -CN, -NO₂, -OH, -OR^a, -OC(=O)R^a, -OC(=O)OR^b, -

OC(=O)NR^cR^d, -SH, -SR^a, -S(=O)R^a, -S(=O)₂R^a, -S(=O)₂NR^cR^d, -NR^cR^d, -NR^bC(=O)NR^cR^d, -

$$\text{NR}^b\text{C}(=\text{O})\text{R}^a, -\text{NR}^b\text{C}(=\text{O})\text{OR}^b, -\text{NR}^b\text{S}(=\text{O})_2\text{R}^a, -\text{C}(=\text{O})\text{R}^a, -\text{C}(=\text{O})\text{C}(=\text{O})\text{R}^a, -\text{C}(=\text{O})\text{OR}^b, -\text{C}(=\text{O})\text{NR}^c\text{R}^d, -$$

C(=O)C(=O)NR^cR^d, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl,

C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, heterocycloalkyl, aryl, or

heteroaryl;

or two R^{Ba} on the same atom are taken together to form an oxo;

m is 0-4;

Ring E is cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

each R^E is independently hydrogen, deuterium, halogen, -CN, -NO₂, -OH, -OR^a, -OC(=O)R^a, -OC(=O)OR^b,

$$-\text{OC}(=\text{O})\text{NR}^{\text{c}}\text{R}^{\text{d}}, -\text{SH}, -\text{SR}^{\text{a}}, -\text{S}(=\text{O})\text{R}^{\text{a}}, -\text{S}(=\text{O})_2\text{R}^{\text{a}}, -\text{S}(=\text{O})_2\text{NR}^{\text{c}}\text{R}^{\text{d}}, -\text{S}(=\text{O})(=\text{NR}^{\text{b}})\text{R}^{\text{a}}, -\text{SiR}^{\text{c}}\text{R}^{\text{d}}\text{OR}^{\text{b}}, -$$

each R^c and R^d are independently hydrogen, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, C₁-C₆alkyl(cycloalkyl), C₁-C₆alkyl(heterocycloalkyl), C₁-C₆alkyl(aryl), or C₁-C₆alkyl(heteroaryl); wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more oxo, deuterium, halogen, -CN, -OH, -OCH₃, -S(=O)CH₃, -S(=O)₂CH₃, -S(=O)₂NH₂, -S(=O)₂NHCH₃, -S(=O)₂N(CH₃)₂, -NH₂, -NHCH₃, -N(CH₃)₂, -C(=O)CH₃, -C(=O)OH, -C(=O)OCH₃, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, or C₁-C₆heteroalkyl; or R^c and R^d are taken together with the atom to which they are attached to form a heterocycloalkyl optionally substituted with one or more oxo, deuterium, halogen, -CN, -OH, -OCH₃, -S(=O)CH₃, -S(=O)₂CH₃, -S(=O)₂NH₂, -S(=O)₂NHCH₃, -S(=O)₂N(CH₃)₂, -NH₂, -NHCH₃, -N(CH₃)₂, -C(=O)CH₃, -C(=O)OH, -C(=O)OCH₃, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, or C₁-C₆heteroalkyl.

[00156] In some embodiments of a compound of Formula (VIII), Ring A is heteroaryl. In some embodiments of a compound of Formula (VIII), Ring A is pyridyl. In some embodiments of a compound of Formula (VIII), Ring A is phenyl.

[00157] In some embodiments of a compound of Formula (VIII), each R^A is independently deuterium, halogen, -CN, -OH, -OR^a, -NR^cR^d, C₁-C₆alkyl, C₁-C₆haloalkyl, or C₁-C₆deuteroalkyl. In some embodiments of a compound of Formula (VIII), each R^A is independently halogen or C₁-C₆alkyl. In some embodiments of a compound of Formula (VIII), each R^A is independently halogen.

[00158] In some embodiments of a compound of Formula (VIII), n is 1 or 2. In some embodiments of a compound of Formula (VIII), n is 1-3. In some embodiments of a compound of Formula (VIII), n is 2. In some embodiments of a compound of Formula (VIII), n is 1.

[00159] In some embodiments of a compound of Formula (VIII), R¹ and R² are independently hydrogen, deuterium, halogen, C₁-C₆alkyl, C₁-C₆haloalkyl, or C₁-C₆deuteroalkyl. In some embodiments of a compound of Formula (VIII), R¹ and R² are independently hydrogen, deuterium, halogen, or C₁-C₆alkyl. In some embodiments of a compound of Formula (VIII), R¹ and R² are hydrogen.

[00160] In some embodiments of a compound of Formula (VIII), X is -O-.

[00161] In some embodiments of a compound of Formula (VIII), R⁵ is hydrogen, deuterium, halogen, -CN, -OH, -OR^a, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkynyl, or cycloalkyl. In some embodiments of a compound of Formula (VIII), R⁵ is hydrogen, deuterium, halogen, -CN, or C₁-C₆alkyl.

[00162] In some embodiments of a compound of Formula (VIII), R⁶ is hydrogen, deuterium, halogen, -CN, -OH, -OR^a, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkynyl, or cycloalkyl. In some embodiments of a compound of Formula (VIII), R⁶ is hydrogen, deuterium, halogen, -CN, or C₁-C₆alkyl.

[00163] In some embodiments of a compound of Formula (VIII), R^7 is hydrogen, deuterium, halogen, -CN, -OH, -OR^a, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkynyl, or cycloalkyl. In some embodiments of a compound of Formula (VIII), R^7 is hydrogen, deuterium, halogen, -CN, or C₁-C₆alkyl.

[00164] In some embodiments of a compound of Formula (VIII), Ring B is a 6-membered heteroaryl. In some embodiments of a compound of Formula (VIII), Ring B is pyridinyl.

[00165] In some embodiments of a compound of Formula (VIII), each R^B is independently hydrogen, deuterium, halogen, -CN, -OH, -OR^a, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkynyl, or cycloalkyl. In some embodiments of a compound of Formula (VIII), each R^B is independently C₁-C₆alkyl.

[00166] In some embodiments of a compound of Formula (VIII), m is 1 or 2. In some embodiments of a compound of Formula (VIII), m is 1-4. In some embodiments of a compound of Formula (VIII), m is 2-4. In some embodiments of a compound of Formula (VIII), m is 1. In some embodiments of a compound of Formula (VIII), m is 2.

[00167] In some embodiments of a compound of Formula (VIII), Ring E is cycloalkyl.

[00168] In some embodiments of a compound of Formula (VIII), each R^E is independently hydrogen, deuterium, halogen, -CN, -OH, -OR^a, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, or C₁-C₆heteroalkyl. In some embodiments of a compound of Formula (VIII), each R^E is independently -OH or C₁-C₆alkyl.

[00169] In some embodiments of a compound of Formula (VIII), p is 1 or 2. In some embodiments of a compound of Formula (VIII), p is 1 or 3. In some embodiments of a compound of Formula (VIII), p is 1. In some embodiments of a compound of Formula (VIII), p is 2.

[00170] In some embodiments of a compound of Formula (VIII), R¹³ is hydrogen, deuterium, halogen, or C₁-C₆alkyl.

[00171] In some embodiments of a compound of Formula (VIII), R¹⁴ is hydrogen, deuterium, halogen, or C₁-C₆alkyl.

[00172] In some embodiments of a compound disclosed herein, each R^a is independently C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein each alkyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more oxo, deuterium, halogen, -CN, -OH, -OCH₃, -S(=O)CH₃, -S(=O)₂CH₃, -S(=O)₂NH₂, -S(=O)₂NHCH₃, -S(=O)₂N(CH₃)₂, -NH₂, -NHCH₃, -N(CH₃)₂, -C(=O)CH₃, -C(=O)OH, -C(=O)OCH₃, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl. In some embodiments of a compound disclosed herein, each R^a is independently C₁-C₆alkyl, C₁-C₆haloalkyl, cycloalkyl, or heterocycloalkyl; wherein each alkyl, cycloalkyl, and heterocycloalkyl is independently optionally substituted with one or more oxo, deuterium, halogen, -CN, -OH, -OCH₃, -S(=O)CH₃, -S(=O)₂CH₃, -S(=O)₂NH₂, -S(=O)₂NHCH₃, -S(=O)₂N(CH₃)₂, -NH₂, -NHCH₃, -N(CH₃)₂, -C(=O)CH₃, -C(=O)OH, -C(=O)OCH₃, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl,

C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl. In some embodiments of a compound disclosed herein, each R^a is independently C₁-C₆alkyl, C₁-C₆haloalkyl, cycloalkyl, or heterocycloalkyl. In some embodiments of a compound disclosed herein, each R^a is independently C₁-C₆alkyl or C₁-C₆haloalkyl. In some embodiments of a compound disclosed herein, each R^a is independently C₁-C₆alkyl.

[00173] In some embodiments of a compound disclosed herein, each R^b is independently hydrogen, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein each alkyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more oxo, deuterium, halogen, -CN, -OH, -OCH₃, -S(=O)CH₃, -S(=O)₂CH₃, -S(=O)₂NH₂, -S(=O)₂NHCH₃, -S(=O)₂N(CH₃)₂, -NH₂, -NHCH₃, -N(CH₃)₂, -C(=O)CH₃, -C(=O)OH, -C(=O)OCH₃, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl. In some embodiments of a compound disclosed herein, each R^b is independently hydrogen, C₁-C₆alkyl, C₁-C₆haloalkyl, cycloalkyl, or heterocycloalkyl; wherein each alkyl, cycloalkyl, and heterocycloalkyl is independently optionally substituted with one or more oxo, deuterium, halogen, -CN, -OH, -OCH₃, -S(=O)CH₃, -S(=O)₂CH₃, -S(=O)₂NH₂, -S(=O)₂NHCH₃, -S(=O)₂N(CH₃)₂, -NH₂, -NHCH₃, -N(CH₃)₂, -C(=O)CH₃, -C(=O)OH, -C(=O)OCH₃, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl. In some embodiments of a compound disclosed herein, each R^b is independently hydrogen, C₁-C₆alkyl, C₁-C₆haloalkyl, cycloalkyl, or heterocycloalkyl. In some embodiments of a compound disclosed herein, each R^b is independently hydrogen, C₁-C₆alkyl, or C₁-C₆haloalkyl. In some embodiments of a compound disclosed herein, each R^b is independently hydrogen or C₁-C₆alkyl.

[00174] In some embodiments of a compound disclosed herein, each R^c and R^d are independently hydrogen, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein each alkyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more oxo, deuterium, halogen, -CN, -OH, -OCH₃, -S(=O)CH₃, -S(=O)₂CH₃, -S(=O)₂NH₂, -S(=O)₂NHCH₃, -S(=O)₂N(CH₃)₂, -NH₂, -NHCH₃, -N(CH₃)₂, -C(=O)CH₃, -C(=O)OH, -C(=O)OCH₃, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl. In some embodiments of a compound disclosed herein, each R^c and R^d are independently hydrogen, C₁-C₆alkyl, C₁-C₆haloalkyl, cycloalkyl, or heterocycloalkyl; wherein each alkyl, cycloalkyl, and heterocycloalkyl is independently optionally substituted with one or more oxo, deuterium, halogen, -CN, -OH, -OCH₃, -S(=O)CH₃, -S(=O)₂CH₃, -S(=O)₂NH₂, -S(=O)₂NHCH₃, -S(=O)₂N(CH₃)₂, -NH₂, -NHCH₃, -N(CH₃)₂, -C(=O)CH₃, -C(=O)OH, -C(=O)OCH₃, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl. In some embodiments of a compound disclosed herein, each R^c and R^d are independently hydrogen, C₁-C₆alkyl, C₁-C₆haloalkyl, cycloalkyl, or heterocycloalkyl. In some embodiments of a compound disclosed herein, each R^c and R^d are independently hydrogen, C₁-C₆alkyl, or C₁-C₆haloalkyl. In some embodiments of a compound disclosed herein, each R^c and R^d are independently hydrogen or C₁-C₆alkyl.

[00175] In some embodiments of a compound disclosed herein, R^c and R^d are taken together with the atom to which they are attached to form a heterocycloalkyl optionally substituted with one or more oxo, deuterium, halogen, -CN, -OH, -OCH₃, -NH₂, -NHCH₃, -N(CH₃)₂, -C(=O)CH₃, -C(=O)OH, -C(=O)OCH₃, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, or C₁-C₆heteroalkyl.

[00176] In some embodiments of a compound disclosed herein, each R^A, R^B, R^C, R^D, R^E, R¹², R^a, R^b, R^c, R^d, and the heterocycloalkyl formed when R^c and R^d are taken together is independently substituted with one, two, three, or four substituents as defined herein. In some embodiments of a compound disclosed herein, each R^A, R^B, R^C, R^D, R^E, R¹², R^a, R^b, R^c, R^d, and the heterocycloalkyl formed when R^c and R^d are taken together is independently substituted with one, two, or three substituents as defined herein. In some embodiments of a compound disclosed herein, each R^A, R^B, R^C, R^D, R^E, R¹², R^a, R^b, R^c, R^d, and the heterocycloalkyl formed when R^c and R^d are taken together is independently substituted with one or two substituents as defined herein. In some embodiments of a compound disclosed herein, each R^A, R^B, R^C, R^D, R^E, R¹², R^a, R^b, R^c, R^d, and the heterocycloalkyl formed when R^c and R^d are taken together is independently substituted with one substituent as defined herein.

[00177] Any combination of the groups described above for the various variables is contemplated herein. Throughout the specification, groups and substituents thereof are chosen by one skilled in the field to provide stable moieties and compounds.

[00178] In some embodiments the compound disclosed herein, or a pharmaceutically acceptable salt, solvate, N-oxide, or stereoisomer thereof, is one of the compounds in Table 1.

TABLE 1

Ex.	Structure
1	
2*	
3*	

Ex.	Structure
3A*	
3B*	
4*	
4A*	
4B*	
5*	
5A*	
5B*	

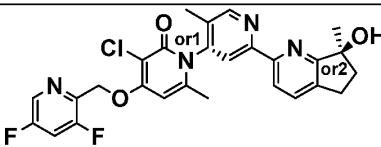
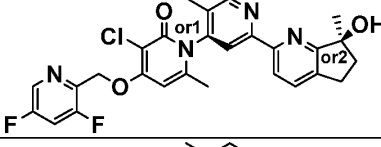
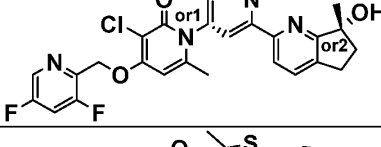
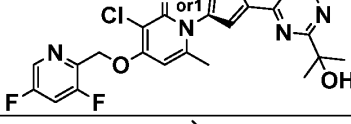
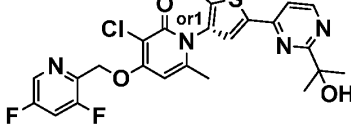
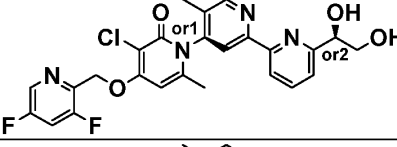
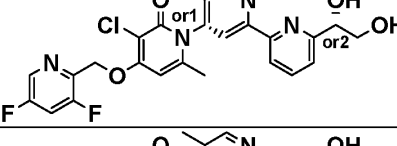
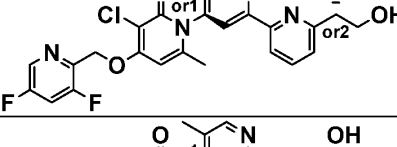
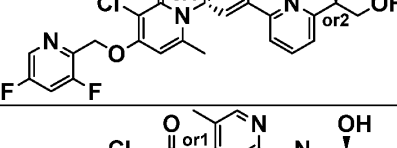
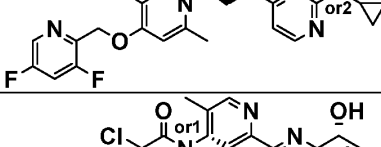
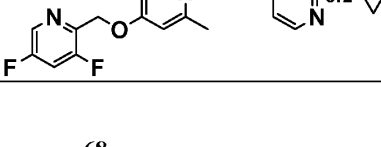
Ex.	Structure
6*	
6A*	
6B*	
6C*	
6D*	
7*	
8*	
9A*	

Ex.	Structure
9B*	
10*	
11*	
12*	
13*	
14*	
15*	
16*	
17*	

Ex.	Structure
18A*	
18B*	
18C*	
18D*	
19A*	
19B*	
20A*	
20B*	
21A*	

Ex.	Structure
21B*	
22A*	
22B*	
23A*	
23B*	
24A*	
24B*	
25*	
25A*	
25B*	
26A*	

Ex.	Structure
26B*	
27A*	
27B*	
28A*	
28B*	
29A*	
29B*	
30*	
31A*	
31B*	
32A*	

Ex.	Structure
32B*	
32C*	
32D*	
33A*	
33B*	
34A*	
34B*	
34C*	
34D*	
35A*	
35B*	

Ex.	Structure
35C*	
35D*	
36A*	
36B*	
36C*	
36D*	
37A*	
37B*	
38A*	
38B*	
39A*	

Ex.	Structure
39B*	
40A*	
40B*	
41A*	
41B*	
42A*	
42B*	
43A*	
43B*	
44A*	

Ex.	Structure
44B*	
45A*	
45B*	
46A*	
46B*	
47A*	
47B*	
48A*	
48B*	
49A*	
49B*	

Ex.	Structure
50A*	
50B*	
51A*	
51B*	
52A*	
52B*	
53A*	
53B*	
54A*	
54B*	
55*	

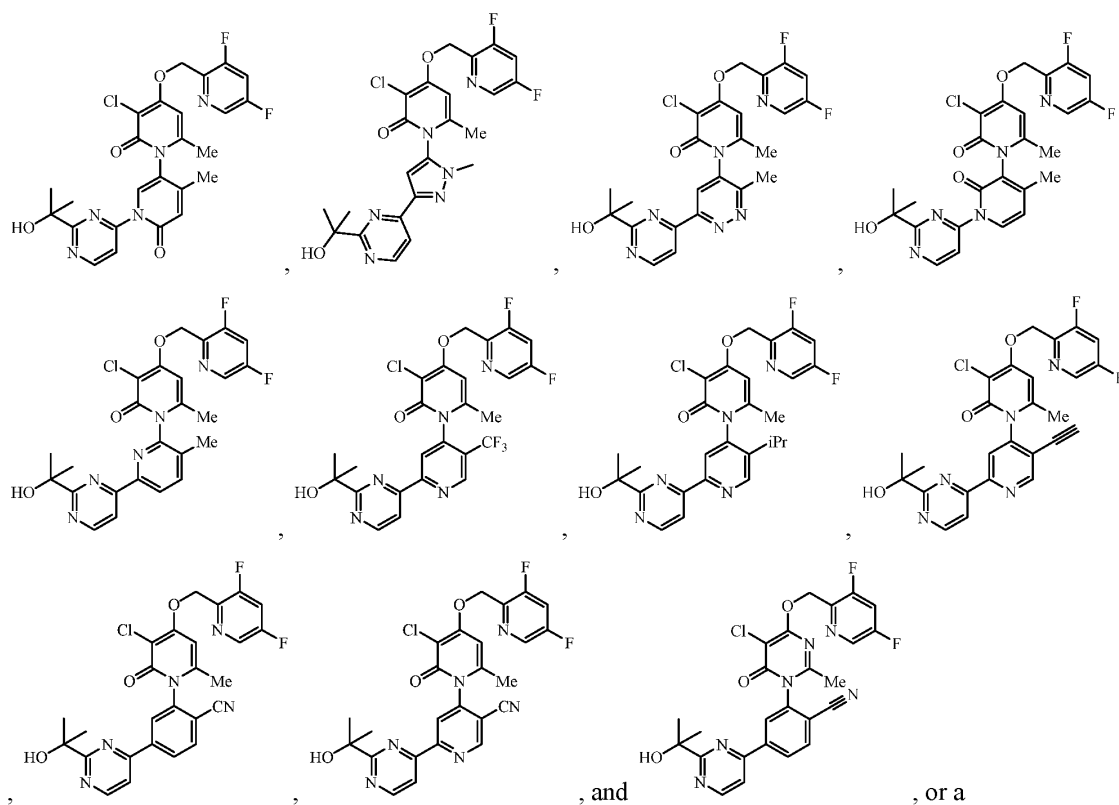
Ex.	Structure
56A*	
56B*	
57A*	
57B*	
58A*	
58B*	
59A*	
59B*	
60A*	
60B*	
61A*	

Ex.	Structure
61B*	
62A*	
62B*	
63A*	
63B*	
64A*	
64B*	
65A*	
65B*	
66A*	
66B*	

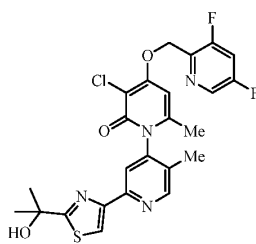
Ex.	Structure
67A*	
67B*	
68A*	
68B*	

* stereochemistry arbitrarily assigned.

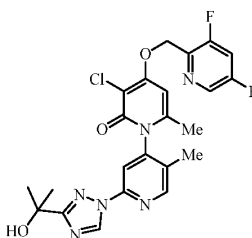
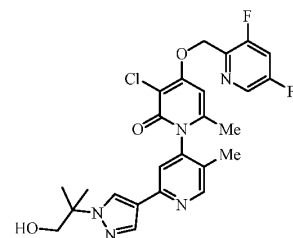
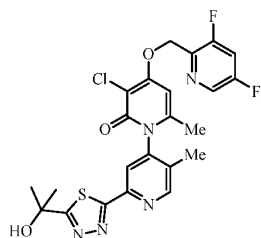
[00179] In some embodiments the compound of Formula (I) is selected from:



pharmaceutically acceptable salt, solvate, N-oxide, or stereoisomer thereof.

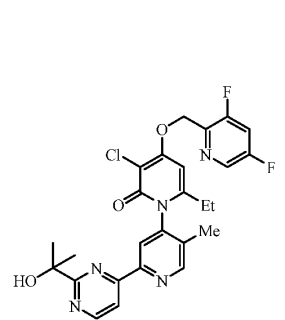
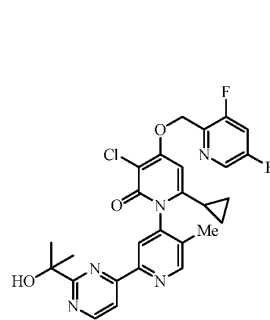
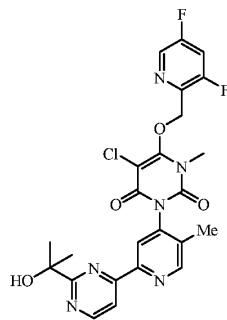
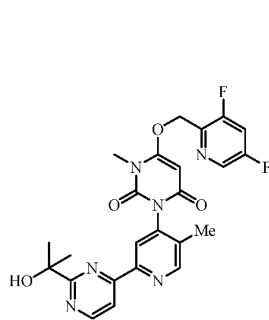
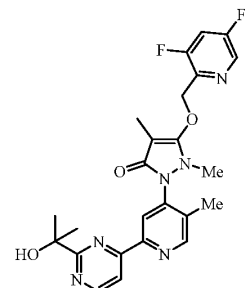
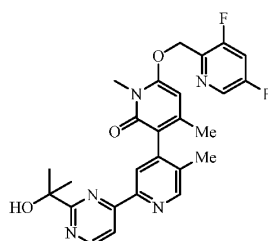
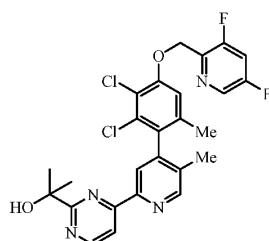
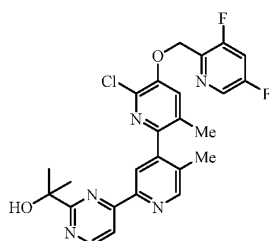
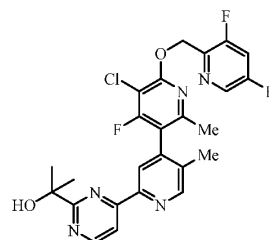
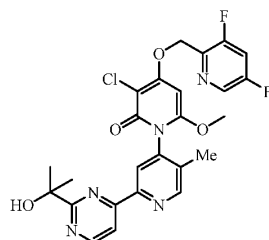
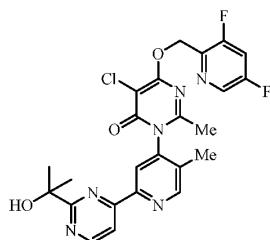


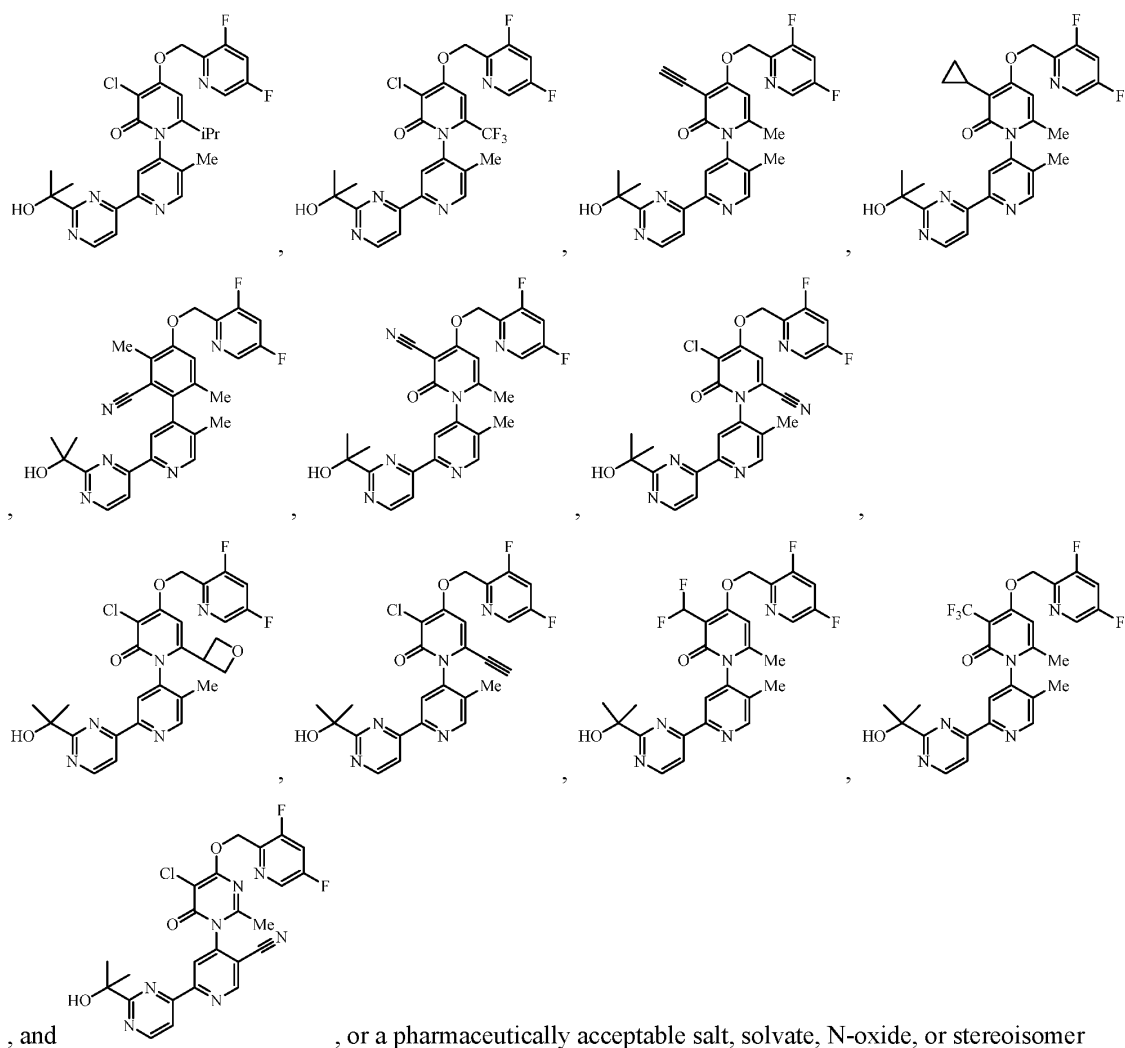
[00180] In some embodiments the compound of Formula (II) is selected from:



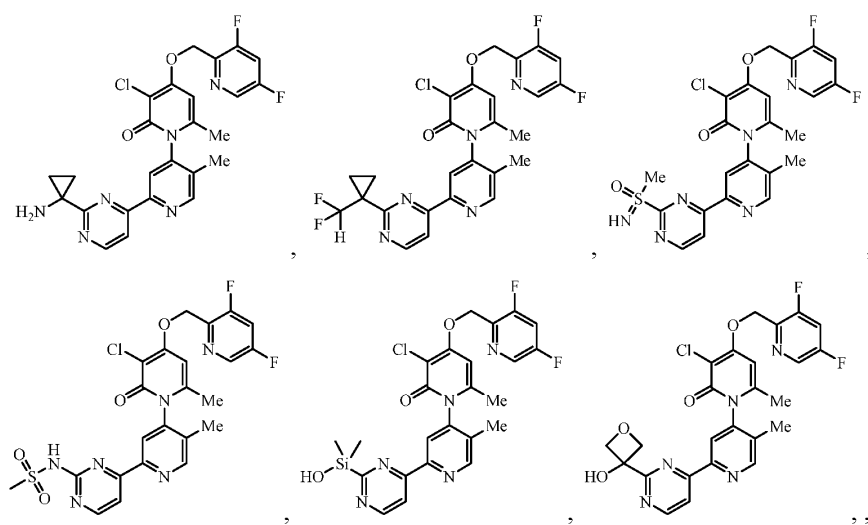
acceptable salt, solvate, N-oxide, or stereoisomer thereof.

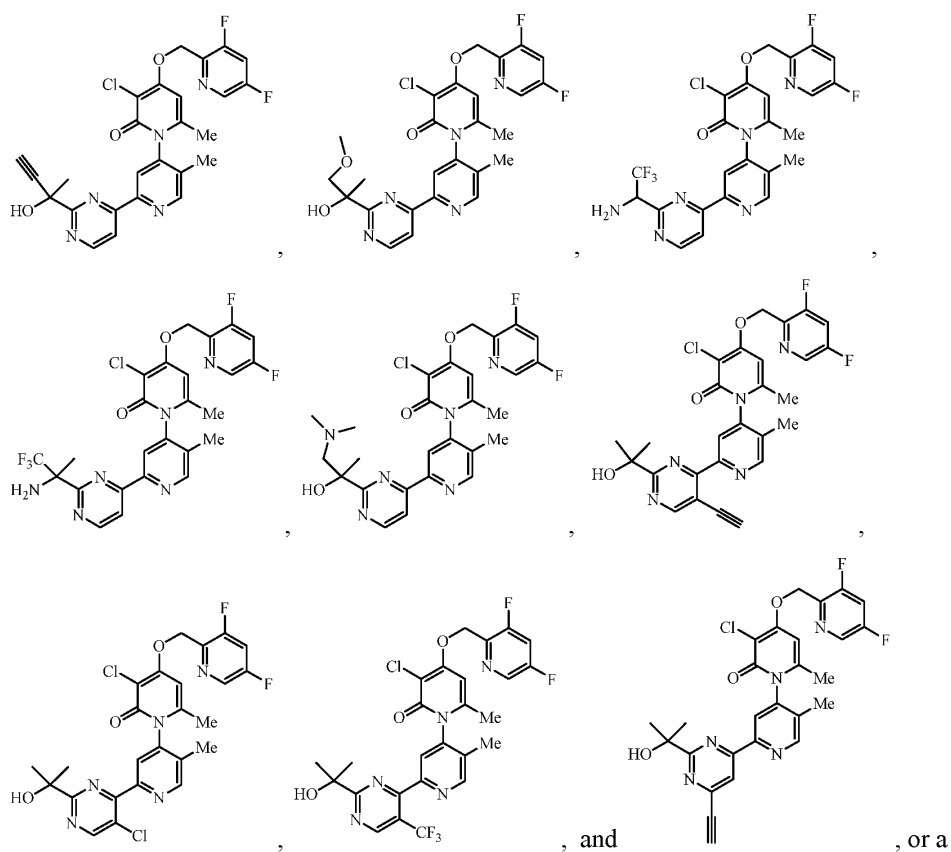
[00181] In some embodiments the compound of Formula (III) is selected from:





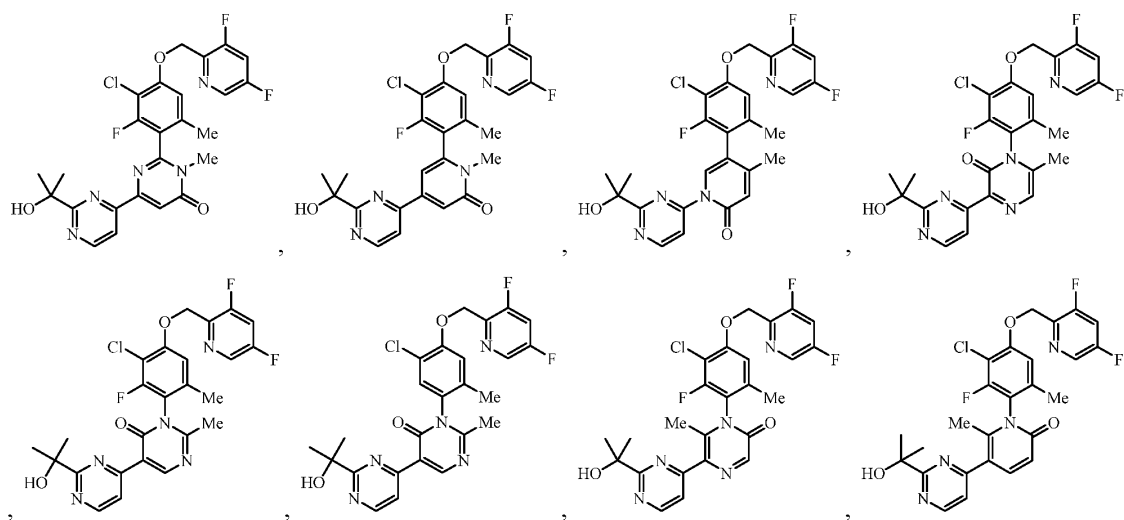
[00182] In some embodiments the compound of Formula (IV) is selected from:

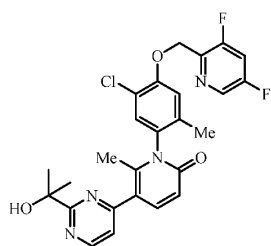




pharmaceutically acceptable salt, solvate, N-oxide, or stereoisomer thereof.

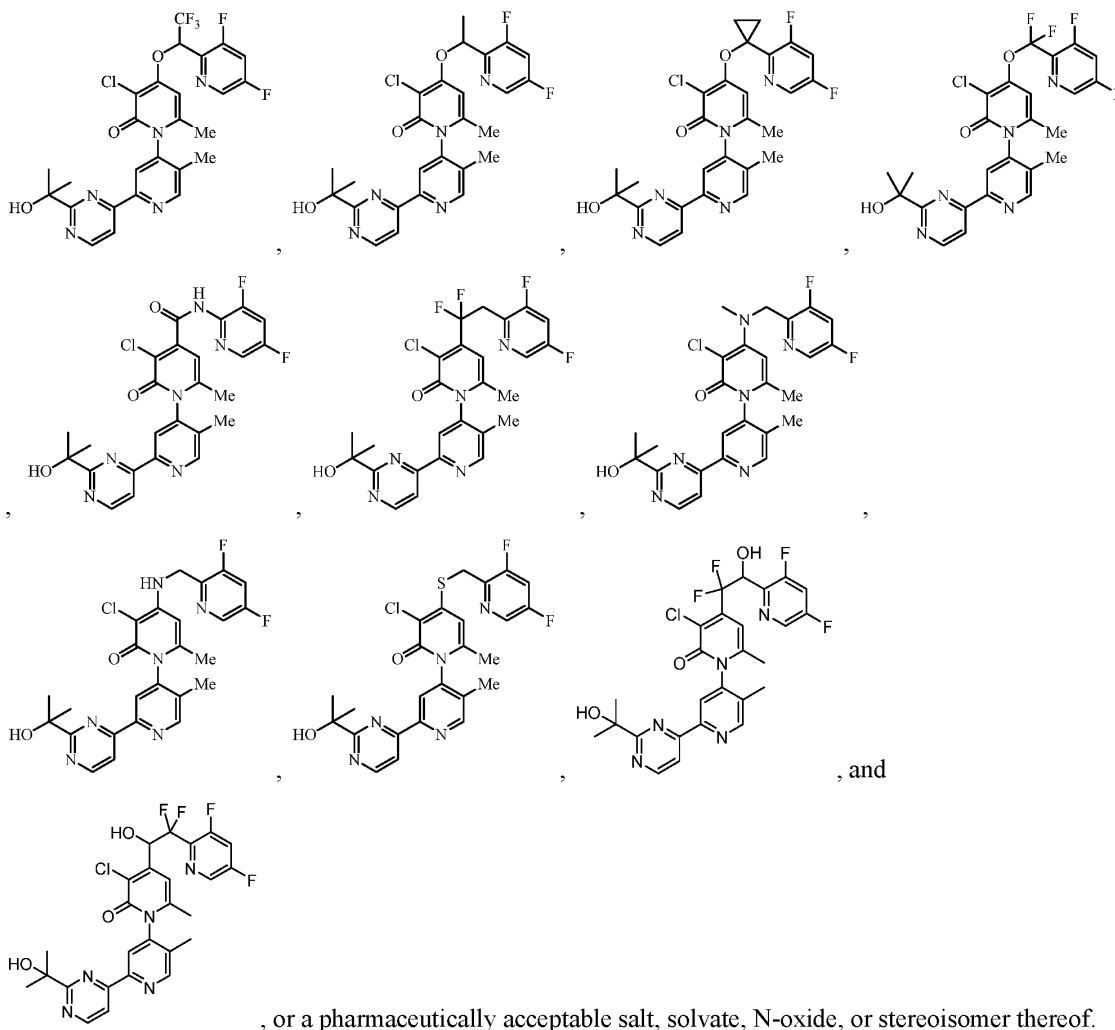
[00183] In some embodiments the compound of Formula (V) is selected from:



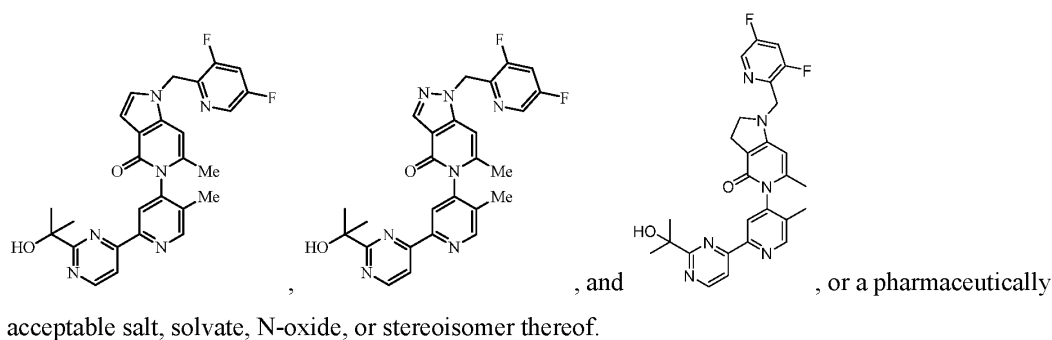


, and , or a pharmaceutically acceptable salt, solvate, N-oxide, or stereoisomer thereof.

[00184] In some embodiments the compound of Formula (VI) is selected from:



[00185] In some embodiments the compound of Formula (VII) is selected from:

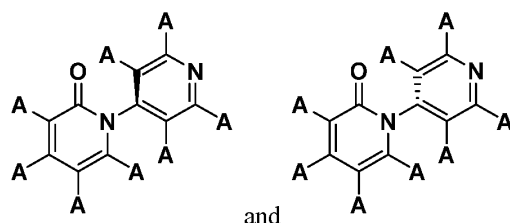


Further Forms of Compounds Disclosed Herein

Isomers/Stereoisomers

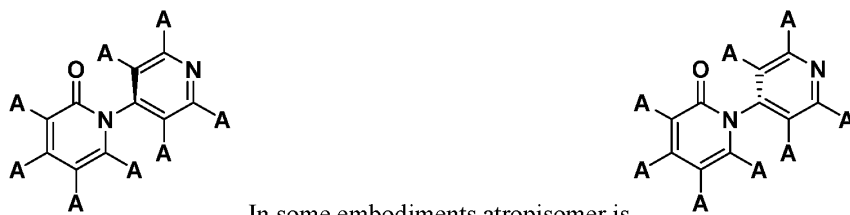
[00186] In some embodiments, the compounds described herein exist as geometric isomers. In some embodiments, the compounds described herein possess one or more double bonds. The compounds presented herein include all *cis*, *trans*, *syn*, *anti*, *entgegen* (*E*), and *zusammen* (*Z*) isomers as well as the corresponding mixtures thereof. In some situations, the compounds described herein possess one or more chiral centers and each center exists in the *R* configuration, or *S* configuration. The compounds described herein include all diastereomeric, enantiomeric, and epimeric forms as well as the corresponding mixtures thereof. In additional embodiments of the compounds and methods provided herein, mixtures of enantiomers and/or diastereoisomers, resulting from a single preparative step, combination, or interconversion are useful for the applications described herein. In some embodiments, the compounds described herein are prepared as their individual stereoisomers by reacting a racemic mixture of the compound with an optically active resolving agent to form a pair of diastereoisomeric compounds, separating the diastereomers and recovering the optically pure enantiomers. In some embodiments, dissociable complexes are preferred. In some embodiments, the diastereomers have distinct physical properties (e.g., melting points, boiling points, solubilities, reactivity, etc.) and are separated by taking advantage of these dissimilarities. In some embodiments, the diastereomers are separated by chiral chromatography, or preferably, by separation/resolution techniques based upon differences in solubility. In some embodiments, the optically pure enantiomer is then recovered, along with the resolving agent, by any practical means that would not result in racemization.

[00187] In some embodiments, the compounds described herein contain bonds with hindered rotation such that two separate rotamers or atropisomers can be isolated. In some embodiments the atropisomers are



wherein each A correspond to the appropriate R group as defined in each of Formula (I) to (VIII). In some embodiments, these atropisomer are separated and are

found to have different biological activity which may be advantageous. In some embodiments atropisomer is



Labeled compounds

[00188] In some embodiments, the compounds described herein exist in their isotopically-labeled forms. In some embodiments, the methods disclosed herein include methods of treating diseases by administering such isotopically-labeled compounds. In some embodiments, the methods disclosed herein include methods of treating diseases by administering such isotopically-labeled compounds as pharmaceutical compositions. Thus, in some embodiments, the compounds disclosed herein include isotopically-labeled compounds, which are identical to those recited herein, but for the fact that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes that can be incorporated into compounds disclosed herein include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, sulfur, fluorine and chloride, such as ^2H , ^3H , ^{13}C , ^{14}C , ^{15}N , ^{18}O , ^{17}O , ^{31}P , ^{32}P , ^{35}S , ^{18}F , and ^{36}Cl , respectively. Compounds described herein, and the pharmaceutically acceptable salts, solvates, or stereoisomers thereof which contain the aforementioned isotopes and/or other isotopes of other atoms are within the scope of this invention. Certain isotopically-labeled compounds, for example those into which radioactive isotopes such as ^3H and ^{14}C are incorporated, are useful in drug and/or substrate tissue distribution assays. Tritiated, i.e., ^3H and carbon-14, i.e., ^{14}C , isotopes are particularly preferred for their ease of preparation and detectability. Further, substitution with heavy isotopes such as deuterium, i.e., ^2H , produces certain therapeutic advantages resulting from greater metabolic stability, for example increased in vivo half-life or reduced dosage requirements.

Pharmaceutically acceptable salts

[00189] In some embodiments, the compounds described herein exist as their pharmaceutically acceptable salts. In some embodiments, the methods disclosed herein include methods of treating diseases by administering such pharmaceutically acceptable salts. In some embodiments, the methods disclosed herein include methods of treating diseases by administering such pharmaceutically acceptable salts as pharmaceutical compositions.

[00190] In some embodiments, the compounds described herein possess acidic or basic groups and therefore react with any of a number of inorganic or organic bases, and inorganic and organic acids, to form a pharmaceutically acceptable salt. In some embodiments, these salts are prepared *in situ* during the final isolation and purification of the compounds disclosed herein, or a solvate, or stereoisomer thereof, or by separately reacting a purified compound in its free form with a suitable acid or base, and isolating the salt thus formed.

[00191] Examples of pharmaceutically acceptable salts include those salts prepared by reaction of the compounds described herein with a mineral, organic acid or inorganic base, such salts including, acetate, acrylate, adipate, alginate, aspartate, benzoate, benzenesulfonate, bisulfate, bisulfite, bromide, butyrate, butyn-1,4-dioate, camphorate, camphorsulfonate, caproate, caprylate, chlorobenzoate, chloride, citrate, cyclopentanepropionate, decanoate, digluconate, dihydrogenphosphate, dinitrobenzoate, dodecylsulfate, ethanesulfonate, formate, fumarate, glucoheptanoate, glycerophosphate, glycolate, hemisulfate, heptanoate, hexanoate, hexyne-1,6-dioate, hydroxybenzoate, γ -hydroxybutyrate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxyethanesulfonate, iodide, isobutyrate, lactate, maleate, malonate, methanesulfonate, mandelate metaphosphate, methanesulfonate, methoxybenzoate, methylbenzoate, monohydrogenphosphate, 1-naphthalenesulfonate, 2-naphthalenesulfonate, nicotinate, nitrate, palmoate, pectinate, persulfate, 3-phenylpropionate, phosphate, picrate, pivalate, propionate, pyrosulfate, pyrophosphate, propiolate, phthalate, phenylacetate, phenylbutyrate, propanesulfonate, salicylate, succinate, sulfate, sulfite, succinate, suberate, sebacate, sulfonate, tartrate, thiocyanate, tosylateundeconate and xylenesulfonate.

[00192] Further, the compounds described herein can be prepared as pharmaceutically acceptable salts formed by reacting the free base form of the compound with a pharmaceutically acceptable inorganic or organic acid, including, but not limited to, inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid metaphosphoric acid, and the like; and organic acids such as acetic acid, propionic acid, hexanoic acid, cyclopentanepropionic acid, glycolic acid, pyruvic acid, lactic acid, malonic acid, succinic acid, malic acid, maleic acid, fumaric acid, p-toluenesulfonic acid, tartaric acid, trifluoroacetic acid, citric acid, benzoic acid, 3-(4-hydroxybenzoyl)benzoic acid, cinnamic acid, mandelic acid, arylsulfonic acid, methanesulfonic acid, ethanesulfonic acid, 1,2-ethanedisulfonic acid, 2-hydroxyethanesulfonic acid, benzenesulfonic acid, 2-naphthalenesulfonic acid, 4-methylbicyclo-[2.2.2]oct-2-ene-1-carboxylic acid, glucoheptonic acid, 4,4'-methylenebis-(3-hydroxy-2-ene-1-carboxylic acid), 3-phenylpropionic acid, trimethylacetic acid, tertiary butylacetic acid, lauryl sulfuric acid, gluconic acid, glutamic acid, hydroxynaphthoic acid, salicylic acid, stearic acid and muconic acid. In some embodiments, other acids, such as oxalic, while not in themselves pharmaceutically acceptable, are employed in the preparation of salts useful as intermediates in obtaining the compounds disclosed herein, solvate, or stereoisomer thereof and their pharmaceutically acceptable acid addition salts.

[00193] In some embodiments, those compounds described herein which comprise a free acid group react with a suitable base, such as the hydroxide, carbonate, bicarbonate, sulfate, of a pharmaceutically acceptable metal cation, with ammonia, or with a pharmaceutically acceptable organic primary, secondary, tertiary, or quaternary amine. Representative salts include the alkali or alkaline earth salts, like lithium, sodium, potassium, calcium, and magnesium, and aluminum salts and the like. Illustrative examples of bases include sodium hydroxide, potassium hydroxide, choline hydroxide, sodium carbonate, $N^+(C_{1-4} \text{ alkyl})_4$, and the like.

[00194] Representative organic amines useful for the formation of base addition salts include ethylamine, diethylamine, ethylenediamine, ethanolamine, diethanolamine, piperazine and the like. It should be understood that the compounds described herein also include the quaternization of any basic nitrogen-

containing groups they contain. In some embodiments, water or oil-soluble or dispersible products are obtained by such quaternization.

Solvates

[00195] In some embodiments, the compounds described herein exist as solvates. The invention provides for methods of treating diseases by administering such solvates. The invention further provides for methods of treating diseases by administering such solvates as pharmaceutical compositions.

[00196] Solvates contain either stoichiometric or non-stoichiometric amounts of a solvent, and, in some embodiments, are formed with pharmaceutically acceptable solvents such as water, ethanol, and the like. Hydrates are formed when the solvent is water, or alcoholates are formed when the solvent is alcohol. Solvates of the compounds described herein can be conveniently prepared or formed during the processes described herein. In addition, the compounds provided herein can exist in unsolvated as well as solvated forms. In general, the solvated forms are considered equivalent to the unsolvated forms for the purposes of the compounds and methods provided herein.

Tautomers

[00197] In some situations, compounds exist as tautomers. The compounds described herein include all possible tautomers within the formulas described herein. Tautomers are compounds that are interconvertible by migration of a hydrogen atom, accompanied by a switch of a single bond and adjacent double bond. In bonding arrangements where tautomerization is possible, a chemical equilibrium of the tautomers will exist. All tautomeric forms of the compounds disclosed herein are contemplated. The exact ratio of the tautomers depends on several factors, including temperature, solvent, and pH.

Method of Treatment

[00198] Described herein are compounds and compositions generally useful for the inhibition of kinase activity of one or more enzymes. Examples of kinases that are inhibited by the compounds and compositions described herein and against which the methods described herein are useful include p38 MAP kinase, MK2, or a mutant thereof.

[00199] MAP kinase-activated protein kinase 2 ("MK2") is an enzyme that in humans is encoded by the MAPKAPK2 gene. This gene encodes a member of the Ser/Thr protein kinase family. This kinase is regulated through direct phosphorylation by p38 MAP kinase. In conjunction with p38 MAP kinase, this kinase is known to be involved in many cellular processes including stress and inflammatory responses, nuclear export, gene expression regulation and cell proliferation. Heat shock protein HSP27 was shown to be one of the substrates of this kinase in vivo. Two transcript variants encoding two different isoforms have been found for this gene.

[00200] MK2 is a multi-domain protein consisting of an N-terminal proline-rich domain, a catalytic domain, an autoinhibitory domain and at the C-terminus a nuclear export signal (NES) and nuclear localization signal (NLS). Two isoforms of human MK2 have been characterized. One isoform consists of 400 amino acids and the other isoform 370 residues which is thought to be a splice variant missing the C-

terminal NLS. MK2 is located in the nucleus of the cell and upon binding and phosphorylation by p38, the MK2 NES becomes functional and both kinases are co-transported out of the nucleus to the cytoplasm. Interestingly, transport of the MK2/p38 complex does not require catalytically active MK2, as the active site mutant, Asp207Ala, is still transported to the cytoplasm. Phosphorylation of human MK2 by p38 on residues T222, S272 and T334 is thought to activate the enzyme by inducing a conformational change of the autoinhibitory domain thus exposing the active site for substrate binding. Mutations of two autoinhibitory domain residues W332A and K326E in murine MK2 demonstrate an increase in basal activity and a C-terminal deletion of the autoinhibitory domain renders the enzyme constitutively active, providing additional evidence to the role of this domain in inhibition of MK2 activity.

[00201] Diseases or disorders associated with MK2 that are treated by compounds disclosed herein include autoimmune disorders, chronic inflammatory disorders, acute inflammatory disorders, auto-inflammatory disorders, fibrotic disorders, metabolic disorders, neoplastic disorders, and cardiovascular or cerebrovascular disorders.

[00202] In some embodiments, the MK2-mediated disease or disorder is an autoimmune disorder, chronic and/or acute inflammatory disorder, and/or auto-inflammatory disorder. Exemplary autoimmune and/or inflammatory and/or auto-inflammatory disorders include: inflammatory bowel diseases (for example, ulcerative colitis or Crohn's disease), multiple sclerosis, psoriasis, arthritis, rheumatoid arthritis, osteoarthritis, juvenile arthritis, psoriatic arthritis, reactive arthritis, ankylosing spondylitis, cryopyrin associated periodic syndromes, Muckle-Wells syndrome, familial cold auto-inflammatory syndrome, neonatal-onset multisystem inflammatory disease, TNF receptor associated periodic syndrome, acute and chronic pancreatitis, atherosclerosis, gout, ankylosing spondylitis, fibrotic disorders (for example, hepatic fibrosis or idiopathic pulmonary fibrosis), nephropathy, sarcoidosis, scleroderma, anaphylaxis, diabetes (for example, diabetes mellitus type 1 or diabetes mellitus type 2), diabetic retinopathy, Still's disease, vasculitis, sarcoidosis, pulmonary inflammation, acute respiratory distress syndrome, wet and dry age-related macular degeneration, autoimmune hemolytic syndromes, autoimmune and inflammatory hepatitis, autoimmune neuropathy, autoimmune ovarian failure, autoimmune orchitis, autoimmune thrombocytopenia, silicone implant associated autoimmune disease, Sjogren's syndrome, familial Mediterranean fever, systemic lupus erythematosus, vasculitis syndromes (for example, temporal, Takayasu's and giant cell arteritis, Behçet's disease or Wegener's granulomatosis), vitiligo, secondary hematologic manifestation of autoimmune diseases (for example, anemias), drug-induced autoimmunity, Hashimoto's thyroiditis, hypophysitis, idiopathic thrombocytic purpura, metal-induced autoimmunity, myasthenia gravis, pemphigus, autoimmune deafness (for example, Meniere's disease), Goodpasture's syndrome, Graves' disease, HW-related autoimmune syndromes, Guillain-Barre disease, Addison's disease, anti-phospholipid syndrome, asthma, atopic dermatitis, Celiac disease, Cushing's syndrome, dermatomyositis, idiopathic adrenal atrophy, idiopathic thrombocytopenia, Kawasaki syndrome, Lambert-Eaton Syndrome, pernicious anemia, pollinosis, polyarteritis nodosa, primary biliary cirrhosis, primary sclerosing cholangitis, Raynaud's, Reiter's Syndrome, relapsing polychondritis, Schmidt's syndrome, thyrotoxicosis, sepsis, septic shock, endotoxic

shock, exotoxin-induced toxic shock, gram negative sepsis, toxic shock syndrome, glomerulonephritis, peritonitis, interstitial cystitis, hyperoxia-induced inflammations, chronic obstructive pulmonary disease (COPD), vasculitis, graft vs. host reaction (for example, graft vs. host disease), allograft rejections (for example, acute allograft rejection or chronic allograft rejection), early transplantation rejection (for example, acute allograft rejection), reperfusion injury, pain (for example, acute pain, chronic pain, neuropathic pain, or fibromyalgia), chronic infections, meningitis, encephalitis, myocarditis, gingivitis, post-surgical trauma, tissue injury, traumatic brain injury, enterocolitis, sinusitis, uveitis, ocular inflammation, optic neuritis, gastric ulcers, esophagitis, peritonitis, periodontitis, dermatomyositis, gastritis, myositis, polymyalgia, pneumonia and bronchitis.

[00203] In some embodiments, the MK2-mediated disease or disorder is a fibrotic disorder. Exemplary fibrotic disorders include systemic sclerosis/scleroderma, lupus nephritis, connective tissue disease, wound healing, surgical scarring, spinal cord injury, CNS scarring, acute lung injury, pulmonary fibrosis (for example, idiopathic pulmonary fibrosis or cystic fibrosis), chronic obstructive pulmonary disease, adult respiratory distress syndrome, acute lung injury, drug-induced lung injury, glomerulonephritis, chronic kidney disease (for example, diabetic nephropathy), hypertension-induced nephropathy, alimentary track or gastrointestinal fibrosis, renal fibrosis, hepatic or biliary fibrosis, liver fibrosis (for example, nonalcoholic steatohepatitis, hepatitis C, or hepatocellular carcinoma), cirrhosis (for example, primary biliary cirrhosis or cirrhosis due to fatty liver disease (for example, alcoholic and nonalcoholic steatosis)), radiation-induced fibrosis (for example, head and neck, gastrointestinal or pulmonary), primary sclerosing cholangitis, restenosis, cardiac fibrosis (for example, endomyocardial fibrosis or atrial fibrosis), ophthalmic scarring, fibrosclerosis, fibrotic cancers, fibroids, fibroma, fibroadenomas, fibrosarcomas, transplant arteriopathy, keloid, mediastinal fibrosis, myelofibrosis, retroperitoneal fibrosis, progressive massive fibrosis, and nephrogenic systemic fibrosis.

[00204] In some embodiments, the MK2-mediated disease or disorder is a metabolic disorder. Exemplary metabolic disorders include obesity, steroid-resistance, glucose intolerance, and metabolic syndrome.

[00205] In some embodiments, the MK2-mediated disease or disorder is a neoplastic disease or disorder. Exemplary neoplastic diseases or disorders include cancers. In some embodiments, exemplary neoplastic diseases or disorders include angiogenesis disorders, multiple myeloma, leukemias (for example, acute lymphocytic leukemia, acute and chronic myelogenous leukemia, chronic lymphocytic leukemia, acute lymphoblastic leukemia, or promyelocytic leukemia), lymphomas (for example, B-cell lymphoma, T-cell lymphoma, mantle cell lymphoma, hairy cell lymphoma, Burkitt's lymphoma, mast cell tumors, Hodgkin's disease or non-Hodgkin's disease), myelodysplastic syndrome, fibrosarcoma, rhabdomyosarcoma; astrocytoma, neuroblastoma, glioma and schwannomas; melanoma, seminoma, teratocarcinoma, osteosarcoma, xenoderma pigmentosum, keratocanthoma, thyroid follicular cancer, Kaposi's sarcoma, melanoma, teratoma, rhabdomyosarcoma, metastatic and bone disorders, as well as cancer of the bone, mouth/pharynx, esophagus, larynx, stomach, intestine, colon, rectum, lung (for example, non-small cell lung cancer or small cell lung cancer), liver, pancreas, nerve, brain (for example, glioma or glioblastoma

multiforme), head and neck, throat, ovary, uterus, prostate, testis, bladder, kidney, breast, gall bladder, cervix, thyroid, prostate, and skin.

[00206] In some embodiments, the MK2-mediated disorder is a cardiovascular or cerebrovascular disorder. Exemplary cardiovascular disorders include atherosclerosis, restenosis of an atherosclerotic coronary artery, acute coronary syndrome, myocardial infarction, cardiac-allograft vasculopathy and stroke. Exemplary cerebrovascular diseases include central nervous system disorders with an inflammatory or apoptotic component, Alzheimer's disease, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, spinal cord injury, neuronal ischemia and peripheral neuropathy.

Dosing

[00207] In certain embodiments, the compositions containing the compound(s) described herein are administered for prophylactic and/or therapeutic treatments. In certain therapeutic applications, the compositions are administered to a patient already suffering from a disease or condition, in an amount sufficient to cure or at least partially arrest at least one of the symptoms of the disease or condition. Amounts effective for this use depend on the severity and course of the disease or condition, previous therapy, the patient's health status, weight, and response to the drugs, and the judgment of the treating physician. Therapeutically effective amounts are optionally determined by methods including, but not limited to, a dose escalation and/or dose ranging clinical trial.

[00208] In prophylactic applications, compositions containing the compounds described herein are administered to a patient susceptible to or otherwise at risk of a particular disease, disorder or condition. Such an amount is defined to be a "prophylactically effective amount or dose." In this use, the precise amounts also depend on the patient's state of health, weight, and the like. When used in patients, effective amounts for this use will depend on the severity and course of the disease, disorder or condition, previous therapy, the patient's health status and response to the drugs, and the judgment of the treating physician. In one aspect, prophylactic treatments include administering to a mammal, who previously experienced at least one symptom of or risk factor for the disease being treated and is currently in remission, a pharmaceutical composition comprising a compound described herein, or a pharmaceutically acceptable salt thereof, in order to prevent a return of the symptoms of the disease or condition.

[00209] In certain embodiments wherein the patient's condition does not improve, upon the doctor's discretion the administration of the compounds are administered chronically, that is, for an extended period of time, including throughout the duration of the patient's life in order to ameliorate or otherwise control or limit the symptoms of the patient's disease or condition.

[00210] In certain embodiments wherein a patient's status does improve, the dose of drug being administered is temporarily reduced or temporarily suspended for a certain length of time (*i.e.*, a "drug holiday"). In specific embodiments, the length of the drug holiday is between 2 days and 1 year, including by way of example only, 2 days, 3 days, 4 days, 5 days, 6 days, 7 days, 10 days, 12 days, 15 days, 20 days, 28 days, or more than 28 days. The dose reduction during a drug holiday is, by way of example only, by

10%-100%, including by way of example only 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, and 100%.

[00211] Once improvement of the patient's conditions has occurred, a maintenance dose is administered if necessary. Subsequently, in specific embodiments, the dosage or the frequency of administration, or both, is reduced, as a function of the symptoms, to a level at which the improved disease, disorder or condition is retained. In certain embodiments, however, the patient requires intermittent or daily treatment on a long-term basis upon any recurrence of symptoms.

[00212] The amount of a given agent that corresponds to such an amount varies depending upon factors such as the particular compound, disease condition and its severity, the identity (*e.g.*, weight, sex) of the subject or host in need of treatment, but nevertheless is determined according to the particular circumstances surrounding the case, including, *e.g.*, the specific agent being administered, the route of administration, the condition being treated, and the subject or host being treated.

[00213] In general, however, doses employed for adult human treatment are typically in the range of 0.01 mg-5000 mg per day. In one aspect, doses employed for adult human treatment are from about 1 mg to about 1000 mg per day. In one embodiment, the desired dose is conveniently presented in a single dose or in divided doses administered simultaneously or at appropriate intervals, for example as two, three, four or more sub-doses per day.

[00214] In one embodiment, the daily dosages appropriate for the compound described herein, or a pharmaceutically acceptable salt thereof, are from about 0.01 to about 50 mg/kg per body weight. In some embodiments, the daily dosage or the amount of active in the dosage form are lower or higher than the ranges indicated herein, based on a number of variables in regard to an individual treatment regime. In various embodiments, the daily and unit dosages are altered depending on a number of variables including, but not limited to, the activity of the compound used, the disease or condition to be treated, the mode of administration, the requirements of the individual subject, the severity of the disease or condition being treated, and the judgment of the practitioner.

[00215] Toxicity and therapeutic efficacy of such therapeutic regimens are determined by standard pharmaceutical procedures in cell cultures or experimental animals, including, but not limited to, the determination of the LD₁₀ and the ED₉₀. The dose ratio between the toxic and therapeutic effects is the therapeutic index and it is expressed as the ratio between LD₅₀ and ED₅₀. In certain embodiments, the data obtained from cell culture assays and animal studies are used in formulating the therapeutically effective daily dosage range and/or the therapeutically effective unit dosage amount for use in mammals, including humans. In some embodiments, the daily dosage amount of the compounds described herein lies within a range of circulating concentrations that include the ED₅₀ with minimal toxicity. In certain embodiments, the daily dosage range and/or the unit dosage amount varies within this range depending upon the dosage form employed and the route of administration utilized.

[00216] In any of the aforementioned aspects are further embodiments in which the effective amount of the compound described herein, or a pharmaceutically acceptable salt thereof, is: (a) systemically

administered to the mammal; and/or (b) administered orally to the mammal; and/or (c) intravenously administered to the mammal; and/or (d) administered by injection to the mammal; and/or (e) administered topically to the mammal; and/or (f) administered non-systemically or locally to the mammal.

[00217] In any of the aforementioned aspects are further embodiments comprising single administrations of the effective amount of the compound, including further embodiments in which (i) the compound is administered once a day; or (ii) the compound is administered to the mammal multiple times over the span of one day.

[00218] In any of the aforementioned aspects are further embodiments comprising multiple administrations of the effective amount of the compound, including further embodiments in which (i) the compound is administered continuously or intermittently: as in a single dose; (ii) the time between multiple administrations is every 6 hours; (iii) the compound is administered to the mammal every 8 hours; (iv) the compound is administered to the subject every 12 hours; (v) the compound is administered to the subject every 24 hours. In further or alternative embodiments, the method comprises a drug holiday, wherein the administration of the compound is temporarily suspended or the dose of the compound being administered is temporarily reduced; at the end of the drug holiday, dosing of the compound is resumed. In one embodiment, the length of the drug holiday varies from 2 days to 1 year.

Routes of Administration

[00219] Suitable routes of administration include, but are not limited to, oral, intravenous, rectal, aerosol, parenteral, ophthalmic, pulmonary, transmucosal, transdermal, vaginal, otic, nasal, and topical administration. In addition, by way of example only, parenteral delivery includes intramuscular, subcutaneous, intravenous, intramedullary injections, as well as intrathecal, direct intraventricular, intraperitoneal, intralymphatic, and intranasal injections.

[00220] In certain embodiments, a compound as described herein is administered in a local rather than systemic manner, for example, via injection of the compound directly into an organ, often in a depot preparation or sustained release formulation. In specific embodiments, long acting formulations are administered by implantation (for example subcutaneously or intramuscularly) or by intramuscular injection. Furthermore, in other embodiments, the drug is delivered in a targeted drug delivery system, for example, in a liposome coated with organ specific antibody. In such embodiments, the liposomes are targeted to and taken up selectively by the organ. In yet other embodiments, the compound as described herein is provided in the form of a rapid release formulation, in the form of an extended release formulation, or in the form of an intermediate release formulation. In yet other embodiments, the compound described herein is administered topically.

Pharmaceutical Compositions/Formulations

[00221] The compounds described herein are administered to a subject in need thereof, either alone or in combination with pharmaceutically acceptable carriers, excipients or diluents, in a pharmaceutical

composition, according to standard pharmaceutical practice. In one embodiment, the compounds of this invention may be administered to animals. The compounds can be administered orally or parenterally, including the intravenous, intramuscular, intraperitoneal, subcutaneous, rectal and topical routes of administration.

[00222] In another aspect, provided herein are pharmaceutical compositions comprising a compound described herein, or a pharmaceutically acceptable salt, solvate, N-oxide, or stereoisomer thereof, and at least one pharmaceutically acceptable excipient. Pharmaceutical compositions are formulated in a conventional manner using one or more pharmaceutically acceptable excipients that facilitate processing of the active compounds into preparations that can be used pharmaceutically. Proper formulation is dependent upon the route of administration chosen. A summary of pharmaceutical compositions described herein can be found, for example, in Remington: The Science and Practice of Pharmacy, Nineteenth Ed (Easton, Pa.: Mack Publishing Company, 1995); Hoover, John E., Remington's Pharmaceutical Sciences, Mack Publishing Co., Easton, Pennsylvania 1975; Liberman, H.A. and Lachman, L., Eds., Pharmaceutical Dosage Forms, Marcel Decker, New York, N.Y., 1980; and Pharmaceutical Dosage Forms and Drug Delivery Systems, Seventh Ed. (Lippincott Williams & Wilkins 1999), herein incorporated by reference for such disclosure.

[00223] In some embodiments, the pharmaceutically acceptable excipient is selected from carriers, binders, filling agents, suspending agents, flavoring agents, sweetening agents, disintegrating agents, dispersing agents, surfactants, lubricants, colorants, diluents, solubilizers, moistening agents, plasticizers, stabilizers, penetration enhancers, wetting agents, anti-foaming agents, antioxidants, preservatives, and any combinations thereof.

[00224] The pharmaceutical compositions described herein are administered to a subject by appropriate administration routes, including, but not limited to, oral, parenteral (e.g., intravenous, subcutaneous, intramuscular), intranasal, buccal, topical, rectal, or transdermal administration routes. The pharmaceutical formulations described herein include, but are not limited to, aqueous liquid dispersions, liquids, gels, syrups, elixirs, slurries, suspensions, self-emulsifying dispersions, solid solutions, liposomal dispersions, aerosols, solid oral dosage forms, powders, immediate release formulations, controlled release formulations, fast melt formulations, tablets, capsules, pills, powders, dragees, effervescent formulations, lyophilized formulations, delayed release formulations, extended release formulations, pulsatile release formulations, multiparticulate formulations, and mixed immediate and controlled release formulations.

[00225] Pharmaceutical compositions including compounds described herein, or a pharmaceutically acceptable salt, solvate, N-oxide, or stereoisomer thereof are manufactured in a conventional manner, such as, by way of example only, by means of conventional mixing, dissolving, granulating, dragee-making, levigating, emulsifying, encapsulating, entrapping, or compression processes.

[00226] Pharmaceutical compositions for oral use are obtained by mixing one or more solid excipient with one or more of the compounds described herein, optionally grinding the resulting mixture, and processing the mixture of granules, after adding suitable auxiliaries, if desired, to obtain tablets or dragee cores.

Suitable excipients include, for example, fillers such as sugars, including lactose, sucrose, mannitol, or sorbitol; cellulose preparations such as, for example, maize starch, wheat starch, rice starch, potato starch, gelatin, gum tragacanth, methylcellulose, microcrystalline cellulose, hydroxypropylmethylcellulose, sodium carboxymethylcellulose; or others such as polyvinylpyrrolidone (PVP or povidone) or calcium phosphate. If desired, disintegrating agents are added, such as the cross-linked croscarmellose sodium, polyvinylpyrrolidone, agar, or alginic acid or a salt thereof such as sodium alginate. In some embodiments, dyestuffs or pigments are added to the tablets or dragee coatings for identification or to characterize different combinations of active compound doses.

[00227] Pharmaceutical compositions that are administered orally include push-fit capsules made of gelatin, as well as soft, sealed capsules made of gelatin and a plasticizer, such as glycerol or sorbitol. The push-fit capsules contain the active ingredients in admixture with filler such as lactose, binders such as starches, and/or lubricants such as talc or magnesium stearate and, optionally, stabilizers. In soft capsules, the active compounds are dissolved or suspended in suitable liquids, such as fatty oils, liquid paraffin, or liquid polyethylene glycols. In some embodiments, stabilizers are added.

[00228] Pharmaceutical compositions for parental use are formulated as infusions or injections. In some embodiments, the pharmaceutical composition suitable for injection or infusion includes sterile aqueous solutions, or dispersions, or sterile powders comprising a compound described herein, or a pharmaceutically acceptable salt, solvate, N-oxide, or stereoisomer thereof. In some embodiments, the pharmaceutical composition comprises a liquid carrier. In some embodiments, the liquid carrier is a solvent or liquid dispersion medium comprising, for example, water, saline, ethanol, a polyol (for example, glycerol, propylene glycol, liquid polyethylene glycols, and the like), vegetable oils, nontoxic glyceryl esters, and any combinations thereof. In some embodiments, the pharmaceutical compositions further comprise a preservative to prevent growth of microorganisms.

Combination

[00229] Disclosed herein are methods of treating an autoimmune disorder, a chronic inflammatory disorder, an acute inflammatory disorder, an auto-inflammatory disorder, a fibrotic disorder, a metabolic disorder, a neoplastic disorder, or a cardiovascular or a cerebrovascular disorder using a compound disclosed herein, or a pharmaceutically acceptable salt, solvate, N-oxide, or stereoisomer thereof, in combination with an additional therapeutic agent.

[00230] In some embodiments, the additional therapeutic agent is selected from the group consisting of anti-inflammatory drugs, anti-atherosclerotic drugs, immunosuppressive drugs, immunomodulatory drugs, cytostatic drugs, anti-proliferative agents, angiogenesis inhibitors, kinase inhibitors, cytokine blockers, and inhibitors of cell adhesion molecules.

[00231] In some embodiments, the additional therapeutic agent is selected from the group consisting of NSAIDs, immunosuppressive drugs, immunomodulatory drugs, cytostatic drugs, antiproliferative agents, angiogenesis inhibitors, biological agents, steroids, vitamin D3 analogs, retinoids, other kinase inhibitors,

cytokine blockers, corticosteroids, and inhibitors of cell adhesion molecules. In some embodiments, the additional therapeutic agent is selected from the group consisting of torcetrapib, aspirin, niacin, HMG CoA reductase inhibitors (e.g., atorvastatin, fluvastatin, lovastatin, pravastatin, rosuvastatin and simvastatin), colessevelam, cholestyramine, colestipol, gemfibrozil, probucol, and clofibrate.

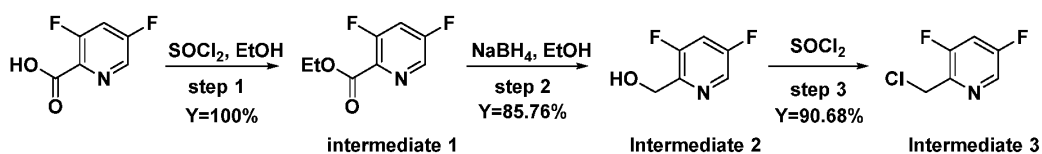
[00232] In some embodiments, the additional therapeutic agent is selected from the group consisting of corticosteroids, nonsteroidal anti-inflammatory drugs (NSAID) (e.g. ibuprofen, naproxen, acetaminophen, aspirin, Fenoprofen (Nalfon), Flurbiprofen (Ansaid), Ketoprofen, Oxaprozin (Daypro), Diclofenac sodium (Voltaren), Diclofenac potassium (Cataflam), Etodolac (Lodine), Indomethacin (Indocin), Ketorolac (Toradol), Sulindac (Clinoril), Tolmetin (Tolectin), Meclofenamate (Meclomen), Mefenamic acid (Ponstel), Nabumetone (Relafen), Piroxicam (Feldene), cox-2 inhibitors (e.g., celecoxib (Celebrex))), immunosuppressants (e.g., methotrexate (Rheumatrex), leflunomide (Arava), azathioprine (Imuran), cyclosporine (Neoral, Sandimmune), tacrolimus and cyclophosphamide (Cytosan), CD20 blockers (Rituximab), Tumor Necrosis Factor (TNF) blockers (e.g., etanercept (Enbrel), infliximab (Remicade) and adalimumab (Humira)), Abatacept (CTLA4-Ig) and interleukin- 1 receptor antagonists (e.g. Anakinra (Kineret), interleukin 6 inhibitors (e.g., Actemra), interleukin 17 inhibitors (e.g., AIN457), Janus kinase inhibitors (e.g., Tasocitinib), syk inhibitors (e.g. R788), and chloroquine and its derivatives.

[00233] In some embodiments, the additional therapeutic agent is selected from the group consisting of an EGFR kinase inhibitor, MEK inhibitor, VEGFR inhibitor, anti-VEGFR2 antibody, KDR antibody, AKT inhibitor, PDK-1 inhibitor, PI3K inhibitor, c-kit/Kdr tyrosine kinase inhibitor, Bcr-Abl tyrosine kinase inhibitor, VEGFR2 inhibitor, PDGFR-beta inhibitor, KIT inhibitor, Flt3 tyrosine kinase inhibitor, PDGF receptor family inhibitor, Flt3 tyrosine kinase inhibitor, RET tyrosine kinase receptor family inhibitor, VEGF-3 receptor antagonist, Raf protein kinase family inhibitor, angiogenesis inhibitor, Erb2 inhibitor, mTOR inhibitor, IGF-1R antibody, NFkB inhibitor, proteasome inhibitor, chemotherapy agent, and glucose reduction agent.

[00234] In some embodiments, the additional therapeutic agent is administered at the same time as the compound disclosed herein. In some embodiments, the additional therapeutic agent and the compound disclosed herein are administered sequentially. In some embodiments, the additional therapeutic agent is administered less frequently than the compound disclosed herein. In some embodiments, the additional therapeutic agent is administered more frequently than the compound disclosed herein. In some embodiments, the additional therapeutic agent is administered prior than the administration of the compound disclosed herein. In some embodiments, the additional therapeutic agent is administered after the administration of the compound disclosed herein.

Example

Intermediates 1, 2, 3



Step 1: Preparation of ethyl 3,5-difluoropicolinate:

[00235] A solution of 3,5-difluoropyridine-2-carboxylic acid (50.00 g, 314.28 mmol, 1.00 equiv) in ethanol (200 ml) was cooled using an ice bath, followed by the addition of SOCl_2 (50 mL, 689.25 mmol, 2.20 equiv) dropwise at 0°C . The resulting mixture was stirred for 3 h at 60°C under nitrogen atmosphere. The reaction was monitored by LCMS. The mixture was allowed to r.t. The resulting mixture was concentrated under vacuum. The residue was purified by silica gel column chromatography to afford ethyl 3,5-difluoropicolinate (59 g, 100%) as a colorless liquid. LC-MS: (ES+H, m/z): $[\text{M}+\text{H}]^+ = 188.1$.

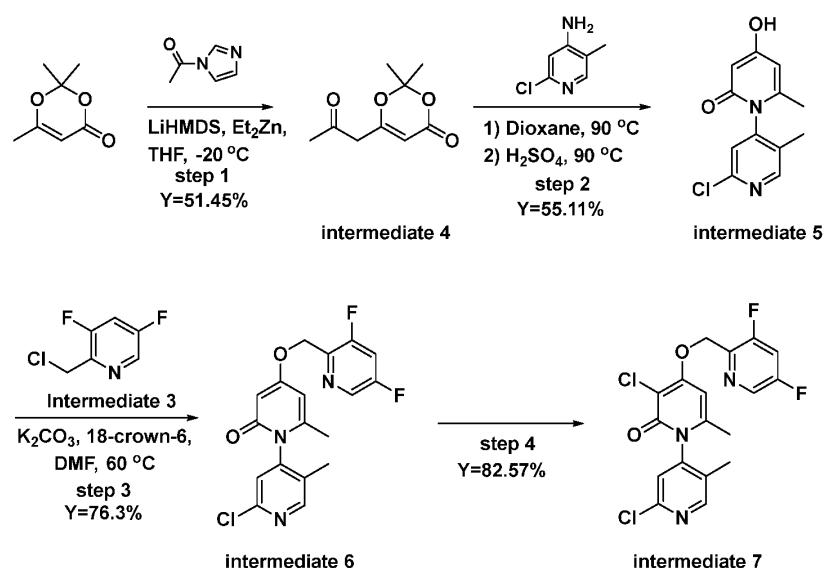
Step 2: Preparation of (3,5-difluoropyridin-2-yl)methanol:

[00236] To a stirred solution of ethyl 3,5-difluoropyridine-2-carboxylate (40.00 g, 213.74 mmol, 1.00 equiv) in ethanol (300 ml) was added NaBH_4 (20.22 g, 534.34 mmol, 2.50 equiv) in portions at 0°C under nitrogen atmosphere. The resulting mixture was stirred for 30 min at 0°C under nitrogen atmosphere. The resulting mixture was stirred for additional 2 h at room temperature under nitrogen atmosphere. The reaction was monitored by LCMS. The reaction was quenched with sat. NH_4Cl (aq.) at 0°C . EtOH was removed under reduced pressure. The aqueous layer was basified to pH 10 with saturated Na_2CO_3 (aq., 300 mL), followed by extracted with EtOAc (3x300 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 . After filtration, the filtrate was concentrated under vacuum to afford (3,5-difluoropyridin-2-yl)methanol (26.6 g, 85.76%) as a colorless liquid. LC-MS: (ES+H, m/z): $[\text{M}+\text{H}]^+ = 146.1$.

Step 3: Preparation of 2-(chloromethyl)-3,5-difluoropyridine:

[00237] To a stirred solution of (3,5-difluoropyridin-2-yl)methanol (34.00 g, 234.31 mmol, 1.00 equiv) in DCM (500ml) was added DMF (160 mg), and then cooled using ice water bath. To the above mixture was added SOCl_2 (40 mL, 551.40 mmol, 2.35 equiv) dropwise under nitrogen atmosphere. The resulting mixture was stirred for 2 h at room temperature under nitrogen atmosphere. The reaction was monitored by LCMS. The resulting mixture was concentrated under vacuum to afford 2-(chloromethyl)-3,5-difluoropyridine (34.75 g, 90.68%) as a brown-yellow semi-solid. LC-MS: (ES+H, m/z): $[\text{M}+\text{H}]^+ = 164.0$. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.35 (d, 1H), 7.28 (td, 1H), 4.73 (d, 2H).

Intermediate 4-7



Step 1: Preparation of 2,2-dimethyl-6-(2-oxopropyl)-1,3-dioxin-4-one:

[00238] A solution of LiHMDS (3.16 L, 3.16 mol, 1.50 equiv, 1M in THF) in THF (1000 mL) was treated with 2,2,6-trimethyl-1,3-dioxin-4-one (300 g, 2.11 mol, 1.00 equiv) for 1 h at -20 °C under nitrogen atmosphere followed by the addition of ZnEt₂ (3.16 L, 3.16 mol, 1.50 equiv, 1M in hexane) dropwise over 2 h at -20 °C. The resulting mixture was stirred for 30 min at -20 °C under nitrogen atmosphere. To the above mixture was added acetylimidazole (348.58 g, 3.16 mol, 1.50 equiv) at -10 °C. The resulting mixture was stirred for additional overnight at room temperature. The reaction was monitored by LCMS. The reaction was quenched by the addition of 1L Water/THF (1:1) at -10 °C. The mixture was acidified to pH 1-2 with 2M HCl (aq.). The resulting mixture was extracted with EtOAc (3 x 5 L). The combined organic layers were washed with brine (3x5L), dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography to afford 2,2-dimethyl-6-(2-oxopropyl)-1,3-dioxin-4-one (200 g, 51.45%) as a Brown yellow solid. LC-MS: (ES+H, m/z): [M+H]⁺ = 185.0. ¹H NMR (400 MHz, DMSO-d₆) δ 5.35(s, 1H), 3.35 (s, 2H), 2.25 (s, 3H), 1.72 (d, 6H).

Step 2: Preparation of 2'-chloro-4-hydroxy-5',6-dimethyl-[1,4'-bipyridin]-2-one:

[00239] A solution of 2,2-dimethyl-6-(2-oxopropyl)-1,3-dioxin-4-one (200.00 g, 1.08 mol, 1.00 equiv) and 2-chloro-5-methylpyridin-4-amine (154.83 g, 1.08 mol, 1.00 equiv) in dioxane (2000 mL) was stirred for 3.5 h at 90 °C under nitrogen atmosphere. The mixture was allowed to cool down to room temperature. The reaction was monitored by LCMS. To the above mixture was added H₂SO₄ (60 mL, 1.12 mol, 1.05 equiv) dropwise. The resulting mixture was stirred for additional 1 h at 90 °C. The mixture was allowed to cool down to room temperature. The reaction was monitored by LCMS. The resulting mixture was concentrated under reduced pressure. The resulting mixture was added H₂O (1000 mL) and stirred for 30 min. The precipitated solids were collected by filtration and washed with Et₂O (3x50 mL). This resulted in 2'-chloro-4-hydroxy-5',6-dimethyl-[1,4'-bipyridin]-2-one (150 g, 55.11%) as a yellow solid. LC-MS: (ES+H, m/z):

$[M+H]^+ = 251.0$. ^1H NMR (300 MHz, DMSO- d_6) δ 10.82 (s, 1H), 8.48 (s, 1H), 7.57 (s, 1H), 5.98 (d, 1H), 5.58 (d, 1H), 1.97 (s, 3H), 1.84 (s, 3H).

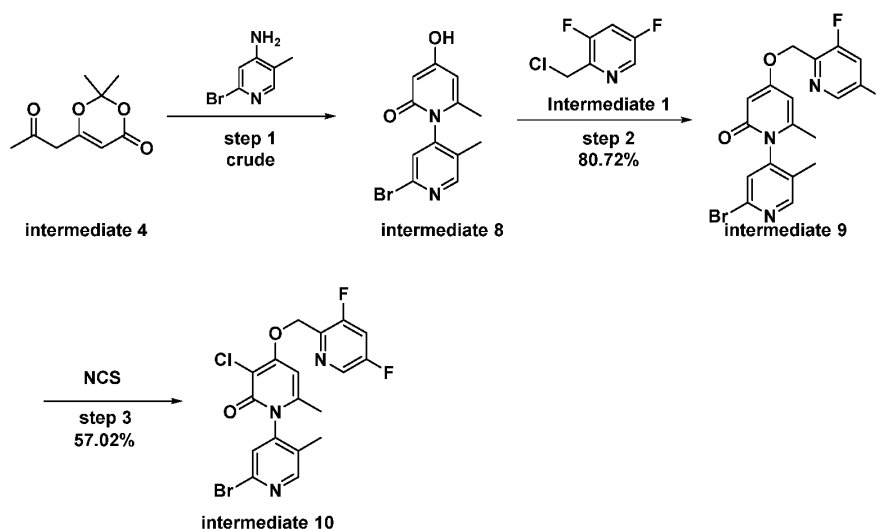
Step 3: Preparation of 2'-chloro-4-((3,5-difluoropyridin-2-yl)methoxy)-5',6-dimethyl-2H-[1,4'-bipyridin]-2-one:

[00240] To a stirred mixture of 2'-chloro-4-hydroxy-5',6-dimethyl-[1,4'-bipyridin]-2-one (20.00 g, 79.78 mmol, 1.00 equiv), 2-(chloromethyl)-3,5-difluoropyridine (15.66 g, 95.74 mmol, 1.20 equiv), K_2CO_3 (33.08 g, 239.35 mmol, 3.00 equiv) and 18-Crown-6 (2.11 g, 7.98 mmol, 0.10 equiv) in DMF (50 mL). The resulting mixture was stirred for 3 h at 60°C under nitrogen atmosphere. The reaction was monitored by LCMS. The residue was dissolved in EA (1500 mL). The organic layer was washed with water (3x400 mL). The organic layer was concentrated under reduced pressure. The residue was purified by silica gel column chromatography to afford 2'-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-5',6-dimethyl-[1,4'-bipyridin]-2-one (23 g, 76.3%) as a yellow solid. LC-MS: (ES+H, m/z): $[M+H]^+ = 378.0$. ^1H NMR (400 MHz, DMSO- d_6) δ 8.59 (s, 1H), 8.49 (s, 1H), 8.13 – 8.01 (m, 1H), 7.61 (s, 1H), 6.13 (d, 1H), 6.03 (d, 1H), 5.25 (s, 2H), 1.99 (s, 3H), 1.85 (s, 3H).

Step 4: Preparation of 2',3-dichloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-5',6-dimethyl-[1,4'-bipyridin]-2-one:

[00241] To a stirred solution of 2'-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-5',6-dimethyl-[1,4'-bipyridin]-2-one (1.00 g, 2.65 mmol, 1.00 equiv) and NCS (0.37 g, 2.78 mmol, 1.05 equiv) in ACN (25 mL) was added 2,2-dichloroacetic acid (0.17 g, 1.32 mmol, 0.50 equiv) dropwise at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 2 h at 60°C under nitrogen atmosphere. The reaction was monitored by LCMS. The resulting mixture was diluted with ethyl acetate (300 mL). The resulting mixture was washed with 2x100 mL of water and brine (100 mL), dried over anhydrous Na_2SO_4 . After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, the pure fraction was concentrated under reduced pressure to afford 2',3-dichloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-5',6-dimethyl-[1,4'-bipyridin]-2-one (901 mg, 82.57%) as a yellow solid. LC-MS: (ES+H, m/z): $[M+H]^+ = 411.9$.

Intermediate 8-10



Step 1: Preparation of 2'-bromo-4-hydroxy-5',6-dimethyl-[1,4'-bipyridin]-2-one:

[00242] A mixture of 2,2-dimethyl-6-(2-oxopropyl)-1,3-dioxin-4-one (22.16 g, 120.296 mmol, 1.5 equiv) and 2-bromo-5-methylpyridin-4-amine (15 g, 80.197 mmol, 1.00 equiv) in 1,4-dioxane (200 mL) was stirred for 2 h at 90°C, to the above mixture was added H₂SO₄ (7.87 g, 80.197 mmol, 1 equiv) dropwise at room temperature under air atmosphere. The resulting mixture was stirred for additional 1 h at 90°C. The reaction was monitored by LCMS. The resulting mixture was concentrated under reduced pressure. To the resulting mixture was added H₂O (40 mL) and the slurry was stirred for 10 min. The precipitated solids were collected by filtration and washed with Et₂O (3x10 mL), then dried under vacuum to afford 2'-bromo-4-hydroxy-5',6-dimethyl-[1,4'-bipyridin]-2-one (22.7 g, crude) as a yellow solid. The crude resulting mixture was used in the next step directly without further purification. LC-MS: (ES+H, m/z): [M+H]⁺=294.9.

Step 2: 2'-chloro-4-[(4-methoxyphenyl)methoxy]-5',6-dimethyl-[1,4'-bipyridin]-2-one:

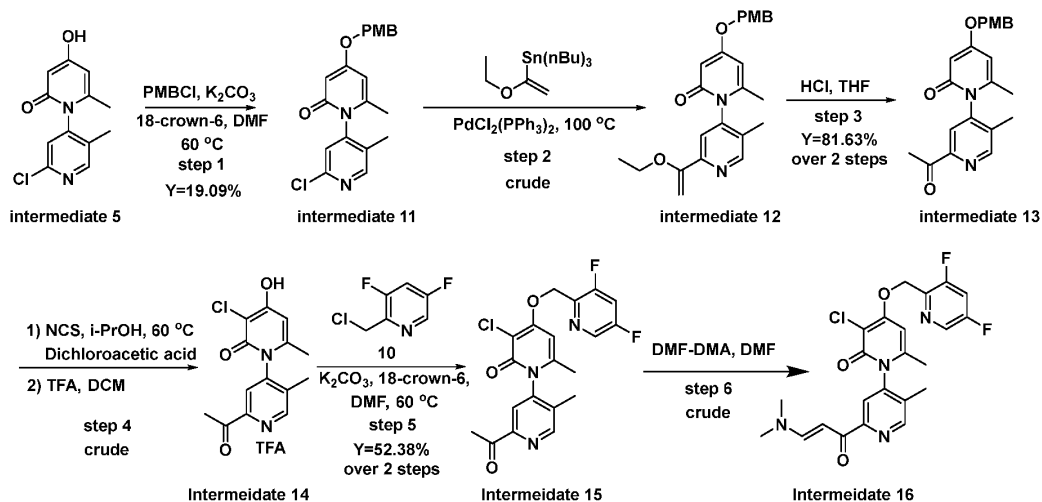
[00243] To a stirred mixture of 2'-bromo-4-hydroxy-5',6-dimethyl-[1,4'-bipyridin]-2-one (42.00 g, 142.307 mmol, 1 equiv) and 2-(chloromethyl)-3,5-difluoropyridine (46.55 g, 284.614 mmol, 2 equiv) in DMF (450 mL) were added K₂CO₃ (98.34 g, 711.535 mmol, 5.00 equiv) and 18-Crown-6 (3.76 g, 14.231 mmol, 0.10 equiv) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 2 h at 60°C under nitrogen atmosphere. The reaction was monitored by LCMS. Desired product could be detected by LCMS. The reaction mixture was partitioned between EA (1000 mL) and water (500 mL). The organic layer was washed with water (500 mL) and brine (500 mL), and then dried over Na₂SO₄. The solution was concentrated under reduced pressure. The residue was purified by silica gel column chromatography to afford 2'-bromo-4-[(3,5-difluoropyridin-2-yl)methoxy]-5',6-dimethyl-[1,4'-bipyridin]-2-one (48.5 g, 80.72%) as a yellow oil. LC-MS: (ES+H, m/z): [M+H]⁺=424.0.

Step 3: Preparation of 2'-bromo-3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-5',6-dimethyl-[1,4'-bipyridin]-2-one:

[00244] To a stirred mixture of 2'-bromo-4-[(3,5-difluoropyridin-2-yl)methoxy]-5',6-dimethyl-[1,4'-bipyridin]-2-one (12 g, 28.421 mmol, 1 equiv) and NCS (3.79 g, 28.421 mmol, 1 equiv) in 2-Propanol (21

mL) were added 2,2-dichloroacetic acid (1.2 mL, 2.870 mmol, 0.10 equiv) dropwise at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 2 h at 60°C under nitrogen atmosphere. The reaction was monitored by LCMS. Desired product could be detected by LCMS. The precipitated solids were collected by filtration and washed with 2-propanol to afford 2'-bromo-3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-5',6-dimethyl-[1,4'-bipyridin]-2-one (7.40 g, 57.02%) as a white solid. LC-MS: (ES+H, m/z): $[M+H]^+ = 457.9$. ^1H NMR (300 MHz, DMSO- d_6) δ 8.60 (d, $J = 2.4$ Hz, 1H), 8.52 (s, 1H), 8.10 (ddd, $J = 10.0, 8.9, 2.4$ Hz, 1H), 7.81 (s, 1H), 6.80 (s, 1H), 5.48 (d, $J = 2.0$ Hz, 2H), 1.98 – 1.94 (m, 6H).

Intermediate 11-16



Step 1: 2'-chloro-4-[(4-methoxyphenyl)methoxy]-5',6-dimethyl-[1,4'-bipyridin]-2-one:

[00245] To a solution of 2'-chloro-4-hydroxy-5',6-dimethyl-[1,4'-bipyridin]-2-one (85.00 g, 339.08 mmol, 1.00 equiv) in DMF (300 mL) was added 4-methoxybenzyl chloride (159.31 g, 1017.23 mmol, 3.00 equiv), K_2CO_3 (187.45 g, 1356.31 mmol, 4.00 equiv) and 18-crown-6 (4.48 g, 16.95 mmol, 0.05 equiv). The mixture was heated at 60°C for 3 h. The reaction was monitored by LCMS. The mixture was allowed to cool down to r.t. The reaction mixture was partitioned between EA (1000 mL) and water (500 mL). The organic layer was washed with water (500 mL) and brine (500 mL), and then dried over Na_2SO_4 . The solution was concentrated under reduced pressure. The residue was purified by silica gel column chromatography to afford 2'-chloro-4-[(4-methoxyphenyl)methoxy]-5',6-dimethyl-[1,4'-bipyridin]-2-one (24 g, 19.09%) as an off-white solid. LC-MS: (ES+H, m/z): $[M+H]^+ = 371.0$.

Step 2: Preparation of 2'-(1-ethoxyethenyl)-4-[(4-methoxyphenyl)methoxy]-5',6-dimethyl-[1,4'-bipyridin]-2-one:

[00246] To a stirred solution of 2'-chloro-4-[(4-methoxyphenyl)methoxy]-5',6-dimethyl-[1,4'-bipyridin]-2-one (24.00 g, 64.72 mmol, 1.00 equiv) and tributyl(1-ethoxyethenyl)stannane (28.05 g, 77.67 mmol, 1.20 equiv) in dioxane (200 mL) was added $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$ (2.27 g, 3.23 mmol, 0.05 equiv). The resulting mixture was stirred for 10 h at 100°C under nitrogen atmosphere. The reaction was monitored by LCMS. The mixture was allowed to cool down to r.t. The resulting mixture was filtered, the filter cake was washed with EA (100 mL). The filtrate was concentrated under reduced pressure. The crude product 2'-(1-ethoxyethenyl)-

4-[(4-methoxyphenyl)methoxy]-5',6-dimethyl-[1,4'-bipyridin]-2-one (32 g) was used in the next step directly without further purification. LC-MS: (ES+H, m/z): $[M+H]^+ = 407.1$.

Step 3: Preparation of 2'-acetyl-4-[(4-methoxyphenyl)methoxy]-5',6-dimethyl-[1,4'-bipyridin]-2-one:

[00247] To a stirred solution 2'-(1-ethoxyethenyl)-4-[(4-methoxyphenyl)methoxy]-5',6-dimethyl-[1,4'-bipyridin]-2-one (32 g, 78.72 mmol, 1.00 equiv) in THF (200 mL) was added conc. HCl (20 mL) dropwise at 0°C under nitrogen atmosphere. The resulting mixture was stirred for 2 h at r.t. under nitrogen atmosphere. The reaction was monitored by LCMS. The mixture was basified to pH 10 with saturated Na_2CO_3 aq. under 0°C. The resulting mixture was extracted with EA (2 x 100 mL). The combined organic layers were washed with saturated NaCl aq. (200 mL), dried over anhydrous Na_2SO_4 . After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography to afford 2'-acetyl-4-[(4-methoxyphenyl)methoxy]-5',6-dimethyl-[1,4'-bipyridin]-2-one (20 g, 81.63%, two steps) as an off-white solid. LC-MS: (ES+H, m/z): $[M+H]^+ = 379.1$.

Step 4: Preparation of 2'-acetyl-3-chloro-4-hydroxy-5',6-dimethyl-[1,4'-bipyridin]-2-one:

[00248] To a stirred mixture of 2'-acetyl-4-[(4-methoxyphenyl)methoxy]-5',6-dimethyl-[1,4'-bipyridin]-2-one (19.00 g, 50.21 mmol, 1.00 equiv) and NCS (7.44 g, 55.72 mmol, 1.10 equiv) in i-PrOH (100.00 mL) was added 2,2-dichloroacetic acid (0.39 g, 3.02 mmol, 0.06 equiv) at room temperature. And the mixture was stirred for 5h at 60°C under nitrogen atmosphere. The reaction was monitored by LCMS. The mixture was allowed to cool down to r.t. The precipitated solids were collected by filtration and washed with cold i-PrOH (10 mL). The resulted solid was dissolved in DCM (100 mL). To the above mixture was added TFA (100 mL) at 0°C. The resulting mixture was stirred for additional 2 h at r.t.. The reaction was monitored by LCMS. The resulting mixture was concentrated under reduced pressure. The residue was purified by trituration with Et_2O (50 mL). This resulted in 2'-acetyl-3-chloro-4-hydroxy-5',6-dimethyl-[1,4'-bipyridin]-2-one (14 g, crude, TFA salt) as a light-yellow solid. LC-MS: (ES+H, m/z): $[M+H]^+ = 293.0$.

Step 5: Preparation of 2'-acetyl-3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-5',6-dimethyl-[1,4'-bipyridin]-2-one:

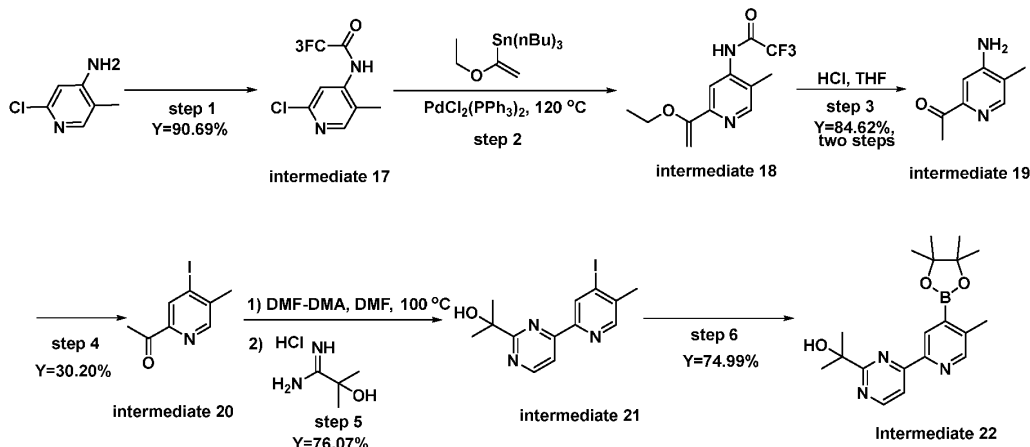
[00249] A mixture of 2'-acetyl-3-chloro-4-hydroxy-5',6-dimethyl-[1,4'-bipyridin]-2-one, TFA salt (14.00 g, 34.42 mmol, 1.00 equiv), K_2CO_3 (14.27 g, 103.25 mmol, 3.00 equiv), 18-crown-6 (0.91 g, 3.44 mmol, 0.10 equiv) and 2-(chloromethyl)-3,5-difluoropyridine (8.44 g, 51.60 mmol, 1.50 equiv) in DMF (100.00 mL) was stirred for 10 h at 60°C under nitrogen atmosphere. The reaction was monitored by LCMS. The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography to afford 2'-acetyl-3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-5',6-dimethyl-[1,4'-bipyridin]-2-one (11 g, 52.38%, two steps) as an off-white solid. LC-MS: (ES+H, m/z): $[M+H]^+ = 420.0$.

Step 6: Preparation of 3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-2'-[(2E)-3-(dimethylamino)prop-2-enoyl]-5',6-dimethyl-[1,4'-bipyridin]-2-one:

[00250] A solution of 2'-acetyl-3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-5',6-dimethyl-[1,4'-bipyridin]-2-one (11.00 g, 26.20 mmol, 1.00 equiv) in DMF-DMA (50 mL) was stirred for 12 h at 100°C

under nitrogen atmosphere. The reaction was monitored by LCMS. The mixture was allowed to cool down to r.t. The resulting mixture was concentrated under reduced pressure.

Intermediate 17-22



Step 1: Preparation of N-(2-chloro-5-methylpyridin-4-yl)-2,2,2-trifluoroacetamide:

[00251] To a stir solution of 2-chloro-5-methylpyridin-4-amine (5.00 g, 35.07 mmol, 1.00 equiv) and Trifluoroacetic anhydride (14.73 g, 70.13 mmol, 2.00 equiv) in DCM (100 mL) was added TEA (14.19 g, 140.26 mmol, 4.00 equiv) dropwise at 0°C under nitrogen atmosphere. The resulting mixture was stirred overnight at room temperature under nitrogen atmosphere. The reaction was monitored by LCMS. The resulting mixture was diluted with water (200mL). The resulting mixture was extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with brine (3x100 mL), dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography to afford N-(2-chloro-5-methylpyridin-4-yl)-2,2,2-trifluoroacetamide (7.60 g, 90.69%) as a light-yellow solid. LC-MS: (ES+H, *m/z*): [M+H]⁺=239.1.

Step 2: Preparation of N-(2-(1-ethoxyvinyl)-5-methylpyridin-4-yl)-2,2,2-trifluoroacetamide:

[00252] To a stirred solution of N-(2-chloro-5-methylpyridin-4-yl)-2,2,2-trifluoroacetamide (7.50 g, 31.44 mmol, 1.00 equiv) and tributyl(1-ethoxyethenyl)stannane (34.06 g, 94.30 mmol, 3.00 equiv) in dioxane (100 mL) was added palladium chloride; bis(triphenylphosphine) (1.10 g, 1.57 mmol, 0.05 equiv) in portions at room temperature under nitrogen atmosphere. The resulting mixture was stirred overnight at 120°C under nitrogen atmosphere. The reaction was monitored by LCMS. The mixture was allowed to cool down to room temperature. The resulting mixture was filtered, the filter cake was washed with EA (100 mL). The filtrate was concentrated under reduced pressure. The crude product was used in the next step directly without further purification. LC-MS: (ES+H, *m/z*): [M+H]⁺=275.0.

Step 3: Preparation of 1-(4-amino-5-methylpyridin-2-yl)ethanone:

[00253] To a stirred solution of N-[2-(1-ethoxyethenyl)-5-methylpyridin-4-yl]-2,2,2-trifluoroacetamide (11 g, 40.11 mmol, 1.00 equiv) in THF (120 mL) was added conc. HCl (10 mL) dropwise at room temperature. The resulting mixture was stirred for 2 h at room temperature. The reaction was monitored by LCMS. The resulting mixture was diluted with water (200 mL). The resulting mixture was washed with Et₂O (8 x

200mL). The aqueous layer was basified to pH 8 with saturated NaHCO_3 (aq.). The resulting mixture was extracted with EtOAc (3 x 200 mL). The combined organic layers were washed with brine (3x200 mL), dried over anhydrous Na_2SO_4 . After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography to afford 1-(4-amino-5-methylpyridin-2-yl)ethanone (4.00 g, 84.62%, two steps) as a brown solid. LC-MS: (ES+H, m/z): $[\text{M}+\text{H}]^+=151.1$. ^1H NMR (300 MHz, DMSO-d_6) δ 8.02 (s, 1H), 7.16 (s, 1H), 6.07 (s, 2H), 2.52 (s, 3H), 2.07 (s, 3H).

Step 4: Preparation of 1-(4-iodo-5-methylpyridin-2-yl)ethanone:

[00254] To a stirred solution of 1-(4-amino-5-methylpyridin-2-yl)ethanone (4.00 g, 26.64 mmol, 1.00 equiv) and triiodomethane (31.46 g, 79.90 mmol, 3.00 equiv) in THF (50 mL) was added tert-butylnitrite (5.49 g, 53.27 mmol, 2.00 equiv) dropwise at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 3h at 80°C under nitrogen atmosphere. The reaction was monitored by LCMS. The mixture was allowed to cool down to room temperature. The resulting mixture was diluted with water (200 mL). The resulting mixture was extracted with EtOAc (3 x 200 mL). The combined organic layers were washed with brine (3x200 mL), dried over anhydrous Na_2SO_4 . After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography to afford 1-(4-iodo-5-methylpyridin-2-yl)ethanone (2.1 g, 30.20%) as a brown solid. LC-MS: (ES+H, m/z): $[\text{M}+\text{H}]^+=261.9$. ^1H NMR (400 MHz, DMSO-d_6) δ 8.54 (s, 1H), 8.27 (s, 1H), 2.60 (s, 3H), 2.42 (s, 3H).

Step 5: Preparation of 2-[4-(4-iodo-5-methylpyridin-2-yl)pyrimidin-2-yl]propan-2-ol:

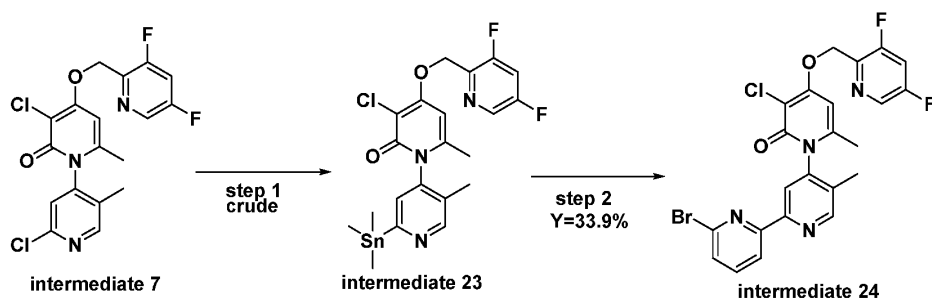
[00255] A mixture of 1-(4-iodo-5-methylpyridin-2-yl)ethanone (2.00 g, 7.66 mmol, 1.00 equiv) in DMF-DMA (20 mL) was stirred for 4h at 100°C under nitrogen atmosphere. The reaction was monitored by LCMS. The mixture was allowed to cool down to room temperature. The resulting mixture was concentrated under reduced pressure. The residue was diluted with DMF (20 mL). To the above mixture was added 2-hydroxy-2-methylpropanimidamide (1.17 g, 11.49 mmol, 1.50 equiv) in portions under nitrogen atmosphere. The resulting mixture was stirred for additional 1.5h at 100°C under nitrogen atmosphere. The reaction was monitored by LCMS. The mixture was allowed to cool down to room temperature. The resulting mixture was diluted with water (150 mL). The resulting mixture was extracted with EtOAc (3 x 150 mL). The combined organic layers were washed with brine (3x150 mL), dried over anhydrous Na_2SO_4 . After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography to afford 2-[4-(4-iodo-5-methylpyridin-2-yl)pyrimidin-2-yl]propan-2-ol (2.07 g, 76.07%) as an off-white solid. LC-MS: (ES+H, m/z): $[\text{M}+\text{H}]^+=355.9$. ^1H NMR (300 MHz, DMSO-d_6) δ 9.09 (s, 1H), 8.93 (d, 1H), 8.58 (s, 1H), 8.17 (d, 1H), 5.31 (s, 1H), 2.44 (s, 3H), 1.56 (s, 6H).

Step 6: Preparation of 2-[4-[5-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-yl]pyrimidin-2-yl]propan-2-ol:

[00256] To a stirred solution of 2-[4-(4-iodo-5-methylpyridin-2-yl)pyrimidin-2-yl]propan-2-ol (200 mg, 0.56 mmol, 1.00 equiv) and bis(pinacolato)diboron (357 mg, 1.41 mmol, 2.50 equiv) in dioxane (5 mL) was added Pd(dppf)Cl_2 (16 mg, 0.03 mmol, 0.05 equiv) and KOAc (221 mg, 2.25 mmol, 4.00 equiv) in portions at room temperature under nitrogen atmosphere. The resulting mixture was stirred overnight at 120°C under

nitrogen atmosphere. The reaction was monitored by LCMS. The mixture was allowed to cool down to room temperature. The resulting mixture was diluted with water (25mL). The resulting mixture was extracted with EtOAc (3 x 25mL). The combined organic layers were washed with brine (3x25 mL), dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography to afford 2-{4-[5-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-yl]pyrimidin-2-yl}propan-2-ol (150 mg, 74.99%) as a brown solid. LC-MS: (ES+H, *m/z*): [M+H]⁺=274.1 (the mass signal of Boric acid). ¹H NMR (300 MHz, DMSO-d₆) δ 8.92 (d, 1H), 8.62-8.66 (m, 2H), 8.19 (d, 1H), 5.19 (s, 1H), 2.53 (s, 3H), 1.57 (s, 6H), 1.36 (s, 12H).

Intermediate 24



Step 1: Preparation of 3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-3',6-dimethyl-2'-(trimethylstannyl)-[1,4'-bipyridin]-2-one:

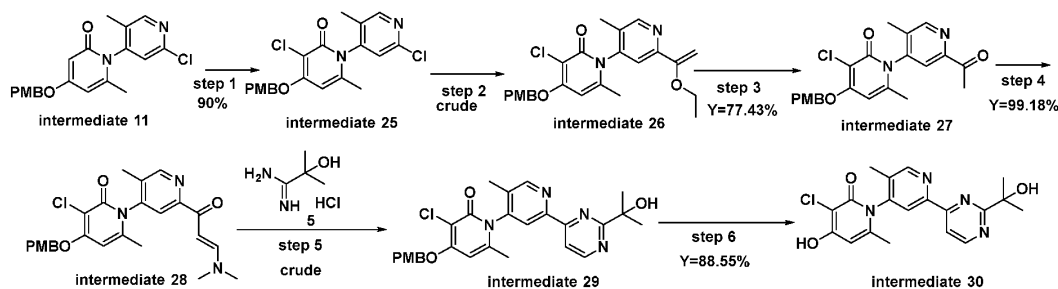
[00257] To a stirred solution of 2',3-dichloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-3',6-dimethyl-[1,4'-bipyridin]-2-one (1.00 g, 2.42 mmol, 1.00 equiv), Sn₂Me₆ (6.36 g, 19.40 mmol, 8.00 equiv) in 1,4-dioxane (20 mL) were added Pd(PPh₃)₂Cl₂ (681 mg, 0.97 mmol, 0.40 equiv) and AsPh₃ (0.29 g, 0.97 mmol, 0.40 equiv). The resulting mixture was stirred for 12 h at 100°C under nitrogen atmosphere. The reaction was monitored by LCMS. The mixture was allowed to cool down to room temperature. The resulting mixture was diluted with EA (200mL). The combined organic layers were washed with KF (aq.) (3 x 100 mL). The organic layer was dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The crude product (1.78 g) was used in the next step directly without further purification. LC-MS: (ES+H, *m/z*): [M+H]⁺=542.3.

Step 2: Preparation of 2'-(6-bromopyridin-2-yl)-3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-5',6-dimethyl-[1,4'-bipyridin]-2-one:

[00258] To a stirred solution 3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-5',6-dimethyl-2'-(trimethylstannyl)-[1,4'-bipyridin]-2-one (2.00 g, 3.70 mmol, 1.00 equiv) and 2,6-dibromo-pyridine (2.63 g, 11.10 mmol, 3.00 equiv) in 1,4-dioxane (20 mL) were added Pd(PPh₃)₂Cl₂ (0.52 g, 0.74 mmol, 0.20 equiv), the resulting mixture was stirred at 80°C for 2 h under nitrogen atmosphere. The reaction was monitored by LCMS. The mixture was allowed to cool down to room temperature. The resulting mixture was diluted with water (200 mL). The resulting mixture was extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with brine (100 mL), dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography to

afford 2'-(6-bromopyridin-2-yl)-3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-5',6-dimethyl-[1,4'-bipyridin]-2-one (670 mg, 33.9%) as a yellow solid. LC-MS: (ES+H, m/z): $[M+H]^+ = 535.1$. ^1H NMR (300 MHz, DMSO- d_6) δ 8.82 (s, 1H), 8.61 (d, $J = 2.4$ Hz, 1H), 8.42 (dd, $J = 7.7, 0.9$ Hz, 1H), 8.16-8.04 (m, 2H), 7.95 (t, $J = 7.8$ Hz, 1H), 7.74 (dd, $J = 7.9, 0.9$ Hz, 1H), 6.81 (s, 1H), 5.49 (d, $J = 2.0$ Hz, 2H), 2.09 (s, 3H), 1.98 (s, 3H). ^{19}F NMR (282 MHz, DMSO- d_6) δ -120.14, -120.17, -122.36, -122.39.

Intermediate 25-30



Step 1: Preparation of 2',3-dichloro-4-[(4-methoxyphenyl)methoxy]-5',6-dimethyl-[1,4'-bipyridin]-2-one:

[00259] To a stirred mixture of 2'-chloro-4-[(4-methoxyphenyl)methoxy]-5',6-dimethyl-[1,4'-bipyridin]-2-one (5 g, 13.483 mmol, 1 equiv) and 2,2-dichloroacetic acid (0.17 mL, 1.348 mmol, 0.1 equiv) in i-PrOH (20.00 mL, 261.705 mmol, 19.41 equiv) were added NCS (1.80 g, 13.483 mmol, 1 equiv) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 2 h at 60°C under nitrogen atmosphere. The reaction was monitored by LCMS. The mixture was allowed to cool down to room temperature. This resulted in 2',3-dichloro-4-[(4-methoxyphenyl)methoxy]-5',6-dimethyl-[1,4'-bipyridin]-2-one (4.9 g, 90%) as a yellow solid. LC-MS: (ES+H, m/z): $[M+H]^+ = 405.1$.

Step 2: 3-chloro-2'-(1-ethoxyethenyl)-4-[(4-methoxyphenyl)methoxy]-5',6-dimethyl-[1,4'-bipyridin]-2-one:

[00260] To a stirred solution of 2',3-dichloro-4-[(4-methoxyphenyl)methoxy]-5',6-dimethyl-[1,4'-bipyridin]-2-one (5 g, 12.33 mmol, 1.00 equiv) and dibutyl(1-ethoxyethenyl)propylstannane (12.85 g, 37.01 mmol, 3.00 equiv) in 1,4-dioxane (55 mL) were added $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$ (0.26 g, 0.37 mmol, 0.03 equiv) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 3 h at 120°C under nitrogen atmosphere. The reaction was monitored by LCMS. The resulting mixture was concentrated under reduced pressure. The crude product was used in the next step directly without further purification. LC-MS: (ES+H, m/z): $[M+H]^+ = 441.1$.

Step 3: 2'-acetyl-3-chloro-4-[(4-methoxyphenyl)methoxy]-5',6-dimethyl-[1,4'-bipyridin]-2-one

[00261] To a stirred mixture of 3-chloro-2'-(1-ethoxyethenyl)-4-[(4-methoxyphenyl)methoxy]-5',6-dimethyl-[1,4'-bipyridin]-2-one (4.00 g, 9.07 mmol, 1.00 equiv) in THF (200 mL) was added HCl (4 mL) dropwise at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 1 h at room temperature under nitrogen atmosphere. The reaction was monitored by LCMS. The resulting mixture was diluted with EtOAc (200 mL). The resulting mixture was washed with 2×200 mL brine. The organic layers

were dried over anhydrous Na_2SO_4 . After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography to afford 2'-acetyl-3-chloro-4-[(4-methoxyphenyl)methoxy]-5',6-dimethyl-[1,4'-bipyridin]-2-one (2.90 g, 77.43%) as a yellow solid. LC-MS: (ES+H, m/z): $[\text{M}+\text{H}]^+ = 413.1$. ^1H NMR (300 MHz, DMSO-d_6) δ 8.83 (s, 1H), 7.88 (s, 1H), 7.48 – 7.40 (m, 2H), 7.07 – 6.95 (m, 2H), 6.79 – 6.73 (m, 1H), 5.27 (s, 2H), 3.79 (s, 3H), 2.67 (s, 3H), 2.09 (s, 3H), 1.92 (s, 3H).

Step 4: 3-chloro-2'-[(2E)-3-(dimethylamino)prop-2-enoyl]-4-[(4-methoxyphenyl)methoxy]-5',6-dimethyl-[1,4'-bipyridin]-2-one:

[00262] To a stirred mixture of 2'-acetyl-3-chloro-4-[(4-methoxyphenyl)methoxy]-5',6-dimethyl-[1,4'-bipyridin]-2-one (2.90 g, 7.02 mmol, 1.00 equiv) in DMF-DMA (25 mL) at room temperature under nitrogen atmosphere. The resulting mixture was stirred overnight at 100°C under nitrogen atmosphere. The reaction was monitored by LCMS. The resulting mixture was concentrated under reduced pressure to afford 3-chloro-2'-[(2E)-3-(dimethylamino)prop-2-enoyl]-4-[(4-methoxyphenyl)methoxy]-5',6-dimethyl-[1,4'-bipyridin]-2-one (3.26 g, 99.18%) as a yellow solid. LC-MS: (ES+H, m/z): $[\text{M}+\text{H}]^+ = 470.1$.

Step 5: 3-chloro-2'-[2-(2-hydroxypropan-2-yl)pyrimidin-4-yl]-4-[(4-methoxyphenyl)methoxy]-5',6-dimethyl-[1,4'-bipyridin]-2-one:

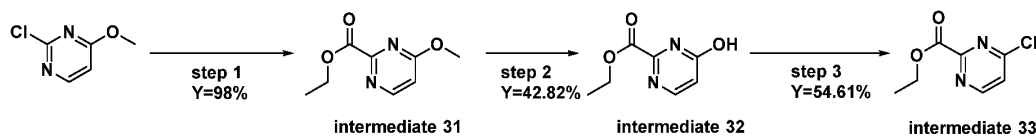
[00263] To a stirred mixture of 3-chloro-2'-[(2E)-3-(dimethylamino)prop-2-enoyl]-4-[(4-methoxyphenyl)methoxy]-5',6-dimethyl-[1,4'-bipyridin]-2-one (3.30 g, 7.05 mmol, 1.00 equiv) and K_2CO_3 (2.92 g, 21.15 mmol, 3.00 equiv) in IPA (33 mL) was added 2-hydroxy-2-methylpropanimidamide hydrochloride (1.95 g, 14.10 mmol, 2.00 equiv) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 2 h at 80°C under nitrogen atmosphere. The reaction was monitored by LCMS. The resulting mixture was diluted with EtOAc (200 mL). The resulting mixture was washed with 2×200 mL brine. The organic layers were dried over anhydrous Na_2SO_4 . After filtration, the filtrate was concentrated under reduced pressure. The resulting mixture was concentrated under reduced pressure. The crude product was used in the next step directly without further purification. LC-MS: (ES+H, m/z): $[\text{M}+\text{H}]^+ = 507.0$.

Step 6: 3-chloro-4-hydroxy-2'-[2-(2-hydroxypropan-2-yl)pyrimidin-4-yl]-5',6-dimethyl-[1,4'-bipyridin]-2-one:

[00264] To a stirred solution of 3-chloro-2'-[2-(2-hydroxypropan-2-yl)pyrimidin-4-yl]-4-[(4-methoxyphenyl)methoxy]-5',6-dimethyl-[1,4'-bipyridin]-2-one (3.70 g, 7.29 mmol, 1.00 equiv) in CH_2Cl_2 (50 mL) was added TFA (15 mL) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 2 h at room temperature under nitrogen atmosphere. The reaction was monitored by LCMS. The resulting mixture was diluted with EtOAc (200 mL). The resulting mixture was washed with 2×200 mL brine. The organic layers were dried over anhydrous Na_2SO_4 . After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography to afford 3-chloro-4-hydroxy-2'-[2-(2-hydroxypropan-2-yl)pyrimidin-4-yl]-5',6-dimethyl-[1,4'-bipyridin]-2-one (2.50 g,

88.55%) as a yellow solid. LC-MS: (ES+H, m/z): $[M+H]^+ = 387.1$. ^1H NMR (400 MHz, DMSO- d_6) δ 11.62 (br, 1H), 8.97 (d, 1H), 8.84 (s, 1H), 8.64 (s, 1H), 8.24 (d, 1H), 6.22 (d, 1H), 5.76 (s, 1H), 2.10 (s, 3H), 1.88 (s, 3H), 1.53 (s, 6H).

Intermediate 31-33



Step 1: Preparation of ethyl 4-methoxypyrimidine-2-carboxylate:

[00265] To a stirred solution of 2-chloro-4-methoxypyrimidine (100.00 g, 691.75 mmol, 1.00 equiv) in EtOH (6.00 L) was added Et₃N (140.00 g, 1383.50 mmol, 2.00 equiv) and Pd(dppf)Cl₂ (10.00 g, 13.66 mmol, 0.05 equiv) in a pressure tank. The mixture was purged with nitrogen for 2 min and then was pressurized to 50 atm with carbon monoxide at 100°C for 12 h. The reaction mixture was cooled to room temperature. The reaction was monitored by LCMS. The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography to afford ethyl 4-methoxypyrimidine-2-carboxylate (123.50 g, 98.00%) as a yellow solid. LC-MS: (ES+H, m/z): $[M+H]^+ = 183.0$. ^1H NMR (300 MHz, DMSO- d_6) δ 8.66 (d, 1H), 7.16 (d, 1H), 4.36 (q, 2H), 3.98 (s, 3H), 1.34 (t, 3H).

Step 2: Preparation of ethyl 4-hydroxypyrimidine-2-carboxylate:

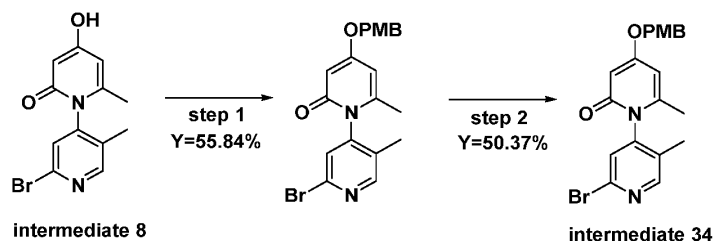
[00266] To a stirred solution of ethyl 4-methoxypyrimidine-2-carboxylate (83.50 g, 458.34 mmol, 1.00 equiv) in MeCN (1.00 L) was added TMSI (262 mL, 1833.36 mmol, 4.00 equiv) dropwise at room temperature under nitrogen atmosphere over 1 h. The resulting mixture was stirred overnight at 50°C. Desired product could be detected by LCMS. The mixture was allowed to cool down to room temperature. The resulting mixture was concentrated under reduced pressure. The residue was re-dissolved in DCM (500 mL) and then concentrated under reduced pressure. Repeat the above steps three times. The residue was purified by trituration with hexane (800 mL). The resulting mixture was concentrated under reduced pressure. This resulted in ethyl 4-hydroxypyrimidine-2-carboxylate (33.00 g, 42.82%) as a yellow solid. LC-MS: (ES+H, m/z): $[M+H]^+ = 169.1$. ^1H NMR (300 MHz, DMSO- d_6) δ 8.14 (d, 1H), 6.60 (d, 1H), 4.34 (q, 2H), 1.32 (t, 3H).

Step 3: Preparation of ethyl 4-chloropyrimidine-2-carboxylate:

[00267] To a stirred mixture of ethyl 4-hydroxypyrimidine-2-carboxylate (33.00 g, 196.25 mmol, 1.00 equiv) in DCE (1.20 L) were added POCl₃ (73 mL, 785.00 mmol, 4.00 equiv) dropwise at 0°C under nitrogen atmosphere over 2 h. The resulting mixture was stirred additional overnight at 50°C. Desired product could be detected by LCMS. The mixture was allowed to cool down to room temperature. The reaction was quenched by the addition of Water/Ice (600 mL) at 0°C. The mixture was basified to pH 7-8 with saturated Na₂CO₃ (aq.). The resulting mixture was extracted with CH₂Cl₂ (3 x 800 mL). The combined organic layers were washed with brine (2 x 800 mL), dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography to afford ethyl 4-chloropyrimidine-2-carboxylate (20.00 g, 54.61%) as a yellow oil. LC-

MS: (ES+H, m/z): $[M+H]^+ = 187.0$. $^1\text{H NMR}$ (400 MHz, DMSO- d_6) δ 8.98 (d, 1H), 7.97 (d, 1H), 4.40 (q, 2H), 1.34 (t, 3H).

Intermediate 34



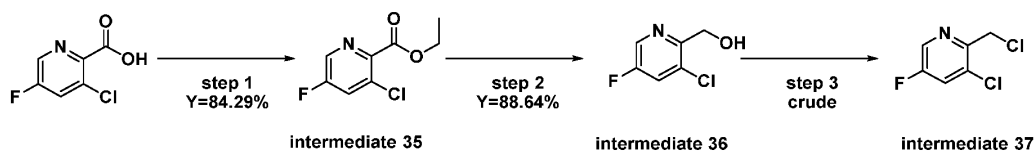
Step 1: Preparation of 2'-bromo-4-[(4-methoxyphenyl)methoxy]-5',6-dimethyl-[1,4'-bipyridin]-2-one:

[00268] To a solution of 2'-bromo-4-hydroxy-5',6-dimethyl-[1,4'-bipyridin]-2-one (7.00 g, 23.72 mmol, 1.00 equiv) in DMF (50 mL) was added PMBCl (11.14 g, 71.15 mmol, 3.00 equiv), K_2CO_3 (13.11 g, 94.872 mmol, 4.00 equiv) and 18-Crown-6 (310 mg, 1.19 mmol, 0.05 equiv). The mixture was stirred at 60°C for 3 h. The reaction was monitored by LCMS. The mixture was allowed to cool down to room temperature. The reaction mixture was partitioned between EA (500 mL) and water (200 mL). The organic layer was washed with water (200 mL) and brine (200 mL), and then dried over Na_2SO_4 . The solution was concentrated under reduced pressure. The residue was purified by silica gel column chromatography to afford 2'-bromo-4-[(4-methoxyphenyl)methoxy]-5',6-dimethyl-[1,4'-bipyridin]-2-one (5.5 g, 55.84%) as an off-white solid. LC-MS: (ES+H, m/z): $[M+H]^+ = 415.0/417.0$. $^1\text{H NMR}$ (300 MHz, DMSO- d_6) δ 8.48 (s, 1H), 7.71 (s, 1H), 7.44 – 7.35 (m, 2H), 7.03 – 6.92 (m, 2H), 6.12 (dd, 1H), 5.93 (d, 1H), 5.04 (s, 2H), 3.78 (s, 3H), 1.96 (s, 3H), 1.85 (s, 3H).

Step 2: Preparation of 2'-bromo-3-chloro-4-[(4-methoxyphenyl)methoxy]-5',6-dimethyl-[1,4'-bipyridin]-2-one:

[00269] To a stirred mixture of 2'-bromo-4-[(4-methoxyphenyl)methoxy]-5',6-dimethyl-[1,4'-bipyridin]-2-one (5.50 g, 13.24 mmol, 1.00 equiv) and NCS (1.95 g, 14.57 mmol, 1.10 equiv) in IPA (20 mL) was added 2,2-dichloroacetic acid (100 mg, 0.80 mmol, 0.06 equiv) at room temperature. The mixture was stirred for 3 h at 60°C under nitrogen atmosphere. The reaction was monitored by LCMS. The mixture was allowed to cool down to room temperature. The precipitated solids were collected by filtration to afford 2'-bromo-3-chloro-4-[(4-methoxyphenyl)methoxy]-5',6-dimethyl-[1,4'-bipyridin]-2-one (3 g, 50.37%) as a white solid. LC-MS: (ES+H, m/z): $[M+H]^+ = 451.1$. $^1\text{H NMR}$ (400 MHz, DMSO- d_6) δ 8.51 (s, 1H), 7.79 (s, 1H), 7.47 – 7.39 (m, 2H), 7.04 – 6.96 (m, 2H), 6.76 (s, 1H), 5.26 (s, 2H), 3.78 (s, 3H), 1.95 (s, 3H), 1.95 (s, 3H).

Intermediate 35-37



Step 1: Preparation of ethyl 3-chloro-5-fluoropyridine-2-carboxylate:

[00270] A solution of 3-chloro-5-fluoropyridine-2-carboxylic acid (4.50 g, 25.63 mmol, 1.00 equiv) in EtOH (100 mL) was cooled with an ice bath. To the above mixture was added SOCl_2 (6.13 g, 51.53 mmol, 2.01 equiv) dropwise over 3 min at 0°C . The resulting mixture was stirred for additional 3 h at room temperature. The reaction was monitored by LCMS. The mixture was allowed to r.t. The resulting mixture was concentrated under vacuum. The residue was purified by silica gel column chromatography to afford ethyl 3-chloro-5-fluoropyridine-2-carboxylate (4.40 g, 84.29%) as a colorless liquid. LC-MS: (ES+H, m/z): $[\text{M}+\text{H}]^+ = 203.9$.

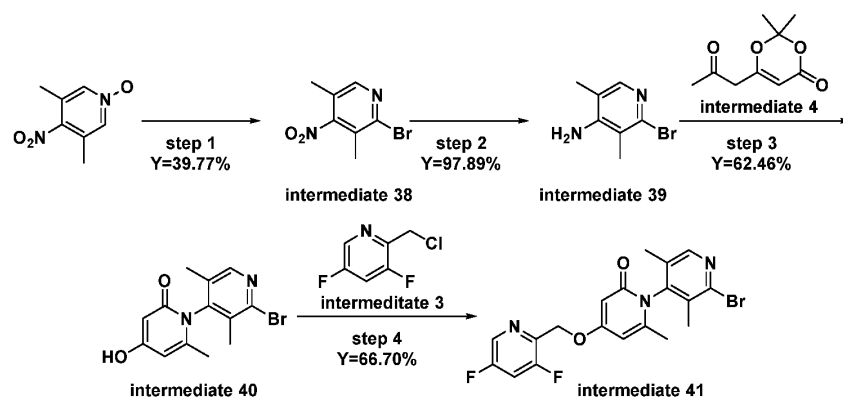
Step 2: Preparation of (3-chloro-5-fluoropyridin-2-yl)methanol :

[00271] To a stirred solution of ethyl 3-chloro-5-fluoropyridine-2-carboxylate (2.10 g, 10.31 mmol, 1.00 equiv) in EtOH (30 mL) was added NaBH_4 (0.98 g, 25.90 mmol, 2.51 equiv) in portions at 0°C under nitrogen atmosphere. The resulting mixture was stirred for 30 min at 0°C under nitrogen atmosphere. The resulting mixture was stirred for additional 2 h at room temperature under nitrogen atmosphere. The reaction was monitored by LCMS. The reaction was quenched with sat. NH_4Cl (aq.) at 0°C . The resulting mixture was concentrated under reduced pressure to remove EtOH, then extracted with EA (3 x 30ml). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 . After filtration, the filtrate was concentrated under vacuum to afford (3-chloro-5-fluoropyridin-2-yl)methanol (2 g, 95.24%) as a yellow oil. LC-MS: (ES+H, m/z): $[\text{M}+\text{H}]^+ = 162.0$.

Step 3: Preparation of 3-chloro-2-(chloromethyl)-5-fluoropyridine:

[00272] To a stirred solution of (3-chloro-5-fluoropyridin-2-yl)methanol (2.10 g, 12.99 mmol, 1.00 equiv) in DCM (30 mL) was added DMF (0.1 mL, 1.30 mmol, 0.10 equiv) at 0°C under nitrogen atmosphere. The SOCl_2 (2.3 mL, 32.49 mmol, 2.50 equiv) was added dropwise under nitrogen atmosphere. The resulting mixture was stirred for 2 h at room temperature. The reaction was monitored by LCMS. The resulting mixture was concentrated under vacuum, to afford 3-chloro-2-(chloromethyl)-5-fluoropyridine (2.00 g, crude) as a brown yellow oil. The crude product was used in the next step directly without further purification. LC-MS: (ES+H, m/z): $[\text{M}+\text{H}]^+ = 179.90$.

Intermediate 38-41



Step 1: Preparation of 2-bromo-3,5-dimethyl-4-nitropyridine:

[00273] To a stirred solution of 3,5-dimethyl-4-nitropyridin-1-ol (5.00 g, 29.38 mmol, 1.00 equiv) in DCE (100 mL) was added POBr₃ (12.64 g, 44.07 mmol, 1.50 equiv) dropwise at 0°C under nitrogen atmosphere. The resulting mixture was stirred for 2 h at 60°C under nitrogen atmosphere. The reaction was monitored by LCMS. The mixture was allowed to r.t. The residue was basified to pH 10 with saturated Na₂CO₃ (aq.) at 0°C. The reaction was poured into water (100 mL) at room temperature. The resulting mixture was extracted with EtOAc (3 x 300 mL). The combined organic layers were concentrated under reduced pressure. The residue was purified by silica gel column chromatography to afford 2-bromo-3,5-dimethyl-4-nitropyridine (5.40 g, 39.77%) as a white solid. LC-MS: (ES+H, m/z): [M+H]⁺ = 231.1/233. ¹H NMR (400 MHz, Chloroform-d) δ 8.24 (s, 1H), 2.35 (s, 3H), 2.25 (s, 3H).

Step 2: Preparation of 2-bromo-3,5-dimethylpyridin-4-amine:

[00274] A mixture of 2-bromo-3,5-dimethyl-4-nitropyridine (5.40 g, 23.37 mmol, 1.00 equiv), Fe (2.61 g, 46.74 mmol, 5.00 equiv) and CaCl₂ (12.97 g, 116.86 mmol, 5.00 equiv) in EtOH (60 mL) was stirred for 3 h at 90°C under nitrogen atmosphere. The reaction was monitored by LCMS. The mixture was allowed to r.t. The resulting mixture was filtered, the filter cake was washed with ethanol (500 mL). The filtrate was concentrated under reduced pressure. The residue was dissolved in EtOAc (500 mL). The EtOAc layer was washed with sat. Na₂CO₃ (aq.) (2 x 300 mL). The organic layers dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. To afford 2-bromo-3,5-dimethylpyridin-4-amine (4.60 g, 97.89%) as a white solid. LC-MS: (ES+H, m/z): [M+H]⁺ = 201.0/203.0. ¹H NMR (400 MHz, DMSO-d₆) δ 7.57 (s, 1H), 5.90 (s, 2H), 2.14 (s, 3H), 1.99 (s, 3H).

Step 3: Preparation of 2'-bromo-4-hydroxy-3',5',6-trimethyl-[1,4'-bipyridin]-2-one:

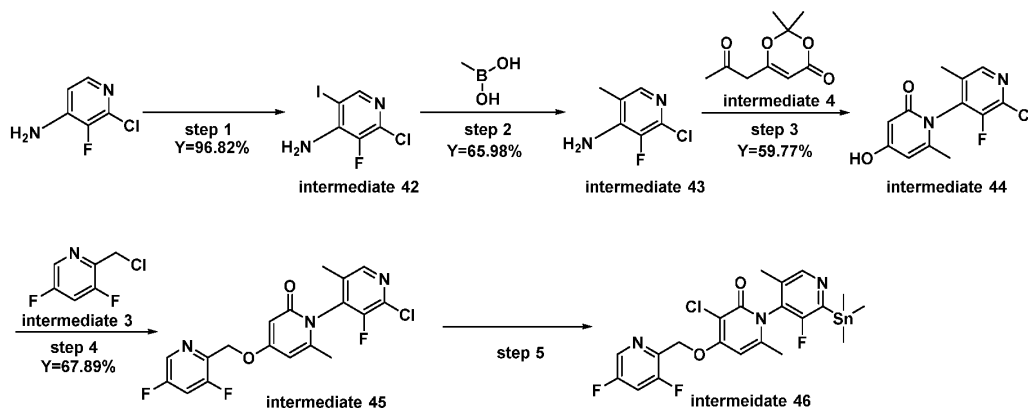
[00275] A solution of 2-bromo-3,5-dimethylpyridin-4-amine (2.30 g, 11.43 mmol, 1.00 equiv) and 2,2-dimethyl-6-(2-oxopropyl)-1,3-dioxin-4-one (2.11 g, 11.43 mmol, 1.00 equiv) in dioxane (15 mL) was stirred for 3.5 h at 90°C under nitrogen atmosphere. The mixture was allowed to cool down to room temperature. The reaction was monitored by LCMS. To the above mixture was added H₂SO₄ (1.12 g, 11.43 mmol, 1.00 equiv) dropwise at 0°C. The resulting mixture was stirred for additional 1 h at 90°C. The reaction was monitored by LCMS. The mixture was allowed to cool down to r.t. The resulting mixture was concentrated under reduced pressure. The residue was purified by reverse flash chromatography to afford 2'-bromo-4-hydroxy-3',5',6-trimethyl-[1,4'-bipyridin]-2-one (1.70 g, 62.46%) as a Brown yellow oil. LC-MS: (ES+H, m/z): [M+H]⁺ = 309.2/311.2. ¹H NMR (400 MHz, Chloroform-d) δ 8.25 (s, 1H), 7.69 – 7.57 (m, 1H), 6.14 (d, 1H), 6.06 (d, 1H), 2.13 (s, 3H), 2.02 (s, 3H), 1.85 (s, 3H).

Step 4: Preparation of 2'-bromo-4-[(3,5-difluoropyridin-2-yl)methoxy]-3',5',6-trimethyl-[1,4'-bipyridin]-2-one:

[00276] A mixture of 2'-bromo-4-hydroxy-3',5',6-trimethyl-[1,4'-bipyridin]-2-one (1.70 g, 5.49 mmol, 1.00 equiv), 2-(chloromethyl)-3,5-difluoropyridine (1.35 g, 8.24 mmol, 1.50 equiv), 18-Crown-6 (0.15 g, 0.55 mmol, 0.10 equiv) and K₂CO₃ (3.04 g, 21.99 mmol, 4.00 equiv) in DMF (15 mL) was stirred for 4 h at 60°C under nitrogen atmosphere. The reaction was monitored by LCMS. The mixture was allowed to cool down to r.t. The residue was dissolved in EA (400 mL). The mixture was washed with water (3 x 200 mL), dried

over anhydrous Na_2SO_4 . After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography to afford 2'-bromo-4-[(3,5-difluoropyridin-2-yl)methoxy]-3',5',6-trimethyl-[1,4'-bipyridin]-2-one (1.60 g, 66.70%) as a yellow green solid. LC-MS: (ES+H, m/z): $[\text{M}+\text{H}]^+ = 436.2/438.2$. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 8.60 (d, 1H), 8.34 (s, 1H), 8.14 – 8.02 (m, 1H), 6.20 (d, 1H), 6.08 (d, 1H), 5.26 (d, 2H), 2.04 (s, 3H), 1.95 (s, 3H), 1.81 (s, 3H).

Intermediate 42-56



Step 1: Preparation of 2-chloro-3-fluoro-5-iodopyridin-4-amine:

[00277] To a stirred solution of 2-chloro-3-fluoropyridin-4-amine (5.00 g, 34.11 mmol, 1.00 equiv) in CH_3CN (150 mL) were added NIS (9.21 g, 40.94 mmol, 1.20 equiv) and 4-methylbenzene-1-sulfonic acid hydrate (0.32 g, 1.70 mmol, 0.05 equiv) in portions at room temperature under nitrogen atmosphere. The resulting mixture was stirred overnight at 70°C under nitrogen atmosphere. The reaction was monitored by LCMS. The mixture was allowed to cool down to room temperature. The resulting mixture was diluted with water (300 mL). The resulting mixture was extracted with EtOAc (3 x 150 mL). The combined organic layers were washed with brine (3x150 mL), dried over anhydrous Na_2SO_4 . After filtration, the filtrate was concentrated under reduced pressure to afford 2-chloro-3-fluoro-5-iodopyridin-4-amine (9.00 g, 96.82%) as a brown solid. LC-MS: (ES+H, m/z): $[\text{M}+\text{H}]^+ = 272.9$. ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 8.10 (s, 1H), 6.69 (s, 2H).

Step 2: Preparation of 2-chloro-3-fluoro-5-methylpyridin-4-amine:

[00278] To a stirred mixture of 2-chloro-3-fluoro-5-iodopyridin-4-amine (9.00 g, 33.03 mmol, 1.00 equiv) and methylboronic acid (3.95 g, 66.06 mmol, 2.00 equiv) in Toluene (200 mL) and H_2O (20 mL) were added Cs_2CO_3 (16.14 g, 49.55 mmol, 1.50 equiv), PCy_3 (0.46 g, 1.65 mmol, 0.05 equiv) and $\text{Pd}(\text{OAc})_2$ (0.37 g, 1.65 mmol, 0.05 equiv) at room temperature under nitrogen atmosphere. The resulting mixture was stirred overnight at 100°C under nitrogen atmosphere. The reaction was monitored by LCMS. The mixture was allowed to cool down to room temperature. The resulting mixture was diluted with water (500 mL). The resulting mixture was extracted with EtOAc (3 x 200 mL). The combined organic layers were washed with brine (3 x 200 mL), dried over anhydrous Na_2SO_4 . After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, the filtrate was concentrated under reduced pressure to afford 2-chloro-3-fluoro-5-methylpyridin-4-amine (3.50 g, 65.98%)

as a yellow solid. LC-MS: (ES+H, m/z): $[M+H]^+ = 161.00$. ^1H NMR (300 MHz, Chloroform-d) δ 7.75 (s, 1H), 4.36 (s, 2H), 2.15 (s, 3H).

Step 3: Preparation of 2'-chloro-3'-fluoro-4-hydroxy-5',6-dimethyl-[1,4'-bipyridin]-2-one:

[00279] To a stirred solution of 2-chloro-3-fluoro-5-methylpyridin-4-amine (3.00 g, 18.68 mmol, 1.00 equiv) in 1,4-dioxane (100 mL) were added 2,2-dimethyl-6-(2-oxopropyl)-1,3-dioxin-4-one (6.88 g, 37.36 mmol, 2.00 equiv) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 2 h at 90°C under nitrogen atmosphere. The mixture was allowed to cool down to room temperature. To the above mixture was added H_2SO_4 (1.83 g, 18.68 mmol, 1.00 equiv) dropwise at room temperature. The resulting mixture was stirred for additional 2 h at 90°C. The reaction was monitored by LCMS. The mixture was allowed to cool down to room temperature. The resulting mixture was concentrated under reduced pressure. The residue was purified by trituration with water (200 mL). The solid was collected by filtration and further purified by trituration with hexane (200 mL) to afford 2'-chloro-3'-fluoro-4-hydroxy-5',6-dimethyl-[1,4'-bipyridin]-2-one (3.00 g, 59.77%) as a brown solid. LC-MS: (ES+ H, m/z): $[M+H]^+ = 269.1$. ^1H NMR (300 MHz, DMSO-d₆) δ 11.03 (s, 1H), 8.42 (s, 1H), 6.05 (d, 1H), 5.61 (d, 1H), 2.06 (s, 3H), 1.89 (s, 3H).

Step 4: Preparation of 2'-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-3'-fluoro-5',6-dimethyl-[1,4'-bipyridin]-2-one:

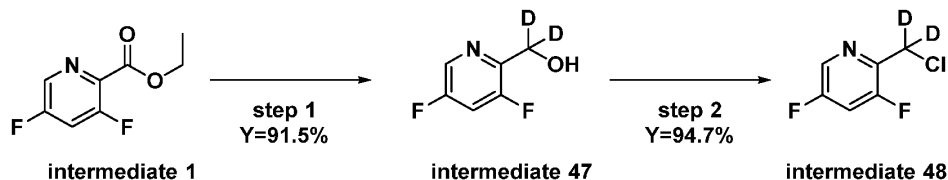
[00280] To a stirred mixture of 2'-chloro-3'-fluoro-4-hydroxy-5',6-dimethyl-[1,4'-bipyridin]-2-one (2.00 g, 7.44 mmol, 1.00 equiv) and 2-(chloromethyl)-3,5-difluoropyridine (1.83 g, 11.16 mmol, 1.50 equiv) in DMF (60 mL) were added Cs_2CO_3 (7.28 g, 22.33 mmol, 3.00 equiv) and 18-Crown-6 (196.7 mg, 0.74 mmol, 0.10 equiv) at room temperature under nitrogen atmosphere. The resulting mixture was stirred overnight at 70°C under nitrogen atmosphere. The reaction was monitored by LCMS. The mixture was allowed to cool down to room temperature. The resulting mixture was diluted with water (150 mL). The resulting mixture was extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with brine (3 x 100 mL), dried over anhydrous Na_2SO_4 . After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, the filtrate was concentrated under reduced pressure to afford 2'-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-3'-fluoro-5',6-dimethyl-[1,4'-bipyridin]-2-one (2.00 g, 67.89%) as a yellow solid. LC-MS: (ES+H, m/z): $[M+H]^+ = 396.1$. ^1H NMR (300 MHz, DMSO-d₆) δ 8.60 (d, 1H), 8.44 (s, 1H), 8.12 – 8.04 (m, 1H), 6.22 (d, 1H), 6.09 (d, 1H), 5.27 (d, 2H), 2.08 (s, 3H), 1.92 (s, 3H).

Step 5: Preparation of 3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-3'-fluoro-5',6-dimethyl-2'-(trimethylstannyl)-[1,4'-bipyridin]-2-one:

[00281] To a stirred solution of 2',3-dichloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-3'-fluoro-5',6-dimethyl-[1,4'-bipyridin]-2-one (500 mg, 1.16 mmol, 1.00 equiv) and Sn_2Me_6 (761.56 mg, 2.32 mmol, 2.00 equiv) in dioxane (8 mL) were added $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$ (163.15 mg, 0.23 mmol, 0.20 equiv) and AsPh_3 (71.18 mg, 0.23 mmol, 0.20 equiv) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 1 h at 80°C under nitrogen atmosphere. The reaction was monitored by LCMS. The mixture was

allowed to cool down to room temperature. The resulting mixture was used in the next step directly without further purification. LC-MS: (ES+H, m/z): $[M+H]^+ = 560.0$.

Intermediate 47-48



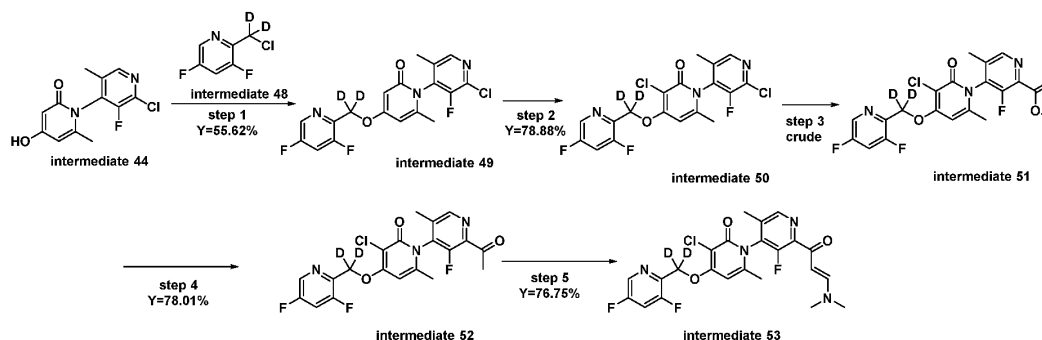
Step 1: Preparation of (3,5-difluoropyridin-2-yl)methan-d₂-ol:

[00282] To a stirred solution of ethyl 5-chloro-3-fluoropyridine-2-carboxylate (500.00 g, 2671.71 mmol, 1.00 equiv) in CD₃OD (500 mL) and THF (1000 mL) was added NaBD₄ (111.84 g, 2671.71 mmol, 1.00 equiv) in portions at 0°C under nitrogen air. The resulting mixture was stirred for 2 hours at room temperature under nitrogen atmosphere. The reaction was monitored by LCMS. The resulting mixture was quenched by the addition of D₂O (200 mL) at 0°C and stirred for 30 min at 0°C. The mixture was diluted with EtOAc (2000 mL) and washed with water (2000 mL) and brine (2000 mL). The organic layers were dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure, to afford (3,5-difluoropyridin-2-yl)methan-d₂-ol methanol (360.00 g, 91.5%) as a yellow oil. LC-MS: (ES+H, m/z): $[M+H]^+ = 148.1$. ¹H NMR (300 MHz, DMSO-d₆) δ 8.44 (d, 1H), 7.88 (ddd, 1H), 5.37 (s, 1H).

Step 2: Preparation of 2-(chloromethyl-d₂)-3,5-difluoropyridine :

[00283] To a stirred solution of (3,5-difluoropyridin-2-yl)methan-d₂-ol (300.00 g, 2039.13 mmol, 1.00 equiv) in DCM (1000 mL) was added DMF (14.91 g, 203.91 mmol, 0.10 equiv) and SOCl₂ (606.44 g, 5097.84 mmol, 2.50 equiv) dropwise under nitrogen atmosphere at 0°C. The resulting mixture was stirred for 2 h at room temperature under nitrogen atmosphere. The reaction was monitored by LCMS. The resulting mixture was concentrated under vacuum to afford 2-(chloromethyl-d₂)-3,5-difluoropyridine (320.00 g, 94.7%) as a yellow oil which was used directly in next step without further purification. LC-MS: (ES+H, m/z): $[M+H]^+ = 166.1$. ¹H NMR (300 MHz, DMSO-d₆) δ 8.48 (d, 1H), 8.04 - 7.93 (m, 1H).

Intermediate 49-53



Step 1: Preparation of 2'-chloro-4-[(3,5-difluoropyridin-2-yl)(2H₂)methoxy]-3'-fluoro-5',6-dimethyl-[1,4'-bipyridin]-2-one:

[00284] To a stirred mixture of 2'-chloro-3'-fluoro-4-hydroxy-5',6-dimethyl-[1,4'-bipyridin]-2-one (1.70 g, 6.32 mmol, 1.00 equiv) and 2-[chloro(2H2) methyl]-3,5-difluoropyridine (1.57 g, 9.49 mmol, 1.50 equiv) in DMF (60 mL) were added Cs₂CO₃ (6.18 g, 18.98 mmol, 3.00 equiv) and 18-Crown-6 (0.17 g, 0.63 mmol, 0.10 equiv) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 2 h at 70°C under nitrogen atmosphere. The reaction was monitored by LCMS. The mixture was allowed to cool down to room temperature. The resulting mixture was diluted with water (150 mL). The resulting mixture was extracted with EtOAc (3 x 100mL). The combined organic layers were washed with brine (3 x 100 mL), dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, the filtrate was concentrated under reduced pressure to afford 2'-chloro-4-[(3,5-difluoropyridin-2-yl) (2H2)methoxy]-3'-fluoro-5',6-dimethyl-[1,4'-bipyridin]-2-one (1.40 g, 55.62%) as a yellow solid. LC-MS: (ES+H, m/z): [M+H]⁺ = 398.1.

Step 2: Preparation of 2',3-dichloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-3'-fluoro-5',6-dimethyl-[1,4'-bipyridin]-2-one:

[00285] To a stirred solution of 2'-chloro-4-[(3,5-difluoropyridin-2-yl)(2H2)methoxy]-3'-fluoro-5',6-dimethyl-[1,4'-bipyridin]-2-one (1.40 g, 3.52 mmol, 1.00 equiv) and NCS (0.61 g, 4.57 mmol, 1.30 equiv) in i-PrOH was added dichloroacetic acid (0.05 g, 0.35 mmol, 0.10 equiv) dropwise at room temperature under nitrogen atmosphere. The resulting mixture was stirred 2 h at 60°C under nitrogen atmosphere. The reaction was monitored by LCMS. The resulting mixture was diluted with water (100 mL). The resulting mixture was extracted with EtOAc (3 x 50mL). The combined organic layers were washed with brine (3 x 50 mL), dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, the filtrate was concentrated under reduced pressure to afford 2',3-dichloro-4-[(3,5-difluoropyridin-2-yl)(2H2)methoxy]-3'-fluoro-5',6-dimethyl-[1,4'-bipyridin]-2-one (1.2 g, 78.88%) as a yellow solid. LC-MS: (ES+H, m/z): [M+H]⁺ = 432.0. ¹H NMR (400 MHz, DMSO-d₆) δ 8.59 (d, 1H), 8.43 (d, 1H), 8.12 – 8.03 (m, 1H), 6.21 (s, 1H), 6.08 (d, 1H), 2.07 (s, 3H), 1.91 (s, 3H).

Step 3: 3-chloro-4-[(3,5-difluoropyridin-2-yl)(2H2)methoxy]-2'-(1-ethoxyethenyl)-3'-fluoro-5',6-dimethyl-[1,4'-bipyridin]-2-one:

[00286] To a stirred solution of 2',3-dichloro-4-[(3,5-difluoropyridin-2-yl)(2H2)methoxy]-3'-fluoro-5',6-dimethyl-[1,4'-bipyridin]-2-one (1.20 g, 2.77 mmol, 1.00 equiv) and tributyl(1-ethoxyethenyl)stannane (2.01 g, 5.55 mmol, 2.00 equiv) in dioxane 24.00 mL were added Pd(PPh₃)₂Cl₂ (0.10 g, 0.14 mmol, 0.05 equiv) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 2h at 120°C under nitrogen atmosphere. The reaction was monitored by LCMS. Desired product could be detected by LCMS. The mixture was allowed to cool down to room temperature. The resulting mixture was used in the next step directly without further purification. LC-MS: (ES+H, m/z): [M+H]⁺ = 468.1.

Step 4: Preparation of 2'-acetyl-3-chloro-4-[(3,5-difluoropyridin-2-yl)(2H2)methoxy]-3'-fluoro-5',6-dimethyl-[1,4'-bipyridin]-2-one:

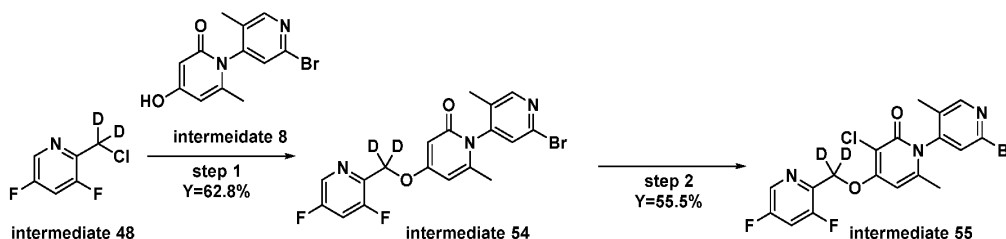
[00287] The above mixture was diluted with 1,4-dioxane (80 mL), then was added HCl (0.94 g, 25.65 mmol, 10.00 equiv) dropwise at 0°C. The resulting mixture was stirred for additional 30 min at room

temperature. Desired product could be detected by LCMS. The mixture was basified to pH 8 with saturated NaHCO_3 (aq.). The resulting mixture was extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with brine (3 x 10 mL), dried over anhydrous Na_2SO_4 . After filtration, The residue was purified by silica gel column chromatography, the filtrate was concentrated under reduced pressure to afford 2'-acetyl-3-chloro-4-[(3,5-difluoropyridin-2-yl)(2H2)methoxy]-3'-fluoro-5',6-dimethyl-[1,4'-bipyridin]-2-one (880 mg, 78.01%) as a yellow solid. LC-MS: (ES+H, m/z): $[\text{M}+\text{H}]^+ = 440.20$.

Step 5: Preparation of 3-chloro-4-[(3,5-difluoropyridin-2-yl)(2H2)methoxy]-2'-[(2E)-3-(dimethylamino)prop-2-enoyl]-3'-fluoro-5',6-dimethyl-[1,4'-bipyridin]-2-one:

[00288] A solution of 2'-acetyl-3-chloro-4-[(3,5-difluoropyridin-2-yl)(2H2)methoxy]-3'-fluoro-5',6-dimethyl-[1,4'-bipyridin]-2-one (880 mg, 2.00 mmol, 1.00 equiv) in DMF-DMA (6 mL) was stirred for 2 h at 100°C under nitrogen atmosphere. Desired product could be detected by LCMS. The mixture was allowed to cool down to room temperature. The precipitated solids were collected by filtration and washed with hexane (3 x 2 mL). This resulted in 3-chloro-4-[(3,5-difluoropyridin-2-yl)(2H2)methoxy]-2'-[(2E)-3-(dimethylamino)prop-2-enoyl]-3'-fluoro-5',6-dimethyl-[1,4'-bipyridin]-2-one (760 mg, 76.75%) as a yellow solid. LC-MS: (ES+H, m/z): $[\text{M}+\text{H}]^+ = 495.1$.

Intermediate 54-55



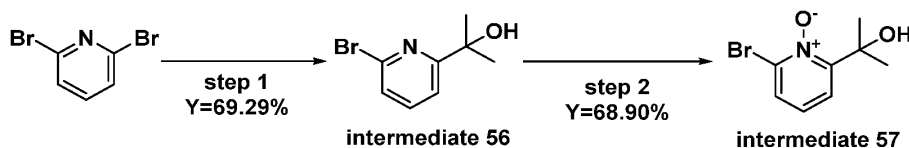
Step 1: Preparation of 2'-bromo-4-((3,5-difluoropyridin-2-yl)methoxy-d2)-5',6-dimethyl-2H-[1,4'-bipyridin]-2-one:

[00289] To a stirred mixture of 2'-bromo-4-hydroxy-5',6-dimethyl-[1,4'-bipyridin]-2-one (100.00 g, 338.82 mmol, 1.00 equiv), 18-Crown-6 (5.37 g, 3.00 mmol, 0.40 equiv) and K_2CO_3 (42.14 g, 304.94 mmol, 3.00 equiv) in DMF (200 mL) was added 2-(chloromethyl-d2)-3,5-difluoropyridine (27.75 g, 152.47 mmol, 1.50 equiv) at r.t.. The resulting mixture was stirred for 2.5 h at 60°C under nitrogen atmosphere. The reaction was monitored by LCMS. The resulting mixture was filtered, the filter cake was washed with EtOAc (3 x 500 mL). The filtrate was diluted with EA (3000 mL). The resulting mixture was washed with brine (3 x 2000 mL) and water (5 x 2000 mL). The organic layer was dried over anhydrous Na_2SO_4 . After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by trituration with Et2O (3x250 mL) and dried under reduced pressure to afford 2'-bromo-4-((3,5-difluoropyridin-2-yl)methoxy-d2)-5',6-dimethyl-2H-[1,4'-bipyridin]-2-one (90 g, 62.8%) as a white solid. LC-MS: (ES+H, m/z): $[\text{M}+\text{H}]^+ = 424.0$. ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 8.59 (d, 1H), 8.48 (s, 1H), 8.08 (ddd, 1H), 7.73 (s, 1H), 6.13 (dd, 1H), 6.03 (d, 1H), 1.97 (s, 3H), 1.85 (s, 3H).

Step 2: Preparation of 2'-bromo-3-chloro-4-((3,5-difluoropyridin-2-yl)methoxy-d2)-5',6-dimethyl-2H-[1,4'-bipyridin]-2-one:

[00290] To a stirred solution of 2'-bromo-4-((3,5-difluoropyridin-2-yl)methoxy-d2)-5',6-dimethyl-2H-[1,4'-bipyridin]-2-one (100.00 g, 235.71 mmol, 1.00 equiv) and NCS (37.77 g, 282.85 mmol, 1.20 equiv) in IPA (500 mL) was added 2,2-dichloroacetic acid (3.04 g, 23.57 mmol, 0.10 equiv) dropwise at room temperature. The resulting mixture was stirred for 1 h at 60°C under nitrogen atmosphere. The reaction was monitored by LCMS. The mixture was allowed to cool down to r.t. The precipitated solids were collected by filtration and washed with cold IPA (4x30 mL), to afford 2'-bromo-3-chloro-4-((3,5-difluoropyridin-2-yl)methoxy-d2)-5',6-dimethyl-2H-[1,4'-bipyridin]-2-one (60.00 g, 55.5%) as a white solid. LC-MS: (ES+H, m/z): [M+H]⁺ = 458.0. ¹H NMR 300 MHz, DMSO-d₆) δ 8.60 (d, 1H), 8.52 (s, 1H), 8.10 (ddd, 1H), 7.81 (s, 1H), 6.80 (d, 1H), 1.96 (s, 6H).

Intermediate 56-57



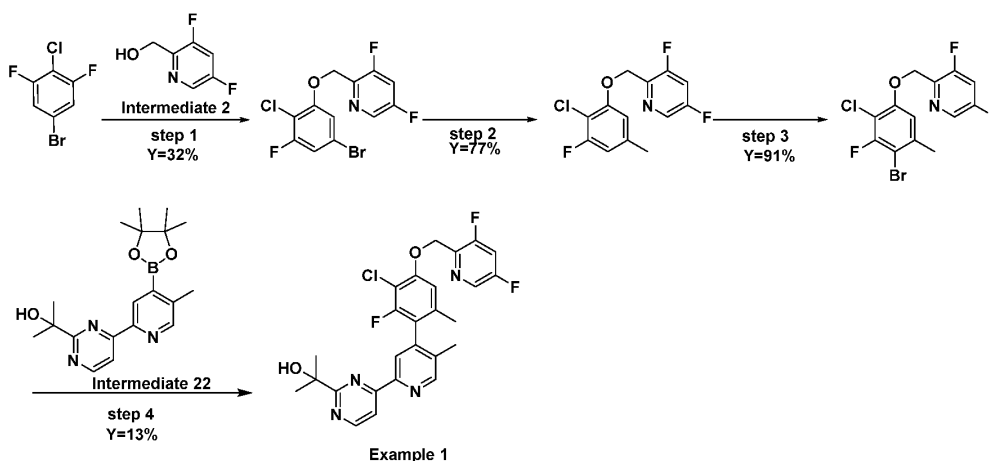
Step 1: Preparation of 2-(6-bromopyridin-2-yl)propan-2-ol:

[00291] To a stirred solution of 2,6-dibromo-pyridine, (25.00 g, 105.53 mmol, 1.00 equiv) in toluene (50 ml) was added n-BuLi (46.43 mL, 116.08 mmol, 1.10 equiv, 2.5M in THF) dropwise at -50°C under nitrogen atmosphere. The resulting mixture was stirred for 30 min at -50°C under nitrogen atmosphere. To the above mixture was added acetone (9.19 g, 158.29 mmol, 1.5 equiv) dropwise over 10 min at -50°C. The resulting mixture was stirred for additional 1 h at -50°C. The reaction was monitored by LCMS. The reaction was quenched with sat. NH₄Cl (aq.) at -10°C. The resulting mixture was extracted with EtOAc (3 x 300 mL). The combined organic layers were concentrated under reduced pressure. The residue was purified by silica gel column chromatography to afford 2-(6-bromopyridin-2-yl)propan-2-ol (15.80 g, 69.29%) as a colorless liquid. LC-MS: (ES+H, m/z): [M+H]⁺ = 216.2/218.2. ¹H NMR (400 MHz, DMSO-d₆) δ 7.73 (t, 1H), 7.68 (dd, 1H), 7.46 (dd, 1H), 5.33 (s, 1H), 1.43 (s, 6H).

Step 2: Preparation of 2-bromo-6-(2-hydroxypropan-2-yl)pyridin-1-ium-1-olate:

[00292] To a stirred solution of 2-(6-bromopyridin-2-yl)propan-2-ol (5.00 g, 23.14 mmol, 1.00 equiv) in DCM (50 ml) was added m-CPBA (11.98 g, 69.42 mmol, 3.00 equiv) in portions at 0°C under nitrogen atmosphere. The resulting mixture was stirred for 24 h at 50°C under nitrogen atmosphere. The reaction was monitored by LCMS. The mixture was allowed to r.t. The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, to afford 2-bromo-6-(2-hydroxypropan-2-yl)pyridin-1-ium-1-olate (3.70 g, 68.90%) as a white solid. LC-MS: (ES+H, m/z): [M+H]⁺ = 232.3/234.3. ¹H NMR (300 MHz, DMSO-d₆) δ 7.91 (dd, 1H), 7.69 (dd, 1H), 7.33 (t, 1H), 6.70 – 6.04 (m, 1H), 1.58 (s, 6H).

Example 1



Step 1: Preparation of 2-(5-bromo-2-chloro-3-fluorophenoxymethyl)-3,5-difluoropyridine:

[00293] A mixture of 5-bromo-2-chloro-1,3-difluorobenzene (6.00 g, 26.38 mmol, 1.00 equiv), (3,5-difluoropyridin-2-yl)methanol (3.83 g, 26.38 mmol, 1.00 equiv), 18-Crown-6 (0.70 g, 2.64 mmol, 0.10 equiv) and K_2CO_3 (10.94 g, 79.15 mmol, 3.00 equiv) in DMF (100 mL) was stirred overnight at 80°C under nitrogen atmosphere. The reaction was monitored by LCMS. The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, and the pure fraction was concentrated under reduced pressure to afford 2-(5-bromo-2-chloro-3-fluorophenoxymethyl)-3,5-difluoropyridine (3.00 g, 32%) as a white solid. LC-MS: (ES+H, m/z): $[M+H]^+ = 351.9/353.9$. 1H NMR (400 MHz, $DMSO-d_6$) δ 8.58 (d, 1H), 8.07 (td, 1H), 7.49 (t, 1H), 7.42 (dd, 1H), 5.41 (d, 2H).

Step 2: Preparation of 2-(2-chloro-3-fluoro-5-methylphenoxymethyl)-3,5-difluoropyridine:

[00294] A mixture of 2-(5-bromo-2-chloro-3-fluorophenoxymethyl)-3,5-difluoropyridine (3.00 g, 8.51 mmol, 1.00 equiv), methylboronic acid (0.76 g, 12.77 mmol, 1.50 equiv), $Pd(dppf)Cl_2$ (313 mg, 0.43 mmol, 0.05 equiv) and K_2CO_3 (3.53 g, 25.53 mmol, 3.00 equiv) in dioxane: $H_2O=10:1$ (100 mL) was stirred overnight at 80°C under nitrogen atmosphere. The reaction was monitored by LCMS. The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography and the pure fraction was concentrated under reduced pressure to afford 2-(2-chloro-3-fluoro-5-methylphenoxymethyl)-3,5-difluoropyridine (1.90 g, 77%) as a white solid. LC-MS: (ES+H, m/z): $[M+H]^+ = 288.1$. 1H NMR (400 MHz, $DMSO-d_6$) δ 8.57 (d, 1H), 8.08 - 8.03 (m, 1H), 7.06 (s, 1H), 6.88 (dd, 1H), 5.30 (d, 2H), 2.32 (s, 3H).

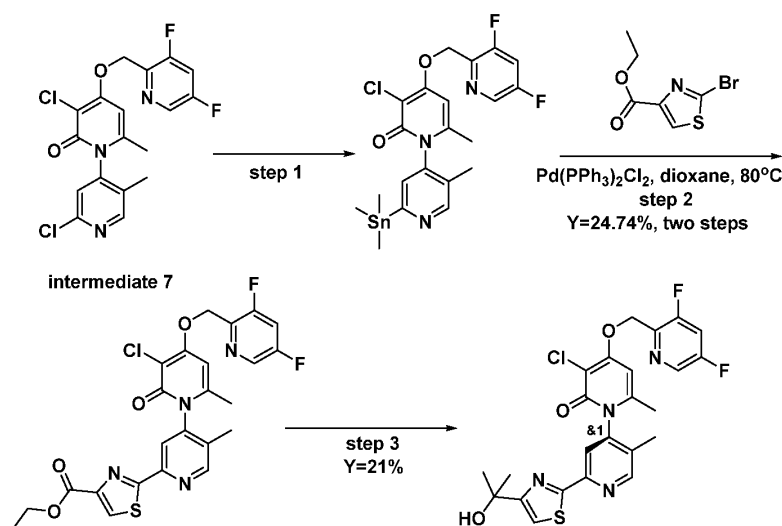
Step 3: Preparation of 2-(4-bromo-2-chloro-3-fluoro-5-methylphenoxymethyl)-3,5-difluoropyridine:

[00295] A mixture of 2-(2-chloro-3-fluoro-5-methylphenoxymethyl)-3,5-difluoropyridine (1.30 g, 4.52 mmol, 1.00 equiv) and NBS (804 mg, 4.52 mmol, 1.00 equiv) in MeCN was stirred overnight at 80°C under nitrogen atmosphere. The reaction was monitored by LCMS. The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography and the pure fraction was concentrated under reduced pressure to afford 2-(4-bromo-2-chloro-3-fluoro-5-methylphenoxymethyl)-3,5-difluoropyridine (1.50 g, 91%) as a white solid. LC-MS: (ES+H, m/z): $[M+H]^+ = 365.9/367.9$. 1H NMR (400 MHz, $DMSO-d_6$) δ 8.57 (d, 1H), 8.09-8.04 (m, 1H), 7.32 (d, 1H), 5.36 (d, 2H), 2.39 (s, 3H).

Step 4: Preparation of 3-{5-chloro-4-[(2,4-difluorophenyl)methoxy]-2-methyl-6-oxypyrimidin-1-yl}-N-methoxy-N,4-dimethylbenzamide:

[00296] A mixture of 2-{4-[5-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-yl]pyrimidin-2-yl}propan-2-ol (50 mg, 0.18 mmol, 1.00 equiv), 2-(4-bromo-2-chloro-3-fluoro-5-methylphenoxy)methyl)-3,5-difluoropyridine (62 mg, 0.17 mmol, 1.20 equiv), Pd(dppf)Cl₂ (10 mg, 0.01 mmol, 0.10 equiv) and Cs₂CO₃ (138 mg, 0.42 mmol, 3.00 equiv) in dioxane:H₂O=20:1 (1 mL) was stirred for 3 h at 100°C under nitrogen atmosphere. The reaction was monitored by LCMS. The resulting mixture was concentrated under reduced pressure. The residue was purified by Prep-TLC to afford 2-[4-(4-{3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-2-fluoro-6-methylphenyl}-5-methylpyridin-2-yl)pyrimidin-2-yl]propan-2-ol (50 mg, crude) as an off-white solid. The crude product (50 mg) was purified by Prep-HPLC and the pure fractions were concentrated and lyophilized to afford 2-[4-(4-{3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-2-fluoro-6-methylphenyl}-5-methylpyridin-2-yl)pyrimidin-2-yl]propan-2-ol (13 mg, 13%) as an off-white solid. LC-MS: (ES+H, *m/z*): [M+H]⁺=515.15. ¹H NMR (400 MHz, DMSO-d₆) δ 8.95 (d, 1H), 8.78 (s, 1H), 8.61 (d, 1H), 8.53 (s, 1H), 8.24 (d, 1H), 8.10 (td, 1H), 7.33 (s, 1H), 5.42 (s, 2H), 5.23 (s, 1H), 2.13 (s, 3H), 2.06 (s, 3H), 1.52 (s, 6H). ¹⁹F NMR (377 MHz, DMSO) δ -115.32, -120.15, -122.47.

Example 2



Example 2

Step 1: Preparation of 3-chloro-4-((3,5-difluoropyridin-2-yl)methoxy)-5',6-dimethyl-2'-(trimethylstannyl)-2H-[1,4'-bipyridin]-2-one:

[00297] To a mixture of 2',3-dichloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-5',6-dimethyl-[1,4'-bipyridin]-2-one (500 mg, 1.21 mmol, 1.00 equiv) and hexamethyldistannane (477 mg, 1.46 mmol, 1.20 equiv) in dioxane (10 mL) was added Pd(PPh₃)₂Cl₂ (170 mg, 0.24 mmol, 0.20 equiv) and AsPh₃ (74 mg, 0.24 mmol, 0.20 equiv) at room temperature under nitrogen. The mixture was stirred overnight at 80°C under nitrogen atmosphere. The reaction was monitored by LCMS. Desired product could be detected by LCMS. The mixture was used directly on the next step. LC-MS: (ES+H, *m/z*): [M+H]⁺=542.1.

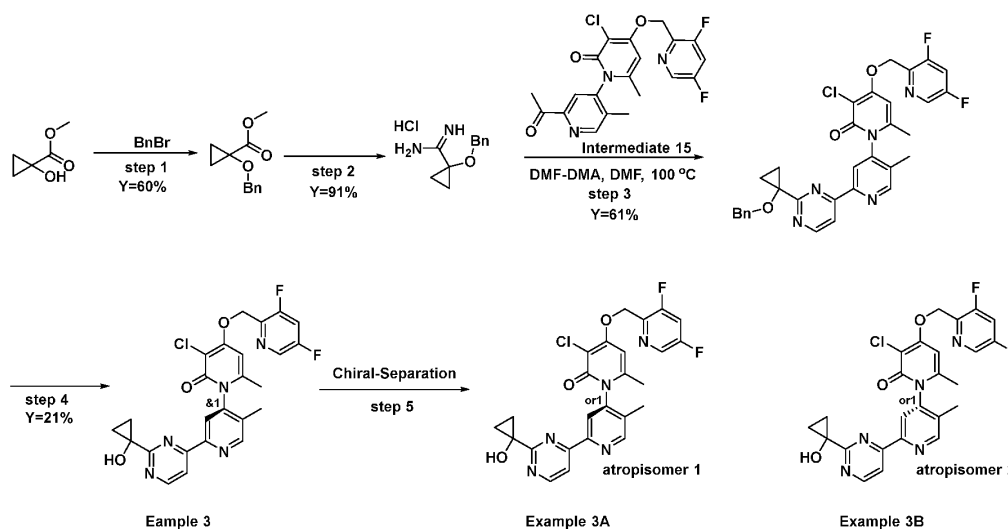
Step 2: Preparation of ethyl 2-{3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-5',6-dimethyl-2-oxo-[1,4'-bipyridin]-2'-yl}-1,3-thiazole-4-carboxylate:

[00298] To the last step of reaction mixture was added ethyl 2-bromo-1,3-thiazole-4-carboxylate (432.59 mg, 1.833 mmol, 1.50 equiv), Pd(PPh₃)₂Cl₂ (170 mg, 0.24 mmol, 0.20 equiv) at room temperature under nitrogen. The mixture was stirred overnight at 80°C under nitrogen atmosphere. The reaction was monitored by LCMS. The mixture was allowed to cool down to room temperature. The resulting mixture was firstly purified by silica gel column chromatography to afford a crude product (210 mg). The crude product (210 mg) was further purified by Prep-HPLC and the pure fractions were concentrated to afford ethyl 2-{3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-5',6-dimethyl-2-oxo-[1,4'-bipyridin]-2'-yl}-1,3-thiazole-4-carboxylate (160 mg, 24.74%, two steps) as a white solid. LC-MS: (ES+H, *m/z*): [M+H]⁺=533.1.

Step 3: Preparation of 3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-2'-[4-(2-hydroxypropan-2-yl)-1,3-thiazol-2-yl]-5',6-dimethyl-[1,4'-bipyridin]-2-one:

[00299] To a mixture of ethyl 2-{3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-5',6-dimethyl-2-oxo-[1,4'-bipyridin]-2'-yl}-1,3-thiazole-4-carboxylate (100 mg, 0.19 mmol, 1.00 equiv) in THF (5 mL) was added CH₃MgBr (0.6 mL, 0.56 mmol, 3.00 equiv) dropwise at 0°C under nitrogen. The mixture was stirred for 3h at room temperature under nitrogen atmosphere. The reaction was monitored by LCMS. The reaction was quenched by MeOH (1 mL). The resulting mixture was concentrated under reduced pressure. The residue was directly purified by Prep-HPLC and the pure fractions were concentrated and lyophilized to afford 3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-2'-[4-(2-hydroxypropan-2-yl)-1,3-thiazol-2-yl]-5',6-dimethyl-[1,4'-bipyridin]-2-one (20.3 mg, 21%) as a white solid. LC-MS: (ES+H, *m/z*): [M+H]⁺=518.8. ¹H NMR (400 MHz, DMSO-d₆) δ 8.72 (s, 1H), 8.61 (d, 1H), 8.10 (ddd, 1H), 8.01 (s, 1H), 7.54 (s, 1H), 6.81 (s, 1H), 5.49 (s, 2H), 5.23 (s, 1H), 2.05 (s, 3H), 1.99 (s, 3H), 1.50 (s, 6H). ¹⁹F NMR (377 MHz, DMSO) δ -120.15, -122.34.

Example 3 and Example 3A and Example 3B



Step 1: Preparation of methyl 1-(benzyloxy)cyclopropane-1-carboxylate:

[00300] A solution of methyl 1-hydroxycyclopropane-1-carboxylate (3.00 g, 25.84 mmol, 1.00 equiv) in DMF (20 mL) was treated with NaH (0.93 g, 38.75 mmol, 1.50 equiv, 60%wt) for 30 min at 0°C under nitrogen atmosphere followed by the addition of benzyl bromide (8.84 g, 51.67 mmol, 2.00 equiv) dropwise at 0°C. The resulting mixture was stirred for 2h at room temperature under nitrogen atmosphere. The reaction was monitored by LCMS and TLC. The reaction was quenched by the addition of Water/Ice (150 mL) at 0°C. The resulting mixture was extracted with EtOAc (3 x 150 mL). The combined organic layers were washed with brine (1x150 mL), dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography to afford methyl 1-(benzyloxy)cyclopropane-1-carboxylate (3.20 g, 60%) as a colorless oil. ¹H NMR (300 MHz, DMSO-d₆) δ 7.47 – 7.23 (m, 5H), 4.60 (s, 2H), 3.69 (s, 3H), 1.37 – 1.16 (m, 4H).

Step 2: Preparation of 1-(benzyloxy)cyclopropane-1-carboximidamide hydrochloride:

[00301] To a stirred mixture of NH₄Cl (2.50 g, 46.74 mmol, 9.64 equiv) in Toluene (20 mL, 188.00 mmol, 38.77 equiv) was added trimethylaluminium (19.25 mL, 534.09 mmol, 110.15 equiv) dropwise at 0°C under nitrogen atmosphere. The resulting mixture was stirred for 30 min at room temperature under nitrogen atmosphere. To the above mixture was added methyl 1-(benzyloxy)cyclopropane-1-carboxylate (1.00 g, 4.85 mmol, 1.00 equiv) in toluene (10 mL) dropwise over 10 min at room temperature. The resulting mixture was stirred for additional overnight at 80°C. The reaction was monitored by LCMS. The reaction was quenched by the addition of MeOH (10 mL) at 0°C. The resulting mixture was filtered, the filter cake was washed with EtOH (5 x 20 mL). The filtrate was concentrated under reduced pressure. This resulted in 1-(benzyloxy)cyclopropane-1-carboximidamide hydrochloride (1.00 g, 91%) as a white solid. LC-MS: (ES+H, *m/z*): [M+H]⁺ = 191.1. ¹H NMR (300 MHz, DMSO-d₆) δ 8.85 (d, 4H), 7.56 – 7.23 (m, 5H), 4.57 (s, 2H), 1.48 (s, 4H).

Step 3: Preparation of 2'-{2-[1-(benzyloxy)cyclopropyl]pyrimidin-4-yl}-3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-5',6-dimethyl-[1,4'-bipyridin]-2-one:

[00302] A solution of 2'-acetyl-3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-5',6-dimethyl-[1,4'-bipyridin]-2-one (200 mg, 0.48 mmol, 1.00 equiv) in DMF-DMA (5 mL) was stirred overnight at 100°C under nitrogen atmosphere. The resulting mixture was concentrated under vacuum. To the above mixture was added 1-(benzyloxy)cyclopropane-1-carboximidamide hydrochloride (324 mg, 1.43 mmol, 3.00 equiv) and K₂CO₃ (395 mg, 2.86 mmol, 6 equiv) in IPA (5 mL). The resulting mixture was stirred for additional overnight at 100°C. The reaction was monitored by LCMS. The resulting mixture was concentrated under reduced pressure. The residue was purified by Prep-TLC (PE/EA=1:3) to afford 2'-{2-[1-(benzyloxy)cyclopropyl]pyrimidin-4-yl}-3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-5',6-dimethyl-[1,4'-bipyridin]-2-one (185 mg, 65%) as a white solid. LC-MS: (ES+H, *m/z*): [M+H]⁺ = 602.2.

Step 4: Preparation of 3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-2'-[2-(1-hydroxycyclopropyl)pyrimidin-4-yl]-5',6-dimethyl-[1,4'-bipyridin]-2-one:

[00303] A mixture of 2'-{2-[1-(benzyloxy)cyclopropyl]pyrimidin-4-yl}-3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-5',6-dimethyl-[1,4'-bipyridin]-2-one (150 mg, 0.25 mmol, 1.00 equiv) and AlCl₃ (199 mg,

1.49 mmol, 6.00 equiv) in Toluene (10 mL) was stirred for 4h at room temperature under nitrogen atmosphere. The reaction was monitored by LCMS. The resulting mixture was filtered, the filter cake was washed with DCM:MeOH=5:1 (3 x 10 mL). The filtrate was concentrated under reduced pressure. The crude product (100 mg) was purified by Prep-HPLC, the pure fractions were concentrated and lyophilized to afford 3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-2'-[2-(1-hydroxycyclopropyl)pyrimidin-4-yl]-5',6-dimethyl-[1,4'-bipyridin]-2-one (26.3 mg, 21%) as a white solid. LC-MS: (ES+H, m/z): $[M+H]^+=511.85$. 1H NMR (400 MHz, DMSO- d_6) δ 8.91 – 8.84 (m, 2H), 8.61 (d, 1H), 8.57 (s, 1H), 8.18 – 8.07 (m, 2H), 6.84 (s, 1H), 6.05 (s, 1H), 5.50 (d, 2H), 2.11 (s, 3H), 1.98 (s, 3H), 1.43 – 1.31 (m, 2H), 1.21-1.18 (m, 2H). ^{19}F NMR (377 MHz, DMSO) δ -120.14 -122.34.

Step 5: Preparation of rel-3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-2'-[2-(1-hydroxycyclopropyl)pyrimidin-4-yl]-5',6-dimethyl-[1,4'-bipyridin]-2-one and rel-3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-2'-[2-(1-hydroxycyclopropyl)pyrimidin-4-yl]-5',6-dimethyl-[1,4'-bipyridin]-2-one:

[00304] 3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-2'-[2-(1-hydroxycyclopropyl)pyrimidin-4-yl]-5',6-dimethyl-[1,4'-bipyridin]-2-one (30 mg, 0.059 mmol, 1.00 equiv) was isolated by prep-Chiral-HPLC. The pure fraction was concentrated and lyophilized to afford rel-3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-2'-[2-(1-hydroxycyclopropyl)pyrimidin-4-yl]-5',6-dimethyl-[1,4'-bipyridin]-2-one (isomer 1, 13.6 mg, ee%=100%) as a white solid and rel-3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-2'-[2-(1-hydroxycyclopropyl)pyrimidin-4-yl]-5',6-dimethyl-[1,4'-bipyridin]-2-one (isomer 2, 11.8 mg, ee%=99.8%) as a white solid.

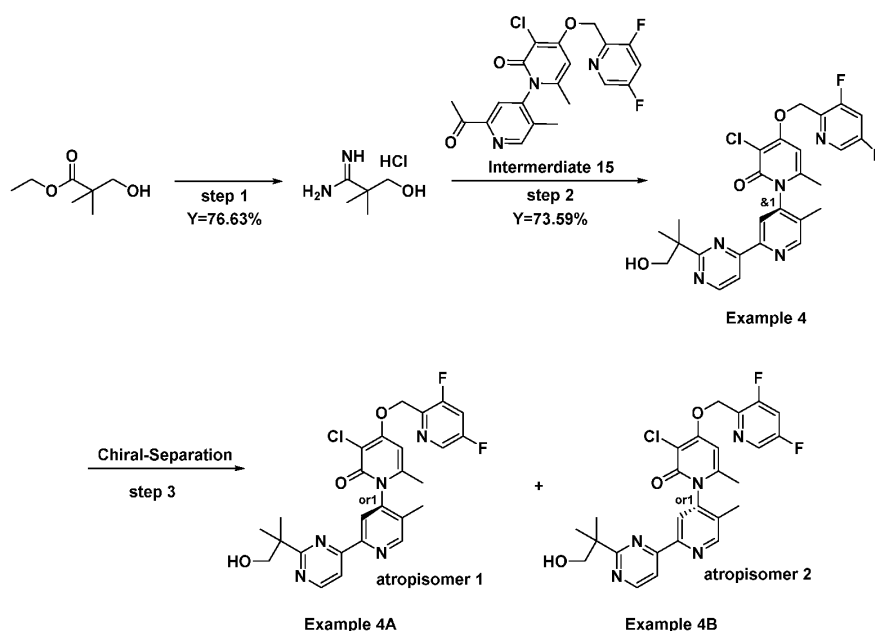
Example 3A (isomer 1):

[00305] LC-MS: (ES+H, m/z): $[M+H]^+=511.80$. 1H NMR (400 MHz, DMSO- d_6) δ 8.90 – 8.83 (m, 2H), 8.61 (d, 1H), 8.57 (s, 1H), 8.15 (d, 1H), 8.11 (td, 1H), 6.85 (s, 1H), 6.05 (s, 1H), 5.50 (d, 2H), 2.11 (s, 3H), 1.98 (s, 3H), 1.43 – 1.30 (m, 2H), 1.18 (d, 2H). ^{19}F NMR (377 MHz, DMSO) δ -120.14, -122.35.

Example 3B (isomer 2):

[00306] LC-MS: (ES+H, m/z): $[M+H]^+=511.80$. 1H NMR (400 MHz, DMSO- d_6) δ 8.90 – 8.83 (m, 2H), 8.61 (d, 1H), 8.57 (s, 1H), 8.15 (d, 1H), 8.11 (td, 1H), 6.85 (s, 1H), 6.05 (s, 1H), 5.50 (d, 2H), 2.11 (s, 3H), 1.98 (s, 3H), 1.43 – 1.30 (m, 2H), 1.18 (d, 2H). ^{19}F NMR (377 MHz, DMSO) δ -120.13, -122.35.

Example 4, 4A, 4B



Step 1: Preparation of 3-hydroxy-2,2-dimethylpropanimidamide hydrochloride:

[00307] To a stirred mixture of NH_4Cl (9.15g, 171.02 mmol, 5.00 equiv) in Toluene (40 mL) was added AlMe_3 (85.51 mL, 2 M in Toluene, 171.02 mmol, 5.00 equiv) dropwise at 0°C under nitrogen atmosphere. The resulting mixture was stirred for 10 min at 0°C under nitrogen atmosphere, and then was stirred at room temperature until no generation of gas. To the above mixture was added a solution of ethyl 3-hydroxy-2,2-dimethylpropanoate (5.00 g, 34.20 mmol, 1.00 equiv) in toluene dropwise at r.t. The resulting mixture was stirred for additional overnight at 80°C . The reaction was monitored by LCMS. The reaction was quenched by the addition of MeOH (30 mL) at 0°C . The resulting mixture was filtered, the filter cake was washed with MeOH (500 mL). The filtrate was concentrated under reduced pressure. The residue was dissolved in EtOH (30 mL). The resulting mixture was filtered, the filter cake was washed with EtOH (15 mL). The filtrate was concentrated under reduced pressure. This resulted in 3-hydroxy-2,2-dimethylpropanimidamide hydrochloride (4 g, crude) as a white solid. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 9.04 (s, 2H), 8.62 (s, 2H), 5.43 (t, 1H), 3.48 (d, 2H), 1.18 (s, 6H).

Step 2: Preparation of 3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-2'-[2-(1-hydroxy-2-methylpropan-2-yl)pyrimidin-4-yl]-5',6-dimethyl-[1,4'-bipyridin]-2-one:

[00308] A solution of 2'-acetyl-3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-5',6-dimethyl-[1,4'-bipyridin]-2-one (450 mg, 0.95 mmol, 1.00 equiv) in DMF-DMA (6 mL) was stirred overnight at 100°C under nitrogen atmosphere. The reaction was monitored by LCMS. The resulting mixture was allowed to r.t. and concentrated under reduced pressure. The crude product (550 mg) was used in the next step directly without further purification. To a solution of the above crude product in IPA (20 mL) was added 3-hydroxy-2,2-dimethylpropanimidamide, HCl salt (1.80 g crude 2, 11.58 mmol, 10.00 equiv) and K_2CO_3 (1.60 g, 11.58 mmol, 10.00 equiv), and then the mixture was stirred overnight at 80°C under nitrogen atmosphere. The reaction was monitored by LCMS. The resulting mixture allowed to r.t. and diluted with EtOAc (100

mL). The combined organic layers were washed with brine (3 x 100 mL), dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography to afford 3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-2'-[2-(1-hydroxy-2-methylpropan-2-yl)pyrimidin-4-yl]-5',6-dimethyl-[1,4'-bipyridin]-2-one (450 mg, 73.59%) as an off-white solid. LC-MS: (ES+H, m/z): [M+H]⁺ = 528.25. ¹H NMR (300 MHz, DMSO-d₆) δ 8.93 (d, 1H), 8.86 (s, 1H), 8.62 (d, 1H), 8.36 (s, 1H), 8.17 (d, 1H), 8.11 (ddd, 1H), 6.84 (s, 1H), 5.50 (d, 2H), 4.56 (t, 1H), 3.73 (d, 2H), 2.10 (s, 3H), 1.98 (s, 3H), 1.35 (s, 6H). ¹⁹F NMR (377 MHz, DMSO) δ -120.11, -120.14, -122.31, -122.336.

Step 3: Preparation of rel-3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-2'-[2-(1-hydroxy-2-methylpropan-2-yl)pyrimidin-4-yl]-5',6-dimethyl-[1,4'-bipyridin]-2-one and rel-3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-2'-[2-(1-hydroxy-2-methylpropan-2-yl)pyrimidin-4-yl]-5',6-dimethyl-[1,4'-bipyridin]-2-one :

[00309] The racemate 3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-2'-[2-(1-hydroxy-2-methylpropan-2-yl)pyrimidin-4-yl]-5',6-dimethyl-[1,4'-bipyridin]-2-one (65 mg) was separated by Prep-Chiral HPLC to afford rel-3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-2'-[2-(1-hydroxy-2-methylpropan-2-yl)pyrimidin-4-yl]-5',6-dimethyl-[1,4'-bipyridin]-2-one (Example 4A, 18 mg, ee%=99.5%) and rel-3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-2'-[2-(1-hydroxy-2-methylpropan-2-yl)pyrimidin-4-yl]-5',6-dimethyl-[1,4'-bipyridin]-2-one (Example 4B, 23 mg, ee%=99.4%) as a white solid.

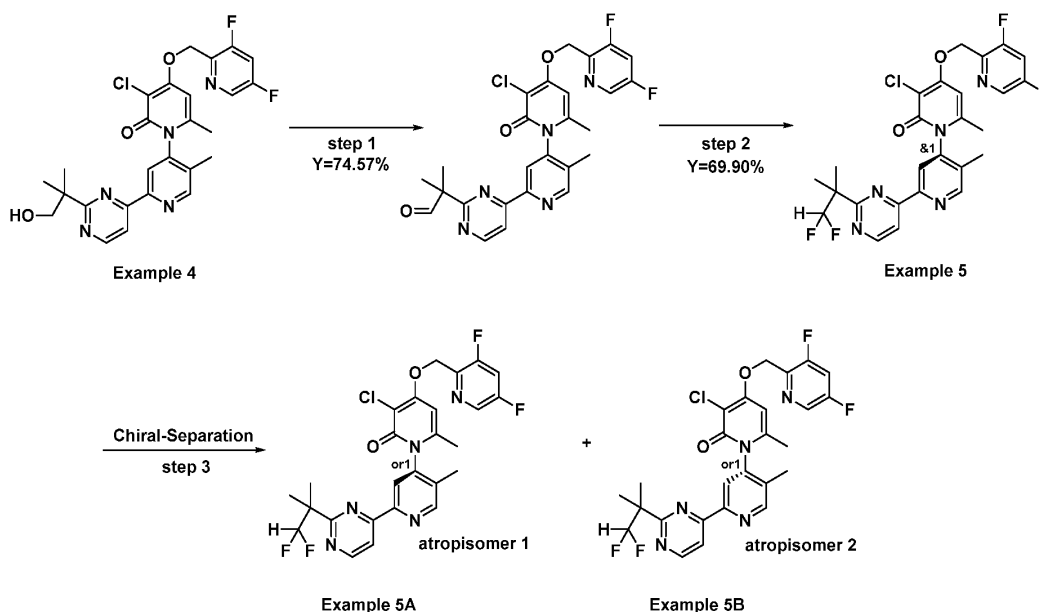
Example 4A:

[00310] LC-MS: (ES+H, m/z): [M+H]⁺ = 528.2. ¹H NMR (400 MHz, DMSO-d₆) δ 8.92 (d, 1H), 8.85 (s, 1H), 8.61 (d, 1H), 8.35 (s, 1H), 8.16 (d, 1H), 8.12 – 8.05 (m, 1H), 6.83 (s, 1H), 5.49 (d, 2H), 4.59 (t, 1H), 3.73 (d, 2H), 2.10 (s, 3H), 1.98 (s, 3H), 1.34 (s, 6H). ¹⁹F NMR (377 MHz, DMSO) δ -120.06, -120.08, -122.20, -122.22.

Example 4B:

[00311] LC-MS: (ES+H, m/z): [M+H]⁺ = 528.2. ¹H NMR (400 MHz, DMSO-d₆) δ 8.92 (d, 1H), 8.85 (s, 1H), 8.60 (d, 1H), 8.34 (s, 1H), 8.16 (d, 1H), 8.10 – 8.03 (m, 1H), 6.82 (s, 1H), 5.48 (d, 2H), 4.62 (t, 1H), 3.72 (d, 2H), 2.09 (s, 3H), 1.97 (s, 3H), 1.33 (s, 6H). ¹⁹F NMR (377 MHz, DMSO) δ -120.03, -120.05, -122.11, -122.13.

Example 5, 5A, 5B



Step 1: Preparation of 2-(4-{3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-5',6-dimethyl-2-oxo-[1,4'-bipyridin]-2'-yl}pyrimidin-2-yl)-2-methylpropanal:

[00312] To a stirred mixture of Dess-Martin (422 mg, 1.00 mmol, 1.50 equiv) in DCM (10 mL) was added a solution of 3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-2'-[2-(1-hydroxy-2-methylpropan-2-yl)pyrimidin-4-yl]-5',6-dimethyl-[1,4'-bipyridin]-2-one (350 mg, 0.66 mmol, 1.00 equiv) in DCM (5 mL) dropwise at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 3 h at room temperature under nitrogen atmosphere. The reaction was monitored by LCMS. The solvent was removed under reduce pressure. The resulting mixture was diluted with EtOAc (100 mL). The resulting mixture was washed with 3 x 100mL of saturated solution of NaHCO₃. The combined organic layers were washed with brine (1 x 100 mL), dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography to afford 2-(4-{3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-5',6-dimethyl-2-oxo-[1,4'-bipyridin]-2'-yl}pyrimidin-2-yl)-2-methylpropanal (260 mg, 74.57%) as a white solid. LC-MS: (ES+H, m/z): [M+H]⁺ = 526.2.

Step 2: Preparation of 3-chloro-2'-[2-(1,1-difluoro-2-methylpropan-2-yl)pyrimidin-4-yl]-4-[(3,5-difluoropyridin-2-yl)methoxy]-5',6-dimethyl-[1,4'-bipyridin]-2-one:

[00313] To a solution of 2-(4-{3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-5',6-dimethyl-2-oxo-[1,4'-bipyridin]-2'-yl}pyrimidin-2-yl)-2-methylpropanal (260 mg, 0.49 mmol, 1.00 equiv) in DCE (10 mL) was added BAST (547 mg, 2.47 mmol, 5.00 equiv) dropwise at 0°C under nitrogen atmosphere, the mixture was then stirred overnight at 80°C. The reaction was monitored by LCMS. The resulting mixture was allowed to r.t. and diluted with EtOAc (100 mL). The combined organic layers were washed with brine (3 x 100 mL), dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography to afford 3-chloro-2'-[2-(1,1-difluoro-2-methylpropan-2-yl)pyrimidin-4-yl]-4-[(3,5-difluoropyridin-2-yl)methoxy]-5',6-dimethyl-[1,4'-bipyridin]-2-

one (195 mg, 69.90%) as a white solid. LC-MS: (ES+H, m/z): $[M+H]^+ = 548.2$. ^1H NMR (400 MHz, DMSO- d_6) δ 9.00 (d, 1H), 8.87 (s, 1H), 8.62 (d, 1H), 8.51 (s, 1H), 8.27 (d, 1H), 8.11 (ddd, 1H), 6.85 (s, 1H), 6.75 (t, 1H), 5.50 (d, 2H), 2.10 (s, 3H), 1.98 (s, 3H), 1.45 (d, 6H). ^{19}F NMR (377 MHz, DMSO) δ -120.11, -120.13, -122.29, -122.31, -128.77.

Step 3: Preparation of rel-3-chloro-2'-[2-(1,1-difluoro-2-methylpropan-2-yl)pyrimidin-4-yl]-4-[(3,5-difluoropyridin-2-yl)methoxy]-5',6-dimethyl-[1,4'-bipyridin]-2-one and rel-3-chloro-2'-[2-(1,1-difluoro-2-methylpropan-2-yl)pyrimidin-4-yl]-4-[(3,5-difluoropyridin-2-yl)methoxy]-5',6-dimethyl-[1,4'-bipyridin]-2-one :

[00314] The racemate 3-chloro-2'-[2-(1,1-difluoro-2-methylpropan-2-yl)pyrimidin-4-yl]-4-[(3,5-difluoropyridin-2-yl)methoxy]-5',6-dimethyl-[1,4'-bipyridin]-2-one (135 mg) was separated by Prep-Chiral HPLC to afford rel-3-chloro-2'-[2-(1,1-difluoro-2-methylpropan-2-yl)pyrimidin-4-yl]-4-[(3,5-difluoropyridin-2-yl)methoxy]-5',6-dimethyl-[1,4'-bipyridin]-2-one (Example 5A, 53 mg, ee%=100%) and rel-3-chloro-2'-[2-(1,1-difluoro-2-methylpropan-2-yl)pyrimidin-4-yl]-4-[(3,5-difluoropyridin-2-yl)methoxy]-5',6-dimethyl-[1,4'-bipyridin]-2-one (Example 5B, 50 mg, ee%=100%) as a white solid.

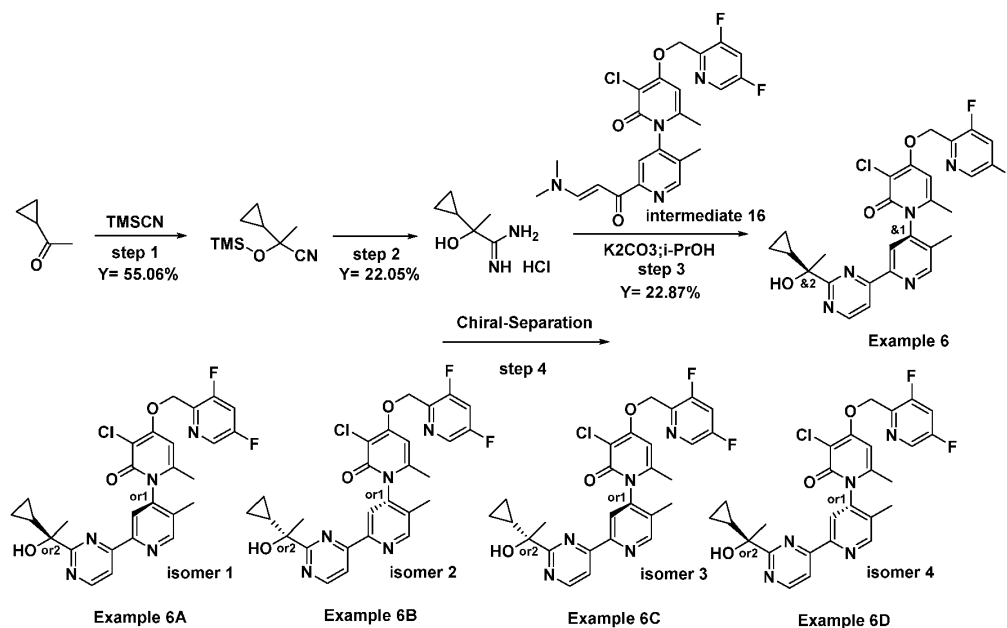
Example 5A:

[00315] LC-MS: (ES+H, m/z): $[M+H]^+ = 548.2$. ^1H NMR (400 MHz, DMSO- d_6) δ 9.00 (d, 1H), 8.88 (s, 1H), 8.62 (d, 1H), 8.51 (s, 1H), 8.28 (d, 1H), 8.18 – 8.05 (m, 1H), 6.98 – 6.54 (m, 2H), 5.50 (d, 2H), 2.11 (s, 3H), 1.98 (s, 3H), 1.45 (s, 6H). ^{19}F NMR (377 MHz, DMSO) δ -120.12, -120.14, -122.29, -122.31, -128.77.

Example 5B:

[00316] LC-MS: (ES+H, m/z): $[M+H]^+ = 548.2$. ^1H NMR (400 MHz, DMSO- d_6) δ 9.00 (d, 1H), 8.88 (s, 1H), 8.62 (d, 1H), 8.51 (s, 1H), 8.28 (d, 1H), 8.16 – 8.07 (m, 1H), 6.95 – 6.55 (m, 2H), 5.50 (d, 2H), 2.11 (s, 3H), 1.98 (s, 3H), 1.45 (s, 6H). ^{19}F NMR (377 MHz, DMSO) δ -120.11, -120.14, -122.28, -122.31, -128.77.

Example 6, 6A, 6B, 6C, 6D



Step 1: Preparation of 2-cyclopropyl-2-[(trimethylsilyl)oxy]propanenitrile:

[00317] To a stirred solution of cyclopropyl methyl ketone (10.00 g, 118.90 mmol, 1.00 equiv) and trimethylsilyl cyanide (14.15 g, 142.60 mmol, 1.20 equiv) in THF (150 mL) was added ZnI₂ (1.90 g, 5.90 mmol, 0.05 equiv) in portions at room temperature under nitrogen atmosphere. The mixture was stirred overnight at room temperature under nitrogen atmosphere. The reaction was monitored by TLC. The resulting mixture was concentrated under reduced pressure. The mixture was diluted with water (50 mL). The resulting mixture was extracted with CH₂Cl₂ (3 x 200 mL). The combined organic layers were washed with brine (2x50 mL), dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography to afford 2-cyclopropyl-2-[(trimethylsilyl)oxy]propanenitrile (12.00 g, 55.06%) as a colorless oil. ¹H NMR (300 MHz, Chloroform-d) δ 1.65 (s, 3H), 1.25 – 1.11 (m, 1H), 0.70 – 0.49 (m, 4H), 0.24 (s, 9H).

Step 2: Preparation of methyl 2-carbamimidoyl-2,2-dimethylacetate HCl salt:

[00318] To a stirred solution of methyl 2-cyano-2,2-dimethylacetate (12.00 g, 94.40 mmol, 1.00 equiv) in MeOH (30 mL) was added HCl (236 mL, 944.0 mmol, 10.00 equiv, 4M in CH₃OH) dropwise at 0°C under nitrogen atmosphere. The mixture was stirred for 7 h at room temperature under nitrogen atmosphere. The resulting mixture was concentrated under vacuum. To the above mixture in CH₃OH (30.00 mL) added NH₃ solution (470 mL, 1.88 mol, 20.00 equiv, 4M in CH₃OH) dropwise over 20 min at 0°C. The resulting mixture was stirred for additional overnight at room temperature. The reaction was monitored by LCMS. The resulting mixture was concentrated under reduced pressure. The product was precipitated by the addition of EtOH (30 mL). The resulting mixture was filtered, the filter cake was washed with EtOH (2 x 30 mL). The filtrate was concentrated under reduced pressure. The residue was purified by trituration with Et₂O (3 x 20mL). This resulted in methyl 2-carbamimidoyl-2,2-dimethylacetate HCl salt (3 g, 22.05%) as a yellow semi-solid. LC-MS: (ES+H, m/z): [M+H]⁺ = 129.3. ¹H NMR (300 MHz, DMSO-d₆) δ 5.94 (s, 1H), 1.50 (s, 3H), 1.40 – 1.24 (m, 1H), 0.58 – 0.30 (m, 4H).

Step 3: Preparation of 3-chloro-2'-[2-(1-cyclopropyl-1-hydroxyethyl)pyrimidin-4-yl]-4-[(3,5-difluoropyridin-2-yl)methoxy]-5',6-dimethyl-[1,4'-bipyridin]-2-one:

[00319] To a stirred mixture of 3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-2'-[(2E)-3-(dimethylamino)prop-2-enoyl]-5',6-dimethyl-[1,4'-bipyridin]-2-one (50 mg, 0.10 mmol, 1.00 equiv) and 2-cyclopropyl-2-hydroxypropanimidamide, HCl salt (108 mg, 0.84 mmol, 8.00 equiv) in i-PrOH (1 mL) were added K₂CO₃ (291 mg, 2.10 mmol, 20.00 equiv) in portions at room temperature under nitrogen atmosphere. The resulting mixture was stirred overnight at 80°C under nitrogen atmosphere. The reaction was monitored by LCMS. The mixture was allowed to cool down to room temperature. The resulting mixture was diluted with water (10 mL). The resulting mixture was extracted with EtOAc (3 x30 mL). The combined organic layers were washed with brine (2 x 5 mL), dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by reversed combi-flash chromatography. The pure fraction was concentrated under vacuum to afford 3-chloro-2'-[2-(1-cyclopropyl-1-hydroxyethyl)pyrimidin-4-yl]-4-[(3,5-difluoropyridin-2-yl)methoxy]-5',6-dimethyl-[1,4'-bipyridin]-2-one

(13.0 mg, 22.87%) as a white solid. LC-MS: (ES+H, m/z): [M+H]⁺ = 539.90. ¹H NMR (400 MHz, DMSO-d₆) δ 9.00 (dd, 1H), 8.86 (s, 1H), 8.78 (d, 1H), 8.61 (d, 1H), 8.26 (dd, 1H), 8.13 – 8.08 (m, 1H), 6.85 (s, 1H), 5.50 (s, 2H), 4.92 (d, 1H), 2.11 (s, 3H), 1.98 (d, 3H), 1.56 (s, 3H), 1.43 – 1.36 (m, 1H), 0.48 – 0.37 (m, 1H), 0.41 – 0.29 (m, 2H), 0.17 – 0.11 (m, 1H). ¹⁹F NMR (377 MHz, DMSO) δ -120.13, -122.30.

Step 4: Preparation of rel-3-chloro-2'-[2-(1-cyclopropyl-1-hydroxyethyl)pyrimidin-4-yl]-4-[(3,5-difluoropyridin-2-yl)methoxy]-5',6-dimethyl-[1,4'-bipyridin]-2-one, rel-3-chloro-2'-[2-(1-cyclopropyl-1-hydroxyethyl)pyrimidin-4-yl]-4-[(3,5-difluoropyridin-2-yl)methoxy]-5',6-dimethyl-[1,4'-bipyridin]-2-one, rel-3-chloro-2'-[2-(1-cyclopropyl-1-hydroxyethyl)pyrimidin-4-yl]-4-[(3,5-difluoropyridin-2-yl)methoxy]-5',6-dimethyl-[1,4'-bipyridin]-2-one, rel-3-chloro-2'-[2-(1-cyclopropyl-1-hydroxyethyl)pyrimidin-4-yl]-4-[(3,5-difluoropyridin-2-yl)methoxy]-5',6-dimethyl-[1,4'-bipyridin]-2-one:

[00320] The racemate 3-chloro-2'-[2-(1-cyclopropyl-1-hydroxyethyl)pyrimidin-4-yl]-4-[(3,5-difluoropyridin-2-yl)methoxy]-5',6-dimethyl-[1,4'-bipyridin]-2-one (200 mg) was separated by Prep-Chiral-HPLC to afford the first eluted peak (80 mg, Example 6A&B) and second eluted peak (80 mg, Example 6C&D).

[00321] The first eluted peak was further separated by Prep-Chiral-HPLC to afford rel-3-chloro-2'-[2-(1-cyclopropyl-1-hydroxyethyl)pyrimidin-4-yl]-4-[(3,5-difluoropyridin-2-yl)methoxy]-5',6-dimethyl-[1,4'-bipyridin]-2-one (Example 6A, 29.3 mg, ee = 95.3%) and rel-3-chloro-2'-[2-(1-cyclopropyl-1-hydroxyethyl)pyrimidin-4-yl]-4-[(3,5-difluoropyridin-2-yl)methoxy]-5',6-dimethyl-[1,4'-bipyridin]-2-one (Example 6B, 32.3 mg, ee = 98.7%) as white solid.

Example 6A:

[00322] LC-MS: (ES+H, m/z): [M+H]⁺ = 539.90. ¹H NMR (300 MHz, DMSO-d₆) δ 9.01 (d, 1H), 8.86 (s, 1H), 8.80 (s, 1H), 8.62 (d, 1H), 8.27 (d, 1H), 8.11 (td, 1H), 6.85 (s, 1H), 5.50 (s, 2H), 4.93 (s, 1H), 2.11 (s, 3H), 1.99 (s, 3H), 1.57 (s, 3H), 1.42 – 1.36 (m, 1H), 0.49 – 0.46 (m, 1H), 0.41 – 0.37 (m, 2H), 0.13 – 0.12 (m, 1H). ¹⁹F NMR (282 MHz, DMSO) δ -120.13, -120.15, -122.30, -122.33.

Example 6B:

[00323] LC-MS: (ES+H, m/z): [M+H]⁺ = 540.10. ¹H NMR (300 MHz, DMSO-d₆) δ 9.00 (d, 1H), 8.86 (s, 1H), 8.78 (s, 1H), 8.61 (d, 1H), 8.26 (d, 1H), 8.10 (td, 1H), 6.85 (s, 1H), 5.50 (s, 2H), 4.91 (s, 1H), 2.11 (s, 3H), 1.98 (s, 3H), 1.56 (s, 3H), 1.44 – 1.38 (m, 1H), 0.49 – 0.46 (m, 1H), 0.41 – 0.37 (m, 2H), 0.13 – 0.12 (m, 1H). ¹⁹F NMR (282 MHz, DMSO) δ -120.14, -120.16, -122.31, -122.33.

[00324] The second eluted peak above was further separated by Prep-Chiral-HPLC to afford rel-3-chloro-2'-[2-(1-cyclopropyl-1-hydroxyethyl)pyrimidin-4-yl]-4-[(3,5-difluoropyridin-2-yl)methoxy]-5',6-dimethyl-[1,4'-bipyridin]-2-one (Example 6C, 28.0 mg, ee = 99.5%) and rel-3-chloro-2'-[2-(1-cyclopropyl-1-hydroxyethyl)pyrimidin-4-yl]-4-[(3,5-difluoropyridin-2-yl)methoxy]-5',6-dimethyl-[1,4'-bipyridin]-2-one (Example 6D, 28.8 mg, ee = 95.1%) as white solid.

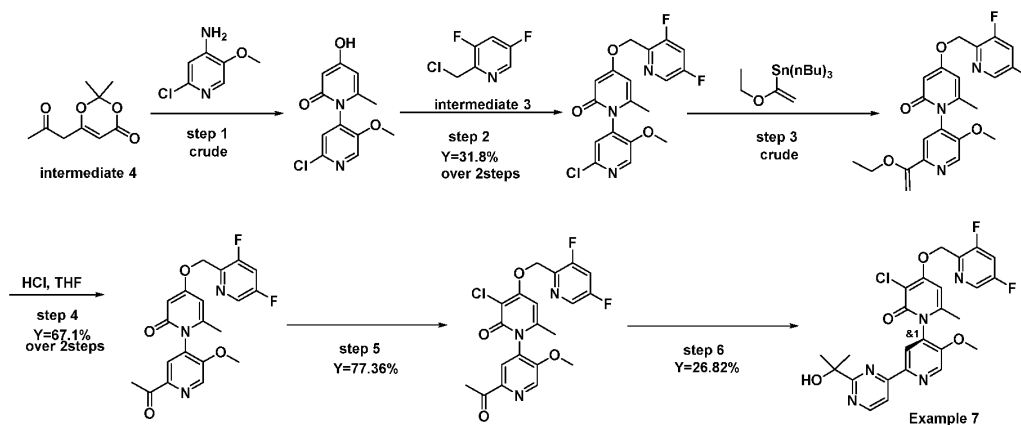
Example 6C:

[00325] LC-MS: (ES+H, m/z): [M+H]⁺ = 540.2. ¹H NMR (300 MHz, DMSO-d₆) δ 9.00 (d, 1H), 8.86 (s, 1H), 8.79 (s, 1H), 8.61 (d, 1H), 8.26 (d, 1H), 8.10 (td, 1H), 6.84 (s, 1H), 5.50 (s, 2H), 4.94 (s, 1H), 2.11 (s, 3H), 1.98 (s, 3H), 1.56 (s, 3H), 1.42 – 1.35 (m, 1H), 0.48 – 0.44 (m, 1H), 0.40 – 0.38 (m, 2H), 0.13 – 0.12 (m, 1H). ¹⁹F NMR (282 MHz, DMSO) δ -120.14, -120.16, -122.32, -122.34.

Example 6D:

[00326] LC-MS: (ES+H, m/z): [M+H]⁺ = 540.2. ¹H NMR (300 MHz, DMSO-d₆) δ 9.00 (d, 1H), 8.86 (s, 1H), 8.78 (s, 1H), 8.61 (d, 1H), 8.26 (d, 1H), 8.10 (td, 1H), 6.85 (s, 1H), 5.50 (s, 2H), 4.94 (s, 1H), 2.11 (s, 3H), 1.98 (s, 3H), 1.56 (s, 3H), 1.44 – 1.38 (m, 1H), 0.50 – 0.48 (m, 1H), 0.39 – 0.34 (m, 2H), 0.13 – 0.12 (m, 1H). ¹⁹F NMR (282 MHz, DMSO) δ -120.14, -120.16, -122.31, -122.33.

Example 7



Step 1: Preparation of 2'-chloro-4-hydroxy-5'-methoxy-6-methyl-[1,4'-bipyridin]-2-one:

[00327] To a stirred solution of 2,2-dimethyl-6-(2-oxopropyl)-1,3-dioxin-4-one (1.16 g, 6.31 mmol, 1.00 equiv) in 1,4-dioxane (17 mL) was added 2-chloro-5-methoxypyridin-4-amine (1.00 g, 6.31 mmol, 1.00 equiv) at rt. The resulting mixture was stirred for 3 h at 90°C under nitrogen atmosphere. The reaction was monitored by LCMS. The mixture was allowed to cool down to RT. To the above mixture was added H₂SO₄ (0.5 mL) at RT. The resulting mixture was stirred for 1 h at 90°C under nitrogen atmosphere. The reaction was monitored by LCMS. The mixture was allowed to cool down to RT. To the above mixture was added H₂O (10 mL) at RT. The resulting mixture was filtered, and the filter cake was washed with diethyl ether (2x10 mL). The filter cake was concentrated under reduced pressure to afford 2'-chloro-4-hydroxy-5'-methoxy-6-methyl-[1,4'-bipyridin]-2-one (990 mg, crude) as a Brown yellow solid. LC-MS: (ES+H, m/z): [M+H]⁺ = 267.1.

Step 2: Preparation of 2'-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-5'-methoxy-6-methyl-[1,4'-bipyridin]-2-one:

[00328] To a stirred solution of 2'-chloro-4-hydroxy-5'-methoxy-6-methyl-[1,4'-bipyridin]-2-one (990 mg, crude) and 2-(chloromethyl)-3,5-difluoropyridine (911 mg, 5.57 mmol, 1.50 equiv) in DMF (20 mL) were added 18-Crown-6 (10 mg, 0.04 mmol, 0.01 equiv) and K₂CO₃ (1.54 g, 11.14 mmol, 3.00 equiv) at RT. The

resulting mixture was stirred for 4 h at 60°C under nitrogen atmosphere. The reaction was monitored by LCMS. The mixture was allowed to cool down to RT. The resulting mixture was concentrated under reduced pressure. The residue was purified by flash chromatography to afford 2'-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-5'-methoxy-6-methyl-[1,4'-bipyridin]-2-one (790 mg, 31.8% over 2steps) as a light yellow solid. LC-MS: (ES+H, *m/z*): [M+H]⁺=394.0.

Step 3: Preparation of 4-[(3,5-difluoropyridin-2-yl)methoxy]-2'-(1-ethoxyethenyl)-5'-methoxy-6-methyl-[1,4'-bipyridin]-2-one :

[00329] To a stirred solution of 2'-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-5'-methoxy-6-methyl-[1,4'-bipyridin]-2-one (790 mg, 2.01 mmol, 1.00 equiv) and tributyl(1-ethoxyethenyl)stannane (1.45 g, 4.01 mmol, 2.00 equiv) in 1,4-dioxane (20 mL) were added Pd(PPh₃)₂Cl₂ (141 mg, 0.20 mmol, 0.10 equiv) at rt. The resulting mixture was stirred for 2 h at 100°C under nitrogen atmosphere. The reaction was monitored by LCMS. The mixture was allowed to cool down to RT. The resulting mixture was filtered, and the filter cake was washed with EA (2 x 20 mL). The filtrate was concentrated under reduced pressure to afford 4-[(3,5-difluoropyridin-2-yl)methoxy]-2'-(1-ethoxyethenyl)-5'-methoxy-6-methyl-[1,4'-bipyridin]-2-one (860 mg, crude) as a yellow oil. LC-MS: (ES+H, *m/z*): [M+H]⁺=430.0.

Step 4: Preparation of 2'-acetyl-4-[(3,5-difluoropyridin-2-yl)methoxy]-5'-methoxy-6-methyl-[1,4'-bipyridin]-2-one:

[00330] To a stirred solution of 4-[(3,5-difluoropyridin-2-yl)methoxy]-2'-(1-ethoxyethenyl)-5'-methoxy-6-methyl-[1,4'-bipyridin]-2-one (860 mg, crude) in THF (10 mL) were added HCl (0.20 mL, 6.59 mmol, 28.27 equiv) dropwise at 0°C. The resulting mixture was stirred for 1h at rt under nitrogen atmosphere. The reaction was monitored by LCMS. The mixture was basified with saturated sodium carbonate solution. The resulting mixture was extracted with EA (3 x 50 mL). The combined organic layers were washed with brine (50 mL), and the combined organic layers were concentrated under reduced pressure. The residue was purified by flash chromatography to afford 2'-acetyl-4-[(3,5-difluoropyridin-2-yl)methoxy]-5'-methoxy-6-methyl-[1,4'-bipyridin]-2-one (540 mg, 67.1% over 2steps) as white solid. LC-MS: (ES+H, *m/z*): [M+H]⁺=402.0.

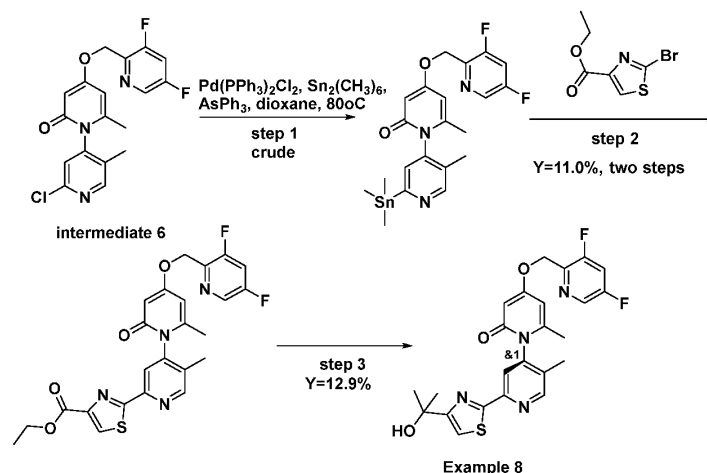
Step 5: Preparation of 2'-acetyl-3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-5'-methoxy-6-methyl-[1,4'-bipyridin]-2-one:

[00331] To a stirred solution of 2'-acetyl-4-[(3,5-difluoropyridin-2-yl)methoxy]-5'-methoxy-6-methyl-[1,4'-bipyridin]-2-one (500 mg, 1.25 mmol, 1.00 equiv) and NCS (175 mg, 1.31 mmol, 1.05 equiv) in MeCN (10 mL) were added 2,2-dichloroacetic acid (16 mg, 0.12 mmol, 0.10 equiv) at RT. The resulting mixture was stirred for 1h at 60°C under nitrogen atmosphere. The reaction was monitored by LCMS. The mixture was allowed to cool down to RT. The resulting mixture was concentrated under reduced pressure. The residue was purified by flash chromatography to afford 2'-acetyl-3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-5'-methoxy-6-methyl-[1,4'-bipyridin]-2-one (420 mg, 77.36%). LC-MS: (ES+H, *m/z*): [M+H]⁺=436.1. ¹H NMR (300 MHz, DMSO-d₆) δ 8.76 (s, 1H), 8.60 (d, 1H), 8.16 – 8.03 (m, 1H), 7.96 (s, 1H), 6.73 (s, 1H), 5.48 (d, 2H), 4.02 (s, 3H), 2.65 (s, 3H), 1.94 (s, 3H).

Step 6: Preparation of 3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-2'-[2-(2-hydroxypropan-2-yl)pyrimidin-4-yl]-5'-methoxy-6-methyl-[1,4'-bipyridin]-2-one:

[00332] A solution of 2'-acetyl-3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-5'-methoxy-6-methyl-[1,4'-bipyridin]-2-one (370 mg, 0.85 mmol, 1.00 equiv) in DMF-DMA (3 mL) was stirred for 12h at 100°C under nitrogen atmosphere. The reaction was monitored by LCMS. The mixture was allowed to cool down to RT. The resulting mixture was concentrated under reduced pressure. To the above mixture in DMF (5 mL) was added 2-hydroxy-2-methylpropanimidamide hydrochloride (353 mg, 2.55 mmol, 3.00 equiv) and K₂CO₃ (587 mg, 4.25 mmol, 5.00 equiv) at rt. The resulting mixture was stirred for additional 4h at 80°C under nitrogen atmosphere. The reaction was monitored by LCMS. The mixture was allowed to cool down to RT. The resulting mixture was concentrated under reduced pressure. The residue was purified by flash chromatography to afford crude product. The crude product was further purified by Prep-HPLC to afford pure fractions. The pure fractions were concentrated under vacuum and then lyophilized to afford 3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-2'-[2-(2-hydroxypropan-2-yl)pyrimidin-4-yl]-5'-methoxy-6-methyl-[1,4'-bipyridin]-2-one (120.9 mg, 26.82%) as a white solid. LC-MS: (ES+H, *m/z*): [M+H]⁺=529.90. ¹H NMR (400 MHz, DMSO-d₆) δ 8.93 (d, 1H), 8.80 (s, 1H), 8.73 (s, 1H), 8.61 (d, 1H), 8.18 (d, 1H), 8.10 (ddd, 1H), 6.77 (s, 1H), 5.50 (s, 2H), 5.23 (s, 1H), 4.01 (s, 3H), 2.00 (s, 3H), 1.53 (d, 6H). ¹⁹F NMR (377 MHz, DMSO) δ -120.16, -122.38.

Example 8



Step 1: Preparation of 4-((3,5-difluoropyridin-2-yl)methoxy)-5',6-dimethyl-2'-(trimethylstannyl)-2H-[1,4'-bipyridin]-2-one:

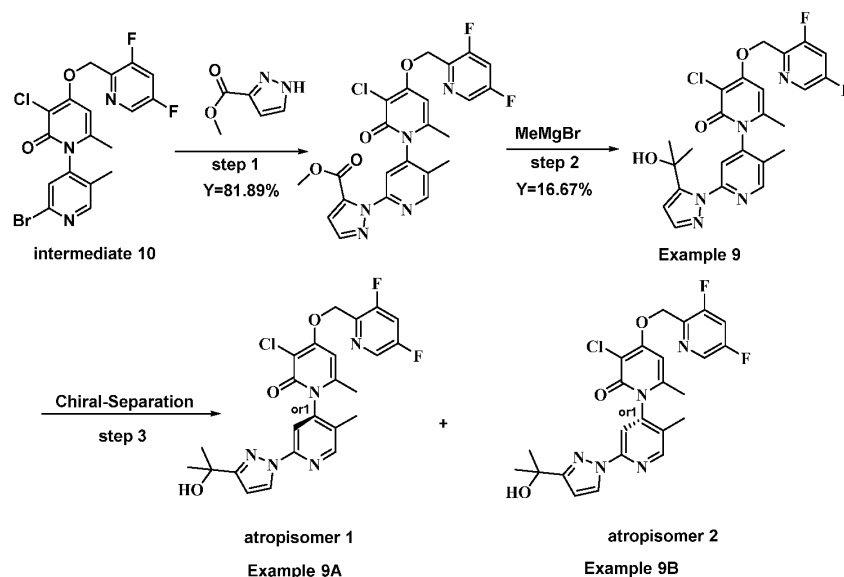
[00333] To a mixture of 2'-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-5',6-dimethyl-[1,4'-bipyridin]-2-one (1.10 g, 2.91 mmol, 1.00 equiv) and hexamethyldistannane (1.14 g, 3.48 mmol, 1.20 equiv) in dioxane (20 mL) was added Pd(PPh₃)₂Cl₂ (0.41 g, 0.58 mmol, 0.20 equiv) and AsPh₃ (0.18 g, 0.58 mmol, 0.20 equiv) at room temperature under nitrogen. The mixture was stirred overnight at 80°C under nitrogen atmosphere. The reaction was monitored by LCMS. Desired product could be detected by LCMS. The mixture was used directly on the next step. LC-MS: (ES+H, *m/z*): [M+H]⁺=508.1.

Step 2: Preparation of 2-(4-bromo-2-chloro-3-fluoro-5-methylphenoxy)methyl)-3,5-difluoropyridine:

[00334] To the last step of reaction mixture was added ethyl 2-bromothiazole-4-carboxylate (680mg, 2.91 mmol, 1.00 equiv), Pd(PPh₃)₂Cl₂ (0.41 g, 0.58 mmol, 0.20 equiv) at room temperature under nitrogen. The mixture was stirred overnight at 80°C under nitrogen atmosphere. The reaction was monitored by LCMS. The mixture was allowed to cool down to room temperature. The resulting mixture was firstly purified by silica gel column chromatography to afford a crude product (300 mg). The crude product (300 mg) was further purified by Prep-HPLC and the pure fractions were concentrated to afford ethyl 2-{4-[(3,5-difluoropyridin-2-yl)methoxy]-2,5'-dimethyl-6-oxo-[1,4'-bipyridin]-2'-yl}-1,3-thiazole-4-carboxylate (160 mg, 11.0%, two steps) as a white solid. LC-MS: (ES+H, *m/z*): [M+H]⁺=499.0.

Step 3: Preparation of 4-[(3,5-difluoropyridin-2-yl)methoxy]-2'-[4-(2-hydroxypropan-2-yl)-1,3-thiazol-2-yl]-5',6-dimethyl-[1,4'-bipyridin]-2-one:

[00335] To a mixture of ethyl 2-{4-[(3,5-difluoropyridin-2-yl)methoxy]-2,5'-dimethyl-6-oxo-[1,4'-bipyridin]-2'-yl}-1,3-thiazole-4-carboxylate (160 mg, 0.32 mmol, 1.00 equiv) in THF (5 mL) was added CH₃MgBr in THF (1.0 mL, 0.96 mmol, 3.00 equiv, 1M) dropwise at 0°C under nitrogen. The mixture was stirred for 3h at room temperature under nitrogen atmosphere. The reaction was monitored by LCMS. The reaction was quenched by MeOH (1 mL). The resulting mixture was concentrated under reduced pressure. The residue was directly purified by Prep-HPLC, and the pure fractions were concentrated and lyophilized to afford 4-[(3,5-difluoropyridin-2-yl)methoxy]-2'-[4-(2-hydroxypropan-2-yl)-1,3-thiazol-2-yl]-5',6-dimethyl-[1,4'-bipyridin]-2-one (20 mg, 12.9%) as a white solid. LC-MS: (ES+H, *m/z*): [M+H]⁺=485.0. ¹H NMR (400 MHz, DMSO-d₆) δ 8.68 (s, 1H), 8.60 (d, 1H), 8.11-8.06 (m, 1H), 7.91 (s, 1H), 7.53 (s, 1H), 6.16 (d, 1H), 6.05 (d, 1H), 5.26 (s, 2H), 5.22 (s, 1H), 2.06 (s, 3H), 1.88 (s, 3H), 1.50 (s, 6H). ¹⁹F NMR (377 MHz, DMSO) δ -120.29, -122.43.

Example 9, 9A, 9B

Step 1: Preparation of methyl 1-(3-chloro-4-((3,5-difluoropyridin-2-yl)methoxy)-5',6-dimethyl-2-oxo-2H-[1,4'-bipyridin]-2'-yl)-1H-pyrazole-5-carboxylate:

[00336] To a stirred solution of 2'-bromo-3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-5',6-dimethyl-[1,4'-bipyridin]-2-one (200 mg, 0.44 mmol, 1.00 equiv) and methyl 1H-pyrazole-3-carboxylate (110 mg, 0.88 mmol, 2.00 equiv) in 1,4-dioxane (5 mL) were added K₂CO₃ (121 mg, 0.88 mmol, 2.00 equiv), CuI (17 mg, 0.09 mmol, 0.20 equiv) and N1,N2-dimethylcyclohexane-1,2-diamine (25 mg, 0.18 mmol, 0.40 equiv) at rt. The resulting mixture was stirred overnight at 90°C under nitrogen atmosphere. The reaction was monitored by LCMS. The mixture was directly purified by reversed combi-flash chromatography. The pure fractions were concentrated under vacuum to afford methyl 1-(3-chloro-4-((3,5-difluoropyridin-2-yl)methoxy)-5',6-dimethyl-2-oxo-2H-[1,4'-bipyridin]-2'-yl)-1H-pyrazole-5-carboxylate (180 mg, 81.89%) as a light yellow solid. LC-MS: (ES+H, m/z): [M+H]⁺ = 502.10. ¹H NMR (400 MHz, DMSO-d₆) δ 8.76 (d, 1H), 8.67 – 8.58 (m, 2H), 8.14 – 8.05 (m, 1H), 8.01 (s, 1H), 7.05 (d, 1H), 6.80 (s, 1H), 5.49 (s, 2H), 3.86 (s, 3H), 2.06 (s, 3H), 2.00 (s, 3H).

Step 2: Preparation of 3-chloro-4-((3,5-difluoropyridin-2-yl)methoxy)-2'-(5-(2-hydroxypropan-2-yl)-1H-pyrazol-1-yl)-5',6-dimethyl-2H-[1,4'-bipyridin]-2-one:

[00337] To a stirred solution of methyl 1-{3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-5',6-dimethyl-2-oxo-[1,4'-bipyridin]-2'-yl}pyrazole-3-carboxylate (150 mg, 0.30 mmol, 1.00 equiv) in THF (8 mL) were added MeMgBr (3 mL, 2.99 mmol, 10.00 equiv, 1M in THF) dropwise at -30°C under nitrogen atmosphere. The resulting mixture was warmed to rt and stirred for 30 min under nitrogen atmosphere. The reaction was monitored by LCMS. The reaction was quenched with sat. NH₄Cl (aq.) at room temperature. The residue was purified by reversed flash chromatography to afford a crude product. The crude product was further purified by Prep-HPLC. The pure fractions were concentrated under vacuum and then lyophilized to afford 3-chloro-4-((3,5-difluoropyridin-2-yl)methoxy)-2'-(5-(2-hydroxypropan-2-yl)-1H-pyrazol-1-yl)-5',6-dimethyl-2H-[1,4'-bipyridin]-2-one (25 mg, 16.67%) as a white solid. LC-MS: (ES+H, m/z): [M+H]⁺ = 502.14 ¹H NMR (400 MHz, DMSO-d₆) δ 8.61 (d, 1H), 8.57 – 8.49 (m, 2H), 8.14 – 8.05 (m, 1H), 7.79 (s, 1H), 6.81 (s, 1H), 6.57 (d, 1H), 5.49 (s, 2H), 5.11 (s, 1H), 2.01 (d, 6H), 1.48 (s, 6H). ¹⁹F NMR (377 MHz, DMSO) δ -120.15, -122.32.

Step 3: Preparation of rel-3-chloro-4-((3,5-difluoropyridin-2-yl)methoxy)-2'-(3-(2-hydroxypropan-2-yl)-1H-pyrazol-1-yl)-5',6-dimethyl-2H-[1,4'-bipyridin]-2-one and rel-3-chloro-4-((3,5-difluoropyridin-2-yl)methoxy)-2'-(3-(2-hydroxypropan-2-yl)-1H-pyrazol-1-yl)-5',6-dimethyl-2H-[1,4'-bipyridin]-2-one :

[00338] The racemate 3-chloro-4-((3,5-difluoropyridin-2-yl)methoxy)-2'-(3-(2-hydroxypropan-2-yl)-1H-pyrazol-1-yl)-5',6-dimethyl-2H-[1,4'-bipyridin]-2-one (80 mg) was separated by Chiral Prep- HPLC. The pure fraction was concentrated under reduced pressure to afford rel-3-chloro-4-((3,5-difluoropyridin-2-yl)methoxy)-2'-(3-(2-hydroxypropan-2-yl)-1H-pyrazol-1-yl)-5',6-dimethyl-2H-[1,4'-bipyridin]-2-one (Example 9A, 34 mg, ee=100%) and rel-3-chloro-4-((3,5-difluoropyridin-2-yl)methoxy)-2'-(3-(2-

hydroxypropan-2-yl)-1H-pyrazol-1-yl)-5',6-dimethyl-2H-[1,4'-bipyridin]-2-one (Example 9B, 32.9 mg, ee=100%) as a white solid.

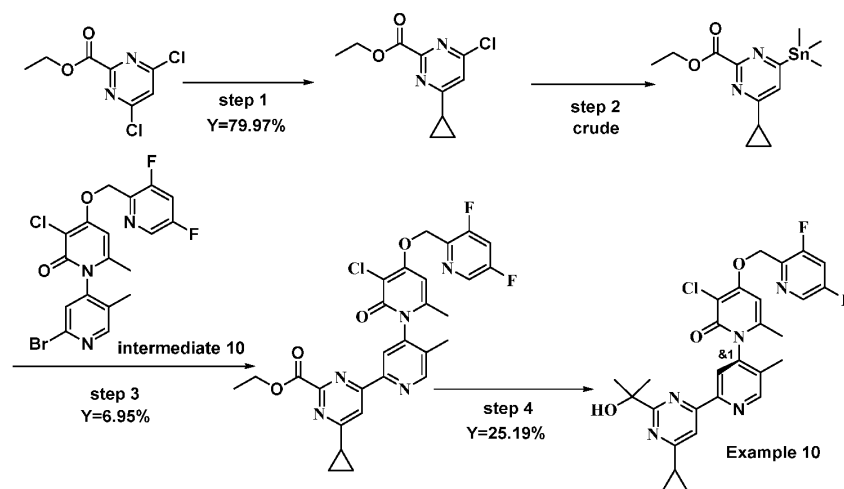
Example 9A:

[00339] LC-MS: (ES+H, m/z): $[M+H]^+ = 502.2$. ^1H NMR (300 MHz, DMSO- d_6) δ 8.60 (d, 1H), 8.54 (s, 1H), 8.51 (d, 1H), 8.14-8.08 (m, 1H), 7.78 (s, 1H), 6.80 (d, 1H), 6.56 (d, 1H), 5.48 (d, 2H), 5.09 (s, 1H), 2.01 (s, 3H), 2.00 (s, 3H), 1.48 (s, 6H). ^{19}F NMR (282 MHz, DMSO) δ -120.15, -120.17, -120.34, -122.37.

Example 9B:

[00340] LC-MS: (ES+H, m/z): $[M+H]^+ = 502.2$. ^1H NMR (300 MHz, DMSO- d_6) δ 8.60 (d, 1H), 8.54 (s, 1H), 8.51 (d, 1H), 8.14-8.08 (m, 1H), 7.78 (s, 1H), 6.80 (d, 1H), 6.56 (d, 1H), 5.48 (d, 2H), 5.09 (s, 1H), 2.01 (s, 3H), 2.00 (s, 3H), 1.48 (s, 6H). ^{19}F NMR (282 MHz, DMSO) δ -120.15, -120.17, -120.34, -122.37.

Example 10



Step 1: Preparation of ethyl 4-chloro-6-cyclopropylpyrimidine-2-carboxylate:

[00341] To a stirred solution of ethyl 4,6-dichloropyrimidine-2-carboxylate (500 mg, 2.262 mmol, 1.00 equiv) and cyclopropylboronic acid (194.30 mg, 2.262 mmol, 1 equiv) in Toluene (5 mL) and H_2O (0.5 mL) was added $\text{Pd}(\text{dppf})\text{Cl}_2$ (37.48 mg, 0.068 mmol, 0.03 equiv) and Cs_2CO_3 (1474.03 mg, 4.524 mmol, 2 equiv) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 1h at 100°C under nitrogen atmosphere. The reaction was monitored by LCMS. The resulting mixture was diluted with water (2mL). The aqueous layer was extracted with EtOAc (3 x 5 mL). The residue was purified by silica gel column chromatography to afford ethyl 4-chloro-6-cyclopropylpyrimidine-2-carboxylate (410 mg, 79.97%) as a yellow oil. MS: (ES+H, m/z): $[M+H]^+ = 227.0$

Step 2: Preparation of ethyl 4-cyclopropyl-6-(trimethylstannyl)pyrimidine-2-carboxylate:

[00342] To a stirred solution of ethyl 4-chloro-6-cyclopropylpyrimidine-2-carboxylate (400 mg, 1.765 mmol, 1.00 equiv) and SnMe_6 (636.01 mg, 1.942 mmol, 1.10 equiv) in 1,4-dioxane (2mL) was added $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$ (247.74 mg, 0.353 mmol, 0.2 equiv) and AsPh_3 (162.13 mg, 0.529 mmol, 0.3 equiv) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for overnight at 80°C under

nitrogen atmosphere. The reaction was monitored by LCMS. The resulting mixture was used in the next step directly without further purification. MS: (ES+H, m/z): $[M+H]^+ = 357.0$

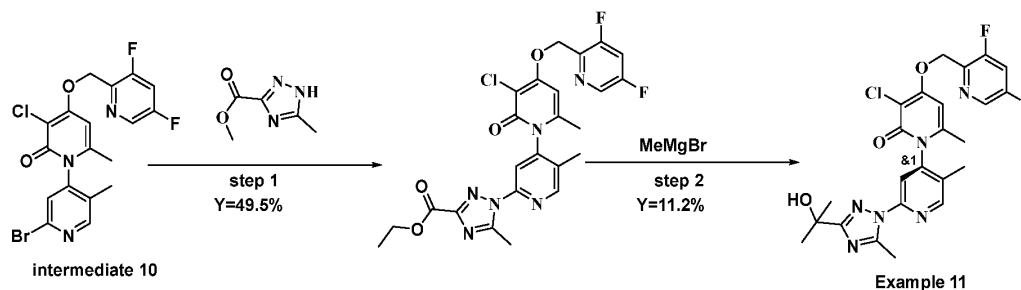
Step 3: Preparation of ethyl 4-{3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-5',6-dimethyl-2-oxo-[1,4'-bipyridin]-2'-yl}-6-cyclopropylpyrimidine-2-carboxylate:

[00343] To a stirred solution of ethyl 4-cyclopropyl-6-(trimethylstannyl)pyrimidine-2-carboxylate (630 mg, 1.775 mmol, 1.00 equiv) in 1,4-dioxane (5 ml) was added 2'-bromo-3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-5',6-dimethyl-[1,4'-bipyridin]-2-one (405.19 mg, 0.887 mmol, 0.50 equiv) and $AsPh_3$ (108.68 mg, 0.355 mmol, 0.2 equiv), $Pd(PPh_3)_2Cl_2$ (373.66 mg, 0.532 mmol, 0.3 equiv) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 2 days at 80°C under nitrogen atmosphere. The reaction was monitored by LCMS. The resulting mixture was diluted with water (5 mL). The aqueous layer was extracted with EtOAc (3x10 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by Prep-TLC (PE / EA 1:1) to afford ethyl 4-{3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-5',6-dimethyl-2-oxo-[1,4'-bipyridin]-2'-yl}-6-cyclopropylpyrimidine-2-carboxylate (70 mg, 6.95%) as a yellow solid. MS: (ES+H, m/z): $[M+H]^+ = 568.3$

Step 4: Preparation of 3-chloro-2'-[6-cyclopropyl-2-(2-hydroxypropan-2-yl)pyrimidin-4-yl]-4-[(3,5-difluoropyridin-2-yl)methoxy]-5',6-dimethyl-[1,4'-bipyridin]-2-one;

[00344] To a stirred solution of ethyl 4-{3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-5',6-dimethyl-2-oxo-[1,4'-bipyridin]-2'-yl}-6-cyclopropylpyrimidine-2-carboxylate (70 mg, 0.123 mmol, 1.00 equiv) in THF (1 ml) was added $MeMgBr$ (44.09 mg, 0.369 mmol, 3 equiv) at 0°C under nitrogen atmosphere. The resulting mixture was stirred for 1 h at 0°C under nitrogen atmosphere. The reaction was monitored by LCMS. The reaction was quenched with sat. NH_4Cl (aq.) at 0°C. The resulting mixture was extracted with EtOAc (3 x 5mL). After filtration, the filtrate was concentrated under reduced pressure. The crude product (60mg) was purified by Prep-HPLC to afford 3-chloro-2'-[6-cyclopropyl-2-(2-hydroxypropan-2-yl)pyrimidin-4-yl]-4-[(3,5-difluoropyridin-2-yl)methoxy]-5',6-dimethyl-[1,4'-bipyridin]-2-one (17.2 mg, 25.19%) as a white solid. MS: (ES+H, m/z): $[M+H]^+ = 554.1$ 1H NMR (300 MHz, $DMSO-d_6$) δ 8.84 (s, 1H), 8.63 (s, 1H), 8.61 (d, 1H), 8.15 (s, 1H), 8.10 (t, 1H), 6.84 (s, 1H), 5.58 – 5.41 (m, 2H), 5.14 (s, 1H), 2.38 – 2.25 (m, 1H), 2.10 (s, 3H), 1.98 (s, 3H), 1.48 (s, 3H), 1.47 (s, 3H), 1.18 - 1.08 (m, 4H). ^{19}F NMR (282 MHz, $DMSO$) δ -120.10, -120.13, -122.24, -122.27.

Example 11



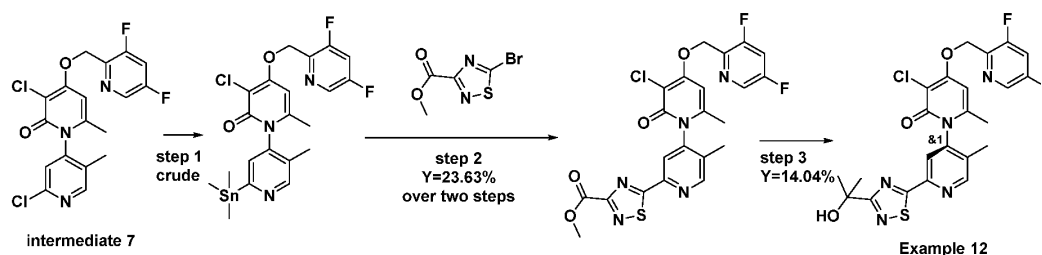
Step 1: Preparation of ethyl 1-{3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-5',6-dimethyl-2-oxo-[1,4'-bipyridin]-2'-yl}-5-methyl-1,2,4-triazole-3-carboxylate:

[00345] A mixture of 2'-bromo-3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-5',6-dimethyl-[1,4'-bipyridin]-2-one (400 mg, 0.876 mmol, 1.00 equiv), ethyl 5-methyl-1H-1,2,4-triazole-3-carboxylate (271.8 mg, 1.752 mmol, 2 equiv), K₂CO₃ (242.12 mg, 1.752 mmol, 2 equiv), (1R,2R)-N1,N2-dimethylcyclohexane-1,2-diamine (249.18 mg, 1.752 mmol, 2.00 equiv) and CuI (41.7 mg, 0.220 mmol, 0.25 equiv) in 1,4-dioxane (6 mL) was stirred for overnight at 100°C under nitrogen atmosphere. The reaction was monitored by LCMS. The reaction was allowed to cool down to room temperature. The resulting mixture was poured into 20 ml of water. The resulting mixture was extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (20 ml), dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography to afford ethyl 1-{3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-5',6-dimethyl-2-oxo-[1,4'-bipyridin]-2'-yl}-5-methyl-1,2,4-triazole-3-carboxylate (240 mg, Y=49.03%) as a yellow solid. LC-MS: (ES+H, m/z): [M+H]⁺=531.1. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.72 (s, 1H), 8.60 (d, 1H), 8.10 (t, 1H), 7.96 (s, 1H), 6.81 (s, 1H), 5.49 (s, 2H), 4.35 (q, 2H), 2.82 (s, 3H), 2.09 (s, 3H), 1.99 (s, 3H), 1.32 (t, 3H).

Step 2: Preparation of 3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-2'-[3-(2-hydroxypropan-2-yl)-5-methyl-1,2,4-triazol-1-yl]-5',6-dimethyl-[1,4'-bipyridin]-2-one:

[00346] To a stirred solution of ethyl 1-{3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-5',6-dimethyl-2-oxo-[1,4'-bipyridin]-2'-yl}-5-methyl-1,2,4-triazole-3-carboxylate (200 mg, 0.377 mmol, 1.00 equiv) in THF (10 mL) was added bromo(methyl)magnesium (3.77 mL, 10 equiv, 1M in THF) dropwise at -30°C under N₂ atmosphere. The resulting mixture was stirred at room temperature under N₂ atmosphere. The reaction was monitored by LCMS. The reaction was quenched by the addition of saturated NH₄Cl (20 mL) at room temperature. The resulting mixture was extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The crude product was purified by Prep-HPLC to afford 3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-2'-[3-(2-hydroxypropan-2-yl)-5-methyl-1,2,4-triazol-1-yl]-5',6-dimethyl-[1,4'-bipyridin]-2-one (22.4 mg, Y=11.2%) as a white solid. LC-MS: (ES+H, m/z): [M+H]⁺=517.25. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.66 (s, 1H), 8.61 (d, 1H), 8.14-8.07 (m, 1H), 7.84 (s, 1H), 6.82 (s, 1H), 5.50 (d, 2H), 5.15 (s, 1H), 2.78 (s, 3H), 2.07 (s, 3H), 2.00 (s, 3H), 1.51 (s, 6H). ¹⁹F NMR (282 MHz, DMSO) δ-120.127, -120.151, -122.289, -122.313.

Example 12



Step 1: Preparation of 3-chloro-4-((3,5-difluoropyridin-2-yl)methoxy)-5',6-dimethyl-2'-H-[1,4'-bipyridin]-2-one:

[00347] To a solution of 2',3-dichloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-5',6-dimethyl-[1,4'-bipyridin]-2-one (500 mg, 1.213 mmol, 1.00 equiv) and hexamethyldistannane (476.88 mg, 1.456 mmol, 1.2 equiv) in 1,4-dioxane (10 ml) was added Pd(PPh₃)₂Cl₂ (170.27 mg, 0.243 mmol, 0.2 equiv) and AsPh₃ (74.29 mg, 0.243 mmol, 0.2 equiv) at room temperature. The resulting mixture was stirred for overnight at 80°C under nitrogen atmosphere. The reaction was monitored by LCMS. The resulting mixture was used in the next step directly without further purification. LC-MS: (ES+H, m/z): [M+H]⁺=542.1.

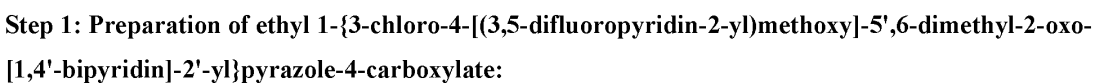
Step 2: Preparation of methyl 5-(3-chloro-4-((3,5-difluoropyridin-2-yl)methoxy)-5',6-dimethyl-2-oxo-2H-[1,4'-bipyridin]-2'-yl)-1,2,4-thiadiazole-3-carboxylate:

[00348] Methyl 5-bromo-1,2,4-thiadiazole-3-carboxylate (136.16 mg, 0.611 mmol, 0.50 equiv), CuI (232.52 mg, 1.221 mmol, 1 equiv) and Pd(PPh₃)₂Cl₂ (171.39 mg, 0.244 mmol, 0.2 equiv) were added to the reaction solution (assumed 100% yield) in the previous step at room temperature. The resulting mixture was stirred for 2 h at 80°C under nitrogen atmosphere. The reaction was monitored by LCMS. The mixture was allowed to cool down to room temperature. The resulting mixture was concentrated under vacuum. The residue was purified by silica gel column chromatography to afford methyl 5-(3-chloro-4-((3,5-difluoropyridin-2-yl)methoxy)-5',6-dimethyl-2-oxo-2H-[1,4'-bipyridin]-2'-yl)-1,2,4-thiadiazole-3-carboxylate (150 mg, 23.63%, over two steps) as a yellow solid. LC-MS: (ES+H, m/z): [M+H]⁺=520.0.

Step 3: Preparation of 3-chloro-4-((3,5-difluoropyridin-2-yl)methoxy)-2'-(3-(2-hydroxypropan-2-yl)-1,2,4-thiadiazol-5-yl)-5',6-dimethyl-2H-[1,4'-bipyridin]-2-one:

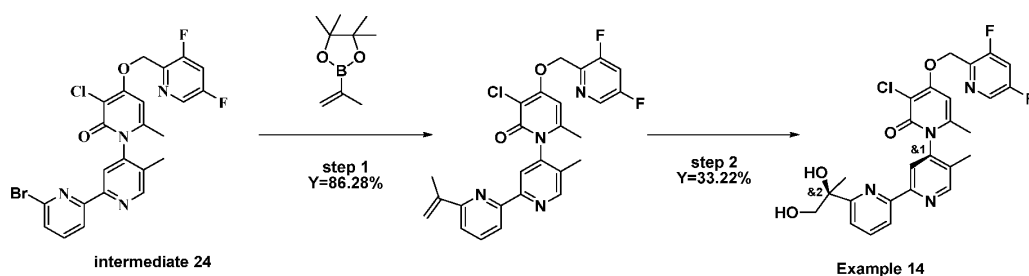
[00349] To a stirred solution of methyl 5-(3-chloro-4-((3,5-difluoropyridin-2-yl)methoxy)-5',6-dimethyl-2-oxo-2H-[1,4'-bipyridin]-2'-yl)-1,2,4-thiadiazole-3-carboxylate (150 mg, 0.289 mmol, 1 equiv) in THF (5 mL) was added CH₃MgBr (0.58 mL, 0.578 mmol, 2 equiv, 1 M in THF) dropwise at 0°C under nitrogen atmosphere. The resulting mixture was stirred for 1 h at 0°C under nitrogen atmosphere. The reaction was monitored by LCMS. The reaction was quenched by the addition of MeOH (5 mL) at 0°C. The resulting mixture was concentrated under reduced pressure. The mixture was purified by Prep-HPLC to afford crude product (50 mg). The crude product was further purified by Prep-HPLC to afford 3-chloro-4-((3,5-difluoropyridin-2-yl)methoxy)-2'-(3-(2-hydroxypropan-2-yl)-1,2,4-thiadiazol-5-yl)-5',6-dimethyl-2H-[1,4'-bipyridin]-2-one (21.3 mg, 14.04%) as a white solid. LC-MS: (ES+H, m/z): [M+H]⁺=520.1. ¹H NMR (400 MHz, DMSO-d₆) δ 8.85 (s, 1H), 8.61 (d, 1H), 8.16 (s, 1H), 8.11 (td, 1H), 6.82 (s, 1H), 5.49 (s, 2H), 5.46 (s,

Example 13



Step 2: Preparation of 3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-2'-[4-(2-hydroxypropan-2-yl)pyrazol-1-yl]-5',6-dimethyl-[1,4'-bipyridin]-2-one:

Example 14



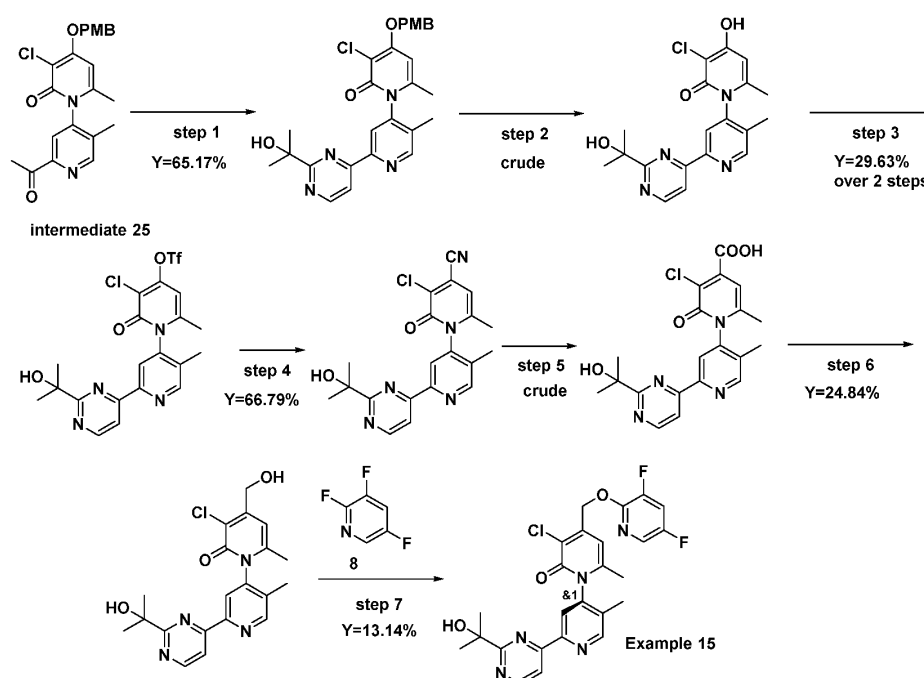
Step 1: Preparation of 3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-5',6-dimethyl-2'-[6-(prop-1-en-2-yl)pyridin-2-yl]-[1,4'-bipyridin]-2-one:

[00352] To a stirred solution of 2'-(6-bromopyridin-2-yl)-3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-5',6-dimethyl-[1,4'-bipyridin]-2-one (150 mg, 0.281 mmol, 1 equiv) and 4,4,5,5-tetramethyl-2-(prop-1-en-2-yl)-1,3,2-dioxaborolane (70.84 mg, 0.422 mmol, 1.5 equiv) in dioxane (2 mL) and H₂O (0.2 mL) were added CsF (85.38 mg, 0.562 mmol, 2 equiv) and Pd(PPh₃)₄ (64.95 mg, 0.056 mmol, 0.2 equiv) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 2 h at 90°C under nitrogen atmosphere. The reaction was monitored by LCMS. The mixture was allowed to cool down to room temperature. The reaction was quenched with saturating NH₄Cl (aq.) (10 mL) at room temperature. The resulting mixture was extracted with EtOAc (3 x 40 mL). The combined organic layers were washed with brine (1 x 50 mL), dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by Prep-TLC (PE / EA 1:1) to afford 3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-5',6-dimethyl-2'-[6-(prop-1-en-2-yl)pyridin-2-yl]-[1,4'-bipyridin]-2-one (200 mg, 86.28%) as a white solid. LC-MS: (ES+H, m/z): [M+H]⁺=495.2.

Step 2: Preparation of 3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-2'-[6-(1,2-dihydroxypropan-2-yl)pyridin-2-yl]-5',6-dimethyl-[1,4'-bipyridin]-2-one:

[00353] To a stirred solution of 3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-5',6-dimethyl-2'-[6-(prop-1-en-2-yl)pyridin-2-yl]-[1,4'-bipyridin]-2-one (200 mg, 0.242 mmol, 1 equiv, 60%) and NMO (56.81 mg, 0.485 mmol, 2.00 equiv) in THF (3 mL) and t-BuOH (1 mL) were added K₂OsO₄·2H₂O (44.67 mg, 0.121 mmol, 0.50 equiv) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 3 h at room temperature under nitrogen atmosphere. The reaction was monitored by LCMS. The resulting mixture was filtered; the filter cake was washed with THF (2 x 3 mL). The filtrate was concentrated under reduced pressure. The residue was purified by reverse flash chromatography. This resulted in 3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-2'-[6-(1,2-dihydroxypropan-2-yl)pyridin-2-yl]-5',6-dimethyl-[1,4'-bipyridin]-2-one (42.6 mg, 33.22%) as a white solid. LC-MS: (ES+H, m/z): [M+H]⁺=529.10. ¹H NMR (400 MHz, DMSO-d₆) δ 8.77 (s, 1H), 8.61 (d, 1H), 8.36 (d, 1H), 8.25 (m, 1H), 8.10 (m, 1H), 7.93 (m, 1H), 7.67 (m, 1H), 6.82 (s, 1H), 5.49 (s, 2H), 5.20-5.16 (m, 1H), 4.59-4.55 (m, 1H), 3.69–3.48 (m, 2H), 2.06 (s, 3H), 1.98 (s, 3H), 1.43 (s, 3H). ¹⁹F NMR (377 MHz, DMSO) δ -120.12, -120.14, -122.33, -122.35.

Example 15



Step 1: Preparation of 3-chloro-2'-[2-(2-hydroxypropan-2-yl)pyrimidin-4-yl]-4-[(4-methoxyphenyl)methoxy]-5',6-dimethyl-[1,4'-bipyridin]-2-one:

[00354] To a stirred solution of 2'-acetyl-3-chloro-4-[(4-methoxyphenyl)methoxy]-5',6-dimethyl-[1,4'-bipyridin]-2-one (2 g, 4.84 mmol, 1.00 equiv) in DMF-DMA (30 mL). The resulting mixture was stirred for 12h at 100°C under nitrogen atmosphere. The reaction was monitored by LCMS. The mixture was allowed to cool down to RT. The resulting mixture was concentrated under reduced pressure. To a stirred solution of the above mixture was added K₂CO₃ (3.35 g, 24.22 mmol, 5 equiv) and 2-hydroxy-2-methylpropanimidamide hydrochloride (2.01 g, 14.53 mmol, 3 equiv) in DMF (30 mL) at RT. The resulting mixture was stirred for 4 h at 80°C under nitrogen atmosphere. The reaction was monitored by LCMS. The resulting mixture was concentrated under reduced pressure. The residue was purified by reverse flash chromatography to afford 3-chloro-2'-[2-(2-hydroxypropan-2-yl)pyrimidin-4-yl]-4-[(4-methoxyphenyl)methoxy]-5',6-dimethyl-[1,4'-bipyridin]-2-one (1.6 g, 65.17%) as a white solid. LC-MS: (ES+H, *m/z*): [M+H]⁺ = 507.1.

Step 2: Preparation of 3-chloro-4-hydroxy-2'-[2-(2-hydroxypropan-2-yl)pyrimidin-4-yl]-5',6-dimethyl-[1,4'-bipyridin]-2-one:

[00355] To a stirred solution of 3-chloro-2'-[2-(2-hydroxypropan-2-yl)pyrimidin-4-yl]-4-[(4-methoxyphenyl)methoxy]-5',6-dimethyl-[1,4'-bipyridin]-2-one (1.6 g, 3.16 mmol, 1.00 equiv) and TFA (5 mL, 67.32 mmol, 21.33 equiv) in DCM (10 mL) at RT. The resulting mixture was stirred for 2 h at RT under nitrogen atmosphere. The reaction was monitored by LCMS. The resulting mixture was concentrated under reduced pressure. The residue was purified by trituration with diethyl ether (10 mL) to afford 3-chloro-4-hydroxy-2'-[2-(2-hydroxypropan-2-yl)pyrimidin-4-yl]-5',6-dimethyl-[1,4'-bipyridin]-2-one (1 g, yellow semi-solid, TFA salt). LC-MS: (ES+H, *m/z*): [M+H]⁺ = 387.0.

Step 3: Preparation of 3-chloro-2'-[2-(2-hydroxypropan-2-yl)pyrimidin-4-yl]-5',6-dimethyl-2-oxo-[1,4'-bipyridin]-4-yl trifluoromethanesulfonate:

[00356] To a stirred solution of 3-chloro-4-hydroxy-2'-[2-(2-hydroxypropan-2-yl)pyrimidin-4-yl]-5',6-dimethyl-[1,4'-bipyridin]-2-one (1 g, assumed 100% yield, 2.58 mmol, 1.00 equiv) lutidine (415.6 mg, 3.88 mmol, 1.5 equiv) and DMAP (31.6 mg, 0.26 mmol, 0.1 equiv) in DCM (10 mL) were added Tf₂O (948.2 mg, 3.36 mmol, 1.3 equiv) dropwise at 0°C. The resulting mixture was stirred for 2 h at RT under nitrogen atmosphere. The reaction was monitored by LCMS. The resulting mixture was concentrated under reduced pressure. The residue was purified by flash chromatography to afford 3-chloro-2'-[2-(2-hydroxypropan-2-yl)pyrimidin-4-yl]-5',6-dimethyl-2-oxo-[1,4'-bipyridin]-4-yltrifluoromethanesulfonate (486 mg, 29.63% over 2 steps) as a yellow oil. LC-MS: (ES+H, *m/z*): [M+H]⁺ = 519.0.

Step 4: Preparation of 2-{3-chloro-2'-[2-(2-hydroxypropan-2-yl)pyrimidin-4-yl]-5',6-dimethyl-2-oxo-[1,4'-bipyridin]-4-yl}acetonitrile :

[00357] To a stirred solution of 3-chloro-2'-[2-(2-hydroxypropan-2-yl)pyrimidin-4-yl]-5',6-dimethyl-2-oxo-[1,4'-bipyridin]-4-yl trifluoromethanesulfonate (360 mg, 0.69 mmol, 1.00 equiv) and Zn(CN)₂ (48.89 mg, 0.42 mmol, 0.6 equiv) in DMF (4 mL) were added Pd(PPh₃)₄ (80.17 mg, 0.07 mmol, 0.1 equiv) at RT. The resulting mixture was stirred for 2 h at 100°C under nitrogen atmosphere. The reaction was monitored by LCMS. The resulting mixture was concentrated under reduced pressure. The residue was purified by flash chromatography to afford 2-{3-chloro-2'-[2-(2-hydroxypropan-2-yl)pyrimidin-4-yl]-5',6-dimethyl-2-oxo-[1,4'-bipyridin]-4-yl}acetonitrile (190 mg, 66.79%) as a yellow solid. LC-MS: (ES+H, *m/z*): [M+H]⁺ = 396.0.

Step 5: Preparation of 3-chloro-2'-[2-(2-hydroxypropan-2-yl)pyrimidin-4-yl]-5',6-dimethyl-2-oxo-[1,4'-bipyridine]-4-carboxylic acid:

[00358] To a stirred solution of 3-chloro-2'-[2-(2-hydroxypropan-2-yl)pyrimidin-4-yl]-5',6-dimethyl-2-oxo-[1,4'-bipyridine]-4-carbonitrile (190 mg, 0.48 mmol, 1.00 equiv) in EtOH (10 mL) was added NaOH (96 mg, 2.40 mmol, 5.00 equiv) in at room temperature under nitrogen atmosphere. The resulting mixture was stirred for additional 2 h at 100°C. The reaction was monitored by LCMS. The mixture was acidified by using citric acid. The resulting mixture was diluted with EA (3 x 50 mL). The resulting mixture was washed with NaCl aq. (50 mL). The organic layers were dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure to afford 3-chloro-2'-[2-(2-hydroxypropan-2-yl)pyrimidin-4-yl]-5',6-dimethyl-2-oxo-[1,4'-bipyridine]-4-carboxylic acid (290 mg, crude) as a white solid, used without further purification. LC-MS: (ES+H, *m/z*): [M+H]⁺ = 415.1.

Step 6: Preparation of 3-chloro-4-(hydroxymethyl)-2'-[2-(2-hydroxypropan-2-yl)pyrimidin-4-yl]-5',6-dimethyl-[1,4'-bipyridin]-2-one:

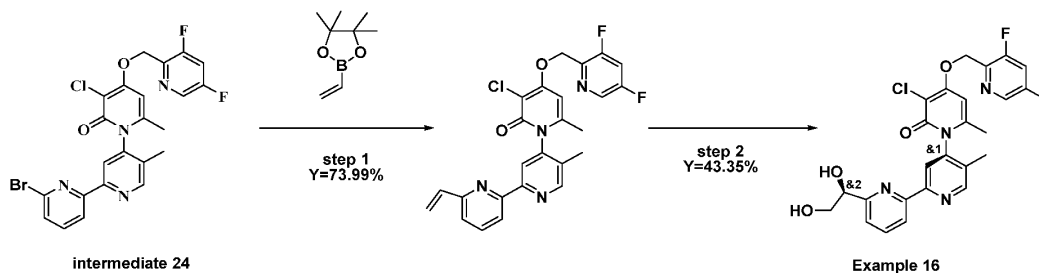
[00359] To a stirred solution of 3-chloro-2'-[2-(2-hydroxypropan-2-yl)pyrimidin-4-yl]-5',6-dimethyl-2-oxo-[1,4'-bipyridine]-4-carboxylic acid (250 mg, 0.603 mmol, 1.00 equiv) in THF (10 mL) was added CDI (117.26 mg, 0.724 mmol, 1.20 equiv) in portions at r.t. under nitrogen atmosphere. The resulting mixture was stirred for 1 h at r.t.. The above mixture was added to a solution of NaBH₄ (68.40 mg, 1.809 mmol, 3.00

equiv) in THF (10 mL) and H₂O (4 mL) dropwise over 5 min at 0°C. The resulting mixture was stirred for additional 1 h at r.t. The reaction was quenched by the addition of sat. NaHCO₃ (20 mL) at 0°C. The resulting mixture was extracted with DCM (3 x 20 mL). The combined organic layers were concentrated under reduced pressure. The residue was purified by reverse flash chromatography to afford 3-chloro-4-(hydroxymethyl)-2'-[2-(2-hydroxypropan-2-yl)pyrimidin-4-yl]-5',6-dimethyl-[1,4'-bipyridin]-2-one (60 mg, 24.84%) as a brown solid. LC-MS: (ES+H, *m/z*): [M+H]⁺ = 401.1. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.98 (d, 1H), 8.87 (s, 1H), 8.69 (s, 1H), 8.25 (d, 1H), 6.66 (s, 1H), 5.74 – 5.65 (m, 1H), 5.26 (s, 1H), 4.60 – 4.50 (m, 2H), 2.10 (s, 3H), 1.98 (s, 3H), 1.53 (s, 3H), 1.52 (s, 3H).

Step 7: Preparation of 3-chloro-4-[(3,5-difluoropyridin-2-yl)oxy]methyl}-2'-[2-(2-hydroxypropan-2-yl)pyrimidin-4-yl]-5',6-dimethyl-[1,4'-bipyridin]-2-one :

[00360] A mixture of 3-chloro-4-(hydroxymethyl)-2'-[2-(2-hydroxypropan-2-yl)pyrimidin-4-yl]-5',6-dimethyl-[1,4'-bipyridin]-2-one (40 mg, 0.100 mmol, 1 equiv) , 2,3,5-trifluoropyridine (26.56 mg, 0.200 mmol, 2 equiv) and Cs₂CO₃ (97.54 mg, 0.300 mmol, 3 equiv) in dioxane (4 mL) was stirred for 5 h at 80°C under nitrogen atmosphere. The reaction was monitored by LCMS. The resulting mixture was diluted with EA (50 mL). The resulting mixture was washed with 2 x 50 mL of NaCl (aq.). The organic layers were dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The crude product was purified by Prep-HPLC to afford 3-chloro-4-[(3,5-difluoropyridin-2-yl)oxy]methyl}-2'-[2-(2-hydroxypropan-2-yl)pyrimidin-4-yl]-5',6-dimethyl-[1,4'-bipyridin]-2-one (7 mg, 13.14%) as a grey solid. LC-MS: (ES+H, *m/z*): [M+H]⁺ = 514.10. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.98 (dd, 1H), 8.88 (s, 1H), 8.72 (s, 1H), 8.31 – 8.21 (m, 1H), 8.13 (d, 1H), 8.07 (ddd, 1H), 6.56 (s, 1H), 5.60 – 5.43 (m, 2H), 5.26 (s, 1H), 2.11 (s, 3H), 1.96 (s, 3H), 1.53 (s, 3H), 1.52 (s, 3H). ¹⁹F NMR (377 MHz, DMSO) δ -133.74, -134.05.

Example 16



Step 1: Preparation of 2'-[2-(2-hydroxypropan-2-yl)pyrimidin-4-yl]-5',6-dimethyl-[1,4'-bipyridin]-2-one:

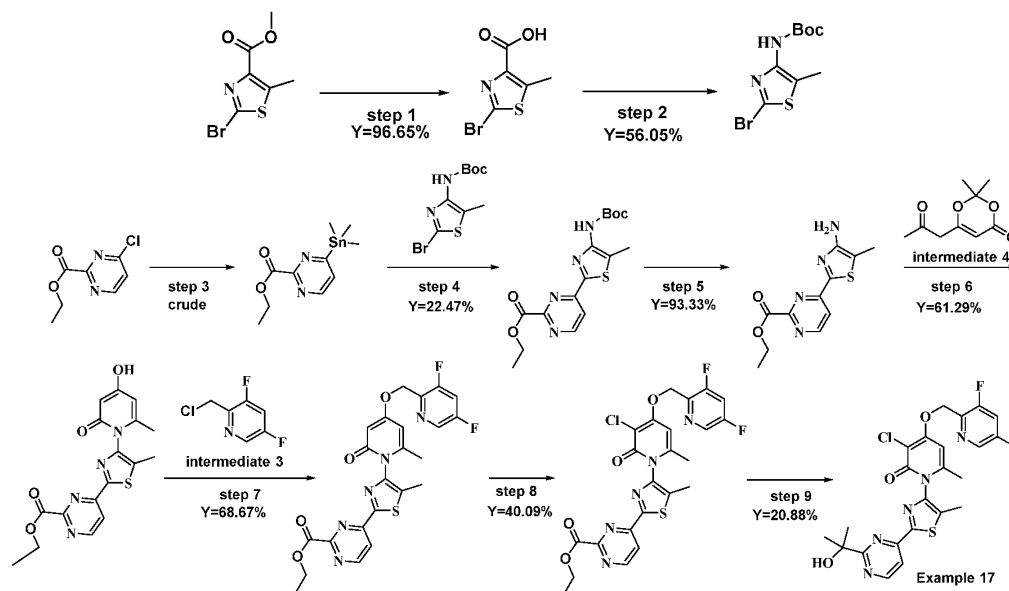
[00361] To a stirred mixture of 2'-[2-(2-hydroxypropan-2-yl)pyrimidin-4-yl]-5',6-dimethyl-[1,4'-bipyridin]-2-one (150 mg, 0.281 mmol, 1 equiv) , K₂CO₃ (77.68 mg, 0.562 mmol, 2 equiv) and 2-ethenyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (86.57 mg, 0.562 mmol, 2 equiv) in 1,4-dioxane (2.5 mL) and H₂O (0.5 mL) was added Pd(dppf)Cl₂·CH₂Cl₂ (22.89 mg, 0.028 mmol, 0.1 equiv) at room temperature. The resulting mixture was stirred for 2 h at 100°C under nitrogen atmosphere. The reaction was monitored by LCMS. The reaction was allowed to cool down to room temperature. The crude product was purified by reverse phase combi-flash to afford 3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-

2'-(6-ethenylpyridin-2-yl)-5',6-dimethyl-[1,4'-bipyridin]-2-one (100 mg, 73.99%) as a white solid. LC-MS: (ES+H, m/z): $[M+H]^+ = 481.12$. ^1H NMR (400 MHz, DMSO- d_6) δ 8.79 (d, 1H), 8.61 (d, 1H), 8.33 (d, 1H), 8.30 (d, 1H), 8.15 – 8.05 (m, 1H), 8.00 – 7.91 (m, 1H), 7.60 – 7.53 (m, 1H), 6.94 – 6.85 (m, 1H), 6.82 (s, 1H), 6.47 – 6.37 (m, 1H), 5.56 – 5.45 (m, 3H), 2.07 (s, 3H), 1.98 (s, 3H).

Step 2: Preparation of 3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-2'-[6-(1,2-dihydroxyethyl)pyridin-2-yl]-5',6-dimethyl-[1,4'-bipyridin]-2-one:

[00362] To a stirred mixture of NMO (48.72 mg, 0.416 mmol, 2 equiv) and 3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-2'-(6-ethenylpyridin-2-yl)-5',6-dimethyl-[1,4'-bipyridin]-2-one (100 mg, 0.208 mmol, 1 equiv) in THF (1.5 mL) and t-BuOH (0.5 mL) was added $\text{K}_2\text{OsO}_4 \cdot 2\text{H}_2\text{O}$ (38.31 mg, 0.104 mmol, 0.5 equiv) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 15 h at room temperature under nitrogen atmosphere. The reaction was monitored by LCMS. The reaction was quenched with sat. sodium thiosulfate (aq.) (40ml), extracted with EtOAc (3 x 40 mL). The combined organic layers were dried over anhydrous Na_2SO_4 . After filtration, the filtrate was concentrated under reduced pressure. The crude product (100 mg) was purified by Prep-HPLC to afford 3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-2'-[6-(1,2-dihydroxyethyl)pyridin-2-yl]-5',6-dimethyl-[1,4'-bipyridin]-2-one (46.6 mg, 43.35%) as a white solid. LC-MS: (ES+H, m/z): $[M+H]^+ = 515.12$. ^1H NMR (400 MHz, DMSO- d_6) δ 8.77 (s, 1H), 8.61 (d, 1H), 8.32 – 8.22 (m, 2H), 8.15 – 8.06 (m, 1H), 7.94 (t, 1H), 7.54 (d, 1H), 6.82 (s, 1H), 5.49 (s, 2H), 5.44 (t, 1H), 4.72 – 4.58 (m, 2H), 3.81 – 3.68 (m, 1H), 3.62 – 3.48 (m, 1H), 2.07 (s, 3H), 1.98 (s, 3H). ^{19}F NMR (377 MHz, DMSO) δ -120.136, -120.154, -122.345, -122.364.

Example 17



Step 1: Preparation of 2-bromo-5-methyl-1,3-thiazole-4-carboxylic acid:

[00363] To a stirred solution of methyl 2-bromo-5-methyl-1,3-thiazole-4-carboxylate (5.5 g, 23.297 mmol, 1.00 equiv) in THF (25 ml) was added LiOH (1.12 g, 46.768 mmol, 2.01 equiv) in water (25 ml) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 30 min at 50°C under nitrogen

atmosphere. The reaction was monitored by LCMS. The mixture was acidified to pH 4 with conc. HCl. The resulting mixture was extracted with EtOAc (3 x 100mL), dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure, to afford 2-bromo-5-methyl-1,3-thiazole-4-carboxylic acid (5 g, 96.65%) as a red solid. LC-MS: (ES+H, m/z): [M+H]⁺=221.9. ¹H NMR (400 MHz, DMSO-d₆) δ 13.17 (s, 1H), 2.67 (s, 3H).

Step 2: Preparation of tert-butyl N-(2-bromo-5-methyl-1,3-thiazol-4-yl)carbamate:

[00364] To a stirred solution of 2-bromo-5-methyl-1,3-thiazole-4-carboxylic acid (5 g, 22.516 mmol, 1.00 equiv) and 2-methylpropan-2-ol (16.69 g, 225.160 mmol, 10.00 equiv) in 1,2-dimethoxyethane (50 mL) was added DPPA (6.82 g, 24.768 mmol, 1.1 equiv) dropwise at 0°C under nitrogen atmosphere. The resulting mixture was stirred for overnight at 90°C under nitrogen atmosphere. The reaction was monitored by LCMS. The resulting mixture was diluted with EA (100mL). The resulting mixture was washed with water (3 x 100mL) and NaCl (aq.) (100mL). the mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography to afford tert-butyl N-(2-bromo-5-methyl-1,3-thiazol-4-yl)carbamate (3.7 g, 56.05%) as a white solid. LC-MS: (ES+H, m/z): [M+H-56]⁺=238.9. ¹H NMR (300 MHz, DMSO-d₆) δ 9.07 (s, 1H), 2.19 (d, 3H), 1.43 (s, 9H).

Step 3: Preparation of ethyl 4-(trimethylstannyl)pyrimidine-2-carboxylate:

[00365] To a stirred solution of ethyl 4-chloropyrimidine-2-carboxylate (1.5 g, 8.039 mmol, 1.00 equiv) and Sn₂Me₆ (6.58 g, 20.084 mmol, 2.50 equiv) in 1,4-dioxane (10 ml) was added Pd(PPh₃)₂Cl₂ (1.69 g, 2.412 mmol, 0.30 equiv) and AsPh₃ (0.49 g, 1.608 mmol, 0.2 equiv) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for overnight at 80°C under nitrogen atmosphere. The reaction was monitored by LCMS. The resulting mixture was diluted with EA (100mL) and washed with 5x100 mL of water and NaCl (aq.) (100 mL). dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The crude product was used in the next step directly without further purification. LC-MS: (ES+H, m/z): [M+H]⁺=317.0

Step 4: Preparation of 4-{4-[(tert-butoxycarbonyl)amino]-5-methyl-1,3-thiazol-2-yl}pyrimidine-2-carboxylate:

[00366] To a stirred solution of ethyl 4-(trimethylstannyl)pyrimidine-2-carboxylate (2.5 g, 7.938 mmol, 1.00 equiv) and tert-butyl N-(2-bromo-5-methyl-1,3-thiazol-4-yl)carbamate (1.86 g, 6.350 mmol, 0.8 equiv) in 1,4-dioxane (20ml) was added CuI (1.51 g, 7.938 mmol, 1 equiv) and Pd(PPh₃)₂Cl₂ (1.11 g, 1.588 mmol, 0.2 equiv) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 2 h at 80°C under nitrogen atmosphere. The mixture was allowed to cool down to room temperature. The reaction was monitored by LCMS. The reaction mixture was partitioned between EA (100 mL) and water (100 mL). The organic layer was extracted with EtOAc (2 x 200mL) the resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography to afford ethyl 4-{4-[(tert-butoxycarbonyl)amino]-5-methyl-1,3-thiazol-2-yl}pyrimidine-2-carboxylate (650 mg, 22.47%) as a white solid. LC-MS: (ES+H, m/z): [M+H-56]⁺=309.1.

Step 5: Preparation of ethyl 4-(4-amino-5-methyl-1,3-thiazol-2-yl)pyrimidine-2-carboxylate:

[00367] To a stirred solution of ethyl 4-{4-[(tert-butoxycarbonyl)amino]-5-methyl-1,3-thiazol-2-yl}pyrimidine-2-carboxylate (650 mg, 1.784 mmol, 1 equiv) in DCM (2ml) was added HCl(gas) in 1,4-dioxane (2ml) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 30 min at room temperature under nitrogen atmosphere. The reaction was monitored by LCMS. The resulting mixture was diluted with EA (100mL). The resulting mixture was washed with water (3 x 100mL), dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure to afford ethyl 4-(4-amino-5-methyl-1,3-thiazol-2-yl)pyrimidine-2-carboxylate (440 mg, 93.33%) as a yellow solid. LC-MS: (ES+H, m/z): [M+H]⁺ = 265.1.

Step 6: Preparation of ethyl 4-[4-(4-hydroxy-2-methyl-6-oxopyridin-1-yl)-5-methyl-1,3-thiazol-2-yl]pyrimidine-2-carboxylate:

[00368] A solution of ethyl 4-(4-amino-5-methyl-1,3-thiazol-2-yl)pyrimidine-2-carboxylate (440 mg, 1.665 mmol, 1 equiv) and 2,2-dimethyl-6-(2-oxopropyl)-1,3-dioxin-4-one (613.27 mg, 3.330 mmol, 2 equiv) in dioxane (5 mL) was stirred for 3 h at 90°C under nitrogen atmosphere. The mixture was allowed to cool down to room temperature. The reaction was monitored by LCMS. To the above mixture was added H₂SO₄ (163.28 mg, 1.665 mmol, 1 equiv) dropwise. The resulting mixture was stirred for additional 1h at 90°C. The mixture was allowed to cool down to room temperature. The reaction was monitored by LCMS. The resulting mixture was concentrated under reduced pressure. The resulting mixture was added H₂O (25 mL) and stirred for 30 min. The precipitated solids were collected by filtration and washed with Et₂O (3x50 mL). This resulted in ethyl 4-[4-(4-hydroxy-2-methyl-6-oxopyridin-1-yl)-5-methyl-1,3-thiazol-2-yl]pyrimidine-2-carboxylate (380 mg, 61.29%) as a yellow solid.

Step 7: Preparation of ethyl 4-(4-{4-[(3,5-difluoropyridin-2-yl)methoxy]-2-methyl-6-oxopyridin-1-yl}-5-methyl-1,3-thiazol-2-yl)pyrimidine-2-carboxylate:

[00369] To a stirred solution of ethyl 4-[4-(4-hydroxy-2-methyl-6-oxopyridin-1-yl)-5-methyl-1,3-thiazol-2-yl]pyrimidine-2-carboxylate (380 mg, 1.020 mmol, 1 equiv) and 2-(chloromethyl)-3,5-difluoropyridine (417.22 mg, 2.550 mmol, 2.5 equiv) in DMF (10ml) was added 18-Crown-6 (80.91 mg, 0.306 mmol, 0.3 equiv) and K₂CO₃ (423.08 mg, 3.060 mmol, 3 equiv) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 2h at 60°C under nitrogen atmosphere. The mixture was allowed to cool down to room temperature. The reaction was monitored by LCMS. The reaction mixture was partitioned between EA (100 mL) and water (100 mL). The organic layer was washed with water (200 mL) and then dried over Na₂SO₄. The solution was concentrated under reduced pressure. The residue was purified by silica gel column chromatography to afford ethyl 4-(4-{4-[(3,5-difluoropyridin-2-yl)methoxy]-2-methyl-6-oxopyridin-1-yl}-5-methyl-1,3-thiazol-2-yl)pyrimidine-2-carboxylate (350 mg, 68.67%) as a white solid. LC-MS: (ES+H, m/z): [M+H]⁺ = 500.1.

Step 8: Preparation of ethyl 4-(4-{3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-6-methyl-2-oxopyridin-1-yl}-5-methyl-1,3-thiazol-2-yl)pyrimidine-2-carboxylate:

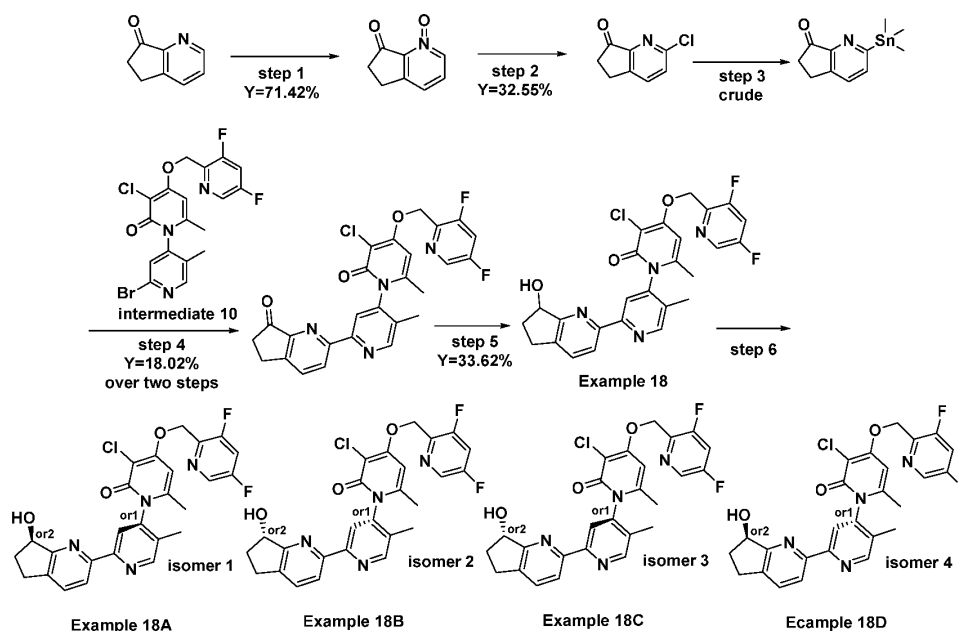
[00370] To a stirred solution of ethyl 4-(4-{4-[(3,5-difluoropyridin-2-yl)methoxy]-2-methyl-6-oxopyridin-1-yl}-5-methyl-1,3-thiazol-2-yl)pyrimidine-2-carboxylate (350 mg, 0.701 mmol, 1 equiv) and NCS (121.64

mg, 0.911 mmol, 1.3 equiv) in IPA(5ml) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 2 h at 50°C under nitrogen atmosphere. The reaction was monitored by LCMS. The mixture was allowed to cool down to room temperature. The reaction mixture was partitioned between EA (10 mL) and water (10 mL). The organic layer was extracted with EtOAc (3 x 50mL). The resulting mixture was concentrated under reduced pressure. The crude product (300mg) was purified by Prep-HPLC to afford ethyl 4-(4-{3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-6-methyl-2-oxypyridin-1-yl}-5-methyl-1,3-thiazol-2-yl)pyrimidine-2-carboxylate (150 mg, 40.09%) as a yellow oil. LC-MS: (ES+H, m/z): $[M+H]^+ = 534.1$. ^1H NMR (300 MHz, DMSO- d_6) δ 9.11 (d, 1H), 8.61 (d, 1H), 8.21 (d, 1H), 8.18 – 8.04 (m, 1H), 6.79 (s, 1H), 5.52 (d, 2H), 4.44 (q, 2H), 2.34 (s, 3H), 2.05 (s, 3H), 1.38 (t, 3H).

Step 9: Preparation of 3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-1-{2-[2-(2-hydroxypropan-2-yl)pyrimidin-4-yl]-5-methyl-1,3-thiazol-4-yl}-6-methylpyridin-2-one:

[00371] To a stirred solution of ethyl 4-(4-{3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-6-methyl-2-oxypyridin-1-yl}-5-methyl-1,3-thiazol-2-yl)pyrimidine-2-carboxylate (150 mg, 0.281 mmol, 1 equiv) in THF was added MeMgBr (335.00 mg, 2.810 mmol, 10 equiv) at 0°C under nitrogen atmosphere. The resulting mixture was stirred for 30min at 0°C under nitrogen atmosphere. The reaction was monitored by LCMS. The reaction was quenched with MeOH at 0°C. The resulting mixture was concentrated under reduced pressure. The crude product (150mg) was purified by Prep-HPLC to afford 3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-1-{2-[2-(2-hydroxypropan-2-yl)pyrimidin-4-yl]-5-methyl-1,3-thiazol-4-yl}-6-methylpyridin-2-one (30.5 mg, 20.88%) as a white solid. LC-MS: (ES+H, m/z): $[M+H]^+ = 520.1$. ^1H NMR (300 MHz, DMSO- d_6) δ 8.97 (d, 1H), 8.61 (d, 1H), 8.17 – 8.04 (m, 1H), 7.89 (d, 1H), 6.78 (s, 1H), 5.52 (d, 2H), 5.17 (s, 1H), 2.32 (s, 3H), 2.05 (d, 3H), 1.57 (s, 6H). ^{19}F NMR (282 MHz, DMSO) δ -120.21, -120.24, -122.44, -122.46.

Example 18A, 18B, 18C, 18D



Step 1: Preparation of 5H,6H-11lambda5-cyclopenta[b]pyridine-1,7-dione:

[00372] To a stirred solution of 5H,6H-cyclopenta[b]pyridin-7-one (5 g, 37.552 mmol, 1.00 equiv) in DCM (150 ml) was added m-CPBA (12.96 g, 75.104 mmol, 2.00 equiv) in portions at 0°C under nitrogen atmosphere. The resulting mixture was stirred for 18 h at room temperature under nitrogen atmosphere. The reaction was monitored by LCMS. The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography to afford 5H,6H-11lambda5-cyclopenta[b]pyridine-1,7-dione (4 g, 71.42%) as a black solid. LC-MS: (ES+H, m/z): [M+H]⁺ = 150.1. ¹H NMR (400 MHz, DMSO-d₆) δ 8.17 (d, 1H), 7.55 (t, 1H), 7.44 (d, 1H), 3.02 (t, 2H), 2.64 (t, 2H).

Step 2: Preparation of 2-chloro-5H,6H-cyclopenta[b]pyridin-7-one:

[00373] To a stirred solution of 5H,6H-11lambda5-cyclopenta[b]pyridine-1,7-dione (3.5 g, 23.466 mmol, 1.00 equiv) in DCE (80 mL) was added POCl₃ (17.99 g, 117.330 mmol, 5 equiv) dropwise at 0°C under nitrogen atmosphere. The resulting mixture was stirred for 2 h at 80°C under nitrogen atmosphere. The reaction was monitored by LCMS. The mixture was allowed to r.t. The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography to afford 2-chloro-5H,6H-cyclopenta[b]pyridin-7-one (1.28 g, 32.55%) as a black solid. LC-MS: (ES+H, m/z): [M+H]⁺ = 168.0. ¹H NMR (400 MHz, DMSO-d₆) δ 8.15 (d, 1H), 7.72 (d, 1H), 3.09 (t, 2H), 2.71 (t, 2H).

Step 3: Preparation of 2-(trimethylstannyl)-5H,6H-cyclopenta[b]pyridin-7-one:

[00374] A mixture of 2-chloro-5H,6H-cyclopenta[b]pyridin-7-one (250 mg, 1.492 mmol, 1 equiv), Pd(PPh₃)₂Cl₂ (209.41 mg, 0.298 mmol, 0.20 equiv), AsPh₃ (91.36 mg, 0.298 mmol, 0.2 equiv) and Sn₂Me₆ (488.74 mg, 1.492 mmol, 1 equiv) in dioxane (8 mL) was stirred for overnight at 80°C under nitrogen atmosphere. The reaction was monitored by LCMS. The resulting mixture was used in the next step directly without further purification. LC-MS: (ES+H, m/z): [M+H]⁺ = 298.0.

Step 4: Preparation of 3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-5',6-dimethyl-2'-[7-oxo-5H,6H-cyclopenta[b]pyridin-2-yl]-[1,4'-bipyridin]-2-one:

[00375] 2'-bromo-3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-5',6-dimethyl-[1,4'-bipyridin]-2-one (328.67 mg, 0.719 mmol, 0.6 equiv), Pd(PPh₃)₂Cl₂ (168.39 mg, 0.240 mmol, 0.20 equiv) and CuI (228.44 mg, 1.199 mmol, 1 equiv) was added to the reaction solution in the previous step at room temperature. The resulting mixture was stirred for 2 h at 80°C under nitrogen atmosphere. The reaction was monitored by LCMS. The mixture was allowed to r.t. The resulting mixture was diluted with EA (200 mL), washed with 3 x 150 mL of sat. NaHCO₃ (aq.). The organic layers were concentrated under reduced pressure. And purified by silica gel column chromatography to afford crude product. The crude product was purified by reverse flash chromatography to afford 3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-5',6-dimethyl-2'-[7-oxo-5H,6H-cyclopenta[b]pyridin-2-yl]-[1,4'-bipyridin]-2-one (110 mg, 18.02%, over two steps) as a white solid. LC-MS: (ES+H, m/z): [M+H]⁺ = 508.8. ¹H NMR (300 MHz, Chloroform-d) δ 8.71 (s, 1H), 8.68 (d, 1H), 8.43 (s, 1H), 8.40 (s, 1H), 8.02 (d, 1H), 7.39 – 7.31 (m, 1H), 6.39 (s, 1H), 5.46 (s, 2H), 3.22 (t, 2H), 2.84 (t, 2H), 2.19 (s, 3H), 2.01 (s, 3H).

Step 5: Preparation of 3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-2'-{7-hydroxy-5H,6H,7H-cyclopenta[b]pyridin-2-yl}-5',6-dimethyl-[1,4'-bipyridin]-2-one:

[00376] To a stirred solution of 3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-5',6-dimethyl-2'-{7-oxo-5H,6H-cyclopenta[b]pyridin-2-yl}-[1,4'-bipyridin]-2-one (400 mg, 0.786 mmol, 1 equiv) in THF (10 ml) was added NaBH₄ (59.47 mg, 1.572 mmol, 2 equiv) in portions at 0°C under nitrogen atmosphere. The resulting mixture was stirred for 1 h at room temperature under nitrogen atmosphere. The reaction was monitored by LCMS. The reaction was quenched with sat. NH₄Cl (aq.) at 0°C. The resulting mixture was extracted with EtOAc. The combined organic layers were concentrated under reduced pressure. The residue was purified by silica gel column chromatography to afford 3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-2'-{7-hydroxy-5H,6H,7H-cyclopenta[b]pyridin-2-yl}-5',6-dimethyl-[1,4'-bipyridin]-2-one (135 mg, 33.62%) as a white solid. LC-MS: (ES+H, m/z): [M+H]⁺=510.8.

Step 6: Preparation of rel-(R)-3-chloro-4-((3,5-difluoropyridin-2-yl)methoxy)-2'-(7-hydroxy-6,7-dihydro-5H-cyclopenta[b]pyridin-2-yl)-5',6-dimethyl-2H-[1,4'-bipyridin]-2-one, rel-(R)-3-chloro-4-((3,5-difluoropyridin-2-yl)methoxy)-2'-(7-hydroxy-6,7-dihydro-5H-cyclopenta[b]pyridin-2-yl)-5',6-dimethyl-2H-[1,4'-bipyridin]-2-one, rel-(R)-3-chloro-4-((3,5-difluoropyridin-2-yl)methoxy)-2'-(7-hydroxy-6,7-dihydro-5H-cyclopenta[b]pyridin-2-yl)-5',6-dimethyl-2H-[1,4'-bipyridin]-2-one and rel-(R)-3-chloro-4-((3,5-difluoropyridin-2-yl)methoxy)-2'-(7-hydroxy-6,7-dihydro-5H-cyclopenta[b]pyridin-2-yl)-5',6-dimethyl-2H-[1,4'-bipyridin]-2-one:

[00377] 3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-2'-{7-hydroxy-5H,6H,7H-cyclopenta[b]pyridin-2-yl}-5',6-dimethyl-[1,4'-bipyridin]-2-one (135 mg, 0.264 mmol, 1 equiv) was isolated by PREP-HPLC to afford 2 peaks. The first peak (53 mg) was separated by prep-chiral-HPLC to afford Example 18A (18.3 mg) and Example 18B (16.9 mg) as a white solid. The second peak (45 mg) was separated by prep-chiral-HPLC to afford Example 18C (14.1 mg) and Example 18D (14.3 mg) as a white solid.

Example 18A:

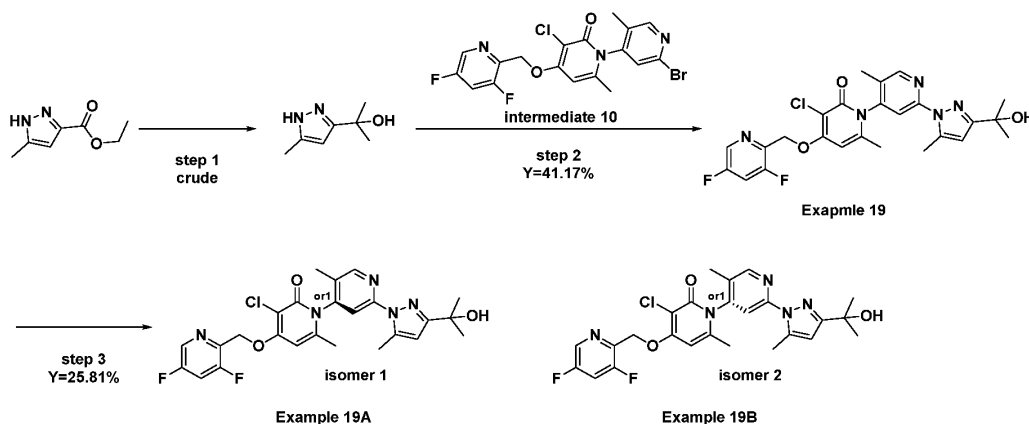
[00378] LC-MS: (ES+H, m/z): [M+H]⁺=510.80. ¹H NMR (400 MHz, DMSO-d₆) δ 8.77 (s, 1H), 8.61 (d, 1H), 8.26 (d, 1H), 8.24 (s, 1H), 8.15 – 8.01 (m, 1H), 7.82 (d, 1H), 6.80 (d, 1H), 5.50 (d, 2H), 5.42 (d, 1H), 5.07 – 4.93 (m, 1H), 3.05 – 2.91 (m, 1H), 2.88 – 2.71 (m, 1H), 2.45 – 2.33 (m, 1H), 2.08 (s, 3H), 1.99 (s, 3H), 1.91 – 1.78 (m, 1H). ¹⁹F NMR (377 MHz, DMSO) δ -120.15, -120.17, -122.34, -122.36.

[00379] **Example 18B:** LC-MS: (ES+H, m/z): [M+H]⁺=510.85. ¹H NMR (400 MHz, DMSO-d₆) δ 8.76 (s, 1H), 8.60 (d, 1H), 8.25 (d, 1H), 8.23 (s, 1H), 8.13 – 8.02 (m, 1H), 7.82 (d, 1H), 6.79 (d, 1H), 5.49 (d, 2H), 5.41 (d, 1H), 5.06 – 4.92 (m, 1H), 3.04 – 2.93 (m, 1H), 2.87 – 2.74 (m, 1H), 2.46 – 2.34 (m, 1H), 2.07 (s, 3H), 1.99 (s, 3H), 1.91 – 1.79 (m, 1H). ¹⁹F NMR (377 MHz, DMSO) δ -120.15, -120.17, -122.36, -122.37.

[00380] **Example 18C:** LC-MS: (ES+H, m/z): [M+H]⁺=510.85. ¹H NMR (400 MHz, DMSO-d₆) δ 8.76 (s, 1H), 8.61 (d, 1H), 8.26 (d, 1H), 8.24 (s, 1H), 8.13 – 8.05 (m, 1H), 7.82 (d, 1H), 6.80 (d, 1H), 5.49 (d, 2H), 5.37 (d, 1H), 5.02 – 4.93 (m, 1H), 3.06 – 2.94 (m, 1H), 2.85 – 2.73 (m, 1H), 2.45 – 2.33 (m, 1H), 2.07 (s, 3H), 1.98 (s, 3H), 1.93 – 1.82 (m, 1H). ¹⁹F NMR (377 MHz, DMSO) δ -120.14, -120.16, -122.34, -122.36.

[00381] Example 18D: LC-MS: (ES+H, m/z): $[M+H]^+ = 510.85$. ^1H NMR (400 MHz, DMSO- d_6) δ 8.76 (s, 1H), 8.61 (d, 1H), 8.26 (d, 1H), 8.25 (s, 1H), 8.13 – 8.06 (m, 1H), 7.83 (d, 1H), 6.80 (d, 1H), 5.49 (d, 2H), 5.39 (d, 1H), 5.02 – 4.93 (m, 1H), 3.06 – 2.94 (m, 1H), 2.85 – 2.73 (m, 1H), 2.45 – 2.33 (m, 1H), 2.07 (s, 3H), 1.98 (s, 3H), 1.91 – 1.86 (m, 1H). ^{19}F NMR (377 MHz, DMSO) δ -120.12, -120.15, -122.31, -122.33.

Example 19A, 19B



Step 1: Preparation of 2-(5-methyl-1H-pyrazol-3-yl)propan-2-ol:

[00382] To a stirred solution of ethyl 5-methyl-1H-pyrazole-3-carboxylate (3 g, 19.459 mmol, 1 equiv) in THF (100 mL) were added MeMgBr (97.30 mL, 97.295 mmol, 5 equiv) dropwise at 0°C under nitrogen atmosphere.

[00383] The reaction was monitored by LCMS. The reaction was quenched with sat. NH_4Cl (aq.) at 0°C, extracted with EtOAc (3 x 1L), dried over anhydrous Na_2SO_4 . After filtration, the filtrate was concentrated under reduced pressure. The crude product 2-(5-methyl-1H-pyrazol-3-yl)propan-2-ol (2.9 g, 88.24%) was used in the next step directly without further purification. LC-MS: (ES+H, m/z): $[M+H]^+ = 141.09$.

Step 2: Preparation of 3-chloro-4-((3,5-difluoropyridin-2-yl)methoxy)-2'-(3-(2-hydroxypropan-2-yl)-5-methyl-1H-pyrazol-1-yl)-5',6-dimethyl-2H-[1,4'-bipyridin]-2-one:

[00384] To a stirred mixture of 2-(5-methyl-1H-pyrazol-3-yl)propan-2-ol (184.18 mg, 1.314 mmol, 2 equiv), K_2CO_3 (181.58 mg, 1.314 mmol, 2 equiv) and 2'-bromo-3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-5',6-dimethyl-[1,4'-bipyridin]-2-one (300 mg, 0.657 mmol, 1.00 equiv) in 1,4-dioxane (5 mL) were added (1S,2S)-N1,N2-dimethylcyclohexane-1,2-diamine (37.38 mg, 0.263 mmol, 0.4 equiv) and CuI (25.02 mg, 0.131 mmol, 0.2 equiv) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for overnight at 100°C under nitrogen atmosphere. After cooling down to r.t., the resulting mixture was poured into water (100 mL), then extracted with EtOAc (3 x 100 mL). The combined organic layers were dried over anhydrous Na_2SO_4 . After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography to afford 240 mg of crude product, which was further purified by Prep-HPLC to afford 3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-2'-[3-(2-

hydroxypropan-2-yl)-5-methylpyrazol-1-yl]-5',6-dimethyl-[1,4'-bipyridin]-2-one (140 mg, 41.17%) as a white solid. LC-MS: (ES+H, m/z): [M+H]⁺ = 516.1.

Step 3: Preparation of rel-3-chloro-4-((3,5-difluoropyridin-2-yl)methoxy)-2'-(3-(2-hydroxypropan-2-yl)-5-methyl-1H-pyrazol-1-yl)-5',6-dimethyl-2H-[1,4'-bipyridin]-2-one and rel-3-chloro-4-((3,5-difluoropyridin-2-yl)methoxy)-2'-(3-(2-hydroxypropan-2-yl)-5-methyl-1H-pyrazol-1-yl)-5',6-dimethyl-2H-[1,4'-bipyridin]-2-one:

[00385] The racemate (3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-2'-[3-(2-hydroxypropan-2-yl)-5-methylpyrazol-1-yl]-5',6-dimethyl-[1,4'-bipyridin]-2-one (140 mg) was separated by Prep-Chiral-HPLC to afford rel-3-chloro-4-((3,5-difluoropyridin-2-yl)methoxy)-2'-(3-(2-hydroxypropan-2-yl)-5-methyl-1H-pyrazol-1-yl)-5',6-dimethyl-2H-[1,4'-bipyridin]-2-one (**Example 19A**, 27.7 mg) and rel-3-chloro-4-((3,5-difluoropyridin-2-yl)methoxy)-2'-(3-(2-hydroxypropan-2-yl)-5-methyl-1H-pyrazol-1-yl)-5',6-dimethyl-2H-[1,4'-bipyridin]-2-one (**Example 19B**, 35.0 mg) as a white solid.

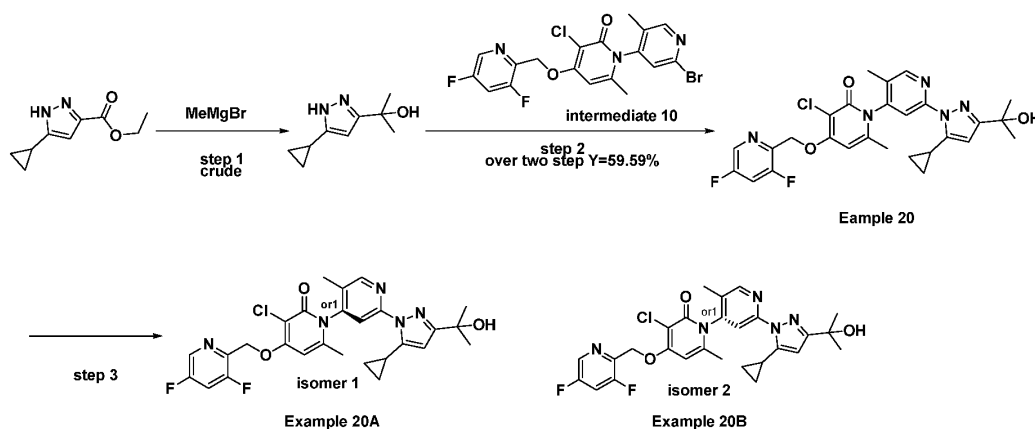
Example 19A:

[00386] LC-MS: (ES+H, m/z): [M+H]⁺ = 516.1. ¹H NMR (400 MHz, DMSO-d₆) δ 8.60 (d, 1H), 8.54 (s, 1H), 8.16 – 8.05 (m, 1H), 7.75 (s, 1H), 6.80 (s, 1H), 6.30 (s, 1H), 5.48 (d, 2H), 4.98 (s, 1H), 2.63 (s, 3H), 2.01 (s, 3H), 1.99 (s, 3H), 1.44 (s, 6H). ¹⁹F NMR (377 MHz, DMSO) δ -120.155, -120.173, -122.342, -122.361.

Example 19B:

[00387] LC-MS: (ES+H, m/z): [M+H]⁺ = 516.1. ¹H NMR (400 MHz, DMSO-d₆) δ 8.60 (d, 1H), 8.54 (s, 1H), 8.16 – 8.05 (m, 1H), 7.75 (s, 1H), 6.80 (s, 1H), 6.30 (s, 1H), 5.48 (d, 2H), 4.98 (s, 1H), 2.63 (s, 3H), 2.01 (s, 3H), 1.99 (s, 3H), 1.44 (s, 6H). ¹⁹F NMR (377 MHz, DMSO) δ -120.150, -120.176, -122.336, -122.362.

Example 20A, 20B



Step 1: Preparation of 2-(5-cyclopropyl-1H-pyrazol-3-yl)propan-2-ol :

[00388] To a stirred solution of ethyl 5-cyclopropyl-1H-pyrazole-3-carboxylate (500 mg, 2.775 mmol, 1 equiv) in THF (10 mL) was added bromo(methyl)magnesium (13.87 mL, 5 equiv, 1 M in THF) dropwise at -30°C under N₂ atmosphere. The resulting mixture was stirred for 1h at r.t. under N₂ atmosphere. The reaction

was monitored by LCMS. The reaction was quenched by the addition of Saturated NH_4Cl (10 mL) at r.t. The resulting mixture was extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 . After filtration, the filtrate was concentrated under reduced pressure to afford 2-(5-cyclopropyl-1H-pyrazol-3-yl)propan-2-ol (517 mg, crude) as a yellow solid. LC-MS: (ES+H, m/z): $[\text{M}+\text{H}]^+ = 167.2$.

Step 2: Preparation of racemate 3-chloro-2'-[5-cyclopropyl-3-(2-hydroxypropan-2-yl)pyrazol-1-yl]-4-[(3,5-difluoropyridin-2-yl)methoxy]-5',6-dimethyl-[1,4'-bipyridin]-2-one:

[00389] A mixture of 2'-bromo-3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-5',6-dimethyl-[1,4'-bipyridin]-2-one (300 mg, 0.657 mmol, 1 equiv), 2-(5-cyclopropyl-1H-pyrazol-3-yl)propan-2-ol (218.39 mg, 1.314 mmol, 2 equiv), (1R,2R)-N1,N2-dimethylcyclohexane-1,2-diamine (186.89 mg, 1.314 mmol, 2 equiv), K_2CO_3 (181.58 mg, 1.314 mmol, 2 equiv) and CuI (31.28 mg, 0.164 mmol, 0.25 equiv) in 1,4-dioxane (3 mL) was stirred for 2 h at 100°C under nitrogen atmosphere. The reaction was monitored by LCMS. The resulting mixture was cooled down to r.t. and poured into 10 mL of water. The resulting mixture was extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na_2SO_4 . After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography to afford crude product, which was further purified by Prep-HPLC to afford 3-chloro-2'-[5-cyclopropyl-3-(2-hydroxypropan-2-yl)pyrazol-1-yl]-4-[(3,5-difluoropyridin-2-yl)methoxy]-5',6-dimethyl-[1,4'-bipyridin]-2-one (230 mg, 59.59%) as a white solid. LC-MS: (ES+H, m/z): $[\text{M}+\text{H}]^+ = 542.2$.

Step 3: Preparation of rel-3-chloro-2'-[5-cyclopropyl-3-(2-hydroxypropan-2-yl)pyrazol-1-yl]-4-[(3,5-difluoropyridin-2-yl)methoxy]-5',6-dimethyl-[1,4'-bipyridin]-2-one (Example 20A) and rel-3-chloro-2'-[5-cyclopropyl-3-(2-hydroxypropan-2-yl)pyrazol-1-yl]-4-[(3,5-difluoropyridin-2-yl)methoxy]-5',6-dimethyl-[1,4'-bipyridin]-2-one (Example 20B):

The racemate (230 mg) was separated by Prep-Chiral-HPLC to afford Example 20A (78.4 mg) as white solid and Example 20B (90.2 mg) as white solid.

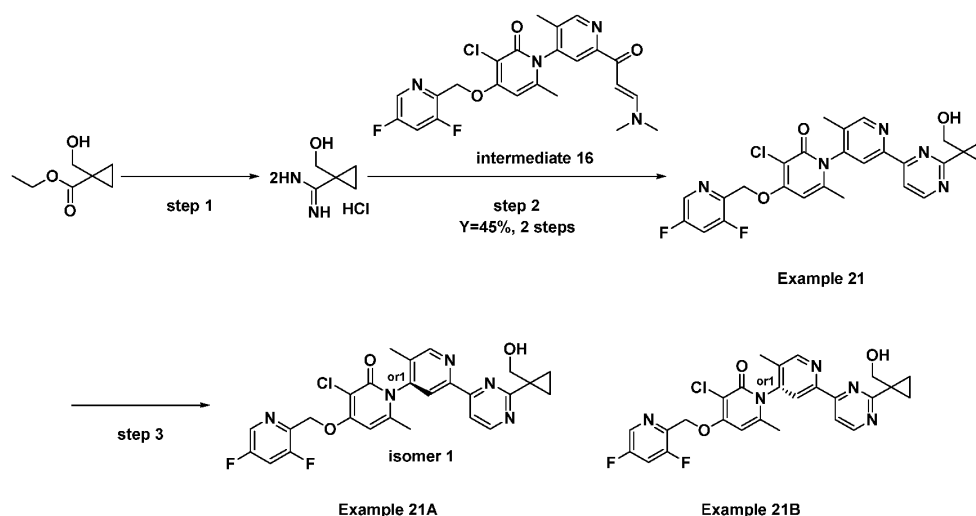
Example 20A:

[00390] LC-MS: (ES+H, m/z): $[\text{M}+\text{H}]^+ = 541.90$. ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 8.61 (d, 1H), 8.57 (s, 1H), 8.15 – 8.06 (m, 1H), 7.74 (s, 1H), 6.81 (s, 1H), 6.12 (s, 1H), 5.49 (d, 2H), 4.96 (s, 1H), 2.81 – 2.73 (m, 1H), 2.03 (s, 3H), 2.01 (s, 3H), 1.42 (s, 6H), 1.04 – 0.93 (m, 2H), 0.74 – 0.62 (m, 2H). ^{19}F NMR (282 MHz, DMSO) δ -120.14, -120.17, -122.33, -122.36.

Example 20B:

[00391] LC-MS: (ES+H, m/z): $[\text{M}+\text{H}]^+ = 541.90$. ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 8.61 (d, 1H), 8.57 (s, 1H), 8.19 – 8.03 (m, 1H), 7.74 (s, 1H), 6.81 (s, 1H), 6.12 (s, 1H), 5.49 (d, 2H), 4.96 (s, 1H), 2.81 – 2.73 (m, 1H), 2.03 (s, 3H), 2.01 (s, 3H), 1.42 (s, 6H), 1.03 – 0.94 (m, 2H), 0.78 – 0.61 (m, 2H). ^{19}F NMR (282 MHz, DMSO) δ -120.14, -120.17, -122.33, -122.35.

Example 21A, 21B



Step 1: Preparation of 1-(hydroxymethyl)cyclopropane-1-carboximidamide hydrochloride:

[00392] To a stirred mixture of NH_4Cl (556.54 mg, 10.405 mmol, 5 equiv) in Toluene (10 mL) was added AlMe_3 (5.2 mL, 10.405 mmol, 5 equiv, 2 M in toluene) dropwise at 0°C under nitrogen atmosphere. The resulting mixture was stirred for 10 min at 0°C under nitrogen atmosphere, and then was stirred at room temperature until no generation of gas. To the above mixture was added a solution of ethyl 1-(hydroxymethyl)cyclopropane-1-carboxylate (300 mg, 2.081 mmol, 1 equiv) in toluene dropwise at room temperature. The resulting mixture was stirred for additional overnight at 80°C . The reaction was monitored by LCMS. The reaction was quenched by the addition of MeOH (10 mL) at 0°C . The resulting mixture was filtered, the filter cake was washed with MeOH (50 mL). The filtrate was concentrated under reduced pressure. The residue was dissolved in MeOH (30 mL). The resulting mixture was filtered, the filter cake was washed with MeOH (15 mL). The filtrate was concentrated under reduced pressure. This resulted in 1-(hydroxymethyl)cyclopropane-1-carboximidamide hydrochloride (230 mg, crude) as a white solid. ^1H NMR (300 MHz, DMSO-d_6) δ 8.99 (s, 2H), 8.72 (s, 2H), 5.41 (t, 1H), 3.52 (d, 2H), 1.21 – 1.12 (m, 2H), 0.99 – 0.90 (m, 2H).

Step 2: Preparation of 3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-2'-[2-[1-(hydroxymethyl)cyclopropyl]pyrimidin-4-yl]-5',6-dimethyl-[1,4'-bipyridin]-2-one:

[00393] To a stirred mixture of 3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-2'-[(2E)-3-(dimethylamino)prop-2-en-1-yl]-5',6-dimethyl-[1,4'-bipyridin]-2-one (150 mg, 0.316 mmol, 1.00 equiv) and 1-(hydroxymethyl)cyclopropane-1-carboximidamide hydrochloride (216.33 mg, 1.896 mmol, 6 equiv, assumed 100% yield) in IPA (3 mL) was added K_2CO_3 (436.53 mg, 1.896 mmol, 10 equiv) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for overnight at 80°C under nitrogen atmosphere. The mixture was allowed to cool down to room temperature. The resulting mixture was filtered, the filter cake was washed with MeOH (3 x 10 mL). The filtrate was concentrated under reduced pressure. The residue was purified by Prep-TLC (PE/EA 1:4) to afford 3-chloro-4-[(3,5-

difluoropyridin-2-yl)methoxy]-2'-{2-[1-(hydroxymethyl)cyclopropyl]pyrimidin-4-yl}-5',6-dimethyl-[1,4'-bipyridin]-2-one (75 mg, 45%) as a light yellow solid. LC-MS: (ES+H, m/z): $[M+H]^+ = 526.1$.

Step3: Preparation of (isomer 1) rel-3-chloro-4-((3,5-difluoropyridin-2-yl)methoxy)-2'-(2-(1-(hydroxymethyl)cyclopropyl)pyrimidin-4-yl)-5',6-dimethyl-2H-[1,4'-bipyridin]-2-one and (isomer 2) rel-3-chloro-4-((3,5-difluoropyridin-2-yl)methoxy)-2'-(2-(1-(hydroxymethyl)cyclopropyl)pyrimidin-4-yl)-5',6-dimethyl-2H-[1,4'-bipyridin]-2-one:

[00394] 3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-2'-{2-[1-(hydroxymethyl)cyclopropyl]pyrimidin-4-yl}-5',6-dimethyl-[1,4'-bipyridin]-2-one (70 mg) was separated by Prep-CHIRAL-HPLC to afford rel-3-chloro-4-((3,5-difluoropyridin-2-yl)methoxy)-2'-(2-(1-(hydroxymethyl)cyclopropyl)pyrimidin-4-yl)-5',6-dimethyl-2H-[1,4'-bipyridin]-2-one (**Example 21A**, isomer 1, 18.4 mg, ee=100%) as a white solid and rel-3-chloro-4-((3,5-difluoropyridin-2-yl)methoxy)-2'-(2-(1-(hydroxymethyl)cyclopropyl)pyrimidin-4-yl)-5',6-dimethyl-2H-[1,4'-bipyridin]-2-one (**Example 21B**, isomer 2, 19.1 mg, ee=99.1%) as a white solid.

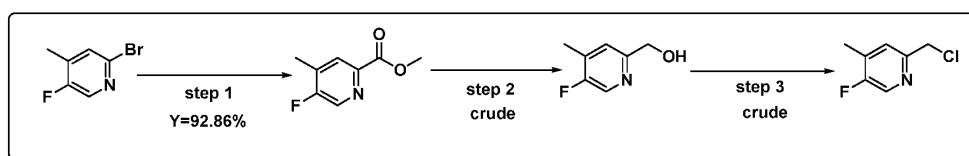
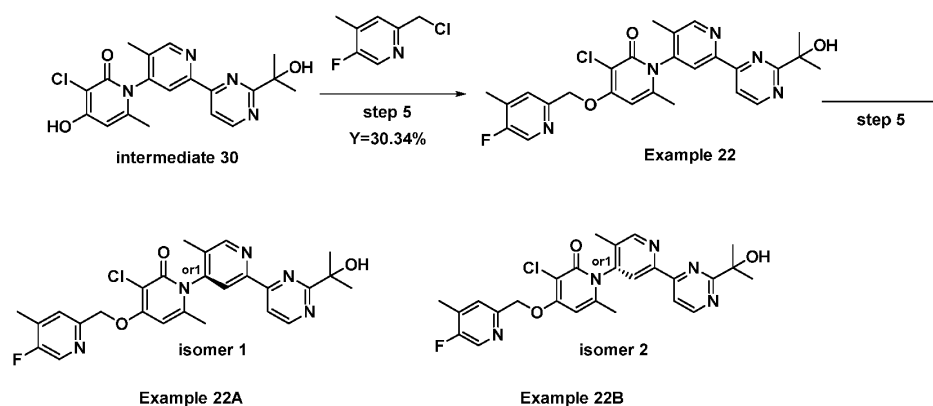
Example 21A:

[00395] LC-MS: (ES+H, m/z): $[M+H]^+ = 526.15$. ^1H NMR (400 MHz, DMSO- d_6) δ 8.85 (t, 2H), 8.62 (d, 1H), 8.36 (s, 1H), 8.15 – 8.06 (m, 2H), 6.84 (s, 1H), 5.49 (d, 2H), 4.56 (t, 1H), 3.97 (d, 2H), 2.09 (s, 3H), 1.97 (s, 3H), 1.38 – 1.32 (m, 1H), 1.26 – 1.20 (m, 1H), 1.10 – 1.04 (m, 2H). ^{19}F NMR (377 MHz, DMSO) δ -120.10, -120.12, -122.31, -122.33.

Example 21B:

[00396] LC-MS: (ES+H, m/z): $[M+H]^+ = 526.15$. ^1H NMR (400 MHz, DMSO- d_6) δ 8.85 (t, 2H), 8.62 (d, 1H), 8.36 (s, 1H), 8.15 – 8.06 (m, 2H), 6.84 (s, 1H), 5.49 (d, 2H), 4.56 (t, 1H), 3.97 (d, 2H), 2.09 (s, 3H), 1.97 (s, 3H), 1.38 – 1.31 (m, 1H), 1.27 – 1.17 (m, 1H), 1.10 – 1.05 (m, 2H). ^{19}F NMR (377 MHz, DMSO) δ -120.10, -120.12, -122.31, -122.32.

Example 22A, 22B



Step 1: methyl 5-fluoro-4-methylpyridine-2-carboxylate:

[00397] To a stirred mixture of 2-bromo-3-fluoro-5-methylpyridine (3.00 g, 15.78 mmol, 1.00 equiv) and DIEA (10.20 g, 78.94 mmol, 5.00 equiv) in MeOH (14 mL) were added Pd(dppf)Cl₂ (0.58 g, 0.78 mmol, 0.05 equiv) at room temperature under air atmosphere. The resulting mixture was stirred for 5 h at 110°C under carbon monoxide atmosphere (30 atm). The reaction was monitored by LCMS. Desired product could be detected by LCMS. The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography to afford ethyl 3-fluoro-5-methylpyridine-2-carboxylate (2.48 g, 92.86%) as an off-white solid. LC-MS: (ES+H, m/z): [M+H]⁺ = 170.2. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.58 (d, 1H), 8.08 (d, 1H), 3.89 (s, 3H), 2.36 (s, 3H).

Step 2: (5-fluoro-4-methylpyridin-2-yl)methanol:

[00398] To a stirred solution of methyl 5-fluoro-4-methylpyridine-2-carboxylate (1.00 g, 5.91 mmol, 1.00 equiv) in THF (8 mL) and MeOH (2 mL) were added NaBH₄ (1.12 g, 29.56 mmol, 5.00 equiv) in portions at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 2 h at room temperature under nitrogen atmosphere. The reaction was monitored by LCMS. Desired product could be detected by LCMS. The reaction was quenched with water (50 mL) at room temperature. The resulting mixture was extracted with EtOAc (100 mL). The combined organic layers were washed with brine (100 mL), dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The crude product (700 mg) was used in the next step directly without further purification. LC-MS: (ES+H, m/z): [M+H]⁺ = 142.2. ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.33 (d, 1H), 7.42 – 7.38 (m, 1H), 5.44 (t, 1H), 4.51 (d, 2H), 2.29 (s, 3H).

Step 3: 2-(chloromethyl)-5-fluoro-4-methylpyridine:

[00399] To a stirred solution of (5-fluoro-4-methylpyridin-2-yl)methanol (700 mg, 2.80 mmol, 1.00 equiv) in DCM (6 mL) were added SOCl₂ (1.5 mL) and DMF (362 mg, 2.80 mmol, 1.00 equiv) dropwise at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 2 h at room temperature under nitrogen atmosphere. The reaction was monitored by LCMS. Desired product could be detected by LCMS. The resulting mixture was concentrated under reduced pressure. The crude product (838 mg) was used in the next step directly without further purification. LC-MS: (ES+H, m/z): [M+H]⁺ = 160.0.

Step 4: 3-chloro-4-[(5-fluoro-4-methylpyridin-2-yl)methoxy]-2'-[2-(2-hydroxypropan-2-yl)pyrimidin-4-yl]-5',6-dimethyl-[1,4'-bipyridin]-2-one:

[00400] To a stirred mixture of 3-chloro-4-hydroxy-2'-[2-(2-hydroxypropan-2-yl)pyrimidin-4-yl]-5',6-dimethyl-[1,4'-bipyridin]-2-one (500 mg, 1.29 mmol, 1.00 equiv) and 2-(chloromethyl)-5-fluoro-4-methylpyridine (778 mg, 4.87 mmol, 4.00 equiv) in DMF (4 mL) were added K₂CO₃ (891 mg, 6.44 mmol, 4.99 equiv) and 18-Crown-6 (34 mg, 0.13 mmol, 0.10 equiv) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 2 h at 60°C under nitrogen atmosphere. The reaction was monitored by LCMS. Desired product could be detected by LCMS. The residue was purified by silica gel column chromatography to afford crude product (280 mg), which was further purified by Prep-HPLC to afford 3-chloro-4-[(5-fluoro-4-methylpyridin-2-yl)methoxy]-2'-[2-(2-hydroxypropan-2-yl)pyrimidin-4-yl]-

5',6-dimethyl-[1,4'-bipyridin]-2-one (200 mg, 30.34%) as a white solid. LC-MS: (ES+H, m/z): $[M+H]^+ = 510.2$.

Step 5: rel-3-chloro-4-[(5-fluoro-4-methylpyridin-2-yl)methoxy]-2'-[2-(2-hydroxypropan-2-yl)pyrimidin-4-yl]-5',6-dimethyl-[1,4'-bipyridin]-2-one and rel-3-chloro-4-[(5-fluoro-4-methylpyridin-2-yl)methoxy]-2'-[2-(2-hydroxypropan-2-yl)pyrimidin-4-yl]-5',6-dimethyl-[1,4'-bipyridin]-2-one:

[00401] The racemate (200 mg) was separated by Prep-Chiral-HPLC to afford **Example 22A** (73 mg, 99.4%, ee=100%) as a white solid and **Example 22B** (69.8 mg, 99.4%, ee=98.8%) as a white solid.

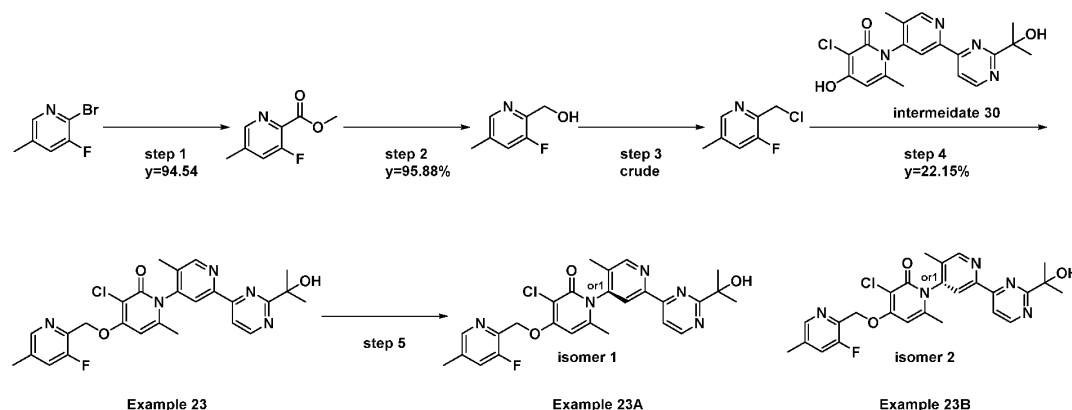
Example 22A:

[00402] LC-MS: (ES+H, m/z): $[M+H]^+ = 510.15$. ^1H NMR (400 MHz, DMSO- d_6) δ 8.97 (d, 1H), 8.86 (s, 1H), 8.68 (s, 1H), 8.51 (d, 1H), 8.24 (d, 1H), 7.58 (d, 1H), 6.81 (s, 1H), 5.38 (d, 2H), 5.25 (s, 1H), 2.35 (d, 3H), 2.11 (s, 3H), 1.98 (s, 3H), 1.53 (s, 6H). ^{19}F NMR (377 MHz, DMSO) δ -133.88.

Example 22B:

[00403] LC-MS: (ES+H, m/z): $[M+H]^+ = 510.10$. ^1H NMR (400 MHz, DMSO- d_6) δ 8.97 (d, 1H), 8.86 (s, 1H), 8.68 (s, 1H), 8.51 (d, 1H), 8.24 (d, 1H), 7.58 (d, 1H), 6.83 – 6.78 (m, 1H), 5.38 (d, 2H), 5.25 (s, 1H), 2.35 (d, 3H), 2.11 (s, 3H), 1.98 (s, 3H), 1.53 (s, 6H). ^{19}F NMR (377 MHz, DMSO) δ -133.88.

Example 23A, 23B



Step 1: Preparation of methyl 3-fluoro-5-methylpyridine-2-carboxylate:

[00404] A mixture of 2-bromo-3-fluoro-5-methylpyridine (3 g, 15.788 mmol, 1 equiv), Pd(dppf)Cl₂ (1.16 g, 1.579 mmol, 0.1 equiv) and DIEA (10.20 g, 78.940 mmol, 5 equiv) in MeOH (30 mL) was stirred for 3 h at 110°C under carbon monoxide atmosphere (30 atm). The reaction was monitored by LCMS. The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography to afford methyl 3-fluoro-5-methylpyridine-2-carboxylate (2.54 g, 94.54%) as an off-white solid. LC-MS: (ES+H, m/z): $[M+H]^+ = 170.1$. ^1H NMR (300 MHz, DMSO- d_6) δ 8.43 – 8.34 (m, 1H), 7.80 – 7.70 (m, 1H), 3.88 (s, 3H), 2.40 (t, 3H).

Step 2: Preparation of (3-fluoro-5-methylpyridin-2-yl)methanol:

[00405] A mixture of methyl 3-fluoro-5-methylpyridine-2-carboxylate (500 mg, 2.956 mmol, 1 equiv) and NaBH₄ (447.32 mg, 11.824 mmol, 4 equiv) in THF (4 mL) and methanol (1 mL) was stirred for 2 h at r.t. The reaction was monitored by LCMS. The reaction was quenched with water at r. t. The resulting mixture

was extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine (30 mL), dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure to afford (3-fluoro-5-methylpyridin-2-yl)methanol (400 mg, 95.88%) as a yellow solid. LC-MS: (ES+H, m/z): [M+H]⁺ = 142.1. ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.22 (d, 1H), 7.56-7.43 (m, 1H), 5.23 (t, 1H), 4.59 – 4.48 (m, 2H), 2.32 (s, 3H).

Step 3: Preparation of 2-(chloromethyl)-3-fluoro-5-methylpyridine:

[00406] A mixture of (3-fluoro-5-methylpyridin-2-yl)methanol (387 mg, 2.742 mmol, 1 equiv), DMF (20.04 mg, 0.274 mmol, 0.1 equiv) and SOCl₂ (1.5 mL, 20.677 mmol, 7.54 equiv) in CH₂Cl₂ (3 mL) was stirred for 2 h at r.t. The reaction was monitored by LCMS. The resulting mixture was concentrated under reduced pressure to afford 2-(chloromethyl)-3-fluoro-5-methylpyridine (638 mg, crude) as a yellow solid. LC-MS: (ES+H, m/z): [M+H]⁺ = 160.0.

Step 4: Preparation of 3-chloro-4-[(3-fluoro-5-methylpyridin-2-yl)methoxy]-2'-[2-(2-hydroxypropan-2-yl)pyrimidin-4-yl]-5',6-dimethyl-[1,4'-bipyridin]-2-one:

[00407] A mixture of 2-(chloromethyl)-3-fluoro-5-methylpyridine (412.55 mg, 2.586 mmol, 2 equiv), 3-chloro-4-hydroxy-2'-[2-(2-hydroxypropan-2-yl)pyrimidin-4-yl]-5',6-dimethyl-[1,4'-bipyridin]-2-one (500 mg, 1.293 mmol, 1.00 equiv), K₂CO₃ (893.17 mg, 6.465 mmol, 5 equiv) and 18-Crown-6 (34.16 mg, 0.129 mmol, 0.1 equiv) in DMF was stirred for overnight at 60°C under nitrogen atmosphere. The reaction was monitored by LCMS. The resulting mixture was cooled down to r.t. and poured into 10 mL of water. The resulting mixture was extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography to afford crude product, which was further purified by Prep-HPLC to afford 3-chloro-4-[(3-fluoro-5-methylpyridin-2-yl)methoxy]-2'-[2-(2-hydroxypropan-2-yl)pyrimidin-4-yl]-5',6-dimethyl-[1,4'-bipyridin]-2-one (149 mg, 22.15%) as a white solid. LC-MS: (ES+H, m/z): [M+H]⁺ = 510.1.

Step 5: Preparation of rel-3-chloro-4-[(3-fluoro-5-methylpyridin-2-yl)methoxy]-2'-[2-(2-hydroxypropan-2-yl)pyrimidin-4-yl]-5',6-dimethyl-[1,4'-bipyridin]-2-one and rel-3-chloro-4-[(3-fluoro-5-methylpyridin-2-yl)methoxy]-2'-[2-(2-hydroxypropan-2-yl)pyrimidin-4-yl]-5',6-dimethyl-[1,4'-bipyridin]-2-one:

[00408] The racemate (149 mg) was separated by Prep-Chiral-HPLC to afford **Example 23A** (64.4 mg, 99.2%, ee=100%) as a white solid and **Example 23B** (57.6 mg, 99.5%, ee=99.8%) as a white solid.

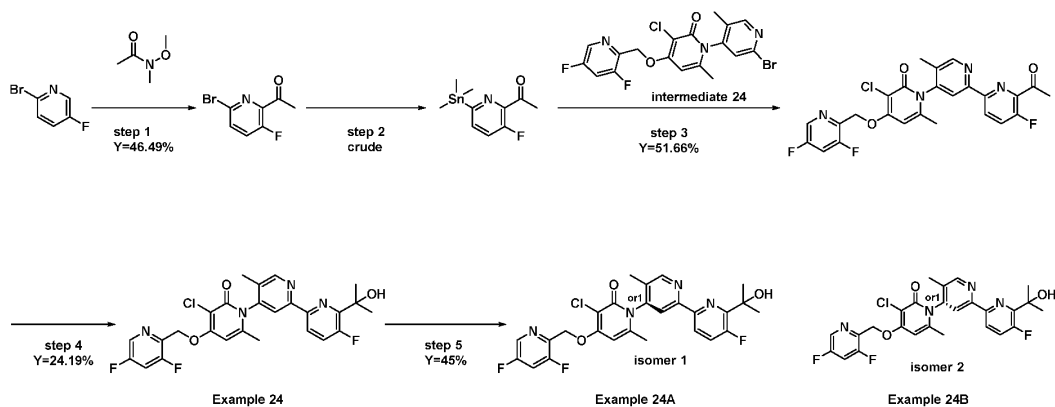
Example 23A:

[00409] LC-MS: (ES+H, m/z): [M+H]⁺ = 510.10. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.97 (d, 1H), 8.86 (s, 1H), 8.69 (s, 1H), 8.36 (s, 1H), 8.24 (d, 1H), 7.75 – 7.67 (m, 1H), 6.85 (s, 1H), 5.45 (d, 2H), 5.25 (s, 1H), 2.39 (s, 3H), 2.11 (s, 3H), 1.98 (s, 3H), 1.54 (s, 3H), 1.53 (s, 3H). ¹⁹F NMR (377 MHz, DMSO) δ -126.190.

Example 23B:

[00410] LC-MS: (ES+H, m/z): $[M+H]^+ = 510.10$. ^1H NMR (400 MHz, DMSO- d_6) δ 8.97 (d, 1H), 8.86 (s, 1H), 8.69 (s, 1H), 8.36 (s, 1H), 8.24 (d, 1H), 7.74 – 7.69 (m, 1H), 6.85 (s, 1H), 5.45 (d, 2H), 5.25 (s, 1H), 2.39 (s, 3H), 2.11 (s, 3H), 1.98 (s, 3H), 1.54 (s, 3H), 1.53 (s, 3H). ^{19}F NMR (282 MHz, DMSO) δ -126.192.

Example 24A, 24B



Step 1: Preparation of 1-(6-bromo-3-fluoropyridin-2-yl)ethanone:

[00411] To a stirred solution of 2-bromo-5-fluoropyridine (20 g, 113.644 mmol, 1 equiv) in Et₂O (500 mL) was added t-BuLi (50.00 mL, 125.008 mmol, 1.1 equiv) dropwise at -78°C under nitrogen atmosphere. The resulting mixture was stirred for 2h at -78°C under nitrogen atmosphere. N-methoxy-N-methylacetamide (12.89 g, 125.008 mmol, 1.1 equiv) was added dropwise to the above solution at -78°C under nitrogen atmosphere. The resulting mixture was stirred for 1h at -78°C under nitrogen atmosphere. The mixture was allowed to warm up to room temperature. The reaction was monitored by LCMS. The reaction was quenched by the addition of sat. NH₄Cl (aq.) (500mL). The organic phase was collected. The aqueous layer was extracted with EtOAc (2x500 mL). The combined organic layers were dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography to afford 1-(6-bromo-3-fluoropyridin-2-yl)ethanone (12 g, 46.49%) as a reddish semi-solid. LC-MS: (ES+H, m/z): $[M+H]^+ = 220.0$. ^1H NMR (400 MHz, DMSO- d_6) δ 8.03 – 7.95 (m, 1H), 7.94 – 7.85 (m, 1H), 2.58 (s, 3H).

Step 2: Preparation of 1-[3-fluoro-6-(trimethylstannyl)pyridin-2-yl]ethanone:

[00412] To a stirred mixture of 1-(6-bromo-3-fluoropyridin-2-yl)ethanone (1.2 g, 5.504 mmol, 1 equiv) and SnMe₄ (7.21 g, 22.016 mmol, 4 equiv) in 1,4-dioxane (20 mL) was added Pd(PPh₃)₂Cl₂ (0.77 g, 1.101 mmol, 0.2 equiv) and AsPh₃ (0.34 g, 1.101 mmol, 0.2 equiv) at room temperature. The resulting mixture was stirred for overnight at 80°C under nitrogen atmosphere. The reaction was monitored by LCMS. The mixture was allowed to cool down to room temperature. The resulting mixture was poured into EA (200 mL) and washed with 5 x 200 mL of KF (aq.). The organic layer was dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure to afford 1-[3-fluoro-6-(trimethylstannyl)pyridin-2-yl]ethanone.

yl]ethanone (crude). The crude product was used in the next step directly without further purification. LC-MS: (ES+H, m/z): [M+H]⁺=304.0

Step 3: Preparation of 1-{6'-acetyl-5'-fluoro-5-methyl-[2,2'-bipyridin]-4-yl}-3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-6-methylpyridin-2-one:

[00413] To a stirred solution of 1-[3-fluoro-6-(trimethylstannyl)pyridin-2-yl]ethanone (1190.10 mg, 3.942 mmol, 3 equiv) and 2'-bromo-3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-5',6-dimethyl-[1,4'-bipyridin]-2-one (600 mg, 1.314 mmol, 1.00 equiv) in 1,4-dioxane (15 mL) were added Pd(PPh₃)₂Cl₂ (92.22 mg, 0.131 mmol, 0.1 equiv) and CuI (250.22 mg, 1.314 mmol, 1 equiv) at room temperature. The resulting mixture was stirred for 3h at 80°C under nitrogen atmosphere. The mixture was allowed to cool down to room temperature. The reaction was monitored by LCMS. The resulting mixture was poured into water (200 ml), and extracted with EtOAc (3 x 200mL). The combined organic layers were dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography to afford 1-{6'-acetyl-5'-fluoro-5-methyl-[2,2'-bipyridin]-4-yl}-3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-6-methylpyridin-2-one (500 mg, 51.66%) as a white solid. LC-MS: (ES+H, m/z): [M+H]⁺=515.1. ¹H NMR (400 MHz, DMSO-d₆) δ 8.81 (s, 1H), 8.70 – 8.64 (m, 1H), 8.64 – 8.59 (m, 1H), 8.34 (s, 1H), 8.15 – 8.07 (m, 1H), 8.07 – 8.00 (m, 1H), 6.83 (s, 1H), 5.49 (s, 2H), 2.73 (s, 3H), 2.08 (s, 3H), 1.98 (s, 3H).

Step 4: Preparation of 3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-1-[5'-fluoro-6'-(2-hydroxypropan-2-yl)-5-methyl-[2,2'-bipyridin]-4-yl]-6-methylpyridin-2-one:

[00414] To a stirred mixture of 1-{6'-acetyl-5'-fluoro-5-methyl-[2,2'-bipyridin]-4-yl}-3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-6-methylpyridin-2-one (450 mg, 0.874 mmol, 1 equiv) in THF (6 mL) was added MeMgBr (2.91 mL, 8.740 mmol, 10 equiv) dropwise at 0°C under nitrogen atmosphere. The resulting mixture was stirred for 1 h at 0°C under nitrogen atmosphere. The reaction was monitored by LCMS. The reaction was quenched with sat. NH₄Cl (aq.) at 0°C. The resulting mixture was extracted with EtOAc (3 x 100 mL). The combined organic layers were dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The crude product was purified by Prep-HPLC to afford 3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-1-[5'-fluoro-6'-(2-hydroxypropan-2-yl)-5-methyl-[2,2'-bipyridin]-4-yl]-6-methylpyridin-2-one (80 mg, 24.19%) as a white solid. LC-MS: (ES+H, m/z): [M+H]⁺=531.1.

Step 5: Preparation of rel-3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-1-[5'-fluoro-6'-(2-hydroxypropan-2-yl)-5-methyl-[2,2'-bipyridin]-4-yl]-6-methylpyridin-2-one and rel-3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-1-[5'-fluoro-6'-(2-hydroxypropan-2-yl)-5-methyl-[2,2'-bipyridin]-4-yl]-6-methylpyridin-2-one :

[00415] The racemate 3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-1-[5'-fluoro-6'-(2-hydroxypropan-2-yl)-5-methyl-[2,2'-bipyridin]-4-yl]-6-methylpyridin-2-one (80 mg) was separated by Prep-Chiral-HPLC to afford rel-3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-1-[5'-fluoro-6'-(2-hydroxypropan-2-yl)-5-methyl-[2,2'-bipyridin]-4-yl]-6-methylpyridin-2-one (**Example 24A**, 18.6 mg, 98.8%, ee=100%) as a white solid

and rel-3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-1-[5'-fluoro-6'-(2-hydroxypropan-2-yl)-5-methyl-[2,2'-bipyridin]-4-yl]-6-methylpyridin-2-one (**Example 24B**, 17.5 mg, 99.7%, ee=98.6%) as a white solid.

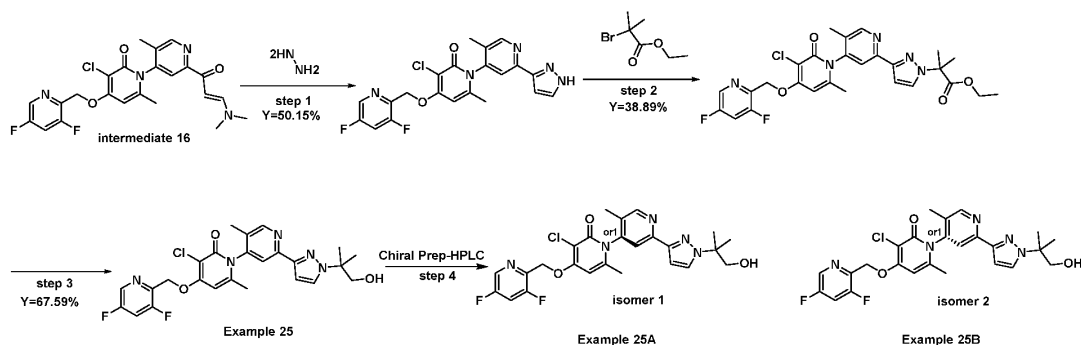
Example 24A:

[00416] LC-MS: (ES+H, m/z): $[M+H]^+ = 531.25$. ^1H NMR (400 MHz, DMSO- d_6) δ 8.77 (s, 1H), 8.62 (d, 1H), 8.49 (s, 1H), 8.43 – 8.35 (m, 1H), 8.17 – 8.05 (m, 1H), 7.90 – 7.78 (m, 1H), 6.83 (s, 1H), 5.49 (s, 2H), 5.46 (s, 1H), 2.07 (s, 3H), 1.99 (s, 3H), 1.55 (s, 6H). ^{19}F NMR (377 MHz, DMSO) δ -119.955, -120.122, -120.148, -122.312, -122.337.

Example 24B:

[00417] LC-MS: (ES+H, m/z): $[M+H]^+ = 531.25$. ^1H NMR (400 MHz, DMSO- d_6) δ 8.77 (s, 1H), 8.62 (d, 1H), 8.49 (s, 1H), 8.43 – 8.35 (m, 1H), 8.17 – 8.05 (m, 1H), 7.90 – 7.78 (m, 1H), 6.83 (s, 1H), 5.49 (s, 2H), 5.46 (s, 1H), 2.06 (s, 3H), 1.99 (s, 3H), 1.55 (s, 6H). ^{19}F NMR (377 MHz, DMSO) δ -119.954, -120.119, -120.144, -122.307, -122.332.

Example 25, 25A, 25B



Step 1: 3-chloro-4-((3,5-difluoropyridin-2-yl)methoxy)-5',6-dimethyl-2'-(1H-pyrazol-3-yl)-2H-[1,4'-bipyridin]-2-one:

[00418] To a stirred solution of 3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-2'-[(2E)-3-(dimethylamino)prop-2-enoyl]-5',6-dimethyl-[1,4'-bipyridin]-2-one (960 mg, 2.022 mmol, 1.00 equiv) and K_2CO_3 (558.77 mg, 4.044 mmol, 2 equiv) in ACN (10 mL) was added hydrazine (20 mL, 1M in THF, 20.220 mmol, 10 equiv) at room temperature. The resulting mixture was stirred for overnight at 80°C under nitrogen atmosphere. The reaction was monitored by LCMS. Desired product could be detected by LCMS. The resulting mixture was diluted with water (20 mL). The resulting mixture was extracted with EtOAc (2 x 20 mL). The combined organic layers were dried over anhydrous Na_2SO_4 . After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by reverse flash chromatography to afford 3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-5',6-dimethyl-2'-(1H-pyrazol-3-yl)-[1,4'-bipyridin]-2-one (450 mg, 50.15%) as a yellow solid. LC-MS: (ES+H, m/z): $[M+H]^+ = 444.1$. ^1H NMR (400 MHz, DMSO- d_6) δ 13.11 (s, 1H), 8.67 (s, 1H), 8.61 (d, 1H), 8.16 – 8.05 (m, 1H), 7.81 (s, 2H), 6.87 (d, 1H), 6.80 (s, 1H), 5.49 (s, 2H), 2.02 (s, 3H), 1.98 (s, 3H).

Step 2: ethyl 2-(3-(3-chloro-4-((3,5-difluoropyridin-2-yl)methoxy)-5',6-dimethyl-2-oxo-2H-[1,4'-bipyridin]-2'-yl)-1H-pyrazol-1-yl)-2-methylpropanoate:

[00419] To a stirred solution of 3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-5',6-dimethyl-2'-(1H-pyrazol-3-yl)-[1,4'-bipyridin]-2-one (450 mg, 1.014 mmol, 1 equiv) and K₂CO₃ (280.25 mg, 2.028 mmol, 2 equiv) in DMF (5 mL) was added ethyl α -bromoisobutyrate (988.82 mg, 5.070 mmol, 5 equiv) dropwise at room temperature. The resulting mixture was stirred for overnight at 80°C under nitrogen atmosphere. The reaction was monitored by LCMS. LCMS was ok. The resulting mixture was diluted with water (20 mL) and extracted with EtOAc (2 x 20 mL). The combined organic layers were dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by reverse flash chromatography to afford ethyl 2-(3-{3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-5',6-dimethyl-2-oxo-[1,4'-bipyridin]-2'-yl}pyrazol-1-yl)-2-methylpropanoate (220 mg, 38.89%) as a yellow solid. LC-MS: (ES+H, m/z): [M+H]⁺ = 558.3. ¹H NMR (400 MHz, DMSO-d₆) δ 8.66 (s, 1H), 8.61 (d, 1H), 8.13 – 8.06 (m, 1H), 8.02 (d, 1H), 7.75 (s, 1H), 6.89 (d, 1H), 6.79 (s, 1H), 5.48 (s, 2H), 4.18 – 4.00 (m, 2H), 2.01 (s, 3H), 1.96 (s, 3H), 1.82 (s, 6H), 1.11 (t, 3H).

Step 3: 3-chloro-4-((3,5-difluoropyridin-2-yl)methoxy)-2'-(1-(1-hydroxy-2-methylpropan-2-yl)-1H-pyrazol-3-yl)-5',6-dimethyl-2H-[1,4'-bipyridin]-2-one:

[00420] To a stirred solution of ethyl 2-(3-{3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-5',6-dimethyl-2-oxo-[1,4'-bipyridin]-2'-yl}pyrazol-1-yl)-2-methylpropanoate (160 mg, 0.287 mmol, 1 equiv) in THF (3 mL) and MeOH (1 mL) was added NaBH₄ (54.24 mg, 1.435 mmol, 5 equiv) at room temperature. The resulting mixture was stirred for 4 h at room temperature under nitrogen atmosphere. The reaction was monitored by LCMS. LCMS was ok. The resulting mixture was quenched by addition of saturated NH₄Cl aq., then poured into water (20 mL). The resulting mixture was extracted with EtOAc (2 x 15 mL). The combined organic layers were dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure to afford 3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-2'-[1-(1-hydroxy-2-methylpropan-2-yl)pyrazol-3-yl]-5',6-dimethyl-[1,4'-bipyridin]-2-one (100 mg, 67.59%) as a pale yellow solid. LC-MS: (ES+H, m/z): [M+H]⁺ = 515.9.

Step 4: rel-3-chloro-4-((3,5-difluoropyridin-2-yl)methoxy)-2'-(1-(1-hydroxy-2-methylpropan-2-yl)-1H-pyrazol-3-yl)-5',6-dimethyl-2H-[1,4'-bipyridin]-2-one and rel-3-chloro-4-((3,5-difluoropyridin-2-yl)methoxy)-2'-(1-(1-hydroxy-2-methylpropan-2-yl)-1H-pyrazol-3-yl)-5',6-dimethyl-2H-[1,4'-bipyridin]-2-one:

[00421] The racemate was separated by Chiral Prep-HPLC to afford rel-3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-2'-[1-(1-hydroxy-2-methylpropan-2-yl)pyrazol-3-yl]-5',6-dimethyl-[1,4'-bipyridin]-2-one (Example 25A, 41.6 mg, ee=100%) as a white solid and rel-3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-2'-[1-(1-hydroxy-2-methylpropan-2-yl)pyrazol-3-yl]-5',6-dimethyl-[1,4'-bipyridin]-2-one (Example 25B, 47.3 mg, ee= 99.9%) as a white solid.

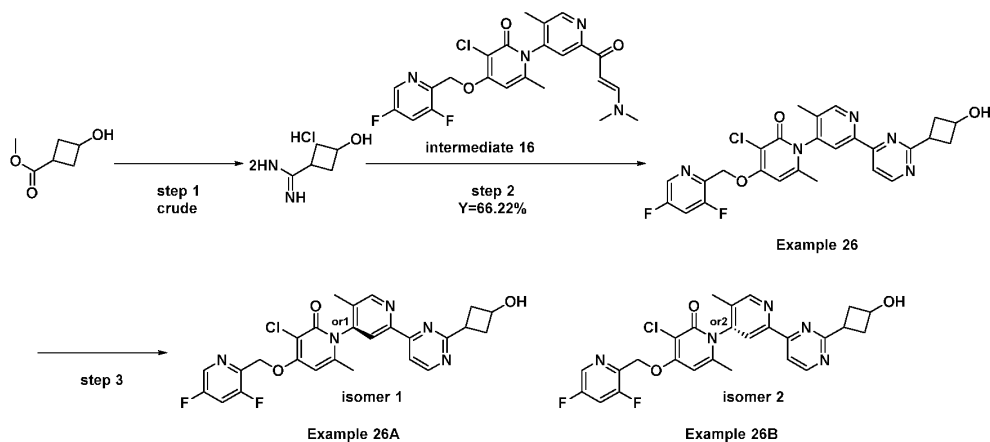
Example 25A:

[00422] LC-MS: (ES+H, m/z): $[M+H]^+ = 516.10$. ^1H NMR (300 MHz, DMSO- d_6) δ 8.65 (s, 1H), 8.61 (d, 1H), 8.16 – 8.07 (m, 1H), 7.88 (d, 1H), 7.77 (s, 1H), 6.87 – 6.73 (m, 2H), 5.49 (s, 2H), 4.99 (t, 1H), 3.70 – 3.57 (m, 2H), 2.01 (s, 3H), 1.98 (s, 3H), 1.51 (s, 6H). ^{19}F NMR (282 MHz, DMSO) δ -120.16, -120.18, -122.36, -122.39.

Example 25B:

[00423] LC-MS: (ES+H, m/z): $[M+H]^+ = 516.15$. ^1H NMR (400 MHz, DMSO- d_6) δ 8.64 (s, 1H), 8.61 (d, 1H), 8.15 – 8.06 (m, 1H), 7.87 (d, 1H), 7.77 (s, 1H), 6.84 – 6.75 (m, 2H), 5.52 – 5.45 (m, 2H), 4.97 (t, 1H), 3.66 – 3.58 (m, 2H), 2.00 (s, 3H), 1.98 (s, 3H), 1.50 (s, 6H). ^{19}F NMR (377 MHz, DMSO) δ -120.16, -120.18, -122.37, -122.39.

Example 26A, 26B



Step 1: Preparation of 3-hydroxycyclobutane-1-carboximidamide:

[00424] To a stirred mixture of NH_4Cl (2.06 g, 38.420 mmol, 5 equiv) in Toluene (10 mL) was added AlMe_3 (19.21 mL, 38.420 mmol, 5 equiv) dropwise at 0°C under nitrogen atmosphere. The resulting mixture was stirred for 10 min at 0°C under nitrogen atmosphere, and then was stirred at room temperature until no generation of gas. To the above mixture was added a solution of methyl 3-hydroxycyclobutane-1-carboxylate (1 g, 7.684 mmol, 1 equiv) in toluene dropwise at r.t.. The resulting mixture was stirred for overnight at 80°C . The reaction was monitored by LCMS. The reaction was quenched by the addition of MeOH (20 mL) at 0°C . The resulting mixture was filtered, the filter cake was washed with MeOH (150 mL). The filtrate was concentrated under reduced pressure. The residue was dissolved in EtOH (20 mL). The resulting mixture was filtered, the filter cake was washed with EtOH (10 mL). The filtrate was concentrated under reduced pressure. This resulted in 3-hydroxycyclobutane-1-carboximidamide (1.1 g, crude) as a white solid. ^1H NMR (400 MHz, DMSO- d_6) δ 8.93 (s, 1H), 8.82 (s, 2H), 5.42 (d, 1H), 4.43 – 4.33 (m, 1H), 2.79 – 2.71 (m, 1H), 2.49 – 2.42 (m, 2H), 2.11 – 2.06 (m, 2H).

Step 2: Preparation of 3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-2'-[2-(3-hydroxycyclobutyl)pyrimidin-4-yl]-5',6-dimethyl-[1,4'-bipyridin]-2-one:

[00425] A mixture of 3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-2'-[(2E)-3-(dimethylamino)prop-2-en-1-yl]-5',6-dimethyl-[1,4'-bipyridin]-2-one (150 mg, 0.316 mmol, 1.00 equiv), K_2CO_3 (873.08 mg, 6.320

mmol, 20 equiv) and 3-hydroxycyclobutane-1-carboximidamide (360.55 mg, 3.160 mmol, 10 equiv) in IPA (8 mL) was stirred for overnight at 80°C under nitrogen atmosphere. The reaction was monitored by LCMS. The resulting mixture was allowed to r.t.. The resulting mixture was diluted with EA (200 mL). The resulting mixture was washed with 2x100 mL of water. The organic layers were concentrated under reduced pressure. The residue was purified by Prep-TLC (EA) to afford 3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-2'-[2-(3-hydroxycyclobutyl)pyrimidin-4-yl]-5',6-dimethyl-[1,4'-bipyridin]-2-one (150 mg, crude). The crude product was further purified by reversed combi-flash chromatography. The pure fraction was concentrated under reduce pressure to afford 3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-2'-[2-(3-hydroxycyclobutyl)pyrimidin-4-yl]-5',6-dimethyl-[1,4'-bipyridin]-2-one (110 mg, 66.22%) as a white solid. LC-MS: (ES+H, m/z): [M+H]⁺=526.3.

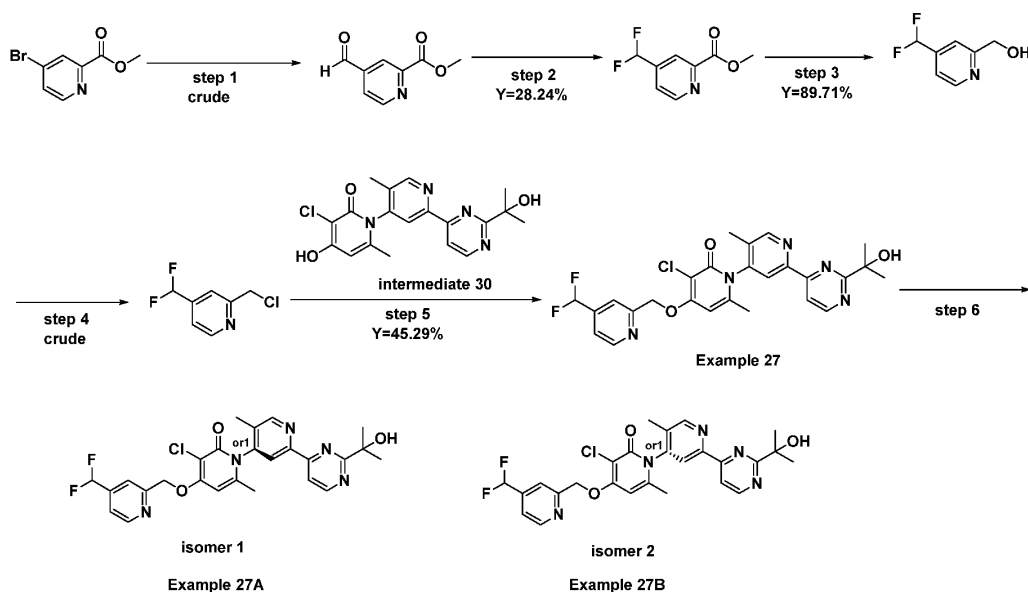
Step 3: Preparation of rel-3-chloro-4-((3,5-difluoropyridin-2-yl)methoxy)-2'-(2-(3-hydroxycyclobutyl)pyrimidin-4-yl)-5',6-dimethyl-2H-[1,4'-bipyridin]-2-one & rel-3-chloro-4-((3,5-difluoropyridin-2-yl)methoxy)-2'-(2-(3-hydroxycyclobutyl)pyrimidin-4-yl)-5',6-dimethyl-2H-[1,4'-bipyridin]-2-one :

[00426] 3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-2'-[2-(3-hydroxycyclobutyl)pyrimidin-4-yl]-5',6-dimethyl-[1,4'-bipyridin]-2-one (100 mg, 0.190 mmol, 1 equiv) was isolated by Prep-Chiral-HPLC to afford rel-3-chloro-4-((3,5-difluoropyridin-2-yl)methoxy)-2'-(2-(3-hydroxycyclobutyl)pyrimidin-4-yl)-5',6-dimethyl-2H-[1,4'-bipyridin]-2-one (**Example 26A**, 40.4 mg, 40.40%) and rel-3-chloro-4-((3,5-difluoropyridin-2-yl)methoxy)-2'-(2-(3-hydroxycyclobutyl)pyrimidin-4-yl)-5',6-dimethyl-2H-[1,4'-bipyridin]-2-one (**Example 26B**, 32.3 mg, 32.3%) as a light pink solid. [the cis/trans=4/1 in the cyclobutene ring]

[00427] Example 26A: LC-MS: (ES+H, m/z): [M+H]⁺=525.85. ¹H NMR (400 MHz, DMSO-d₆) δ 8.92 (d, 1H), 8.87 (s, 1H), 8.61 (d, 1H), 8.32 (s, 1H), 8.18 (d, 1H), 8.13 – 8.04 (m, 1H), 6.83 (d, 1H), 5.50 (d, 2H), 5.18 (d, 1H), 4.14 – 4.04 (m, 1H), 3.23 – 3.14 (m, 1H), 2.60 – 2.55 (m, 2H), 2.33 – 2.23 (m, 2H), 2.10 (s, 3H), 1.98 (s, 3H). ¹⁹F NMR (377 MHz, DMSO) δ -120.10, -120.12, -122.28, -122.30.

[00428] Example 26B: LC-MS: (ES+H, m/z): [M+H]⁺=525.85. ¹H NMR (400 MHz, DMSO-d₆) δ 8.92 (d, 1H), 8.87 (s, 1H), 8.61 (d, 1H), 8.33 (s, 1H), 8.18 (d, 1H), 8.14 – 8.02 (m, 1H), 6.83 (d, 1H), 5.50 (d, 2H), 5.16 (d, 1H), 4.15 – 4.04 (m, 1H), 3.23 – 3.15 (m, 1H), 2.63 – 2.55 (m, 2H), 2.33 – 2.22 (m, 2H), 2.10 (s, 3H), 1.98 (s, 3H). ¹⁹F NMR (377 MHz, DMSO) δ -120.11, -120.13, -122.32, -122.34.

Example 27A, 27B



Step 1: Preparation of methyl 4-formylpyridine-2-carboxylate:

[00429] To a stirred solution of methyl 4-bromopyridine-2-carboxylate (10 g, 46.28 mmol, 1.00 equiv) and TMEDA (10.76 g, 92.57 mmol, 2.00 equiv) in Toluene (130 mL) were added $\text{Pd}(\text{AcO})_2$ (1.04 g, 4.62 mmol, 0.10 equiv) and bis(adamantan-1-yl)(butyl)phosphane (3.32 g, 9.25 mmol, 0.20 equiv) at room temperature under nitrogen atmosphere. The resulting mixture was stirred overnight at 100°C under carbon monoxide/ hydrogen (15atm/15atm) atmosphere. Desired product could be detected by LCMS. The resulting mixture was cooled down to r.t. The resulting mixture was concentrated under reduced pressure. The resulting mixture was filtered, the filter cake was washed with EtOAc (3 x 20 mL). The filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography to afford methyl 4-formylpyridine-2-carboxylate (1.70 g, crude) as a yellow solid. LC-MS: (ES+H, m/z): $[\text{M}+\text{H}+\text{H}_2\text{O}]^+ = 183.8$

Step 2: Preparation of methyl 4-(difluoromethyl)pyridine-2-carboxylate:

[00430] To a stirred solution of methyl crude 4-formylpyridine-2-carboxylate (1.50 g, 9.08 mmol, 1.00 equiv) in DCM (8 mL) was added BAST (6.03 g, 27.24 mmol, 3.00 equiv) dropwise at room temperature under **nitrogen** atmosphere. The resulting mixture was stirred for 2 h at room temperature under nitrogen atmosphere. The reaction was monitored by LCMS. The resulting mixture was slowly poured into ice water (50 mL). The resulting mixture was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were dried over anhydrous Na_2SO_4 . After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography to afford methyl 4-(difluoromethyl)pyridine-2-carboxylate (480 mg, 28.24%) as a light yellow oil. LC-MS: (ES+H, m/z): $[\text{M}+\text{H}]^+ = 188.1$. ^1H NMR (300 MHz, DMSO- d_6) δ 8.94 – 8.86 (m, 1H), 8.19 (s, 1H), 7.90 – 7.82 (m, 1H), 7.22 (t, 1H), 3.92 (s, 3H).

Step 3: Preparation of [4-(difluoromethyl)pyridin-2-yl]methanol:

[00431] A mixture of methyl 4-(difluoromethyl)pyridine-2-carboxylate (430 mg, 2.29 mmol, 1.00 equiv) and NaBH₄ (347 mg, 9.19 mmol, 4.00 equiv) in THF (4 mL) and methanol (1 mL) was stirred for 2 h at room temperature under nitrogen atmosphere. The reaction was monitored by LCMS. The reaction was quenched with water (10 mL) at r.t. The resulting mixture was extracted with EtOAc (3 x 30 mL). The combined **organic** layers were washed with brine (30 mL), dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure to afford [4-(difluoromethyl)pyridin-2-yl]methanol (328 mg, 89.71%) as a yellow solid. LC-MS: (ES+H, m/z): [M+H]⁺=160.1. ¹H NMR (400 MHz, DMSO-d₆) δ 8.65 (d, 1H), 7.64 (s, 1H), 7.43 (d, 1H), 7.13 (t, 1H), 5.59 (t, 1H), 4.63 (d, 2H)

Step 4: Preparation of 2-(chloromethyl)-4-(difluoromethyl)pyridine:

[00432] A mixture of [4-(difluoromethyl)pyridin-2-yl]methanol (328 mg, 2.06 mmol, 1.00 equiv), DMF (15 mg, 0.20 mmol, 0.1 equiv) and SOCl₂ (1.5 mL) in CH₂Cl₂ (3 mL) was stirred for 2 h at r.t. The reaction was monitored by LCMS. The resulting mixture was concentrated under reduced pressure to afford 2-(chloromethyl)-4-(difluoromethyl)pyridine (700 mg, crude) as a yellow solid. LC-MS: (ES+H, m/z): [M+H]⁺=178.0.

Step 5: Preparation of 3-chloro-4-{[4-(difluoromethyl)pyridin-2-yl]methoxy}-2'-[2-(2-hydroxypropan-2-yl)pyrimidin-4-yl]-5',6-dimethyl-[1,4'-bipyridin]-2-one:

[00433] A mixture of 2-(chloromethyl)-4-(difluoromethyl)pyridine (201 mg, 1.13 mmol, 2.00 equiv), 3-chloro-4-hydroxy-2'-[2-(2-hydroxypropan-2-yl)pyrimidin-4-yl]-5',6-dimethyl-[1,4'-bipyridin]-2-one (220 mg, 0.57 mmol, 1.00 equiv), K₂CO₃ (392 mg, 2.84 mmol, 5.00 equiv) and 18-Crown-6 (15 mg, 0.06 mmol, 0.10 equiv) in DMF (3 mL) was stirred overnight at 60°C under nitrogen atmosphere. The reaction was monitored by LCMS. The resulting mixture was cooled down to r.t. and poured into 10 mL of water. The resulting mixture was extracted with EtOAc (3 x 30 mL). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography to afford crude product, which was further purified by Prep-HPLC to afford 3-chloro-4-{[4-(difluoromethyl)pyridin-2-yl]methoxy}-2'-[2-(2-hydroxypropan-2-yl)pyrimidin-4-yl]-5',6-dimethyl-[1,4'-bipyridin]-2-one (136 mg, 45.29%). LC-MS: (ES+H, m/z): [M+H]⁺=528.2.

Step 6: Preparation of rel-3-chloro-4-{[4-(difluoromethyl)pyridin-2-yl]methoxy}-2'-[2-(2-hydroxypropan-2-yl)pyrimidin-4-yl]-5',6-dimethyl-[1,4'-bipyridin]-2-one and rel-3-chloro-4-{[4-(difluoromethyl)pyridin-2-yl]methoxy}-2'-[2-(2-hydroxypropan-2-yl)pyrimidin-4-yl]-5',6-dimethyl-[1,4'-bipyridin]-2-one :

[00434] The racemate (136 mg) was separated by Prep-Chiral-HPLC to afford **Example 27A** (56.3 mg, 99.6%, ee=100%) as a white solid and **Example 27B** (53.3 mg, 99.4%, ee=99.2%) as a white solid.

Example 27A:

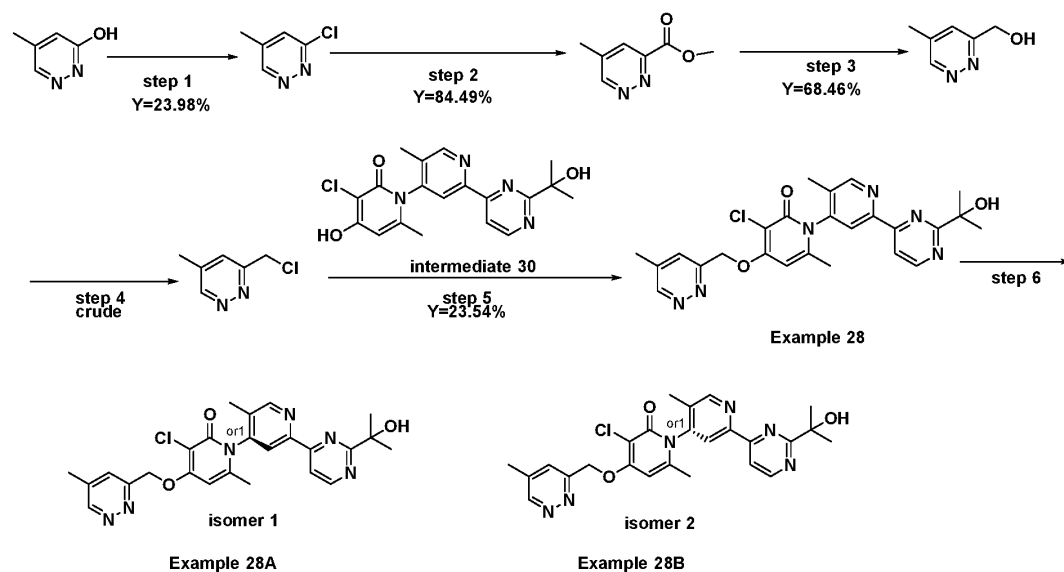
[00435] LC-MS: (ES+H, m/z): [M+H]⁺=528.10. ¹H NMR (300 MHz, DMSO-d₆) δ 8.98 (d, 1H), 8.87 (s, 1H), 8.82 (d, 1H), 8.70 (s, 1H), 8.25 (d, 1H), 7.79 (s, 1H), 7.61 (d, 1H), 7.42-7.02 (t, 1H) 6.84 (s, 1H), 5.54

(s, 2H), 5.26 (s, 1H), 2.11 (s, 3H), 1.99 (s, 3H), 1.54 (s, 3H), 1.53 (s, 3H). ^{19}F NMR (282 MHz, DMSO) δ -115.08.

Example 27B:

[00436] LC-MS: (ES+H, m/z): $[\text{M}+\text{H}]^+ = 528.10$. ^1H NMR (300 MHz, DMSO- d_6) δ 8.98 (d, 1H), 8.87 (s, 1H), 8.82 (d, 1H), 8.70 (s, 1H), 8.25 (d, 1H), 7.79 (s, 1H), 7.61 (d, 1H), 7.41-7.02 (t, 1H), 6.84 (s, 1H), 5.54 (s, 2H), 5.26 (s, 1H), 2.11 (s, 3H), 1.99 (s, 3H), 1.54 (s, 3H), 1.53 (s, 3H). ^{19}F NMR (282 MHz, DMSO) δ -115.08.

Example 28A, 28B



Step 1: Preparation of 3-chloro-5-methylpyridazine:

[00437] A solution of 5-methylpyridazin-3-ol (5.00 g) in POCl_3 (50 mL) was stirred for 3 h at 80°C under nitrogen atmosphere. The reaction was monitored by LCMS. The reaction was quenched with ice at room temperature. The mixture was basified to pH 9 with NaOH aq. The resulting mixture was extracted with EtOAc (3 x 100 mL). The combined organic layers were dried over anhydrous Na_2SO_4 . After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography to afford 3-chloro-5-methylpyridazine (1.4 g, 23.98%) as a brown liquid. LC-MS: (ES+H, m/z): $[\text{M}+\text{H}]^+ = 129.1$. ^1H NMR (400 MHz, DMSO- d_6) δ 9.14 (d, 1H), 7.81 (d, 1H), 2.37 (s, 3H).

Step 2: Preparation of methyl 5-methylpyridazine-3-carboxylate:

[00438] To a stirred solution of DIEA (2.01 g, 15.55 mmol, 2.00 equiv) and 3-chloro-5-methylpyridazine (1.00 g, 7.77 mmol, 1.00 equiv) in MeOH (10 mL) was added $\text{Pd}(\text{dppf})\text{Cl}_2\text{CH}_2\text{Cl}_2$ (0.63 g, 0.77 mmol, 0.10 equiv) at room temperature under nitrogen atmosphere. The resulting mixture was stirred overnight at 100°C under carbon monoxide atmosphere. The reaction was monitored by LCMS. The resulting mixture was cooled down to r.t. The resulting mixture was concentrated under vacuum. The residue was purified by silica gel column chromatography to afford methyl 5-methylpyridazine-3-carboxylate (1.00 g, 84.49%) as

a light-yellow solid. LC-MS: (ES+H, m/z): [M+H]⁺ = 153.2. ¹H NMR (400 MHz, DMSO-d₆) δ 9.32 (d, 1H), 8.12-8.06 (m, 1H), 3.96 (s, 3H), 2.42 (s, 3H).

Step 3: Preparation of (5-methylpyridazin-3-yl)methanol:

[00439] To a stirred solution of methyl 5-methylpyridazine-3-carboxylate (500 mg, 3.28 mmol, 1.00 equiv) in THF (3 mL) and MeOH (1 mL) was added NaBH₄ (621 mg, 16.43 mmol, 5.00 equiv) at room temperature. The resulting mixture was stirred for 2 h at room temperature. The reaction was monitored by LCMS. The resulting mixture was diluted with water (10 mL). The resulting mixture was extracted with CHCl₃ and isopropanol (3:1) (3 x 10 mL). The combined organic layers were dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure to afford (5-methylpyridazin-3-yl)methanol (280 mg, 68.64%) as pale yellow solid. LC-MS: (ES+H, m/z): [M+H]⁺ = 125.2. ¹H NMR (400 MHz, DMSO-d₆) δ 8.98 (d, 1H), 7.54 (d, 1H), 5.60 (s, 1H), 4.72 (s, 2H), 2.34 (s, 3H).

Step 4: Preparation of 3-(chloromethyl)-5-methylpyridazine:

[00440] A mixture of (5-methylpyridazin-3-yl)methanol (280 mg, 2.25 mmol, 1.00 equiv), DMF (16 mg, 0.22 mmol, 0.10 equiv) and SOCl₂ (1.5 mL) in CH₂Cl₂ (3 mL) was stirred for 2 h at r.t. The reaction was monitored by LCMS. The resulting mixture was concentrated under reduced pressure to afford 3-(chloromethyl)-5-methylpyridazine (280 mg, crude) as a yellow solid. LC-MS: (ES+H, m/z): [M+H]⁺ = 143.1.

Step 5: Preparation of 3-chloro-2'-[2-(2-hydroxypropan-2-yl)pyrimidin-4-yl]-5',6-dimethyl-4-[(5-methylpyridazin-3-yl)methoxy]-[1,4'-bipyridin]-2-one:

[00441] A mixture of 3-(chloromethyl)-5-methylpyridazine (147 mg, 1.03 mmol, 2 equiv), 3-chloro-4-hydroxy-2'-[2-(2-hydroxypropan-2-yl)pyrimidin-4-yl]-5',6-dimethyl-[1,4'-bipyridin]-2-one (200 mg, 0.51 mmol, 1.00 equiv), K₂CO₃ (357 mg, 2.58 mmol, 5.00 equiv) and 18-Crown-6 (13 mg, 0.05 mmol, 0.10 equiv) in DMF (2 mL) was stirred overnight at 60°C under nitrogen atmosphere. The reaction was monitored by LCMS. The resulting mixture was cooled down to r.t. and poured into 10 mL of water. The resulting mixture was extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, to afford crude product, which was further purified by Prep-HPLC to afford 3-chloro-2'-[2-(2-hydroxypropan-2-yl)pyrimidin-4-yl]-5',6-dimethyl-4-[(5-methylpyridazin-3-yl)methoxy]-[1,4'-bipyridin]-2-one (60 mg, 23.54%) as a white solid. LC-MS: (ES+H, m/z): [M+H]⁺ = 493.1.

Step 6: Preparation of rel-3-chloro-2'-[2-(2-hydroxypropan-2-yl)pyrimidin-4-yl]-5',6-dimethyl-4-[(5-methylpyridazin-3-yl)methoxy]-[1,4'-bipyridin]-2-one and rel-3-chloro-2'-[2-(2-hydroxypropan-2-yl)pyrimidin-4-yl]-5',6-dimethyl-4-[(5-methylpyridazin-3-yl)methoxy]-[1,4'-bipyridin]-2-one :

[00442] The racemate (60 mg) was separated by Prep-Chiral-HPLC to afford **Example 28A** (19.1 mg, 98.7%, ee=100%) as a white solid and **Example 28B** (18.4 mg, 98.7%, ee=100%) as a white solid.

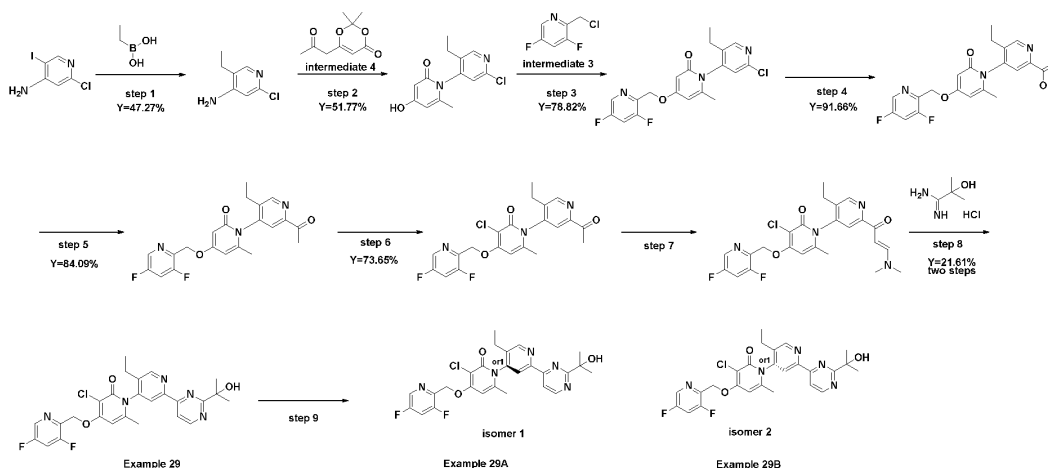
Example 28A:

[00443] LC-MS: (ES+H, m/z): $[M+H]^+ = 493.20$. ^1H NMR (400 MHz, DMSO- d_6) δ 9.15 (s, 1H), 8.97 (d, 1H), 8.87 (s, 1H), 8.69 (s, 1H), 8.24 (d, 1H), 7.71 (s, 1H), 6.86 (s, 1H), 5.63 (s, 2H), 5.27 (s, 1H), 2.41 (s, 3H), 2.11 (s, 3H), 1.99 (s, 3H), 1.54 (s, 3H), 1.53 (s, 3H).

Example 28B:

[00444] LC-MS: (ES+H, m/z): $[M+H]^+ = 493.25$. ^1H NMR (400 MHz, DMSO- d_6) δ 9.15 (s, 1H), 8.98 (d, 1H), 8.87 (s, 1H), 8.69 (s, 1H), 8.24 (d, 1H), 7.71 (s, 1H), 6.86 (s, 1H), 5.63 (s, 2H), 5.27 (s, 1H), 2.42 (s, 3H), 2.11 (s, 3H), 1.99 (s, 3H), 1.54 (s, 3H), 1.53 (s, 3H).

Example 29A, 28B



Step1: Preparation of 2-chloro-5-ethylpyridin-4-amine:

[00445] To a stirred mixture of 2-chloro-5-iodopyridin-4-amine (5.50 g, 21.61 mmol, 1.00 equiv) and boronic acid, ethyl- (3.19 g, 43.22 mmol, 2.00 equiv) in Toluene (500 mL) and H₂O (50 mL) were added Cs₂CO₃ (21.13 g, 64.84 mmol, 3.00 equiv) and Pd(dppf)Cl₂ (880.38 mg, 1.08 mmol, 0.05 equiv) at room temperature under nitrogen atmosphere. The resulting mixture was stirred overnight at 100°C under nitrogen atmosphere. The reaction was monitored by LCMS. The mixture was allowed to cool down to room temperature. The reaction was poured into water (1.5L) at room temperature. The resulting mixture was extracted with EtOAc (2 x 500 mL). The combined organic layers were washed with brine (500 mL), dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography the pure fraction was concentrated under reduced pressure to afford 2-chloro-5-ethylpyridin-4-amine (1.60 g, 47.27%) as a white solid. LC-MS: (ES+H, m/z): $[M+H]^+ = 157.1$. ^1H NMR (400 MHz, Chloroform- d) δ 7.87 (s, 1H), 6.55 (s, 1H), 4.33 (br, 2H), 2.46 (q, 2H), 1.24 (t, 3H).

Step2: Preparation of 2'-chloro-5'-ethyl-4-hydroxy-6-methyl-[1,4'-bipyridin]-2-one:

[00446] To a stirred solution of 2-chloro-5-ethylpyridin-4-amine (1.60 g, 10.21 mmol, 1.00 equiv) in 1,4-dioxane (40 mL) was added 2,2-dimethyl-6-(2-oxopropyl)-1,3-dioxin-4-one (3.76 g, 20.43 mmol, 2.00 equiv) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 2 h at 90°C under nitrogen atmosphere. The mixture was allowed to cool down to room temperature. To the above

mixture was added conc. H_2SO_4 (1.00 g, 10.21 mmol, 1.00 equiv) dropwise at room temperature. The resulting mixture was stirred for additional 2 h at 90°C . The reaction was monitored by LCMS. The mixture was allowed to cool down to room temperature. The resulting mixture was concentrated under reduced pressure. The resulting mixture was diluted with water (50 mL). The precipitated solids were collected by filtration and washed with water (3x20 mL). The residue was purified by trituration with hexane (200 mL) to afford 2'-chloro-5'-ethyl-4-hydroxy-6-methyl-[1,4'-bipyridin]-2-one (1.4 g, 51.77%) as a brown solid. LC-MS: (ES+H, m/z): $[\text{M}+\text{H}]^+ = 265.2$. ^1H NMR (300 MHz, DMSO-d_6) δ 10.86 (br, 1H), 8.50 (s, 1H), 7.55 (s, 1H), 5.98 (d, 1H), 5.59 (d, 1H), 2.41 – 2.26 (m, 2H), 1.84 (s, 3H), 1.07 (t, 3H).

Step3: Preparation of 2'-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-5'-ethyl-6-methyl-[1,4'-bipyridin]-2-one:

[00447] To a stirred solution of 2'-chloro-5'-ethyl-4-hydroxy-6-methyl-[1,4'-bipyridin]-2-one (1.20 g, 4.53 mmol, 1.00 equiv) and 2-(chloromethyl)-3,5-difluoropyridine (1.11 g, 6.80 mmol, 1.50 equiv) in DMF (50 mL) were added 18-Crown-6 (0.12 g, 0.45 mmol, 0.10 equiv) and K_2CO_3 (1.25 g, 9.06 mmol, 2.00 equiv) at room temperature under nitrogen atmosphere. The resulting mixture was stirred overnight at 60°C under nitrogen atmosphere. The reaction was monitored by LCMS. The mixture was allowed to cool down to room temperature. The reaction was quenched with water (50 mL) at room temperature. The resulting mixture was extracted with EtOAc (3 x 50mL). The combined organic layers were washed with brine (50 mL), dried over anhydrous Na_2SO_4 . After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography the pure fraction was concentrated under reduced pressure to afford 2'-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-5'-ethyl-6-methyl-[1,4'-bipyridin]-2-one (1.40 g, 78.82%) as a yellow solid. LC-MS: (ES+H, m/z): $[\text{M}+\text{H}]^+ = 392.1$. ^1H NMR (300 MHz, DMSO-d_6) δ 8.60 (d, 1H), 8.53 (s, 1H), 8.12 – 8.04 (m, 1H), 7.60 (s, 1H), 6.14 (dd, 1H), 6.04 (d, 1H), 5.25 (d, 2H), 2.45 – 2.23 (m, 2H), 1.86 (s, 3H), 1.08 (t, 3H).

Step 4: Preparation of 4-[(3,5-difluoropyridin-2-yl)methoxy]-2'-(1-ethoxyethenyl)-5'-ethyl-6-methyl-[1,4'-bipyridin]-2-one:

[00448] To a stirred solution of 2'-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-5'-ethyl-6-methyl-[1,4'-bipyridin]-2-one (1.40 g, 3.57 mmol, 1.00 equiv) and tributyl(1-ethoxyethenyl)stannane (2.58 g, 7.14 mmol, 2.00 equiv) in 1,4-dioxane (20 mL) were added $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$ (125 mg, 0.18 mmol, 0.05 equiv) at room temperature under nitrogen atmosphere. The resulting mixture was stirred overnight at 100°C under nitrogen atmosphere. The reaction was monitored by LCMS. The mixture was allowed to cool down to room temperature. The reaction was quenched with water (100 mL) at room temperature. The resulting mixture was extracted with EtOAc (3 x 50mL). The combined organic layers were washed with brine (100 mL), dried over anhydrous Na_2SO_4 . After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography the pure fraction was concentrated under reduced pressure to afford 4-[(3,5-difluoropyridin-2-yl)methoxy]-2'-(1-ethoxyethenyl)-5'-ethyl-6-methyl-[1,4'-bipyridin]-2-one (1.40 g, 91.66%) as a yellow solid. LC-MS: (ES+H, m/z): $[\text{M}+\text{H}]^+ = 428.1$.

Step 5: Preparation of 2'-acetyl-4-[(3,5-difluoropyridin-2-yl)methoxy]-5'-ethyl-6-methyl-[1,4'-bipyridin]-2-one:

[00449] To a stirred solution of 4-[(3,5-difluoropyridin-2-yl)methoxy]-2'-(1-ethoxyethenyl)-5'-ethyl-6-methyl-[1,4'-bipyridin]-2-one (1.40 g, 3.27 mmol, 1.00 equiv) in THF (10 mL) was added conc. HCl (1 mL) dropwise at 0°C. The resulting mixture was stirred for 1h at room temperature. The reaction was monitored by LCMS. The reaction was poured into water (50 mL) at room temperature. The resulting mixture was extracted with EtOAc (3x30 mL). The combined organic layers were washed with brine (40 mL). The resulting mixture was concentrated under vacuum. The residue was purified by silica gel column chromatography the pure fraction was concentrated under vacuum to afford 2'-acetyl-4-[(3,5-difluoropyridin-2-yl)methoxy]-5'-ethyl-6-methyl-[1,4'-bipyridin]-2-one (1.10 g, 84.09%) as a brown oil. LC-MS: (ES+H, m/z): [M+H]⁺=400.1. ¹H NMR (400 MHz, DMSO-d₆) δ 8.84 (s, 1H), 8.59 (d, 1H), 8.10 – 8.05 (m, 1H), 7.77 (s, 1H), 6.14 (dd, 1H), 6.04 (d, 1H), 5.25 (d, 2H), 2.67 (s, 3H), 2.48 – 2.34 (m, 2H), 1.81 (s, 3H), 1.12 (t, 3H).

Step 6: Preparation of 2'-acetyl-3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-5'-ethyl-6-methyl-[1,4'-bipyridin]-2-one:

[00450] To a stirred solution of 2'-acetyl-4-[(3,5-difluoropyridin-2-yl)methoxy]-5'-ethyl-6-methyl-[1,4'-bipyridin]-2-one (1.00 g, 2.50 mmol, 1.00 equiv) in isopropyl alcohol (20 mL) were added NCS (0.37 g, 2.75 mmol, 1.10 equiv) and dichloroacetic acid (0.02 g, 0.15 mmol, 0.06 equiv) dropwise at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 1.5 h at 60°C under nitrogen atmosphere. The reaction was monitored by LCMS. The reaction was quenched by the addition of water (60 mL) at room temperature. The resulting mixture was extracted with EtOAc (3 x 25mL). The combined organic layers were washed with brine (30 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, the pure fraction was concentrated under vacuum to afford 2'-acetyl-3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-5'-ethyl-6-methyl-[1,4'-bipyridin]-2-one (800 mg, 73.65%) as a yellow solid. LC-MS: (ES+H, m/z): [M+H]⁺=434.2. ¹H NMR (300 MHz, DMSO-d₆) δ 8.88 (s, 1H), 8.61 (d, 1H), 8.14 – 8.07 (m, 1H), 7.88 (s, 1H), 6.80 (s, 1H), 5.48 (d, 2H), 2.68 (s, 3H), 2.47 - 2.30 (m, 2H), 1.91 (s, 3H), 1.12 (t, 3H).

Step 7: Preparation of 3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-2'-[(2E)-3-(dimethylamino)prop-2-enoyl]-5'-ethyl-6-methyl-[1,4'-bipyridin]-2-one:

[00451] Into DMF-DMA (4 mL) was added 2'-acetyl-3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-5'-ethyl-6-methyl-[1,4'-bipyridin]-2-one (400 mg, 0.92 mmol, 1.00 equiv) at room temperature under nitrogen atmosphere. The resulting mixture was stirred overnight at 100°C under nitrogen atmosphere. The reaction was monitored by LCMS. The mixture was allowed to cool down to room temperature. The resulting mixture was concentrated under reduced pressure. The crude product was used in the next step directly without further purification. LC-MS: (ES+H, m/z): [M+H]⁺=489.2.

Step 8: Preparation of 3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-5'-ethyl-2'-[2-(2-hydroxypropan-2-yl)pyrimidin-4-yl]-6-methyl-[1,4'-bipyridin]-2-one:

[00452] To a stirred solution of 3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-2'-[(2E)-3-(dimethylamino)prop-2-enoyl]-5'-ethyl-6-methyl-[1,4'-bipyridin]-2-one (450 mg, 0.92 mmol, assumed 100% yield, 1.00 equiv) in dimethylformamide (10 mL) were added 2-hydroxy-2-methylpropanimidamide hydrochloride (1.27 g, 2.76 mmol, 10.00 equiv) and K₂CO₃ (1.28 g, 2.76 mmol, 10.00 equiv) at room temperature under nitrogen atmosphere. The resulting mixture was stirred overnight at 80°C under nitrogen atmosphere. The reaction was monitored by LCMS. The reaction was poured into water (100mL) at room temperature. The resulting mixture was extracted with EtOAc (3x100 mL). The combined organic layers were washed with brine (5x100 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by Prep-TLC, the residue was concentrated under reduced pressure. The crude product was purified by Prep-HPLC, the pure fraction was concentrated under reduced pressure to afford 3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-5'-ethyl-2'-[2-(2-hydroxypropan-2-yl)pyrimidin-4-yl]-6-methyl-[1,4'-bipyridin]-2-one (105 mg, 21.61%) as a white solid. LC-MS: (ES+H, *m/z*): [M+H]⁺ = 528.3. ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.98 (d, 1H), 8.90 (s, 1H), 8.68 (s, 1H), 8.61 (d, 1H), 8.25 (d, 1H), 8.16 – 8.03 (m, 1H), 6.85 (s, 1H), 5.50 (s, 2H), 5.27(s, 1H), 2.50-2.35 (m, 2H), 1.99 (s, 3H), 1.54 (s, 3H), 1.53 (s, 3H), 1.15 (s, 3H).

Step 9: Preparation of (Example 29A, isomer 1) rel-3-chloro-4-((3,5-difluoropyridin-2-yl)methoxy)-5'-ethyl-2'-(2-(2-hydroxypropan-2-yl)pyrimidin-4-yl)-6-methyl-2H-[1,4'-bipyridin]-2-one and (Example 28B, isomer 2) rel-3-chloro-4-((3,5-difluoropyridin-2-yl)methoxy)-5'-ethyl-2'-(2-(2-hydroxypropan-2-yl)pyrimidin-4-yl)-6-methyl-2H-[1,4'-bipyridin]-2-one:

[00453] The race-mixture (100 mg) was separated by Prep-CHIRAL-HPLC, the pure fraction was concentrated under reduced pressure and then lyophilized to afford rel-3-chloro-4-((3,5-difluoropyridin-2-yl)methoxy)-5'-ethyl-2'-(2-(2-hydroxypropan-2-yl)pyrimidin-4-yl)-6-methyl-2H-[1,4'-bipyridin]-2-one (Example 29A, isomer 1, 36.2 mg, ee=100%) as a white solid and rel-3-chloro-4-((3,5-difluoropyridin-2-yl)methoxy)-5'-ethyl-2'-(2-(2-hydroxypropan-2-yl)pyrimidin-4-yl)-6-methyl-2H-[1,4'-bipyridin]-2-one (Example 29B, isomer 2, 32.3 mg, ee=100%) as a white solid.

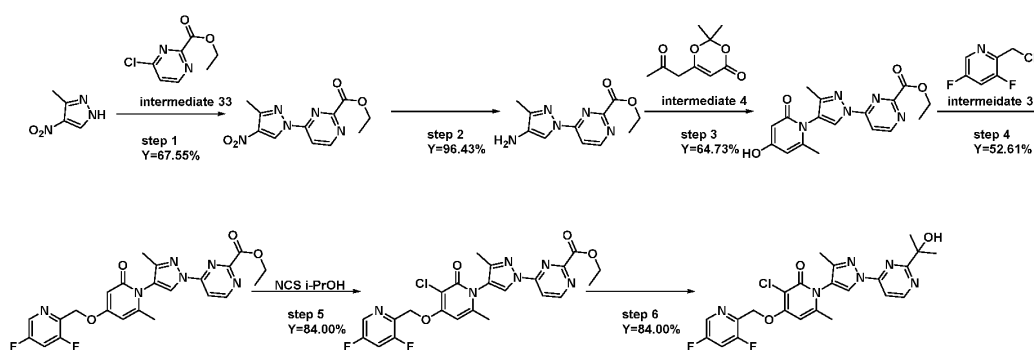
Example 29A:

[00454] LC-MS: (ES+H, *m/z*): [M+H]⁺ = 528.10. ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.98 (d, 1H), 8.90 (s, 1H), 8.68 (s, 1H), 8.61 (d, 1H), 8.24 (d, 1H), 8.16 – 8.03 (m, 1H), 6.85 (s, 1H), 5.50 (s, 2H), 5.25(s, 1H), 2.50-2.34 (m, 2H), 1.98 (s, 3H), 1.54 (s, 3H), 1.53 (s, 3H), 1.15 (t, 3H).
¹⁹F NMR (282 MHz, DMSO) δ -120.12, -120.15, -122.31, -122.34.

Example 29B:

[00455] LC-MS: (ES+H, *m/z*): [M+H]⁺ = 528.10. ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.98 (d, 1H), 8.90 (s, 1H), 8.68 (s, 1H), 8.61 (d, 1H), 8.24 (d, 1H), 8.16 – 8.03 (m, 1H), 6.85 (s, 1H), 5.50 (s, 2H), 5.25(s, 1H), 2.51-2.37 (m, 2H), 1.98 (s, 3H), 1.54 (s, 3H), 1.53 (s, 3H), 1.15 (t, 3H).
¹⁹F NMR (282 MHz, DMSO) δ -120.12, -120.15, -122.32, -122.34.

Example 30



Example 30

Step 1: Preparation of ethyl 4-(3-methyl-4-nitropyrrol-1-yl)pyrimidine-2-carboxylate:

[00456] To a stirred solution of ethyl 4-chloropyrimidine-2-carboxylate (1.00 g, 5.35 mmol, 1.00 equiv) and 3-methyl-4-nitro-1H-pyrazole (0.89 g, 7.02 mmol, 1.31 equiv) in DMF (10 mL) was added Cs_2CO_3 (3.49 g, 10.71 mmol, 2.00 equiv) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 3 h at 50°C under nitrogen atmosphere. The mixture was allowed to cool down to room temperature. The reaction was quenched with saturating NH_4Cl (aq.) at room temperature. The resulting mixture was extracted with EtOAc (3x20 mL). The combined organic layers were washed with brine (30 mL), dried over anhydrous Na_2SO_4 . After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography to afford ethyl 4-(3-methyl-4-nitropyrrol-1-yl)pyrimidine-2-carboxylate (1.00 g, 67.55%) as a white solid. LC-MS: (ES+H, m/z): $[\text{M}+\text{H}]^+ = 278.1$.

Step 2: Preparation of ethyl 4-(4-amino-3-methylpyrazol-1-yl)pyrimidine-2-carboxylate:

[00457] To a solution of ethyl 4-(3-methyl-4-nitropyrrol-1-yl)pyrimidine-2-carboxylate (1.00 g, 3.60 mmol, 1.00 equiv) in 15 mL EtOH was added Pd/C (0.38 g, enough, 10wt%) in a pressure tank. The mixture was hydrogenated at room temperature under 30 atm of hydrogen pressure for 40 min, the reaction was monitored by LCMS. The resulting mixture was filtered through a Celite pad and concentrated under reduced pressure. The residue was purified by trituration with diethyl ether (5 mL). The precipitated solids were collected by filtration. This resulted in ethyl 4-(4-amino-3-methylpyrazol-1-yl)pyrimidine-2-carboxylate (0.86 g, 96.43%) as a yellow solid. LC-MS: (ES+H, m/z): $[\text{M}+\text{H}]^+ = 248.1$. ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 8.76 (d, 1H), 7.79 (d, 1H), 7.77 (s, 1H), 4.54 (br, 2H), 4.38 (q, 2H), 2.19 (s, 3H), 1.35 (t, 3H).

Step 3: Preparation of ethyl 4-[4-(4-hydroxy-2-methyl-6-oxopyridin-1-yl)-3-methylpyrazol-1-yl]pyrimidine-2-carboxylate:

[00458] A solution of ethyl 4-(4-amino-3-methylpyrazol-1-yl)pyrimidine-2-carboxylate (0.86 g, 3.47 mmol, 1.00 equiv) and 2,2-dimethyl-6-(2-oxopropyl)-1,3-dioxin-4-one (1.60 g, 8.69 mmol, 2.50 equiv) in dioxane (10 mL) was stirred for 3 h at 80°C under nitrogen atmosphere. The mixture was allowed to cool down to room temperature. To the above mixture was added conc. H_2SO_4 (0.29 mL, 35.48 mmol, 1.00 equiv) dropwise at room temperature. The resulting mixture was stirred for additional 1 h at 80°C. The mixture was allowed to cool down to room temperature. The resulting mixture was concentrated under vacuum. The residue was dissolved in water (1 mL). The residue was purified by reverse combi-flash

chromatography. This resulted in ethyl 4-[4-(4-hydroxy-2-methyl-6-oxopyridin-1-yl)-3-methylpyrazol-1-yl]pyrimidine-2-carboxylate (0.80 g, 64.73%) as a brown solid. LC-MS: (ES+H, m/z): [M+H]⁺ = 356.1. ¹H NMR (300 MHz, DMSO-d₆) δ 10.75 (br, 1H), 9.02 (d, 1H), 8.81 (s, 1H), 8.07 (d, 1H), 5.94 (s, 1H), 5.57 (d, 1H), 4.40 (q, 2H), 2.07 (s, 3H), 2.00 (s, 3H), 1.36 (t, 3H).

Step 4: Preparation of ethyl 4-(4-{4-[(3,5-difluoropyridin-2-yl)methoxy]-2-methyl-6-oxopyridin-1-yl}-3-methylpyrazol-1-yl)pyrimidine-2-carboxylate:

[00459] To a stirred solution of ethyl 4-[4-(4-hydroxy-2-methyl-6-oxopyridin-1-yl)-3-methylpyrazol-1-yl]pyrimidine-2-carboxylate (0.70 g, 1.97 mmol, 1.00 equiv) and Na₂CO₃ (0.42 g, 3.94 mmol, 2.00 equiv) in DMF (5 mL) were added 2-(chloromethyl)-3,5-difluoropyridine (0.48 g, 2.95 mmol, 1.50 equiv) and 18-Crown-6 (0.20 g, 0.78 mmol, 0.40 equiv) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 2 h at 60°C under nitrogen atmosphere. The mixture was allowed to cool down to room temperature. The reaction was quenched with saturating NH₄Cl (aq.) at room temperature. The resulting mixture was extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (30 mL), dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography to afford ethyl 4-(4-{4-[(3,5-difluoropyridin-2-yl)methoxy]-2-methyl-6-oxopyridin-1-yl}-3-methylpyrazol-1-yl)pyrimidine-2-carboxylate (0.50 g, 52.61%) as a yellow solid. LC-MS: (ES+H, m/z): [M+H]⁺ = 483.2

Step 5: Preparation of ethyl 4-(4-{3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-6-methyl-2-oxopyridin-1-yl}-3-methylpyrazol-1-yl)pyrimidine-2-carboxylate:

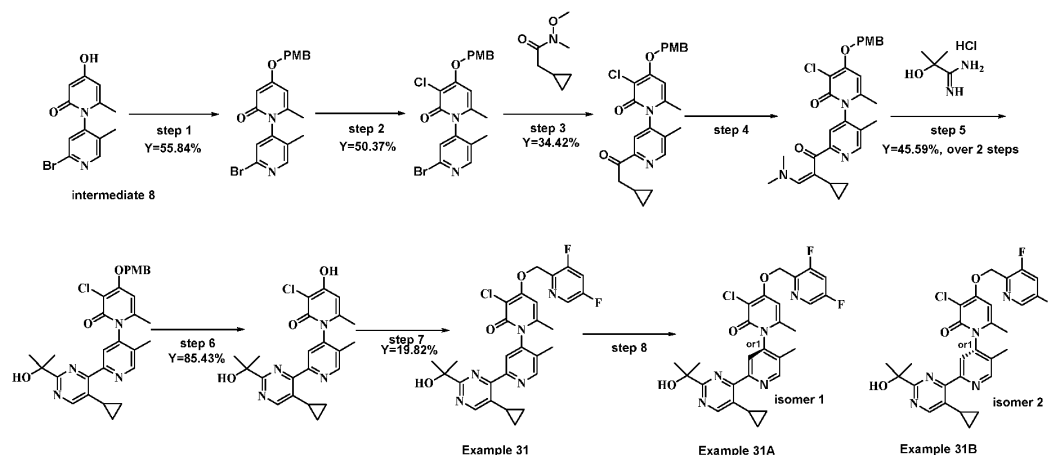
[00460] To a stirred solution of ethyl 4-(4-{4-[(3,5-difluoropyridin-2-yl)methoxy]-2-methyl-6-oxopyridin-1-yl}-3-methylpyrazol-1-yl)pyrimidine-2-carboxylate (0.50 g, 1.03 mmol, 1.00 equiv) and dichloroacetic acid (13 mg, 0.10 mmol, 0.10 equiv) in propan-2-ol (2 mL) was added NCS (0.15 g, 1.14 mmol, 1.10 equiv) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 2 h at 60°C under nitrogen atmosphere. The mixture was allowed to cool down to room temperature. The precipitated solids were collected by filtration and washed with 2-propanol (3x1 mL). This resulted in ethyl 4-(4-{3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-6-methyl-2-oxopyridin-1-yl}-3-methylpyrazol-1-yl)pyrimidine-2-carboxylate (0.45 g, 84.00%) as a white solid. LC-MS: (ES+H, m/z): [M+H]⁺ = 517.1

Step 6: Preparation of 3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-1-{1-[2-(2-hydroxypropan-2-yl)pyrimidin-4-yl]-3-methylpyrazol-4-yl}-6-methylpyridin-2-one:

[00461] To a stirred solution of ethyl 4-(4-{3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-6-methyl-2-oxopyridin-1-yl}-3-methylpyrazol-1-yl)pyrimidine-2-carboxylate (330 mg, 0.64 mmol, 1.00 equiv) in THF (2 mL) was added MeMgBr (3.2 mL, 6.40 mmol, 10 equiv, 2M in THF) dropwise at -10°C under nitrogen atmosphere. The resulting mixture was stirred for 20 min at 0°C under nitrogen atmosphere. The reaction was quenched with saturating NH₄Cl (aq.) at room temperature. The resulting mixture was extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by reverse combi-flash chromatography. This resulted in 3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-1-{1-[2-(2-hydroxypropan-2-yl)pyrimidin-4-yl]-3-methylpyrazol-4-yl}-6-methylpyridin-2-one.

[2-(2-hydroxypropan-2-yl)pyrimidin-4-yl]-3-methylpyrazol-4-yl]-6-methylpyridin-2-one (77 mg, 24.08%) as a white solid. LC-MS: (ES+H, m/z): [M+H]⁺=503.05. ¹H NMR (300 MHz, DMSO-d₆) δ 9.20 (s, 1H), 8.90 (d, 1H), 8.60 (d, 1H), 8.10 (m, 1H), 7.76 (d, 1H), 6.77 (s, 1H), 5.49 (d, 2H), 5.17 (s, 1H), 2.13 (s, 3H), 2.10 (s, 3H), 1.53 (s, 3H), 1.52 (s, 3H). ¹⁹F NMR (282 MHz, DMSO) δ -120.19, -120.21, -122.42, -122.44.

Example 31A, 31B



Step 1: Preparation of 2'-bromo-4-[(4-methoxyphenyl)methoxy]-5',6-dimethyl-[1,4'-bipyridin]-2-one:

[00462] To a solution of 2'-bromo-4-hydroxy-5',6-dimethyl-[1,4'-bipyridin]-2-one (7.00 g, 23.72 mmol, 1.00 equiv) in DMF (50 mL) was added PMBCl (11.14 g, 71.15 mmol, 3.00 equiv), K₂CO₃ (13.11 g, 94.872 mmol, 4.00 equiv) and 18-Crown-6 (310 mg, 1.19 mmol, 0.05 equiv). The mixture was stirred at 60°C for 3 h. The reaction was monitored by LCMS. The mixture was allowed to cool down to room temperature. The reaction mixture was partitioned between EA (500 mL) and water (200 mL). The organic layer was washed with water (200 mL) and brine (200 mL), and then dried over Na₂SO₄. The solution was concentrated under reduced pressure. The residue was purified by silica gel column chromatography to afford 2'-bromo-4-[(4-methoxyphenyl)methoxy]-5',6-dimethyl-[1,4'-bipyridin]-2-one (5.5 g, 55.84%) as an off-white solid. LC-MS: (ES+H, m/z): [M+H]⁺=415.0/417.0. ¹H NMR (300 MHz, DMSO-d₆) δ 8.48 (s, 1H), 7.71 (s, 1H), 7.44 – 7.35 (m, 2H), 7.03 – 6.92 (m, 2H), 6.12 (dd, 1H), 5.93 (d, 1H), 5.04 (s, 2H), 3.78 (s, 3H), 1.96 (s, 3H), 1.85 (s, 3H).

Step 2: Preparation of 2'-bromo-3-chloro-4-[(4-methoxyphenyl)methoxy]-5',6-dimethyl-[1,4'-bipyridin]-2-one:

[00463] To a stirred mixture of 2'-bromo-4-[(4-methoxyphenyl)methoxy]-5',6-dimethyl-[1,4'-bipyridin]-2-one (5.50 g, 13.24 mmol, 1.00 equiv) and NCS (1.95 g, 14.57 mmol, 1.10 equiv) in IPA (20 mL) was added 2,2-dichloroacetic acid (100 mg, 0.80 mmol, 0.06 equiv) at room temperature. The mixture was stirred for 3h at 60°C under nitrogen atmosphere. The reaction was monitored by LCMS. The mixture was allowed to cool down to room temperature. The precipitated solids were collected by filtration to afford 2'-bromo-3-chloro-4-[(4-methoxyphenyl)methoxy]-5',6-dimethyl-[1,4'-bipyridin]-2-one (3 g, 50.37%) as a white solid. LC-MS: (ES+H, m/z): [M+H]⁺=451.1. ¹H NMR (400 MHz, DMSO-d₆) δ 8.51 (s, 1H), 7.79 (s, 1H), 7.47 – 7.39 (m, 2H), 7.04 – 6.96 (m, 2H), 6.76 (s, 1H), 5.26 (s, 2H), 3.78 (s, 3H), 1.95 (s, 3H), 1.95 (s, 3H).

Step3: Preparation of 3-chloro-2'-(2-cyclopropylacetyl)-4-[(4-methoxyphenyl)methoxy]-5',6-dimethyl-[1,4'-bipyridin]-2-one:

[00464] To a stirred mixture of 2'-bromo-3-chloro-4-[(4-methoxyphenyl)methoxy]-5',6-dimethyl-[1,4'-bipyridin]-2-one (1.50 g, 3.34 mmol, 1.00 equiv) in Toluene (50 mL) were added i-PrMgCl (3.34 mL, 6.67 mmol, 2 equiv, 2M in THF) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 2h at room temperature under nitrogen atmosphere. To the above mixture was added 2-cyclopropyl-N-methoxy-N-methylacetamide (22.39 g, 16.68 mmol, 5.00 equiv) dropwise over 5 min at room temperature. The resulting mixture was stirred overnight at room temperature. The reaction was monitored by LCMS. The reaction was quenched by the addition of sat. NH₄Cl (aq.) (10 mL) at 0°C. The resulting mixture was extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with brine (2 x 100 mL), dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography to afford 3-chloro-2'-(2-cyclopropylacetyl)-4-[(4-methoxyphenyl)methoxy]-5',6-dimethyl-[1,4'-bipyridin]-2-one (520 mg, 34.42%) as a yellow solid. LC-MS: (ES+H, m/z): [M+H]⁺ = 453.2.

Step 4/5: Preparation of 3-chloro-2'-[5-cyclopropyl-2-(2-hydroxypropan-2-yl)pyrimidin-4-yl]-4-[(4-methoxyphenyl)methoxy]-5',6-dimethyl-[1,4'-bipyridin]-2-one:

[00465] A solution of 3-chloro-2'-(2-cyclopropylacetyl)-4-[(4-methoxyphenyl)methoxy]-5',6-dimethyl-[1,4'-bipyridin]-2-one (520 mg, 1.15 mmol, 1.00 equiv) in DMF-DMA (4 mL) was stirred overnight at 100°C under nitrogen atmosphere. The reaction was monitored by LCMS. The mixture was allowed to cool down to room temperature. The resulting mixture was concentrated under reduced pressure, to afford 3-chloro-2'-[(2Z)-2-cyclopropyl-3-(dimethylamino)prop-2-enoyl]-4-[(4-methoxyphenyl)methoxy]-5',6-dimethyl-[1,4'-bipyridin]-2-one (550 mg, crude). The crude product was used in the next step directly without further purification.

The above crude (assumed 100% yield, 1.00 equiv) was re-dissolved in IPA (3 mL) and added 2-hydroxy-2-methylpropanimidamide hydrochloride (1.11 g, 10.83 mmol, 10.00 equiv) and K₂CO₃ (1.50 g, 10.83 mmol, 10.00 equiv). The resulting mixture was stirred for 12 h at 80°C. The reaction was monitored by LCMS. The mixture was allowed to cool down to room temperature. The resulting mixture was filtered, the filter cake was washed with MeOH (3 x 10 mL). The filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography to afford 3-chloro-2'-[5-cyclopropyl-2-(2-hydroxypropan-2-yl)pyrimidin-4-yl]-4-[(4-methoxyphenyl)methoxy]-5',6-dimethyl-[1,4'-bipyridin]-2-one (270 mg, 45.59%) as a light yellow solid. LC-MS: (ES+H, m/z): [M+H]⁺ = 547.2.

Step 6: Preparation of 3-chloro-2'-[5-cyclopropyl-2-(2-hydroxypropan-2-yl)pyrimidin-4-yl]-4-hydroxy-5',6-dimethyl-[1,4'-bipyridin]-2-one:

[00466] To a stirred solution of 3-chloro-2'-[5-cyclopropyl-2-(2-hydroxypropan-2-yl)pyrimidin-4-yl]-4-[(4-methoxyphenyl)methoxy]-5',6-dimethyl-[1,4'-bipyridin]-2-one (270 mg, 0.49 mmol, 1.00 equiv) in DCM (3 mL) was added TFA (1 mL) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 1h at room temperature under nitrogen atmosphere. The reaction was monitored by LCMS. The

resulting mixture was concentrated under reduced pressure. The residue was purified by trituration with hexane (10 mL) to afford 3-chloro-2'-[5-cyclopropyl-2-(2-hydroxypropan-2-yl)pyrimidin-4-yl]-4-hydroxy-5',6-dimethyl-[1,4'-bipyridin]-2-one (180 mg, 85.43%) as a yellow oil. LC-MS: (ES+H, m/z): [M+H]⁺=427.2.

Step 7: Preparation of 3-chloro-2'-[5-cyclopropyl-2-(2-hydroxypropan-2-yl)pyrimidin-4-yl]-4-[(3,5-difluoropyridin-2-yl)methoxy]-5',6-dimethyl-[1,4'-bipyridin]-2-one:

[00467] To a stirred mixture of 3-chloro-2'-[5-cyclopropyl-2-(2-hydroxypropan-2-yl)pyrimidin-4-yl]-4-hydroxy-5',6-dimethyl-[1,4'-bipyridin]-2-one (175 mg, 0.41 mmol, 1.00 equiv) and 2-(chloromethyl)-3,5-difluoropyridine (74 mg, 0.45 mmol, 1.10 equiv) in DMF (2 mL) was added 18-Crown-6 (5.42 mg, 0.02 mmol, 0.05 equiv) and K₂CO₃ (169.96 mg, 1.23 mmol, 3.00 equiv) at room temperature under nitrogen atmosphere. The resulting mixture was stirred overnight at 60°C under nitrogen atmosphere. The mixture was allowed to cool down to room temperature. The resulting mixture was diluted with EA (20 mL), then washed with H₂O (3x20 mL), the organic layer was concentrated under reduced pressure. The resulting mixture was purified by Prep-HPLC to afford 3-chloro-2'-[5-cyclopropyl-2-(2-hydroxypropan-2-yl)pyrimidin-4-yl]-4-[(3,5-difluoropyridin-2-yl)methoxy]-5',6-dimethyl-[1,4'-bipyridin]-2-one (45 mg, 19.82%) as a light yellow solid. LC-MS: (ES+H, m/z): [M+H]⁺=554.1.

Step 8: Preparation of (Example 31A, isomer 1) rel-3-chloro-2'-(5-cyclopropyl-2-(2-hydroxypropan-2-yl)pyrimidin-4-yl)-4-[(3,5-difluoropyridin-2-yl)methoxy]-5',6-dimethyl-2H-[1,4'-bipyridin]-2-one and rel-3-chloro-2'-(5-cyclopropyl-2-(2-hydroxypropan-2-yl)pyrimidin-4-yl)-4-[(3,5-difluoropyridin-2-yl)methoxy]-5',6-dimethyl-2H-[1,4'-bipyridin]-2-one:

[00468] 3-chloro-2'-[5-cyclopropyl-2-(2-hydroxypropan-2-yl)pyrimidin-4-yl]-4-[(3,5-difluoropyridin-2-yl)methoxy]-5',6-dimethyl-[1,4'-bipyridin]-2-one (racemate, 40 mg) was separated by Prep-CHIRAL-HPLC to afford **Example 31A** (11.1 mg, ee=98.5%) as a light yellow solid and **Example 31B** (11.1 mg, ee=99.6%) as a light yellow solid.

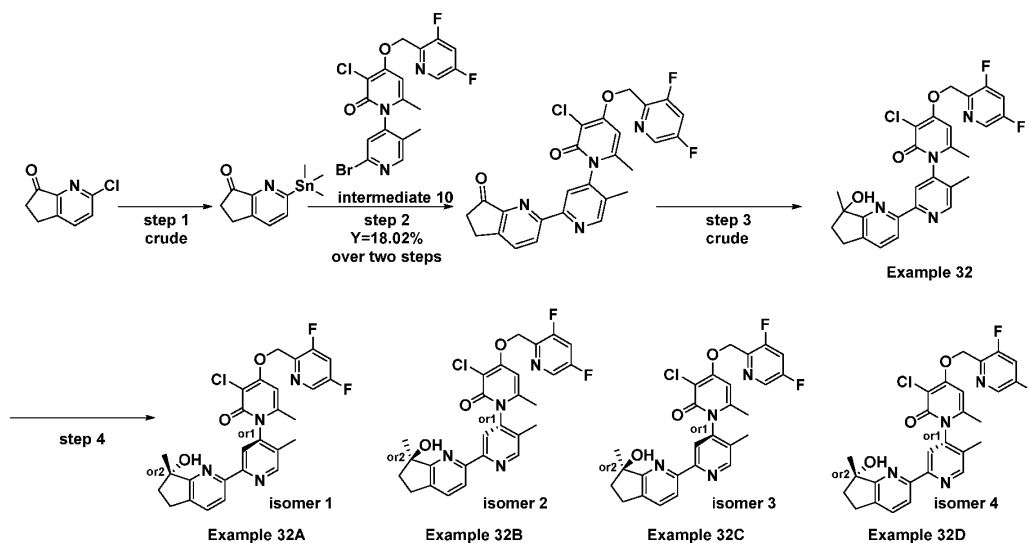
Example 31A:

[00469] LC-MS: (ES+H, m/z): [M+H]⁺=554.30. ¹H NMR (400 MHz, DMSO-d₆) δ 8.81 (s, 1H), 8.60 (d, 1H), 8.57 (s, 1H), 8.18 (s, 1H), 8.15 – 8.05 (m, 1H), 6.83 (s, 1H), 5.49 (d, 2H), 5.08 (s, 1H), 2.75 (td, 1H), 2.10 (s, 3H), 2.00 (s, 3H), 1.50 (s, 3H), 1.50 (s, 3H), 1.01 – 0.90 (m, 2H), 0.82 – 0.75 (m, 2H). ¹⁹F NMR (377 MHz, DMSO) δ -120.14, -120.16, -122.33, -122.35.

Example 31B:

[00470] LC-MS: (ES+H, m/z): [M+H]⁺=554.10. ¹H NMR (400 MHz, DMSO-d₆) δ 8.81 (s, 1H), 8.60 (d, 1H), 8.57 (s, 1H), 8.18 (s, 1H), 8.10 (ddd, 1H), 6.83 (s, 1H), 5.49 (d, 2H), 5.08 (s, 1H), 2.81 – 2.70 (m, 1H), 2.10 (s, 3H), 2.00 (s, 3H), 1.50 (s, 3H), 1.50 (s, 3H), 1.02 – 0.88 (m, 2H), 0.84 – 0.73 (m, 2H). ¹⁹F NMR (377 MHz, DMSO) δ -120.14, -120.16, -122.34, -122.36.

Example 32A, 32B, 32C, 32D



Step 1: Preparation of 2-(trimethylstannyl)-5H,6H-cyclopenta[b]pyridin-7-one:

[00471] A mixture of 2-chloro-5H,6H-cyclopenta[b]pyridin-7-one (250 mg, 1.492 mmol, 1.00 equiv), $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$ (209 mg, 0.298 mmol, 0.20 equiv), AsPh_3 (91 mg, 0.298 mmol, 0.20 equiv) and Sn_2Me_6 (488 mg, 1.492 mmol, 1.00 equiv) in dioxane (8 mL) was stirred for overnight at 80°C under nitrogen atmosphere. The reaction was monitored by LCMS. The resulting mixture was used in the next step directly without further purification. LC-MS: (ES+H, m/z): $[\text{M}+\text{H}]^+ = 298.0$.

Step 2: Preparation of 3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-5',6-dimethyl-2'-[7-oxo-5H,6H-cyclopenta[b]pyridin-2-yl]-[1,4'-bipyridin]-2-one:

[00472] 2'-bromo-3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-5',6-dimethyl-[1,4'-bipyridin]-2-one (328 mg, 0.719 mmol, 0.6 equiv), $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$ (168 mg, 0.240 mmol, 0.20 equiv) and CuI (228 mg, 1.199 mmol, 1 equiv) was added to the reaction solution in the previous step at room temperature. The resulting mixture was stirred for 2 h at 80°C under nitrogen atmosphere. The reaction was monitored by LCMS. The mixture was allowed to r.t.. The resulting mixture was diluted with EA (200 mL), washed with 3x150 mL of sat. NaHCO_3 (aq.). The organic layers were concentrated under reduced pressure and purified by silica gel column chromatography to afford crude product. The crude product was further purified by reverse combi-flash chromatography to afford 3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-5',6-dimethyl-2'-[7-oxo-5H,6H-cyclopenta[b]pyridin-2-yl]-[1,4'-bipyridin]-2-one (110 mg, 18.02%, over two steps) as a white solid. LC-MS: (ES+H, m/z): $[\text{M}+\text{H}]^+ = 508.8$. ^1H NMR (300 MHz, Chloroform-d) δ 8.71 (s, 1H), 8.68 (d, 1H), 8.43 (s, 1H), 8.40 (s, 1H), 8.02 (d, 1H), 7.39 – 7.31 (m, 1H), 6.39 (s, 1H), 5.46 (s, 2H), 3.22 (t, 2H), 2.84 (t, 2H), 2.19 (s, 3H), 2.01 (s, 3H).

Step 3: Preparation of 3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-2'-[7-hydroxy-7-methyl-5H,6H-cyclopenta[b]pyridin-2-yl]-5',6-dimethyl-[1,4'-bipyridin]-2-one:

[00473] To a stirred solution of 3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-5',6-dimethyl-2'-[7-oxo-5H,6H-cyclopenta[b]pyridin-2-yl]-[1,4'-bipyridin]-2-one (200 mg, 0.393 mmol, 1.00 equiv) in THF (10 mL) was added MeMgBr (1.31 mL, 3.93 mmol, 10.00 equiv, 3M in THF) dropwise at -10°C under nitrogen

atmosphere. The resulting mixture was stirred for 1 h at -10°C under nitrogen atmosphere. The reaction was monitored by LCMS. The reaction was quenched by addition of sat. NH_4Cl (aq.) (20 mL) at -10°C. The resulting mixture was extracted with EtOAc (3 x 50 mL). The combined organic layers were dried over anhydrous Na_2SO_4 . After filtration, the filtrate was concentrated under reduced pressure, to afford 3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-2'-{7-hydroxy-7-methyl-5H,6H-cyclopenta[b]pyridin-2-yl}-5',6-dimethyl-[1,4'-bipyridin]-2-one (220 mg, crude) as a yellow solid. LC-MS: (ES+H, m/z): $[\text{M}+\text{H}]^+ = 525.2$.

Step 4: Preparation of rel-(R)-3-chloro-4-((3,5-difluoropyridin-2-yl)methoxy)-2'-(7-hydroxy-7-methyl-6,7-dihydro-5H-cyclopenta[b]pyridin-2-yl)-5',6-dimethyl-2H-[1,4'-bipyridin]-2-one & rel-(R)-3-chloro-4-((3,5-difluoropyridin-2-yl)methoxy)-2'-(7-hydroxy-7-methyl-6,7-dihydro-5H-cyclopenta[b]pyridin-2-yl)-5',6-dimethyl-2H-[1,4'-bipyridin]-2-one & rel-(R)-3-chloro-4-((3,5-difluoropyridin-2-yl)methoxy)-2'-(7-hydroxy-7-methyl-6,7-dihydro-5H-cyclopenta[b]pyridin-2-yl)-5',6-dimethyl-2H-[1,4'-bipyridin]-2-one & rel-(R)-3-chloro-4-((3,5-difluoropyridin-2-yl)methoxy)-2'-(7-hydroxy-7-methyl-6,7-dihydro-5H-cyclopenta[b]pyridin-2-yl)-5',6-dimethyl-2H-[1,4'-bipyridin]-2-one:

[00474] 3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-2'-{7-hydroxy-7-methyl-5H,6H-cyclopenta[b]pyridin-2-yl}-5',6-dimethyl-[1,4'-bipyridin]-2-one (220 mg, crude) was isolated by Prep-HPLC to afford 2 fractions. The first peak (50 mg) was separated by prep-chiral-HPLC to afford **Example 32A** (17.8 mg, 95.7% purity, ee=100%) and **Example 32B** (17.3 mg, 95.0% purity, ee=97.17%) as a white solid. The second peak (60 mg) was separated by prep-chiral-HPLC to afford **Example 32C** (22.8 mg, 97.8% purity, ee=98.67%) and **Example 32D** (23.5 mg, 97.3% purity, ee=96.46%) as a white solid.

Example 32A:

[00475] LC-MS: (ES+H, m/z): $[\text{M}+\text{H}]^+ = 525.1$. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 8.76 (s, 1H), 8.61 (d, 1H), 8.26 (d, 1H), 8.24 (d, 1H), 8.15 – 8.04 (m, 1H), 7.80 (d, 1H), 6.83 (d, 1H), 5.50 (d, 2H), 5.12 (s, 1H), 3.03 – 2.88 (m, 1H), 2.86 – 2.73 (m, 1H), 2.19 – 2.09 (m, 2H), 2.07 (s, 3H), 1.98 (s, 3H), 1.47 (s, 3H). ^{19}F NMR (377 MHz, DMSO) δ -120.13, -120.15, -122.31, -122.33.

Example 32B:

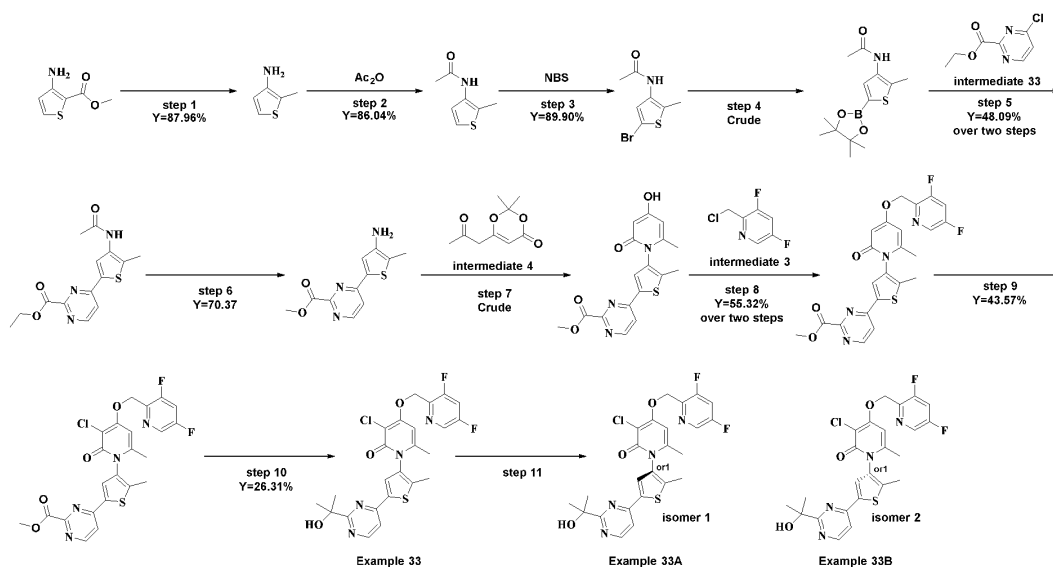
[00476] LC-MS: (ES+H, m/z): $[\text{M}+\text{H}]^+ = 525.1$. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 8.76 (s, 1H), 8.61 (d, 1H), 8.26 (d, 1H), 8.24 (d, 1H), 8.15 – 7.99 (m, 1H), 7.80 (d, 1H), 6.83 (d, 1H), 5.50 (d, 2H), 5.13 (s, 1H), 3.02 – 2.87 (m, 1H), 2.86 – 2.75 (m, 1H), 2.20 – 2.10 (m, 2H), 2.07 (s, 3H), 1.98 (s, 3H), 1.47 (s, 3H). ^{19}F NMR (377 MHz, DMSO) δ -120.12, -120.14, -122.28, -122.30.

Example 32C:

[00477] LC-MS: (ES+H, m/z): $[\text{M}+\text{H}]^+ = 525.1$. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 8.76 (s, 1H), 8.61 (d, 1H), 8.27 (d, 1H), 8.25 (d, 1H), 8.15 – 8.04 (m, 1H), 7.80 (d, 1H), 6.82 (d, 1H), 5.49 (d, 2H), 5.12 (s, 1H), 3.05 – 2.89 (m, 1H), 2.83 – 2.74 (m, 1H), 2.15 – 2.09 (m, 2H), 2.07 (s, 3H), 1.98 (s, 3H), 1.50 (s, 3H). ^{19}F NMR (377 MHz, DMSO) δ -120.14, -120.16, -122.33, -122.35.

Example 32D:

[00478] LC-MS: (ES+H, m/z): [M+H]⁺=525.1. ¹H NMR (400 MHz, DMSO-d₆) δ 8.76 (s, 1H), 8.61 (d, 1H), 8.27 (d, 1H), 8.25 (d, 1H), 8.13 – 8.04 (m, 1H), 7.80 (d, 1H), 6.82 (d, 1H), 5.49 (d, 2H), 5.12 (s, 1H), 3.03 – 2.87 (m, 1H), 2.85 – 2.73 (m, 1H), 2.19 – 2.08 (m, 2H), 2.07 (s, 3H), 1.98 (s, 3H), 1.50 (s, 3H). ¹⁹F NMR (377 MHz, DMSO) δ -120.14, -120.16, -122.33, -122.35.

Example 33A, 33B**Step 1: Preparation of 2-methylthiophen-3-amine:**

[00479] To a stirred solution of LAH (14.49 g, 381.70 mmol, 2.00 equiv) in 1,4-dioxane was added methyl 3-aminothiophene-2-carboxylate (30.00 g, 190.85 mmol, 1.00 equiv) in 1,4-dioxane dropwise at 95°C under nitrogen atmosphere. The resulting mixture was stirred for 1.5 h at 95°C under nitrogen atmosphere. The mixture was allowed to cool down to room temperature. The reaction was monitored by LCMS. LCMS was OK. The mixture was allowed to cool down to 0°C. To the above mixture was added water (14.5 mL), 15% aqueous NaOH (43.5 mL) and water (14.5 mL). The resulting mixture was stirred for 1 h at room temperature. The resulting mixture was filtered, the filter cake was washed with EtOAc (3x50 mL). The filtrate was concentrated under reduced pressure to afford 2-methylthiophen-3-amine (19.00 g, 87.96%) as a black oil. LC-MS: (ES+H, m/z): [M+H]⁺=114.0. ¹H NMR (300 MHz, DMSO-d₆) δ 6.94 (d, 1H), 6.50 (d, 1H), 4.48 (br, 2H), 2.11 (s, 3H).

Step 2: Preparation of N-(2-methylthiophen-3-yl)acetamide:

[00480] To a stirred solution of 2-methylthiophen-3-amine (10.00 g, 88.35 mmol, 1.00 equiv) and CH₃COOK (11.27 g, 114.86 mmol, 1.30 equiv) in toluene was added Ac₂O (10.86 mL, 114.86 mmol, 1.30 equiv) in portions at room temperature. The resulting mixture was stirred for 1 h at room temperature. The resulting mixture was concentrated under reduced pressure. The residue was dissolved in DCM (30 mL). The combined organic layers were washed with brine (3 x 30 mL), dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column

chromatography to afford N-(2-methylthiophen-3-yl)acetamide (11.80 g, 86.04%) as a yellow solid. LC-MS: (ES+H, m/z): [M+H]⁺ = 156.1. ¹H NMR (300 MHz, DMSO-d₆) δ 9.41 (s, 1H), 7.22 – 7.11 (m, 2H), 2.27 (s, 3H), 2.01 (s, 3H).

Step 3: Preparation of N-(5-bromo-2-methylthiophen-3-yl)acetamide:

[00481] To a stirred solution of N-(2-methylthiophen-3-yl)acetamide (11.80 g, 76.02 mmol, 1.00 equiv) and 1-bromopyrrolidine-2,5-dione (13.53 g, 76.02 mmol, 1.00 equiv) in acetonitrile at room temperature under air atmosphere. The resulting mixture was stirred for 3h at room temperature. The reaction was monitored by LCMS. The resulting mixture was concentrated under reduced pressure. The resulting mixture was diluted with brine (50 mL) and extracted with CH₂Cl₂ (3 x 20mL). Then organic layer was dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to afford N-(5-bromo-2-methylthiophen-3-yl)acetamide (16.00 g, 89.90%) as a yellow solid. LC-MS: (ES+H, m/z): [M+H]⁺ = 233.9. ¹H NMR (400 MHz, DMSO-d₆) δ 9.52 (s, 1H), 7.25 (s, 1H), 2.22 (s, 3H), 2.00 (s, 3H).

Step 4: Preparation of N-[2-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)thiophen-3-yl]acetamide:

[00482] To a stirred solution of N-(5-bromo-2-methylthiophen-3-yl)acetamide (10.00 g, 42.71 mmol, 1.00 equiv) and 4,4,5,5-tetramethyl-2-(tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (14.10 g, 55.53 mmol, 1.30 equiv) in 1,4-dioxane (50 mL) were added CH₃COOK (12.58 g, 128.14 mmol, 3.00 equiv) and Pd(dppf)Cl₂ (1.56 g, 2.13 mmol, 0.10 equiv) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 12 h at 100°C under nitrogen atmosphere. The mixture was allowed to cool down to room temperature. The reaction was monitored by LCMS. The resulting mixture was filtered, the filter cake was washed with 1,4-dioxane (3x10 mL). The filtrate was concentrated under reduced pressure to afford N-[2-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)thiophen-3-yl]acetamide (11.00 g, crude) as a black solid. The crude product was used in the next step directly without further purification. LC-MS: (ES+H, m/z): [M+H]⁺ = 282.2.

Step 5: Preparation of ethyl 4-(4-acetamido-5-methylthiophen-2-yl)pyrimidine-2-carboxylate:

[00483] To a stirred solution of N-[2-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)thiophen-3-yl]acetamide (9.00 g, 32.00 mmol, assumed 100% yield, 1.00 equiv) and ethyl 4-chloropyrimidine-2-carboxylate (7.76 g, 41.61 mmol, 1.30 equiv) in 1,4-dioxane/H₂O (50mL /10 mL) were added K₂CO₃ (13.27 g, 96.02 mmol, 3.00 equiv) and Pd(dppf)Cl₂.CH₂Cl₂ (2.61 g, 3.20 mmol, 0.10 equiv) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 2 h at 80°C under nitrogen atmosphere. The reaction was monitored by LCMS. The resulting mixture was concentrated under reduced pressure. The resulting mixture was diluted with brine (50 mL) and extracted with DCM (3 x 50 mL). Then organic layer was dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to afford ethyl 4-(4-acetamido-5-methylthiophen-2-yl)pyrimidine-2-carboxylate (4.70 g, 48.09%) as a brown solid. LC-MS: (ES+H, m/z): [M+H]⁺ = 306.1. ¹H NMR (300 MHz,

DMSO- d_6) δ 9.64 (s, 1H), 8.85 (d, 1H), 8.18 (s, 1H), 8.03 (d, 1H), 4.44-4.32 (m, 2H), 2.38 (s, 3H), 2.07 (s, 3H), 1.38-1.31 (m, 3H).

Step 6: Preparation of methyl 4-(4-amino-5-methylthiophen-2-yl)pyrimidine-2-carboxylate:

[00484] To a stirred solution of ethyl 4-(4-acetamido-5-methylthiophen-2-yl)pyrimidine-2-carboxylate (4.70 g, 15.39 mmol, 1.00 equiv) HCl(g) in MeOH (10 mL, 4M in MeOH) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 2 h at room temperature under nitrogen atmosphere. The reaction was monitored by LCMS. The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography to afford methyl 4-(4-amino-5-methylthiophen-2-yl)pyrimidine-2-carboxylate (2.70 g, 70.37%) as a brown solid. LC-MS: (ES+H, m/z): $[M+H]^+ = 250.0$. ^1H NMR (300 MHz, DMSO- d_6) δ 8.78 (d, 1H), 7.84 (d, 1H), 7.46 (s, 1H), 4.81 (s, 2H), 3.91 (s, 3H), 2.22 (s, 3H).

Step 7: Preparation of methyl 4-[4-(4-hydroxy-2-methyl-6-oxopyridin-1-yl)-5-methylthiophen-2-yl]pyrimidine-2-carboxylate:

[00485] To a stirred solution of methyl 4-(4-amino-5-methylthiophen-2-yl)pyrimidine-2-carboxylate (1.70 g, 6.81 mmol, 1.00 equiv) and 2,2-dimethyl-6-(2-oxopropyl)-1,3-dioxin-4-one (1.63 g, 8.86 mmol, 1.30 equiv) in 1,4-dioxane (30 mL) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 2 h at 90°C under nitrogen atmosphere. The mixture was allowed to cool down to room temperature. To the above mixture was added conc. H_2SO_4 (0.67 g, 6.81 mmol, 1.00 equiv) dropwise over 1 min at room temperature. The resulting mixture was stirred for additional 1 h at 90°C. The mixture was allowed to cool down to room temperature. The reaction was monitored by LCMS. The resulting mixture was concentrated under reduced pressure. The residue was purified by trituration with Et_2O (100 mL). The precipitated solid was collected by filtration and washed with Et_2O (5 x 6 mL), to afford methyl 4-[4-(4-hydroxy-2-methyl-6-oxopyridin-1-yl)-5-methylthiophen-2-yl]pyrimidine-2-carboxylate (2.00 g, 82.06%) as a brown solid. LC-MS: (ES+H, m/z): $[M+H]^+ = 358.0$. ^1H NMR (400 MHz, DMSO- d_6) δ 10.75 (s, 1H), 8.94 – 8.91 (m, 1H), 8.12 – 8.08 (m, 1H), 8.01 (d, 1H), 5.95 (d, 1H), 5.59 (d, 1H), 3.93 (s, 3H), 2.20 (s, 3H), 1.94 (s, 3H).

Step 8: Preparation of methyl 4-(4-{4-[(3,5-difluoropyridin-2-yl)methoxy]-2-methyl-6-oxopyridin-1-yl}-5-methylthiophen-2-yl)pyrimidine-2-carboxylate:

[00486] To a stirred solution of methyl 4-[4-(4-hydroxy-2-methyl-6-oxopyridin-1-yl)-5-methylthiophen-2-yl]pyrimidine-2-carboxylate (1.20 g, 3.35 mmol, 1.00 equiv) and 2-(chloromethyl)-3,5-difluoropyridine (600.42 mg, 3.69 mmol, 1.10 equiv) in DMF (3 mL) were added 18-crown-6 (90.12 mg, 0.33 mmol, 0.10 equiv) and K_2CO_3 (2.32 g, 16.79 mmol, 5.00 equiv) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 3 h at 60°C under nitrogen atmosphere. The mixture was allowed to cool down to room temperature. The reaction was monitored by LCMS. The resulting mixture was poured into water (20 mL), then extracted with EtOAc (3x10 mL). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na_2SO_4 . After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography to afford methyl 4-(4-{4-[(3,5-

difluoropyridin-2-yl)methoxy]-2-methyl-6-oxopyridin-1-yl}-5-methylthiophen-2-yl)pyrimidine-2-carboxylate (900 mg, 55.32%) as a brown solid. LC-MS: (ES+H, m/z): $[M+H]^+ = 485.0$.

Step 9: Preparation of methyl 4-(4-{3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-6-methyl-2-oxopyridin-1-yl}-5-methylthiophen-2-yl)pyrimidine-2-carboxylate:

[00487] To a stirred solution of methyl 4-(4-{4-[(3,5-difluoropyridin-2-yl)methoxy]-2-methyl-6-oxopyridin-1-yl}-5-methylthiophen-2-yl)pyrimidine-2-carboxylate (900 mg, 1.85 mmol, 1.00 equiv) and NCS (322 mg, 2.41 mmol, 1.30 equiv) in IPA (4 mL) was added 2,2-dichloroacetic acid (24 mg, 0.18 mmol, 0.10 equiv) dropwise at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 1 h at 60°C under nitrogen atmosphere. The mixture was allowed to cool down to room temperature. The reaction was monitored by LCMS. The resulting mixture was poured into brine (50 mL) and extracted with DCM (3 x 50 mL). Then organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by reverse combi-flash chromatography to afford methyl 4-(4-{3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-6-methyl-2-oxopyridin-1-yl}-5-methylthiophen-2-yl)pyrimidine-2-carboxylate (420 mg, 43.57%) as a yellow solid. LC-MS: (ES+H, m/z): $[M+H]^+ = 519.0$. ^1H NMR (400 MHz, DMSO-d_6) δ 8.94 (d, 1H), 8.60 (d, 1H), 8.13 – 8.08 (m, 1H), 8.08 (d, 1H), 8.07 (d, 1H), 6.77 – 6.74 (m, 1H), 5.48 (d, 2H), 3.94 (s, 3H), 2.23 (s, 3H), 2.06 (s, 3H).

Step 10: Preparation of 3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-1-{5-[2-(2-hydroxypropan-2-yl)pyrimidin-4-yl]-2-methylthiophen-3-yl}-6-methylpyridin-2-one:

[00488] To a stirred solution of methyl 4-(4-{3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-6-methyl-2-oxopyridin-1-yl}-5-methylthiophen-2-yl)pyrimidine-2-carboxylate (380 mg, 0.73 mmol, 1.00 equiv) in THF (3 mL) was added MeMgBr (3.66 mL, 7.32 mmol, 10.00 equiv, 2M in THF) dropwise at 0°C under nitrogen atmosphere. The resulting mixture was stirred for 1 h at 0°C under nitrogen atmosphere. The reaction was monitored by LCMS. The reaction was quenched by the addition of sat. NH_4Cl (aq.) (20 mL) at 0°C. The resulting mixture was extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (40 mL), dried over anhydrous Na_2SO_4 . After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by reverse combi-flash chromatography to afford crude 3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-1-{5-[2-(2-hydroxypropan-2-yl)pyrimidin-4-yl]-2-methylthiophen-3-yl}-6-methylpyridin-2-one (154 mg, crude) as a light yellow solid. The crude product (154 mg) was further purified by Prep-HPLC to afford 3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-1-{5-[2-(2-hydroxypropan-2-yl)pyrimidin-4-yl]-2-methylthiophen-3-yl}-6-methylpyridin-2-one (100 mg, 26.31%) as a light yellow solid. LC-MS: (ES+H, m/z): $[M+H]^+ = 519.1$. ^1H NMR (300 MHz, DMSO-d_6) δ 8.80 (d, 1H), 8.60 (d, 1H), 8.16 – 8.03 (m, 1H), 7.99 (s, 1H), 7.75 (d, 1H), 6.75 (s, 1H), 5.48 (s, 2H), 5.03 (s, 1H), 2.22 (s, 3H), 2.06 (s, 3H), 1.52 (s, 6H).

Step 11: Preparation of rel-3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-1-{5-[2-(2-hydroxypropan-2-yl)pyrimidin-4-yl]-2-methylthiophen-3-yl}-6-methylpyridin-2-one and rel-3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-1-{5-[2-(2-hydroxypropan-2-yl)pyrimidin-4-yl]-2-methylthiophen-3-yl}-6-methylpyridin-2-one:

[00489] The race-mixture (100.00 mg) was separated by Prep-HPLC to afford rel-3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-1-{5-[2-(2-hydroxypropan-2-yl)pyrimidin-4-yl]-2-methylthiophen-3-yl}-6-methylpyridin-2-one (Example 33A, isomer 1, 26.20 mg, ee=100%) as a light yellow solid and rel-3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-1-{5-[2-(2-hydroxypropan-2-yl)pyrimidin-4-yl]-2-methylthiophen-3-yl}-6-methylpyridin-2-one (Example 33B, isomer 2, 33.50 mg, ee=99.70%) as a white solid.

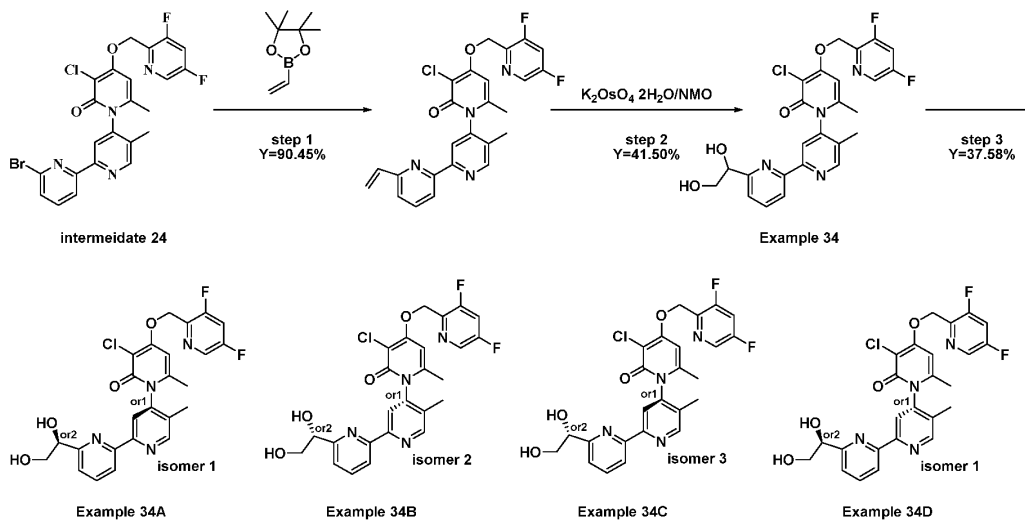
Example 33A:

[00490] LC-MS: (ES+H, m/z): $[M+H]^+=519.0$. ^1H NMR (300 MHz, DMSO- d_6) δ 8.80 (d, 1H), 8.61 (d, 1H), 8.15-8.06 (m, 1H), 8.00 (s, 1H), 7.76 (d, 1H), 6.76 (s, 1H), 5.48 (s, 2H), 5.03 (s, 1H), 2.22 (s, 3H), 2.07 (s, 3H), 1.53 (s, 6H). ^{19}F NMR (282 MHz, DMSO) δ -120.17, -120.20, -122.40, -122.43.

Example 33B:

[00491] LC-MS: (ES+H, m/z): $[M+H]^+=519.0$. ^1H NMR (300 MHz, DMSO- d_6) δ 8.80 (d, 1H), 8.61 (d, 1H), 8.17 – 8.04 (m, 1H), 8.00 (s, 1H), 7.75 (d, 1H), 6.76 (s, 1H), 5.48 (s, 2H), 5.03 (s, 1H), 2.22 (s, 3H), 2.07 (s, 3H), 1.53 (s, 6H). ^{19}F NMR (282 MHz, DMSO) δ -120.17, -120.20, -122.40, -122.43.

Example 34A, 34B, 34C, 34D



Step 1: Preparation of 3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-2'-(6-ethenylpyridin-2-yl)-5',6-dimethyl-[1,4'-bipyridin]-2-one:

[00492] To a stirred mixture of 2'-(6-bromopyridin-2-yl)-3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-5',6-dimethyl-[1,4'-bipyridin]-2-one (220 mg, 0.41 mmol, 1.00 equiv), K_2CO_3 (114 mg, 0.82 mmol, 2.00 equiv) and 2-ethenyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (128 mg, 0.82 mmol, 2.00 equiv) in 1,4-dioxane (3.50 mL) and H_2O (0.70 mL) was added $\text{Pd}(\text{dppf})\text{Cl}_2\text{CH}_2\text{Cl}_2$ (35 mg, 0.04 mmol, 0.10 equiv) at room temperature. The resulting mixture was stirred for 2 h at 100°C under nitrogen atmosphere. The mixture was allowed to cool down to room temperature. The reaction was monitored by LCMS. The mixture was purified by reverse phase combi-flash to afford 3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-2'-(6-ethenylpyridin-2-yl)-5',6-dimethyl-[1,4'-bipyridin]-2-one (180 mg, 90.45%) as a white solid. LC-MS: (ES+H, m/z): $[M+H]^+=481.0$.

Step 2: Preparation of 3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-2'-[6-(1,2-dihydroxyethyl)pyridin-2-yl]-5',6-dimethyl-[1,4'-bipyridin]-2-one:

[00493] To a stirred mixture of NMO (88 mg, 0.75 mmol, 2.00 equiv) and 3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-2'-(6-ethenylpyridin-2-yl)-5',6-dimethyl-[1,4'-bipyridin]-2-one (180 mg, 0.38 mmol, 1.00 equiv) in THF (2 mL) and t-BuOH (0.66 mL) was added K₂OsO₄·2H₂O (78 mg, 0.19 mmol, 0.50 equiv) at room temperature. The resulting mixture was stirred for 15 h at room temperature under nitrogen atmosphere. The reaction was monitored by LCMS. The reaction was quenched with sat. sodium thiosulfate (aq.) (30ml), extracted with EtOAc (3 x 40 mL). The combined organic layers were dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The crude product (150 mg) was purified by Prep-HPLC to afford 3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-2'-[6-(1,2-dihydroxyethyl)pyridin-2-yl]-5',6-dimethyl-[1,4'-bipyridin]-2-one (80 mg, 41.50%) as a white solid. LC-MS: (ES+H, m/z): [M+H]⁺ = 515.1.

Step 3: Preparation of rel-3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-2'-[6-(1,2-dihydroxyethyl)pyridin-2-yl]-5',6-dimethyl-[1,4'-bipyridin]-2-one and rel-3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-2'-[6-(1,2-dihydroxyethyl)pyridin-2-yl]-5',6-dimethyl-[1,4'-bipyridin]-2-one and rel-3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-2'-[6-(1,2-dihydroxyethyl)pyridin-2-yl]-5',6-dimethyl-[1,4'-bipyridin]-2-one and rel-3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-2'-[6-(1,2-dihydroxyethyl)pyridin-2-yl]-5',6-dimethyl-[1,4'-bipyridin]-2-one :

[00494] The racemate 3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-2'-[6-(1,2-dihydroxyethyl)pyridin-2-yl]-5',6-dimethyl-[1,4'-bipyridin]-2-one (120 mg) was separated by Prep-Chiral-HPLC to afford two peaks. The first peak was separated by Prep-Chiral-SFC to afford **Example 34A** (10.2 mg, ee=99.32%) and **Example 34B** (8.3 mg, ee=96.92%) as a white solid. The second peak was separated by Prep-Chiral-SFC to afford **Example 34C** (16 mg, ee=100%) and **Example 34D** (10.6 mg, ee=98.18%) as a white solid.

Example 34A:

[00495] LC-MS: (ES+H, m/z): [M+H]⁺ = 515.05. ¹H NMR (400 MHz, DMSO-d₆) δ 8.77 (s, 1H), 8.61 (d, 1H), 8.30 (s, 1H), 8.26 (d, 1H), 8.11 (td, 1H), 7.94 (t, 1H), 7.54 (d, 1H), 6.82 (s, 1H), 5.49 (d, 2H), 5.45 (d, 1H), 4.74 – 4.58 (m, 2H), 3.83 – 3.69 (m, 1H), 3.62 – 3.48 (m, 1H), 2.07 (s, 3H), 1.97 (s, 3H). ¹⁹F NMR (377 MHz, DMSO) δ -120.13, -120.15, -122.34, -122.36.

Example 34B:

[00496] LC-MS: (ES+H, m/z): [M+H]⁺ = 515.10. ¹H NMR (400 MHz, DMSO-d₆) δ 8.77 (s, 1H), 8.61 (d, 1H), 8.30 (s, 1H), 8.26 (d, 1H), 8.11 (td, 1H), 7.94 (t, 1H), 7.54 (d, 1H), 6.82 (s, 1H), 5.49 (d, 2H), 5.45 (d, 1H), 4.74 – 4.58 (m, 2H), 3.83 – 3.69 (m, 1H), 3.62 – 3.48 (m, 1H), 2.07 (s, 3H), 1.97 (s, 3H). ¹⁹F NMR (377 MHz, DMSO) δ -120.13, -120.15, -122.34, -122.36.

Example 34C:

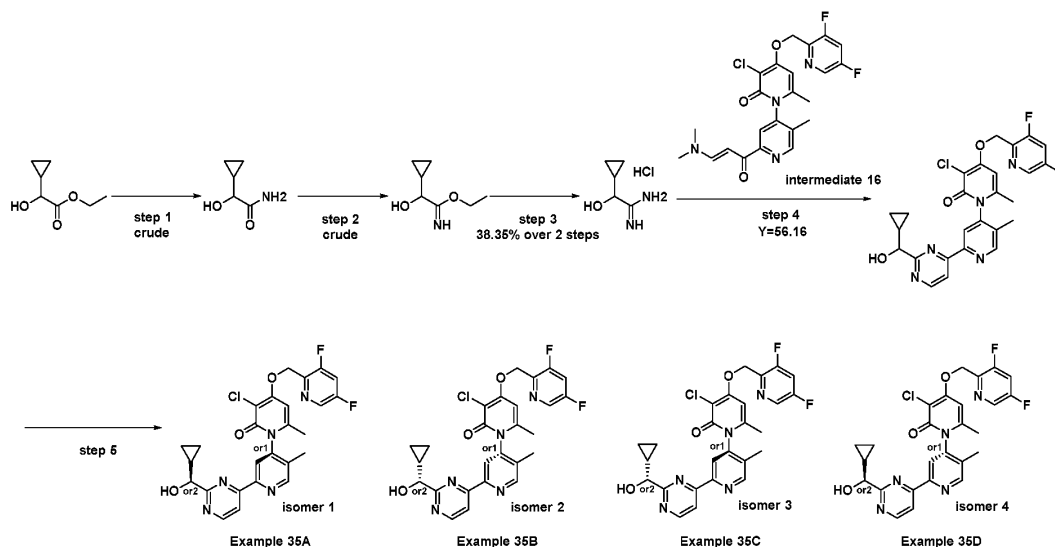
[00497] LC-MS: (ES+H, m/z): [M+H]⁺ = 515.10. ¹H NMR (300 MHz, DMSO-d₆) δ 8.78 (s, 1H), 8.62 (d, 1H), 8.30 (s, 1H), 8.29 – 8.23 (m, 1H), 8.11 (ddd, 1H), 7.95 (t, 1H), 7.55 (d, 1H), 6.83 (s, 1H), 5.50 (d, 2H),

5.45 (d, 1H), 4.74 – 4.55 (m, 2H), 3.83 – 3.72 (m, 1H), 3.66 – 3.47 (m, 1H), 2.07 (s, 3H), 1.98 (s, 3H). ^{19}F NMR (377 MHz, DMSO) δ -120.13, -120.15, -122.34, -122.36.

Example 34D:

[00498] LC-MS: (ES+H, m/z): $[\text{M}+\text{H}]^+ = 515.05$. ^1H NMR (300 MHz, DMSO- d_6) δ 8.78 (s, 1H), 8.62 (d, 1H), 8.30 (s, 1H), 8.29 – 8.23 (m, 1H), 8.11 (ddd, 1H), 7.95 (t, 1H), 7.55 (d, 1H), 6.83 (s, 1H), 5.50 (d, 2H), 5.45 (d, 1H), 4.74 – 4.55 (m, 2H), 3.83 – 3.72 (m, 1H), 3.66 – 3.47 (m, 1H), 2.07 (s, 3H), 1.98 (s, 3H). ^{19}F NMR (377 MHz, DMSO) δ -120.13, -120.15, -122.34, -122.36.

Example 35A, 35B, 35C, 35D



Step 1: Preparation of 2-cyclopropyl-2-hydroxyacetamide:

[00499] To a stirred solution of ethyl 2-cyclopropyl-2-hydroxyacetate (1.20 g, 8.33 mmol, 1.00 equiv) in acetone (20 mL) and H_2O (20 mL) was added MnO_2 (1.45 g, 16.66 mmol, 2.00 equiv) at room temperature under nitrogen atmosphere. The resulting mixture was stirred overnight at room temperature under nitrogen atmosphere. The reaction was monitored by TLC (PE:EA=1:1, R_f =0.2). The resulting mixture was filtrated, and the filtrate was concentrated under vacuum to afford 2-cyclopropyl-2-hydroxyacetamide (1.00 g, crude) as white solid. ^1H NMR (300 MHz, DMSO- d_6) δ 7.24 – 6.91 (m, 2H), 5.16 (s, 1H), 3.56 – 3.41 (m, 1H), 1.17 – 0.87 (m, 1H), 0.43 – 0.23 (m, 4H).

Step 2&3: Preparation of 2-cyclopropyl-2-hydroxyethanimidamide hydrochloride:

[00500] To a stirred solution of 2-cyclopropyl-2-hydroxyacetamide (800 mg, 6.949 mmol, 1.00 equiv) in THF (10 mL) was added tetrafluoroborane; triethyloxidanium (1716 mg, 9.034 mmol, 1.30 equiv) at 0°C under nitrogen atmosphere. The resulting mixture was stirred for 3 h at r.t. under nitrogen atmosphere. The resulting mixture was concentrated under reduced pressure to afford crude ethyl 2-cyclopropyl-2-hydroxyethanimidate. The above residue was dissolved in methanol (20 mL), To the above mixture was added $\text{NH}_3(\text{g})$ in MeOH (20 mL) at 0°C over 5 min. The resulting mixture was stirred for additional 1 h at

r.t. The resulting mixture was concentrated under reduced pressure. The residue was dissolved in EA (20 mL). The resulting mixture was filtered, to the filtrate was added HCl(gas) in 1,4-dioxane (5 mL) at 0°C, the resulting mixture was stirred for 2 h at 0°C under nitrogen atmosphere. The precipitated solids were collected by filtration and washed with EA (3x10 mL). This resulted in 2-cyclopropyl-2-hydroxyethanimidamide hydrochloride (400 mg, 38.35%) as a white solid. ¹H NMR (300 MHz, DMSO-d₆) δ 9.21 – 8.54 (m, 4H), 6.69 – 5.55 (m, 1H), 3.94 (d, 1H), 1.21 – 1.01 (m, 1H), 0.68 – 0.52 (m, 1H), 0.54 – 0.25 (m, 3H).

Step 4: Preparation of 3-chloro-2'-{2-[cyclopropyl(hydroxy)methyl]pyrimidin-4-yl}-4-[(3,5-difluoropyridin-2-yl)methoxy]-5',6-dimethyl-[1,4'-bipyridin]-2-one:

[00501] A mixture of 2-cyclopropyl-2-hydroxyethanimidamide hydrochloride (285 mg, 1.89 mmol, 3.00 equiv), 3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-2'-[(2E)-3-(dimethylamino)prop-2-enoyl]-5',6-dimethyl-[1,4'-bipyridin]-2-one (300 mg, 0.63 mmol, 1.00 equiv) and K₂CO₃ (873 mg, 6.32 mmol, 10.00 equiv) in IPA was stirred overnight at 80°C under nitrogen atmosphere. The reaction was monitored by LCMS. The resulting mixture was cooled down to r.t. and poured into 10 mL of water. The resulting mixture was extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography to afford crude product, which was further purified by Prep-HPLC to afford 3-chloro-2'-{2-[cyclopropyl(hydroxy)methyl]pyrimidin-4-yl}-4-[(3,5-difluoropyridin-2-yl)methoxy]-5',6-dimethyl-[1,4'-bipyridin]-2-one (190 mg, 56.16%) as a white solid. LC-MS: (ES+H, m/z): [M+H]⁺=526.0.

Step 5: Preparation of rel-3-chloro-2'-{2-[cyclopropyl(hydroxy)methyl]pyrimidin-4-yl}-4-[(3,5-difluoropyridin-2-yl)methoxy]-5',6-dimethyl-[1,4'-bipyridin]-2-one (Example 35A&B&C&D):

The racemate (190 mg) was separated by Prep-Chiral-HPLC to afford a mixture of **Example 35A&B** (90 mg) as a white solid and a mixture of **Example 35C&D** (85 mg) as a white solid.

The first racemate (90 mg) was separated by Prep-Chiral-HPLC to afford **Example 35A** (33.4 mg, 99.2%, ee=100%) as a white solid and **Example 35B** (30.3 mg, 99.7%, ee=100%) as a white solid.

The second racemate (85 mg) was separated by Prep-Chiral-HPLC to afford **Example 35C** (26.7 mg, 99.8%, ee=100%) as a white solid and **Example 35D** (23.8 mg, 99.4%, ee=100%) as a white solid.

Example 35A:

[00502] LC-MS: (ES+H, m/z): [M+H]⁺=526.1. ¹H NMR (300 MHz, DMSO-d₆) δ 8.97 (d, 1H), 8.87 (s, 1H), 8.62 (d, 1H), 8.59 (s, 1H), 8.26 (d, 1H), 8.16 – 8.06 (m, 1H), 6.85 (s, 1H), 5.50 (d, 2H), 5.22 (d, 1H), 4.20 (t, 1H), 2.12 (s, 3H), 1.98 (s, 3H), 1.39 – 1.29 (m, 1H), 0.50 – 0.37 (m, 4H). ¹⁹F NMR (282 MHz, DMSO) δ -120.14, -120.17, -122.32, -122.35.

Example 35B:

[00503] LC-MS: (ES+H, m/z): [M+H]⁺=526.1. ¹H NMR (300 MHz, DMSO-d₆) δ 8.97 (d, 1H), 8.87 (s, 1H), 8.62 (d, 1H), 8.56 (s, 1H), 8.26 (d, 1H), 8.16 – 8.06 (m, 1H), 6.85 (s, 1H), 5.50 (d, 2H), 5.23 (d, 1H),

4.20 (t, 1H), 2.12 (s, 3H), 1.99 (s, 3H), 1.38 – 1.24 (m, 1H), 0.49 – 0.34 (m, 4H). ^{19}F NMR (282 MHz, DMSO) δ -120.14, -120.16, -122.32, -122.34.

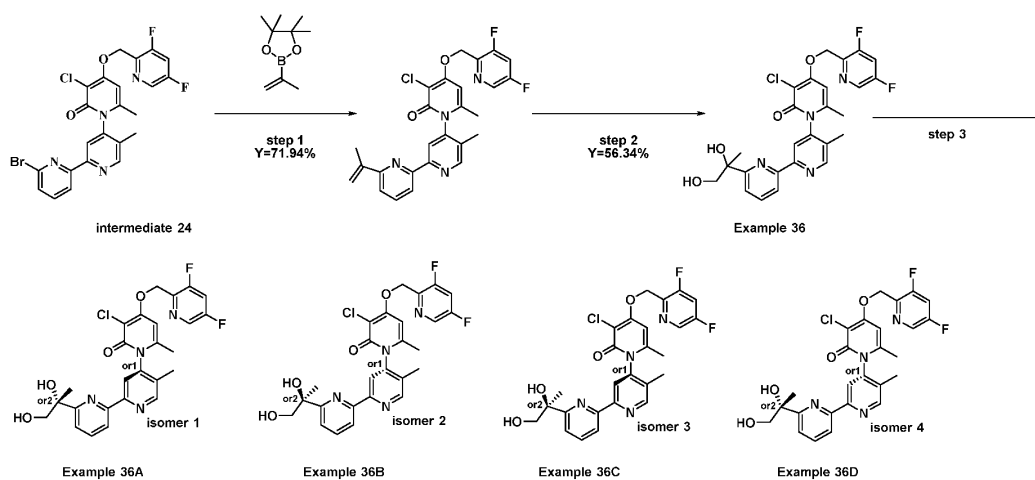
Example 35C:

[00504] LC-MS: (ES+H, m/z): $[\text{M}+\text{H}]^+ = 526.1$. ^1H NMR (300 MHz, DMSO- d_6) δ 8.97 (d, 1H), 8.87 (s, 1H), 8.61 (d, 1H), 8.56 (s, 1H), 8.26 (d, 1H), 8.16 – 8.04 (m, 1H), 6.84 (s, 1H), 5.50 (d, 2H), 5.23 (d, 1H), 4.20 (t, 1H), 2.11 (s, 3H), 1.98 (s, 3H), 1.40 – 1.29 (m, 1H), 0.49 – 0.36 (m, 4H). ^{19}F NMR (282 MHz, DMSO) δ -120.14, -120.16, -122.32, -122.34.

Example 35D:

[00505] LC-MS: (ES+H, m/z): $[\text{M}+\text{H}]^+ = 526.1$. ^1H NMR (300 MHz, DMSO- d_6) δ 8.97 (d, 1H), 8.88 (s, 1H), 8.62 (d, 1H), 8.60 (s, 1H), 8.27 (d, 1H), 8.16 – 8.04 (m, 1H), 6.85 (s, 1H), 5.51 (d, 2H), 5.22 (d, 1H), 4.20 (t, 1H), 2.12 (s, 3H), 1.99 (s, 3H), 1.39 – 1.28 (m, 1H), 0.46 – 0.38 (m, 4H). ^{19}F NMR (282 MHz, DMSO) δ -120.14, -120.17, -122.32, -122.35.

Example 36A, 36B, 36C, 36D



Step 1: Preparation of 3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-5',6-dimethyl-2'-[6-(prop-1-en-2-yl)pyridin-2-yl]-[1,4'-bipyridin]-2-one:

[00506] To a stirred solution of 2'-(6-bromopyridin-2-yl)-3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-5',6-dimethyl-[1,4'-bipyridin]-2-one (300 mg, 0.56 mmol, 1.00 equiv) and 4,4,5,5-tetramethyl-2-(prop-1-en-2-yl)-1,3,2-dioxaborolane (142 mg, 0.84 mmol, 1.50 equiv) in dioxane (4 mL) and H_2O (0.4 mL) were added CsF (170 mg, 1.12 mmol, 2.00 equiv) and $\text{Pd}(\text{PPh}_3)_4$ (130 mg, 0.11 mmol, 0.20 equiv) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 2 h at 90°C under nitrogen atmosphere. The mixture was allowed to cool down to room temperature. The reaction was poured into sat. NH_4Cl (aq.) (20 mL) at room temperature. The resulting mixture was extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na_2SO_4 . After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by Prep-TLC to

afford 3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-5',6-dimethyl-2'-[6-(prop-1-en-2-yl)pyridin-2-yl]-[1,4'-bipyridin]-2-one (200 mg, 71.94%) as a white solid. LC-MS: (ES+H, m/z): [M+H]⁺=495.2

Step 2: Preparation of 3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-2'-[6-(1,2-dihydroxypropan-2-yl)pyridin-2-yl]-5',6-dimethyl-[1,4'-bipyridin]-2-one:

[00507] To a stirred solution of 3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-5',6-dimethyl-2'-[6-(prop-1-en-2-yl)pyridin-2-yl]-[1,4'-bipyridin]-2-one (200 mg, 0.24 mmol, 1.00 equiv,) and NMO (57 mg, 0.48 mmol, 2.00 equiv) in THF (3 mL) and t-BuOH (1 mL) were added K₂OsO₄·2H₂O (45 mg, 0.12 mmol, 0.50 equiv) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 3 h at room temperature under nitrogen atmosphere. The resulting mixture was filtered, the filter cake was washed with THF (2 x 3 mL). The filtrate was concentrated under reduced pressure. The residue was purified by reverse combi-flash chromatography. This resulted in 3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-2'-[6-(1,2-dihydroxypropan-2-yl)pyridin-2-yl]-5',6-dimethyl-[1,4'-bipyridin]-2-one (120 mg, 56.34%) as a white solid. LC-MS: (ES+H, m/z): [M+H]⁺=529.10. ¹H NMR (400 MHz, DMSO-d₆) δ 8.77 (s, 1H), 8.61 (d, 1H), 8.36 (d, 1H), 8.25 (m, 1H), 8.10 (m, 1H), 7.93 (m, 1H), 7.67 (m, 1H), 6.82 (s, 1H), 5.49 (s, 2H), 5.19 (d, 1H), 4.59 (m, 1H), 3.69 – 3.48 (m, 2H), 2.49 (s, 3H), 2.06 (s, 3H), 1.43 (s, 3H). ¹⁹F NMR (377 MHz, DMSO) δ -120.12, -120.14, -122.33, -122.35.

Step 3: Preparation of rel-3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-2'-[6-(1,2-dihydroxypropan-2-yl)pyridin-2-yl]-5',6-dimethyl-[1,4'-bipyridin]-2-one & rel-3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-2'-[6-(1,2-dihydroxypropan-2-yl)pyridin-2-yl]-5',6-dimethyl-[1,4'-bipyridin]-2-one & rel-3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-2'-[6-(1,2-dihydroxypropan-2-yl)pyridin-2-yl]-5',6-dimethyl-[1,4'-bipyridin]-2-one & rel-3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-2'-[6-(1,2-dihydroxypropan-2-yl)pyridin-2-yl]-5',6-dimethyl-[1,4'-bipyridin]-2-one:

[00508] 3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-2'-[6-(1,2-dihydroxypropan-2-yl)pyridin-2-yl]-5',6-dimethyl-[1,4'-bipyridin]-2-one (120 mg) was separated by Prep-Chiral-HPLC to afford **Example 36A** (11.6 mg, ee=100%), **Example 36B** (13.1 mg, ee=99.34%) and mixture of **Example 36C&D** (56.0 mg) as a white solid. The mixture of **Example 36C&D** (56.0 mg) was further separated by Prep-Chiral-HPLC to afford **Example 36C** (10.4 mg, ee=100%), and **Example 36D** (11.5 mg, ee=99.78%) as a white solid.

Example 36A:

[00509] LC-MS: (ES+H, m/z): [M+H]⁺=529.05. ¹H NMR (300 MHz, DMSO-d₆) δ 8.77 (s, 1H), 8.62 (d, 1H), 8.36 (d, 1H), 8.26 (m, 1H), 8.11 (m, 1H), 7.94 (m, 1H), 7.67 (m, 1H), 6.83 (s, 1H), 5.49 (d, 2H), 5.20 (d, 1H), 4.60 (m, 1H), 3.60 (m, 2H), 2.07 (s, 3H), 1.98 (s, 3H), 1.44 (s, 3H). ¹⁹F NMR (282 MHz, DMSO) δ -120.11, -120.14, -122.30, -122.33.

Example 36B:

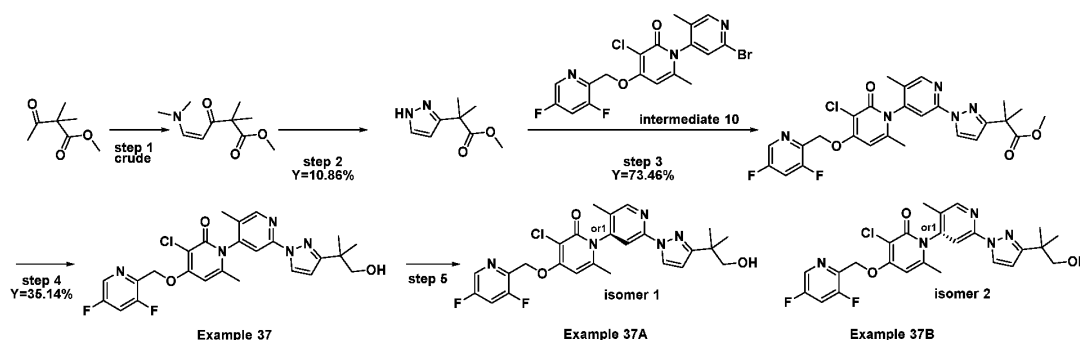
[00510] LC-MS: (ES+H, m/z): [M+H]⁺=529.05. ¹H NMR (300 MHz, DMSO-d₆) δ 8.77 (s, 1H), 8.62 (d, 1H), 8.36 (d, 1H), 8.26 (m, 1H), 8.11 (m, 1H), 7.94 (m, 1H), 7.67 (m, 1H), 6.83 (s, 1H), 5.49 (d, 2H), 5.20 (d, 1H), 4.60 (m, 1H), 3.60 (m, 2H), 2.07 (s, 3H), 1.98 (s, 3H), 1.44 (s, 3H). ¹⁹F NMR (282 MHz, DMSO) δ -120.11, -120.14, -122.31, -122.33.

Example 36C:

[00511] LC-MS: (ES+H, m/z): $[M+H]^+ = 529.10$. ^1H NMR (300 MHz, DMSO- d_6) δ 8.76 (s, 1H), 8.60 (d, 1H), 8.35 (s, 1H), 8.25 (d, 1H), 8.16 – 7.98 (m, 1H), 7.94 (m, 1H), 7.66 (m, 1H), 6.82 (s, 1H), 5.48 (d, 2H), 5.24 (s, 1H), 4.64 (m, 1H), 3.60 (m, 2H), 2.06 (s, 3H), 1.98 (s, 3H), 1.43 (s, 3H). ^{19}F NMR (282 MHz, DMSO) δ -120.04, -120.06, -122.13, -122.16.

Example 36D:

[00512] LC-MS: (ES+H, m/z): $[M+H]^+ = 529.10$. ^1H NMR (300 MHz, DMSO- d_6) δ 8.76 (s, 1H), 8.60 (d, 1H), 8.35 (s, 1H), 8.25 (d, 1H), 8.16 – 7.98 (m, 1H), 7.94 (m, 1H), 7.66 (m, 1H), 6.82 (s, 1H), 5.48 (d, 2H), 5.24 (s, 1H), 4.64 (m, 1H), 3.60 (m, 2H), 2.06 (s, 3H), 1.98 (s, 3H), 1.43 (s, 3H). ^{19}F NMR (282 MHz, DMSO) δ -120.09, -120.11, -122.26, -122.28.

Example 37A, 37B**Step 1: Preparation of methyl (4Z)-5-(dimethylamino)-2,2-dimethyl-3-oxopent-4-enoate:**

[00513] Into a 250 mL round-bottom flask were added methyl 2,2-dimethyl-3-oxobutanoate (4 g, 27.745 mmol, 1 equiv) and DMF-DMA (25 mL) at room temperature. The resulting mixture was stirred overnight at 100°C under nitrogen atmosphere. The mixture was allowed to cool down to room temperature. The reaction was monitored by LCMS. The resulting mixture was concentrated under reduced pressure. The crude product was used in the next step directly without further purification. LC-MS: (ES+H, m/z): $[M+H]^+ = 200.1$.

Step 2: Preparation of methyl 2-methyl-2-(1H-pyrazol-3-yl)propanoate:

[00514] Into a 100mL round-bottom flask were added methyl (4Z)-5-(dimethylamino)-2,2-dimethyl-3-oxopent-4-enoate (1.50 g, crude) and hydrazine (10 mL, 1M in THF) at room temperature. The resulting mixture was stirred overnight at room temperature under nitrogen atmosphere. The reaction was monitored by LCMS. The resulting mixture was concentrated under reduced pressure. The residue was purified by reverse combi-flash chromatography. This resulted in methyl 2-methyl-2-(1H-pyrazol-3-yl)propanoate (500 mg, 10.86%) as a colorless oil. LC-MS: (ES+H, m/z): $[M+H]^+ = 169.2$. ^1H NMR (300 MHz, Chloroform- d) δ 7.60 – 7.53 (m, 1H), 7.25 – 6.98 (m, 1H), 6.30 – 6.21 (m, 1H), 3.72 (s, 3H), 1.64 (s, 6H).

Step 3: Preparation of methyl 2-(1-{3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-5',6-dimethyl-2-oxo-[1,4'-bipyridin]-2'-yl}pyrazol-3-yl)-2-methylpropanoate:

[00515] To a solution of methyl 2-methyl-2-(1H-pyrazol-3-yl)propanoate (220 mg, 1.31 mmol, 1.50 equiv) and 2'-bromo-3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-5',6-dimethyl-[1,4'-bipyridin]-2-one (400 mg, 0.87 mmol, 1.00 equiv) in 1,4-dioxane (6 mL) were added CuI (33 mg, 0.17 mmol, 0.20 equiv), K₂CO₃ (185 mg, 1.75 mmol, 2.00 equiv) and (1S,2S)-N1,N2-dimethylcyclohexane-1,2-diamine (49 mg, 0.35 mmol, 0.40 equiv) at room temperature. The resulting mixture was stirred for 3 h at 80°C under nitrogen atmosphere. The reaction was monitored by LCMS. The mixture was allowed to cool down to room temperature. The reaction was poured into water (100 mL) and was extracted with EtOAc (3 x 100 mL). The combined organic layers were dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography to afford methyl 2-(1-{3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-5',6-dimethyl-2-oxo-[1,4'-bipyridin]-2'-yl}pyrazol-3-yl)-2-methylpropanoate (350 mg, 73.46%) as a white solid. LC-MS: (ES+H, m/z): [M+H]⁺=544.3. ¹H NMR (400 MHz, Chloroform-*d*) δ 8.47 – 8.43 (m, 1H), 8.43 – 8.40 (m, 1H), 8.38 (s, 1H), 7.73 (s, 1H), 7.36 – 7.30 (m, 1H), 6.43 – 6.35 (m, 2H), 5.45 – 5.40 (m, 2H), 3.68 (s, 3H), 2.09 (s, 3H), 2.03 (s, 3H), 1.62 (s, 3H), 1.60 (s, 3H).

Step 4: Preparation of 3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-2'-[3-(1-hydroxy-2-methylpropan-2-yl)pyrazol-1-yl]-5',6-dimethyl-[1,4'-bipyridin]-2-one:

[00516] To a stirred solution of methyl 2-(1-{3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-5',6-dimethyl-2-oxo-[1,4'-bipyridin]-2'-yl}pyrazol-3-yl)-2-methylpropanoate (300 mg, 0.55 mmol, 1.00 equiv) in DCM (3 mL) and MeOH (3 mL) was added NaBH₄ (625 mg, 16.56 mmol, 30.00 equiv) in portions at 0°C. The resulting mixture was stirred overnight at room temperature. The reaction was poured into water (100 mL) and extracted with CH₂Cl₂ (3 x 100 mL). The combined organic layers were dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography to afford 3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-2'-[3-(1-hydroxy-2-methylpropan-2-yl)pyrazol-1-yl]-5',6-dimethyl-[1,4'-bipyridin]-2-one (100 mg, 35.14%) as a white solid. LC-MS: (ES+H, m/z): [M+H]⁺=516.3.

Step 5: Preparation of rel-3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-2'-[3-(1-hydroxy-2-methylpropan-2-yl)pyrazol-1-yl]-5',6-dimethyl-[1,4'-bipyridin]-2-one and rel-3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-2'-[3-(1-hydroxy-2-methylpropan-2-yl)pyrazol-1-yl]-5',6-dimethyl-[1,4'-bipyridin]-2-one :

[00517] The racemate 3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-2'-[3-(1-hydroxy-2-methylpropan-2-yl)pyrazol-1-yl]-5',6-dimethyl-[1,4'-bipyridin]-2-one (80 mg) was separated by Prep-Chiral-SFC to afford rel-3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-2'-[3-(1-hydroxy-2-methylpropan-2-yl)pyrazol-1-yl]-5',6-dimethyl-[1,4'-bipyridin]-2-one (**Example 37A**, 28.6 mg, ee=97.82%) as a white solid and rel-3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-2'-[3-(1-hydroxy-2-methylpropan-2-yl)pyrazol-1-yl]-5',6-dimethyl-[1,4'-bipyridin]-2-one (**Example 37B**, 22.8 mg, ee=98.44%) as a white solid.

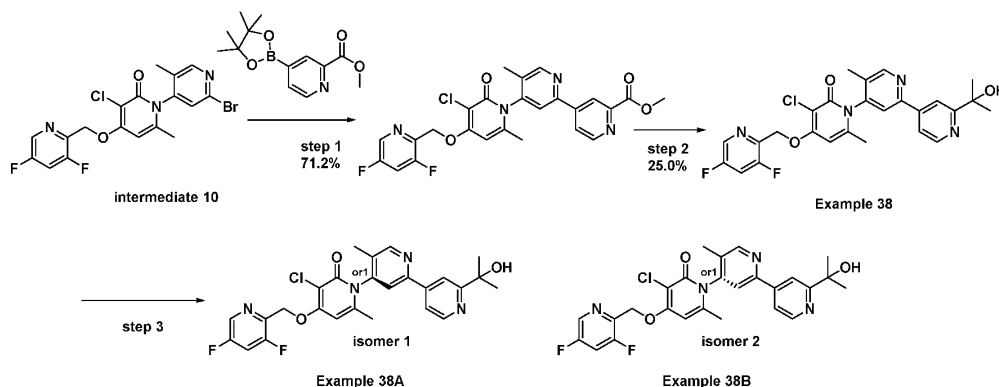
Example 37A:

[00518] LC-MS: (ES+H, m/z): $[M+H]^+ = 516.05$. ^1H NMR (300 MHz, DMSO- d_6) δ 8.67 – 8.59 (m, 1H), 8.54 (s, 1H), 8.52 – 8.45 (m, 1H), 8.17 – 8.03 (m, 1H), 7.80 (s, 1H), 6.81 (s, 1H), 6.57 – 6.45 (m, 1H), 5.49 (s, 2H), 4.64 (t, 1H), 3.47 (d, 2H), 2.01 (s, 6H), 1.25 (s, 6H). ^{19}F NMR (377 MHz, DMSO) δ -120.148, -120.173, -122.343, -122.369.

Example 37B:

[00519] LC-MS: (ES+H, m/z): $[M+H]^+ = 516.05$. ^1H NMR (300 MHz, DMSO- d_6) δ 8.69 – 8.59 (m, 1H), 8.54 (s, 1H), 8.52 – 8.47 (m, 1H), 8.17 – 8.06 (m, 1H), 7.80 (s, 1H), 6.81 (s, 1H), 6.56 – 6.46 (m, 1H), 5.49 (s, 2H), 4.64 (t, 1H), 3.47 (d, 2H), 2.01 (s, 6H), 1.25 (s, 6H). ^{19}F NMR (377 MHz, DMSO) δ -120.145, -120.170, -122.340, -122.365.

Example 38A, 38B



Step 1: Preparation of methyl 4-{3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-5',6-dimethyl-2-oxo-[1,4'-bipyridin]-2'-yl}pyridine-2-carboxylate:

[00520] To a stirred mixture of 2'-bromo-3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-5',6-dimethyl-[1,4'-bipyridin]-2-one (500 mg, 1.09 mmol, 1.00 equiv) and methyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine-2-carboxylate (576 mg, 2.19 mmol, 2.00 equiv) in dioxane (15 mL) and H_2O (3 mL) were added CsF (332 mg, 2.19 mmol, 2.00 equiv) and $\text{Pd}(\text{dppf})\text{Cl}_2$ (80 mg, 0.11 mmol, 0.10 equiv) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for additional 2 h at 100°C . The reaction was monitored by LCMS. The mixture was allowed to cool down to room temperature. The resulting mixture was filtered, the filter cake was washed with EtOAc (3x50 mL). The filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography to afford methyl 4-{3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-5',6-dimethyl-2-oxo-[1,4'-bipyridin]-2'-yl}pyridine-2-carboxylate (400 mg, 71.23%) as a yellow solid. LC-MS: (ES+H, m/z): $[M+H]^+ = 513.1$.

Step 2: Preparation of 3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-2'-[2-(2-hydroxypropan-2-yl)pyridin-4-yl]-5',6-dimethyl-[1,4'-bipyridin]-2-one:

[00521] To a stirred solution of methyl 4-{3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-5',6-dimethyl-2-oxo-[1,4'-bipyridin]-2'-yl}pyridine-2-carboxylate (400 mg, 0.78 mmol, 1.00 equiv) in THF (20 mL) was added MeMgBr (2.60 mL, 7.80 mmol, 10.00 equiv, 3M in THF) dropwise at 0°C under nitrogen atmosphere. The resulting mixture was stirred for 1 h at 0°C under nitrogen atmosphere. The reaction was

quenched by the addition of sat. NH_4Cl (aq.) (20 mL) at 0°C . The resulting mixture was extracted with EtOAc (3 x 40 mL). The combined organic layers were washed with brine (1 x 200 mL), dried over anhydrous Na_2SO_4 . After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by PREP-HPLC. This resulted in 3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-2'-[2-(2-hydroxypropan-2-yl)pyridin-4-yl]-5',6-dimethyl-[1,4'-bipyridin]-2-one (100 mg, 25.00%) as a white solid. LC-MS: (ES+H, m/z): $[\text{M}+\text{H}]^+ = 512.9$.

Step 3: Preparation of rel-3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-2'-[2-(2-hydroxypropan-2-yl)pyridin-4-yl]-5',6-dimethyl-[1,4'-bipyridin]-2-one & rel-3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-2'-[2-(2-hydroxypropan-2-yl)pyridin-4-yl]-5',6-dimethyl-[1,4'-bipyridin]-2-one :

[00522] 3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-2'-[2-(2-hydroxypropan-2-yl)pyridin-4-yl]-5',6-dimethyl-[1,4'-bipyridin]-2-one (140 mg) was separated by prep-chiral-HPLC to afford **Example 38A** (41.3 mg, ee=100%) and **Example 38B** (43.8 mg, ee=100%) as a white solid.

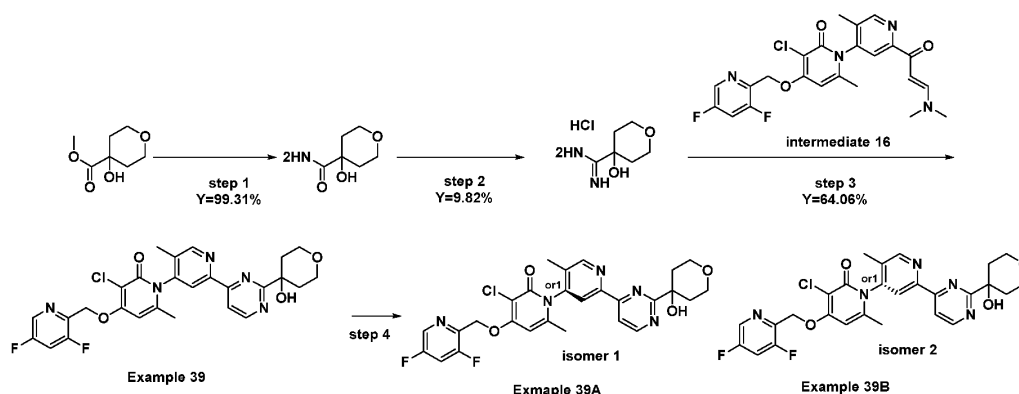
Example 38A:

[00523] LC-MS: (ES+H, m/z): $[\text{M}+\text{H}]^+ = 513.10$. ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 8.84 (s, 1H), 8.65 – 8.57 (m, 2H), 8.39 (d, 1H), 8.18 (s, 1H), 8.11 (td, 1H), 7.92 (dd, 1H), 6.83 (s, 1H), 5.50 (d, 2H), 5.33 (s, 1H), 2.08 (s, 3H), 1.99 (s, 3H), 1.50 (s, 3H), 1.49 (s, 3H). ^{19}F NMR (282 MHz, DMSO) δ -120.14, -120.16, -122.33, -122.36.

Example 38B:

[00524] LC-MS: (ES+H, m/z): $[\text{M}+\text{H}]^+ = 513.10$. ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 8.84 (s, 1H), 8.65 – 8.57 (m, 2H), 8.39 (t, 1H), 8.18 (s, 1H), 8.11 (ddd, 1H), 7.91 (dd, 1H), 6.83 (s, 1H), 5.50 (d, 2H), 5.32 (s, 1H), 2.08 (s, 3H), 1.99 (s, 3H), 1.50 (s, 3H), 1.49 (s, 3H). ^{19}F NMR (282 MHz, DMSO) δ -120.14, -120.16, -122.33, -122.36.

Example 39A, 39B



Step 1: Preparation of 4-hydroxyoxane-4-carboxamide:

[00525] A solution of methyl 4-hydroxyoxane-4-carboxylate (3 g, 18.73 mmol, 1.00 equiv) in $\text{NH}_3(\text{g})$ in MeOH (30 mL, 4M) was stirred for 2 h at 80°C under nitrogen atmosphere. The resulting mixture was allowed to cool down to room temperature. The resulting mixture was concentrated under vacuum, to afford

4-hydroxyoxane-4-carboxamide (2.70 g, 99.31%) as a white solid. ¹H NMR (400 MHz, DMSO-d₆) δ 7.15 (d, 2H), 5.30 (s, 1H), 3.83 – 3.48 (m, 4H), 2.09 – 1.75 (m, 2H), 1.42 – 1.17 (m, 2H).

Step 2: Preparation of 4-hydroxyoxane-4-carboximidamide hydrochloride:

[00526] A solution of 4-hydroxyoxane-4-carboxamide (2.70 g, 18.60 mmol, 1.00 equiv) in THF (60 mL) was added tetrafluoroborane; triethyloxidanium (5.30 g, 27.90 mmol, 1.50 equiv) in portions at 0°C under nitrogen atmosphere. The resulting mixture was stirred for 3 h at room temperature under nitrogen atmosphere. The resulting mixture was concentrated under reduced pressure. The residue was dissolved in MeOH (40 mL). To the above solution was added NH₃(g) in MeOH (30 mL, 4M) dropwise at 0°C. The resulting mixture was stirred for additional 3 h at room temperature. The resulting mixture was concentrated under reduced pressure. The residue was dissolved in EA (50 mL). To the above solution was added HCl(gas) in 1,4-dioxane (10 mL, 7M) dropwise at 0°C. The resulting mixture was stirred for additional 30 min at room temperature. The precipitated solids were collected by filtration and washed with EA (10 mL). The filter cake was concentrated under vacuum. To afford 4-hydroxyoxane-4-carboximidamide hydrochloride (330 mg, 9.82%) as a white solid.

Step 3: Preparation of 3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-2'-[2-(4-hydroxyoxan-4-yl)pyrimidin-4-yl]-5',6-dimethyl-[1,4'-bipyridin]-2-one:

[00527] A mixture of 4-hydroxyoxane-4-carboximidamide hydrochloride (380 mg, 2.10 mmol, 5.00 equiv), K₂CO₃ (580 mg, 4.20 mmol, 10.00 equiv) and 3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-2'-[(2E)-3-(dimethylamino)prop-2-en-1-yl]-5',6-dimethyl-[1,4'-bipyridin]-2-one (200 mg, 0.42 mmol, 1.00 equiv) in IPA (5 mL) was stirred overnight at 80°C under nitrogen atmosphere. The reaction was monitored by LCMS. The resulting mixture was allowed to cool down to room temperature. The resulting mixture was diluted with EA (200 mL). The resulting mixture was washed with water (2x100 mL). The organic layers were concentrated under reduced pressure. The residue was purified by Prep-TLC (EA 0.1%Et₃N) to afford 3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-2'-[2-(4-hydroxyoxan-4-yl)pyrimidin-4-yl]-5',6-dimethyl-[1,4'-bipyridin]-2-one (200 mg, crude). The crude product was further purified by Prep-HPLC to afford 3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-2'-[2-(4-hydroxyoxan-4-yl)pyrimidin-4-yl]-5',6-dimethyl-[1,4'-bipyridin]-2-one (150 mg, 64.06%) as a white solid. LC-MS: (ES+H, m/z): [M+H]⁺=556.1. ¹H NMR (400 MHz, DMSO-d₆) δ 9.07 (s, 2H), 8.76 (s, 2H), 6.29 (br, 1H), 3.81 – 3.70 (m, 2H), 3.69 – 3.64 (m, 2H), 2.20 – 1.95 (m, 2H), 1.58 – 1.52 (m, 2H).

Step 4: Preparation of rel-3-chloro-4-((3,5-difluoropyridin-2-yl)methoxy)-2'-(2-(4-hydroxytetrahydro-2H-pyran-4-yl)pyrimidin-4-yl)-5',6-dimethyl-2H-[1,4'-bipyridin]-2-one & rel-3-chloro-4-((3,5-difluoropyridin-2-yl)methoxy)-2'-(2-(4-hydroxytetrahydro-2H-pyran-4-yl)pyrimidin-4-yl)-5',6-dimethyl-2H-[1,4'-bipyridin]-2-one :

[00528] 3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-2'-[2-(4-hydroxyoxan-4-yl)pyrimidin-4-yl]-5',6-dimethyl-[1,4'-bipyridin]-2-one (150 mg) was isolated by Prep-CHIRAL-HPLC to afford rel-3-chloro-4-((3,5-difluoropyridin-2-yl)methoxy)-2'-(2-(4-hydroxytetrahydro-2H-pyran-4-yl)pyrimidin-4-yl)-5',6-dimethyl-2H-[1,4'-bipyridin]-2-one (**Example 39A, isomer 1**, 37.2 mg, ee=99.58%) and rel-3-chloro-4-

((3,5-difluoropyridin-2-yl)methoxy)-2'-(2-(4-hydroxytetrahydro-2H-pyran-4-yl)pyrimidin-4-yl)-5',6-dimethyl-2H-[1,4'-bipyridin]-2-one (**Example 39B, isomer 2**, 35.3 mg, ee=99.63%) as a white solid.

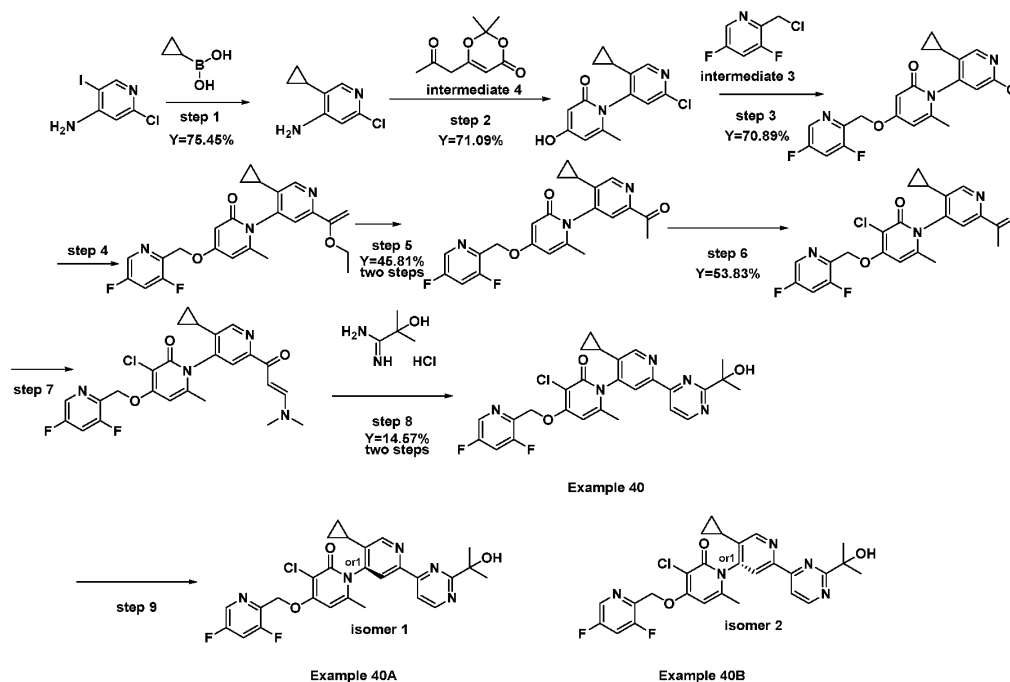
Example 39A:

[00529] LC-MS: (ES+H, m/z): [M+H]⁺=555.85. ¹H NMR (400 MHz, DMSO-d₆) δ 9.01 (d, 1H), 8.87 (s, 1H), 8.64 (d, 1H), 8.61 (d, 1H), 8.26 (d, 1H), 8.15 – 8.06 (m, 1H), 6.85 (d, 1H), 5.50 (d, 2H), 5.33 (s, 1H), 3.88 – 3.67 (m, 4H), 2.35 – 2.15 (m, 2H), 2.11 (s, 3H), 1.98 (s, 3H), 1.72 – 1.60 (m, 2H). ¹⁹F NMR (377 MHz, DMSO) δ -120.13, -120.15, -122.31, -122.32.

Example 39B:

[00530] LC-MS: (ES+H, m/z): [M+H]⁺=555.90. ¹H NMR (400 MHz, DMSO-d₆) δ 9.01 (d, 1H), 8.87 (s, 1H), 8.64 (d, 1H), 8.61 (d, 1H), 8.26 (d, 1H), 8.14 – 8.06 (m, 1H), 6.85 (d, 1H), 5.50 (d, 2H), 5.33 (s, 1H), 3.85 – 3.67 (m, 4H), 2.35 – 2.16 (m, 2H), 2.11 (s, 3H), 1.98 (s, 3H), 1.75 – 1.60 (m, 2H). ¹⁹F NMR (377 MHz, DMSO) δ -120.13, -120.15, -122.30, -122.32.

Example 40A, 40B



Step1: Preparation of 2-chloro-5-cyclopropylpyridin-4-amine:

[00531] To a stirred solution of 2-chloro-5-iodopyridin-4-amine (5.00 g, 19.64 mmol, 1.00 equiv), cyclopropylboronic acid (1.69 g, 19.64 mmol, 1.00 equiv) in Toluene (30 mL) and H₂O (3 mL) was added Pd(dppf)Cl₂ (0.72 g, 0.98 mmol, 0.05 equiv) at room temperature under nitrogen atmosphere. The resulting mixture was stirred overnight at 100°C under nitrogen atmosphere. The reaction was monitored by TLC. The mixture was allowed to cool down to room temperature. The reaction was quenched by the addition of water (50mL) at room temperature. The resulting mixture was extracted with EtOAc (3 x 30mL). The combined organic layers were washed with brine (100 mL). The filtrate was concentrated under reduced

pressure. The residue was purified by silica gel column chromatography, the pure fraction was concentrated under vacuum to afford 2-chloro-5-cyclopropylpyridin-4-amine (2.50 g, 75.45%) as a yellow oil. ¹H NMR (300 MHz, DMSO-d₆) δ 7.60 (s, 1H), 6.51 (s, 1H), 6.28 (s, 2H), 1.67-1.43 (m, 1H), 0.98 – 0.75 (m, 2H), 0.64 – 0.43 (m, 2H).

Step2: Preparation of 2'-chloro-5'-cyclopropyl-4-hydroxy-6-methyl-[1,4'-bipyridin]-2-one:

[00532] To a stirred solution of 2-chloro-5-cyclopropylpyridin-4-amine (2.40 g, 14.23 mmol, 1.00 equiv) and 2,2-dimethyl-6-(2-oxopropyl)-1,3-dioxin-4-one (5.24 g, 28.46 mmol, 2.00 equiv) in 1,4-dioxane (72 mL) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 2h at 90°C under nitrogen atmosphere. The mixture was allowed to cool down to room temperature. To the above mixture was added H₂SO₄ (1.40 g, 14.23 mmol, 1.00 equiv) dropwise at room temperature. The resulting mixture was stirred for additional 1 h at 90°C. The reaction was monitored by LCMS. The mixture was allowed to cool down to room temperature then concentrated to remove the solvent, followed by additions of water (20 mL). The precipitated solids were collected by filtration and washed with Et₂O (3x10 mL) to afford 2'-chloro-5'-cyclopropyl-4-hydroxy-6-methyl-[1,4'-bipyridin]-2-one (2.80 g, 71.09%) as a white solid. LC-MS: (ES+H, *m/z*): [M+H]⁺=277.1. ¹H NMR (400 MHz, DMSO-d₆) δ 10.84 (br, 1H), 8.20 (s, 1H), 7.52 (s, 1H), 6.04-5.91 (m, 1H), 5.66-5.54 (m, 1H), 1.88 (s, 3H), 1.51-1.35 (m, 1H), 1.00 – 0.80 (m, 3H), 0.73 – 0.55 (m, 1H).

Step3: Preparation of 2'-chloro-5'-cyclopropyl-4-[(3,5-difluoropyridin-2-yl)methoxy]-6-methyl-[1,4'-bipyridin]-2-one:

[00533] To a stirred solution of 2'-chloro-5'-cyclopropyl-4-hydroxy-6-methyl-[1,4'-bipyridin]-2-one (2.90 g, 10.48 mmol, 1.00 equiv) and 2-(chloromethyl)-3,5-difluoropyridine (3.43 g, 20.96 mmol, 2.00 equiv) in DMF (50 mL) were added K₂CO₃ (5.79 g, 41.92 mmol, 4.00 equiv) and 18-Crown-6 (277 mg, 1.04 mmol, 0.10 equiv) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 1h at 60°C under nitrogen atmosphere. The reaction was monitored by LCMS. The mixture was allowed to cool down to room temperature. The reaction was poured into water (100 mL) at room temperature. The resulting mixture was extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with brine (5 x 100 mL), the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography the pure fraction was concentrated under vacuum to afford 2'-chloro-5'-cyclopropyl-4-[(3,5-difluoropyridin-2-yl)methoxy]-6-methyl-[1,4'-bipyridin]-2-one (3.00 g, 70.89%) as a yellow solid. LC-MS: (ES+H, *m/z*): [M+H]⁺=404.1. ¹H NMR (400 MHz, DMSO-d₆) δ 8.62-8.57 (m, 1H), 8.22 (s, 1H), 8.13-8.02 (m, 1H), 7.57 (s, 1H), 6.19-6.11 (m, 1H), 6.08-6.01 (m, 1H), 5.29-5.17 (m, 2H), 1.90 (s, 3H), 1.48-1.34 (m, 1H), 0.99 – 0.90 (m, 1H), 0.91 – 0.82 (m, 2H), 0.74 – 0.60 (m, 1H).

Step4: Preparation of 5'-cyclopropyl-4-[(3,5-difluoropyridin-2-yl)methoxy]-2'-(1-ethoxyethenyl)-6-methyl-[1,4'-bipyridin]-2-one:

[00534] To a stirred solution of 2'-chloro-5'-cyclopropyl-4-[(3,5-difluoropyridin-2-yl)methoxy]-6-methyl-[1,4'-bipyridin]-2-one (3.00 g, 7.42 mmol, 1.00 equiv) and tributyl(1-ethoxyethenyl)stannane (5.37 g, 14.85 mmol, 2.00 equiv) in 1,4-dioxane (30 mL) were added Pd(PPh₃)Cl₂ (260 mg, 0.37 mmol, 0.05 equiv) at room temperature under nitrogen atmosphere. The resulting mixture was stirred overnight at 100°C under

nitrogen atmosphere. The reaction was monitored by TLC. The mixture was allowed to cool down to room temperature. The resulting mixture was filtrated and concentrated under reduced pressure to afford 5'-cyclopropyl-4-[(3,5-difluoropyridin-2-yl)methoxy]-2'-(1-ethoxyethenyl)-6-methyl-[1,4'-bipyridin]-2-one (1.80 g, crude) as a yellow solid.

Step 5: Preparation of 2'-acetyl-5'-cyclopropyl-4-[(3,5-difluoropyridin-2-yl)methoxy]-6-methyl-[1,4'-bipyridin]-2-one:

[00535] To a stirred solution of 5'-cyclopropyl-4-[(3,5-difluoropyridin-2-yl)methoxy]-2'-(1-ethoxyethenyl)-6-methyl-[1,4'-bipyridin]-2-one (1.80 g, 4.09 mmol, 1.00 equiv) in THF (20 mL) were added conc. HCl (2 mL) dropwise at 0°C under nitrogen atmosphere. The resulting mixture was stirred for 2 h at room temperature under nitrogen atmosphere. The reaction was monitored by LCMS. The reaction was poured into Water(40ml) at room temperature. The resulting mixture was extracted with EtOAc (3 x 30mL). The combined organic layers were washed with brine (3x50 mL), the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, the pure fraction was concentrated under vacuum to afford 2'-acetyl-5'-cyclopropyl-4-[(3,5-difluoropyridin-2-yl)methoxy]-6-methyl-[1,4'-bipyridin]-2-one (1.40 g, 45.81%, two steps) as a yellow solid. LC-MS: (ES+H, m/z): [M+H]⁺ =412.1. ¹H NMR (400 MHz, DMSO-d₆) δ 8.63-8.57 (m, 1H), 8.47 (s, 1H), 8.12-8.04 (m, 1H), 7.75 (s, 1H), 6.18-6.11 (m, 1H), 6.08-6.02 (m, 1H), 5.24 (d, 2H), 2.64 (s, 3H), 1.86 (s, 3H), 1.56-1.43 (m, 1H), 1.14 – 0.94 (m, 3H), 0.88 – 0.76 (m, 1H).

Step 6: Preparation of 2'-acetyl-3-chloro-5'-cyclopropyl-4-[(3,5-difluoropyridin-2-yl)methoxy]-6-methyl-[1,4'-bipyridin]-2-one:

[00536] To a stirred solution of 2'-acetyl-5'-cyclopropyl-4-[(3,5-difluoropyridin-2-yl)methoxy]-6-methyl-[1,4'-bipyridin]-2-one (1.20 g, 2.91 mmol, 1.00 equiv) and NCS (506 mg, 3.79 mmol, 1.30 equiv) in DCM (10 mL) were added 2,2-dichloroacetic acid (18 mg, 0.14 mmol, 0.05 equiv) at room temperature under nitrogen atmosphere. The resulting mixture was stirred overnight at room temperature under nitrogen atmosphere. The reaction was monitored by LCMS. The reaction was poured into Water (30ml) at room temperature. The resulting mixture was extracted with CH₂Cl₂ (3 x20 mL). The combined organic layers were washed with brine (3x30 mL), the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, the pure fraction was concentrated under vacuum to afford 2'-acetyl-3-chloro-5'-cyclopropyl-4-[(3,5-difluoropyridin-2-yl)methoxy]-6-methyl-[1,4'-bipyridin]-2-one (700 mg, 53.83%) as a yellow solid. LC-MS: (ES+H, m/z): [M+H]⁺ =446.0. ¹H NMR (300 MHz, DMSO-d₆) δ 8.66-8.57 (m, 1H), 8.51 (s, 1H), 8.16-8.03 (m, 1H), 7.86 (s, 1H), 6.81 (s, 1H), 5.47 (s, 2H), 2.65 (s, 3H), 1.96 (s, 3H), 1.57 – 1.40 (m, 1H), 1.15-1.05 (m, 1H), 1.04-0.95 (m, 2H), 0.91-0.75 (m, 1H).

Step 7: Preparation of 3-chloro-5'-cyclopropyl-4-[(3,5-difluoropyridin-2-yl)methoxy]-2'-[(2E)-3-(dimethylamino)prop-2-enoyl]-6-methyl-[1,4'-bipyridin]-2-one:

[00537] To a stirred solution of 2'-acetyl-3-chloro-5'-cyclopropyl-4-[(3,5-difluoropyridin-2-yl)methoxy]-6-methyl-[1,4'-bipyridin]-2-one (680 mg, 1.52 mmol, 1.00 equiv) in DMF-DMA (20 mL) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 3 h at 100°C under nitrogen atmosphere.

The reaction was monitored by LCMS. The mixture was allowed to cool down to room temperature. The resulting mixture was concentrated under reduced pressure to afford 3-chloro-5'-cyclopropyl-4-[(3,5-difluoropyridin-2-yl)methoxy]-2'-[(2E)-3-(dimethylamino)prop-2-enoyl]-6-methyl-[1,4'-bipyridin]-2-one (440 mg, crude) as a yellow solid. The crude product mixture was used in the next step directly without further purification. LC-MS: (ES+H, *m/z*): [M+H]⁺ = 501.2.

Step 8: Preparation of 3-chloro-5'-cyclopropyl-4-[(3,5-difluoropyridin-2-yl)methoxy]-2'-[2-(2-hydroxypropan-2-yl)pyrimidin-4-yl]-6-methyl-[1,4'-bipyridin]-2-one:

[00538] To a stirred solution of 3-chloro-5'-cyclopropyl-4-[(3,5-difluoropyridin-2-yl)methoxy]-2'-[(2E)-3-(dimethylamino)prop-2-enoyl]-6-methyl-[1,4'-bipyridin]-2-one (440 mg, 0.87 mmol, 1.00 equiv) and 2-hydroxy-2-methylpropanimidamide hydrochloride (608 mg, 4.39 mmol, 5.00 equiv) in DMF (5 mL) were added K₂CO₃ (364 mg, 2.63 mmol, 3.00 equiv) at room temperature under nitrogen atmosphere. The resulting mixture was stirred overnight at 80°C under nitrogen atmosphere. The reaction was monitored by LCMS. The mixture was allowed to cool down to room temperature. The resulting mixture was poured into water (40 mL) at 0°C. The resulting mixture was extracted with EtOAc (3 x 30 mL). The combined organic layers were washed with brine (5x50 mL), the filtrate was concentrated under reduced pressure. The residue was purified by Prep-TLC, the pure fraction was concentrated under vacuum to afford 3-chloro-5'-cyclopropyl-4-[(3,5-difluoropyridin-2-yl)methoxy]-2'-[2-(2-hydroxypropan-2-yl)pyrimidin-4-yl]-6-methyl-[1,4'-bipyridin]-2-one (120 mg, 14.57%, over two steps) as a white solid. LC-MS: (ES+H, *m/z*): [M+H]⁺ = 540.1.

Step 9: Preparation of rel-3-chloro-5'-cyclopropyl-4-[(3,5-difluoropyridin-2-yl)methoxy]-2'-[2-(2-hydroxypropan-2-yl)pyrimidin-4-yl]-6-methyl-[1,4'-bipyridin]-2-one and rel-3-chloro-5'-cyclopropyl-4-[(3,5-difluoropyridin-2-yl)methoxy]-2'-[2-(2-hydroxypropan-2-yl)pyrimidin-4-yl]-6-methyl-[1,4'-bipyridin]-2-one:

[00539] The racemate (100 mg) was separated by Prep-Chiral-HPLC to afford Example 40A (30.9 mg, 98.2% purity, ee=100%) as a white solid and Example 40B (37.7 mg, 96.9% purity, ee=99.48%) as a white solid.

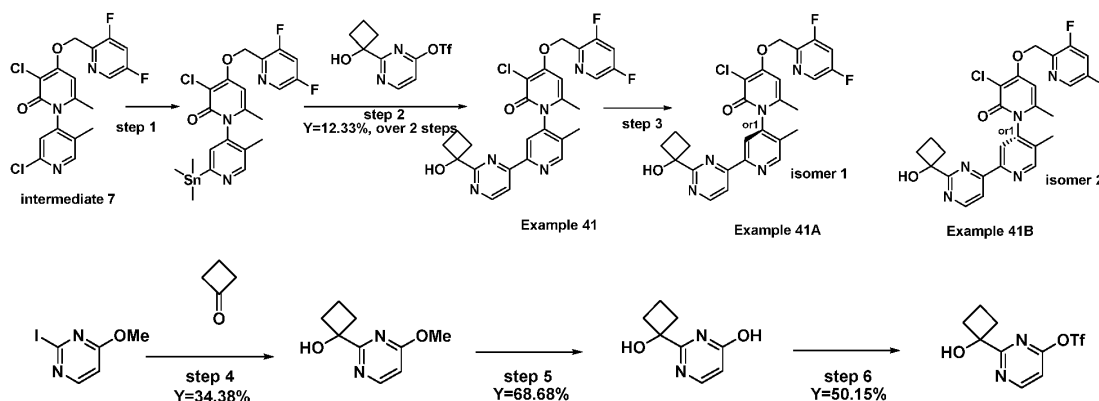
Example 40A:

[00540] LC-MS: (ES+H, *m/z*): [M+H]⁺ = 540.10. ¹H NMR (300 MHz, DMSO-*d*₆) δ 9.00-8.93 (m, 1H), 8.66(s, 1H), 8.63 – 8.60 (m, 1H), 8.56(s, 1H) 8.25-8.18 (m, 1H), 8.15-8.07 (m, 1H), 6.86 (s, 1H), 5.52-5.48 (m, 2H), 5.26 (s, 1H), 2.03 (s, 3H), 1.56-1.50 (m, 7H), 1.14-1.07 (m, 1H), 1.03-0.95 (m, 2H), 0.87-0.78 (m, 1H). ¹⁹F NMR (282 MHz, DMSO) δ -120.11, -120.13, -122.29, -122.31.

Example 40B:

[00541] LC-MS: (ES+H, *m/z*): [M+H]⁺ = 539.85. ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.99-8.94 (m, 1H), 8.66 (s, 1H), 8.63-8.60 (m, 1H), 8.56 (s, 1H), 8.23-8.19 (m, 1H), 8.15-8.06 (m, 1H), 6.86 (s, 1H), 5.54-5.45 (m, 2H), 5.26 (s, 1H), 2.03 (s, 3H), 1.57-1.50 (m, 7H), 1.17-1.05 (m, 1H), 1.02 – 0.93 (m, 2H), 0.88-0.77 (m, 1H). ¹⁹F NMR (282 MHz, DMSO) δ -120.10, -120.12, -122.27, -122.29.

Example 41A, 41B



Step 1: Preparation of 3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-5',6-dimethyl-2'-(trimethylstannyl)-[1,4'-bipyridin]-2-one:

[00542] To a stirred mixture of 2',3-dichloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-5',6-dimethyl-[1,4'-bipyridin]-2-one (500 mg, 1.21 mmol, 1.00 equiv) and SnMe_6 (1.59 g, 4.85 mmol, 4.00 equiv) in dioxane (10 mL) was added AsPh_3 (185 mg, 0.61 mmol, 0.50 equiv) and $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$ (170 mg, 0.24 mmol, 0.20 equiv) at room temperature under nitrogen atmosphere. The resulting mixture was stirred overnight at 80°C under nitrogen atmosphere. The mixture was allowed to cool down to room temperature. The resulting mixture was diluted with ethyl acetate (50 mL). The resulting mixture was washed with 5x20 mL of sat. KF aq.. The combined organic layers were washed with brine (50 mL), dried over anhydrous Na_2SO_4 . After filtration, the filtrate was concentrated under reduced pressure, to afford 3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-5',6-dimethyl-2'-(trimethylstannyl)-[1,4'-bipyridin]-2-one (700 mg, crude) as a brown semi-solid. LC-MS: (ES+H, m/z): $[\text{M}+\text{H}]^+ = 541.9$.

Step 2: Preparation of 3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-2'-[2-(1-hydroxycyclobutyl)pyrimidin-4-yl]-5',6-dimethyl-[1,4'-bipyridin]-2-one:

[00543] To a stirred mixture of 3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-5',6-dimethyl-2'-(trimethylstannyl)-[1,4'-bipyridin]-2-one (700 mg, assumed 100% yield, 0.93 mmol, 1.00 equiv) and 2-(1-hydroxycyclobutyl)pyrimidin-4-yl trifluoromethanesulfonate (827 mg, 2.78 mmol, 3.00 equiv) in dioxane (10 mL) was added $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$ (194 mg, 0.29 mmol, 0.30 equiv) and CuI (176 mg, 0.96 mmol, 1.00 equiv) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 2 h at 100°C under nitrogen atmosphere. The mixture was allowed to cool down to room temperature. The resulting mixture was diluted with water (50 mL). The resulting mixture was extracted with EtOAc (3x100 mL). The combined organic layers were washed with brine (100 mL), dried over anhydrous Na_2SO_4 . After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography to afford the crude product (200 mg), which was further purified by Prep-HPLC to afford 3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-2'-[2-(1-hydroxycyclobutyl)pyrimidin-4-yl]-5',6-dimethyl-

[1,4'-bipyridin]-2-one (60 mg, 12.33%, over 2 steps) as a white solid. LC-MS: (ES+H, m/z): [M+H]⁺ =526.2.

Step3: Preparation of rel-3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-2'-[2-(1-hydroxycyclobutyl)pyrimidin-4-yl]-5',6-dimethyl-[1,4'-bipyridin]-2-one and rel-3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-2'-[2-(1-hydroxycyclobutyl)pyrimidin-4-yl]-5',6-dimethyl-[1,4'-bipyridin]-2-one :

[00544] The racemate 3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-2'-[2-(1-hydroxycyclobutyl)pyrimidin-4-yl]-5',6-dimethyl-[1,4'-bipyridin]-2-one (60 mg) was separated by Prep-Chiral-HPLC to afford **Example 41A** (21.6 mg, ee=100%) as an off-white solid and **Example 41B** (20.7 mg, ee=100%) as an off-white solid.

Example 41A:

[00545] LC-MS: (ES+H, m/z): [M+H]⁺ =526.20. ¹H NMR (400 MHz, DMSO-d₆) δ 9.02 (d, 1H), 8.87 (s, 1H), 8.63 (s, 1H), 8.62 – 8.60 (d, 1H), 8.26 (d, 1H), 8.15 – 8.05 (m, 1H), 6.84 (s, 1H), 5.68 (s, 1H), 5.50 (s, 2H), 2.72 – 2.58 (m, 2H), 2.34 – 2.24 (m, 2H), 2.11 (s, 3H), 1.98 (s, 3H), 1.96 – 1.76 (m, 2H). ¹⁹F NMR (377 MHz, DMSO) δ -120.13, -120.15, -122.30, -122.32.

Example 41B:

[00546] LC-MS: (ES+H, m/z): [M+H]⁺ =526.15. ¹H NMR (400 MHz, DMSO-d₆) δ 9.02 (d, 1H), 8.87 (s, 1H), 8.63 (s, 1H), 8.62 – 8.60 (d, 1H), 8.26 (d, 1H), 8.11 (ddd, 1H), 6.84 (s, 1H), 5.68 (s, 1H), 5.50 (s, 2H), 2.71 – 2.59 (m, 2H), 2.35 – 2.54 (m, 2H), 2.11 (s, 3H), 1.98 (s, 3H), 1.96 – 1.78 (m, 2H). ¹⁹F NMR (377 MHz, DMSO) δ -120.13, -120.15, -122.31, -122.33.

Step 4: Preparation of 1-(4-methoxypyrimidin-2-yl)cyclobutan-1-ol:

[00547] To a stirred solution of 2-iodo-4-methoxypyrimidine (8.00 g, 33.90 mmol, 1.00 equiv) in toluene (50 mL) was added i-PrMgCl (3.83 g, 37.29 mmol, 1.10 equiv, 2M in THF) dropwise at 0°C under nitrogen atmosphere. The resulting mixture was stirred for 30min at 0°C under nitrogen atmosphere. To the above mixture was added cyclobutanone (3.09 g, 44.07 mmol, 1.30 equiv) in toluene (2 mL) dropwise over 2 min at 0°C. The resulting mixture was stirred for additional 1h at room temperature. The reaction was monitored by LCMS. The reaction was quenched with sat. NH₄Cl (aq.) at 0°C. The resulting mixture was extracted with EtOAc (3x100 mL). The combined organic layers were washed with brine (2x100 mL), dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography to afford 1-(4-methoxypyrimidin-2-yl)cyclobutan-1-ol (2.10 g, 34.38%) as a yellow oil. LC-MS: (ES+H, m/z): [M+H]⁺ =183.0.

Step 5: Preparation of 2-(1-hydroxycyclobutyl)pyrimidin-4-ol:

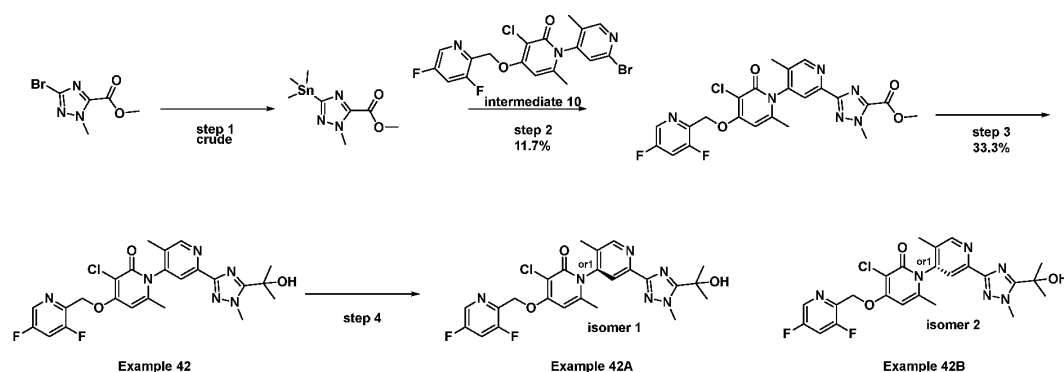
[00548] To a stirred solution of 1-(4-methoxypyrimidin-2-yl)cyclobutan-1-ol (2.10 g, 11.65 mmol, 1.00 equiv) in MeCN (20 mL) was added TMSI (9.33 g, 46.61 mmol, 4.00 equiv) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for overnight at room temperature under nitrogen atmosphere. The mixture was allowed to cool down to room temperature. The resulting mixture was concentrated under reduced pressure. The residue was purified by trituration with hexane/EA (3/1) (3x20

mL), to afford 2-(1-hydroxycyclobutyl)pyrimidin-4-ol (1.33 g, 68.68%) as a light yellow solid. LC-MS: (ES+H, m/z): $[M+H]^+ = 167.1$.

Step 6: Preparation of 2-(1-hydroxycyclobutyl)pyrimidin-4-yl trifluoromethanesulfonate:

[00549] To a stirred mixture of 2-(1-hydroxycyclobutyl)pyrimidin-4-ol (1 g, 6.018 mmol, 1 equiv) and Pyridine (1.43 g, 18.05 mmol, 3 equiv) in DCM (10 mL) was added Tf_2O (3.40 g, 12.04 mmol, 2 equiv) dropwise at 0°C under nitrogen atmosphere. The resulting mixture was stirred for 5 min at 0°C under nitrogen atmosphere. The reaction was monitored by LCMS. The residue was purified by silica gel column chromatography, to afford 2-(1-hydroxycyclobutyl)pyrimidin-4-yl trifluoromethanesulfonate (900 mg, 50.15%) as a yellow oil. LC-MS: (ES+H, m/z): $[M+H]^+ = 299.1$.

Example 42A, 42B



Step 1: Preparation of methyl 2-methyl-5-(trimethylstannyl)-1,2,4-triazole-3-carboxylate:

[00550] To a stirred solution of methyl 5-bromo-2-methyl-1,2,4-triazole-3-carboxylate (500 mg, 2.27 mmol, 1.00 equiv) and Sn_2Me_6 (2.98 g, 9.08 mmol, 4.00 equiv) in 1,4-dioxane was added $Pd(PPh_3)_2Cl_2$ (478 mg, 0.68 mmol, 0.30 equiv) and $AsPh_3$ (208 mg, 0.68 mmol, 0.30 equiv) at room temperature under nitrogen atmosphere. The resulting mixture was stirred overnight at 80°C. The reaction was monitored by LCMS. The mixture was allowed to cool down to room temperature. The resulting mixture was diluted with EtOAc (100mL). The residue was washed with KF (5 x 300 mL). The combined organic layers were washed with brine (200 mL), dried over anhydrous Na_2SO_4 . After filtration, the filtrate was concentrated under reduced pressure. The crude product was used in the next step directly without further purification. LC-MS: (ES+H, m/z): $[M+H]^+ = 306.1$.

Step 2: Preparation of methyl 5-{3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-5',6-dimethyl-2-oxo-[1,4'-bipyridin]-2'-yl}-2-methyl-1,2,4-triazole-3-carboxylate:

[00551] To a stirred mixture of methyl 2-methyl-5-(trimethylstannyl)-1,2,4-triazole-3-carboxylate (500 mg, 1.64 mmol, 1.00 equiv) and 2'-bromo-3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-5',6-dimethyl-[1,4'-bipyridin]-2-one (450 mg, 0.98 mmol, 0.60 equiv) in dioxane (40 mL) were added $Pd(PPh_3)_2Cl_2$ (230 mg, 0.32 mmol, 0.20 equiv) and CuI (313 mg, 1.64 mmol, 1.00 equiv) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 2 h at 80°C under nitrogen atmosphere. The reaction was monitored by LCMS. The mixture was allowed to cool down to room temperature. The residue was purified

by silica gel column chromatography to afford methyl 5-{3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-5',6-dimethyl-2-oxo-[1,4'-bipyridin]-2'-yl}-2-methyl-1,2,4-triazole-3-carboxylate (100 mg, 11.76%) as a yellow solid. LC-MS: (ES+H, m/z): [M+H]⁺ = 517.2

Step 3: Preparation of 3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-2'-[5-(2-hydroxypropan-2-yl)-1-methyl-1,2,4-triazol-3-yl]-5',6-dimethyl-[1,4'-bipyridin]-2-one:

[00552] To a stirred solution of methyl 5-{3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-5',6-dimethyl-2-oxo-[1,4'-bipyridin]-2'-yl}-2-methyl-1,2,4-triazole-3-carboxylate (300 mg, 0.58 mmol, 1.00 equiv) in THF (30 mL) was added MeMgBr (1.93 mL, 5.80 mmol, 10.00 equiv) dropwise at 0°C under nitrogen atmosphere. The resulting mixture was stirred for 1 h at 0°C under nitrogen atmosphere. The reaction was monitored by LCMS. The reaction was quenched by the addition of sat. NH₄Cl (aq.) (10 mL) at 0°C. The resulting mixture was extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with brine (200 mL), dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by PREP-HPLC. This resulted in 3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-2'-[5-(2-hydroxypropan-2-yl)-1-methyl-1,2,4-triazol-3-yl]-5',6-dimethyl-[1,4'-bipyridin]-2-one (100 mg, 33.33%) as a white solid. LC-MS: (ES+H, m/z): [M+H]⁺ = 517.4.

Step 3: Preparation of rel-3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-2'-[5-(2-hydroxypropan-2-yl)-1-methyl-1,2,4-triazol-3-yl]-5',6-dimethyl-[1,4'-bipyridin]-2-one & rel-3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-2'-[5-(2-hydroxypropan-2-yl)-1-methyl-1,2,4-triazol-3-yl]-5',6-dimethyl-[1,4'-bipyridin]-2-one :

[00553] The racemate 3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-2'-[5-(2-hydroxypropan-2-yl)-1-methyl-1,2,4-triazol-3-yl]-5',6-dimethyl-[1,4'-bipyridin]-2-one (55 mg) was separated by prep-chiral-HPLC to afford **Example 42A** (26.2 mg, 99.0% purity, ee=100%) and **Example 42B** (26.0 mg, 99.4% purity, ee=100%) as a white solid.

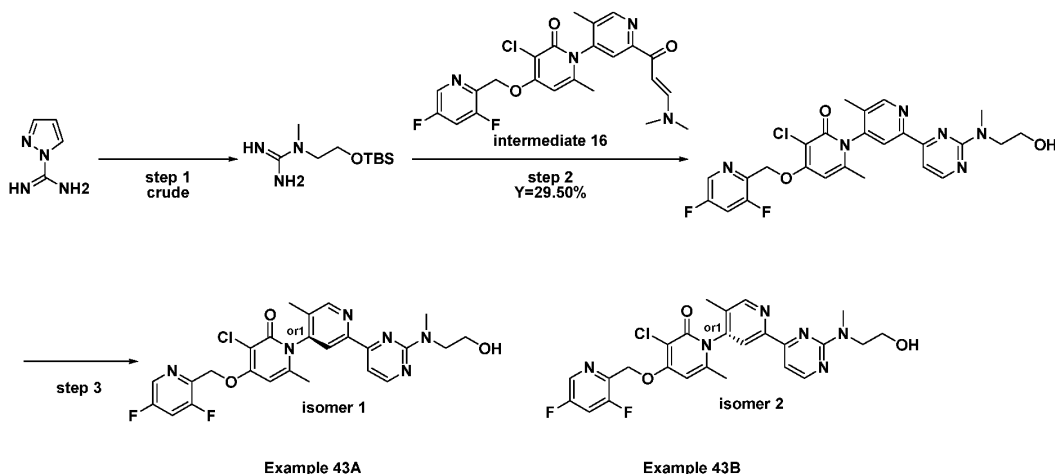
Example 42A:

[00554] LC-MS: (ES+H, m/z): [M+H]⁺ = 517.10. ¹H NMR (300 MHz, DMSO-d₆) δ 8.70-8.76 (m, 1H), 8.56-8.66 (m, 1H), 8.11 (t, 1H), 7.84 (s, 1H), 6.80 (s, 1H), 5.73 (s, 1H), 5.49 (s, 2H), 4.09 (s, 3H), 2.05 (s, 3H), 1.96 (s, 3H), 1.59 (s, 6H). ¹⁹F NMR (282 MHz, DMSO) δ -120.14, -120.16, -122.33, -122.36.

Example 42B:

[00555] LC-MS: (ES+H, m/z): [M+H]⁺ = 517.10. ¹H NMR (300 MHz, DMSO-d₆) δ 8.73 (s, 1H), 8.61 (s, 1H), 8.10 (t, 1H), 7.84 (s, 1H), 6.80 (s, 1H), 5.73 (s, 1H), 5.48 (s, 2H), 4.09 (s, 3H), 2.05 (s, 3H), 1.96 (s, 3H), 1.58 (s, 6H). ¹⁹F NMR (282 MHz, DMSO) δ -120.13, -120.16, -122.32, -122.35.

Example 43A, 43B



Step 1: Preparation of N-{2-[(tert-butyldimethylsilyl)oxy]ethyl}-N-methylguanidine:

[00556] To a mixture of pyrazole-1-carboximidamide (1.00 g, 9.08 mmol, 1.00 equiv) and {2-[(tert-butyldimethylsilyl)oxy]ethyl}(methyl)amine (1.72 g, 9.08 mmol, 1.00 equiv) in MeCN (15 mL) was added TEA (2.76 g, 27.24 mmol, 3.00 equiv) at room temperature. The resulting mixture was stirred overnight at 60°C under nitrogen atmosphere. The mixture was allowed to cool down to room temperature. The reaction was monitored by LCMS. The resulting mixture was concentrated under reduced pressure. The crude product was used in the next step directly without further purification. LC-MS: (ES+H, m/z): [M+H]⁺ = 232.1.

Step 2: Preparation of 3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-2'-{2-[(2-hydroxyethyl)(methyl)amino]pyrimidin-4-yl}-5',6-dimethyl-[1,4'-bipyridin]-2-one:

[00557] To a solution of N-{2-[(tert-butyldimethylsilyl)oxy]ethyl}-N-methylguanidine (682 mg, 2.94 mmol, 2.00 equiv) and 3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-2'-[(2E)-3-(dimethylamino)prop-2-enoyl]-5',6-dimethyl-[1,4'-bipyridin]-2-one (700 mg, 1.47 mmol, 1.00 equiv) in IPA (15 mL) was added K₂CO₃ (2037 mg, 14.74 mmol, 10.00 equiv) at room temperature. The resulting mixture was stirred overnight at 80°C under nitrogen atmosphere. The mixture was allowed to cool down to room temperature. The reaction was monitored by LCMS. The reaction was poured into water (300 mL), extracted with CH₂Cl₂ (3 x 300 mL). The combined organic layers were dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by reverse flash chromatography to afford 3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-2'-{2-[(2-hydroxyethyl)(methyl)amino]pyrimidin-4-yl}-5',6-dimethyl-[1,4'-bipyridin]-2-one (230 mg, 29.50%) as a white solid. LC-MS: (ES+H, m/z): [M+H]⁺ = 529.2.

Step 3: Preparation of rel-3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-2'-{2-[(2-hydroxyethyl)(methyl)amino]pyrimidin-4-yl}-5',6-dimethyl-[1,4'-bipyridin]-2-one (Example 43A) and rel-3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-2'-{2-[(2-hydroxyethyl)(methyl)amino]pyrimidin-4-yl}-5',6-dimethyl-[1,4'-bipyridin]-2-one (Example 43B):

[00558] The racemate 3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-2'-{2-[(2-hydroxyethyl)(methyl)amino]pyrimidin-4-yl}-5',6-dimethyl-[1,4'-bipyridin]-2-one (230 mg) was separated by Prep-Chiral-SFC to afford rel-3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-2'-{2-[(2-hydroxyethyl)(methyl)amino]pyrimidin-4-yl}-5',6-dimethyl-[1,4'-bipyridin]-2-one (**Example 43A**, 90.1 mg, ee=100.00%) as a white solid and rel-3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-2'-{2-[(2-hydroxyethyl)(methyl)amino]pyrimidin-4-yl}-5',6-dimethyl-[1,4'-bipyridin]-2-one (**Example 43B**, 83.3 mg, ee=99.58%) as a white solid.

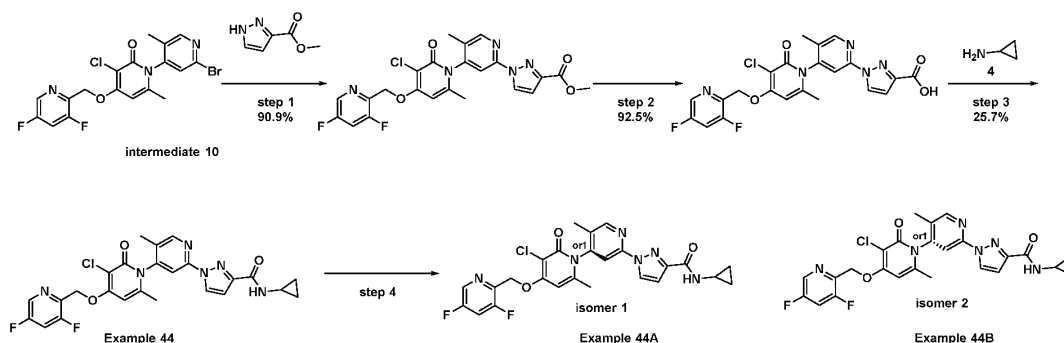
Example 43A:

[00559] LC-MS: (ES+H, m/z): $[M+H]^+ = 529.1$. 1H NMR (300 MHz, DMSO- d_6) δ 8.81 (s, 1H), 8.66 – 8.58 (m, 1H), 8.55 – 8.47 (m, 1H), 8.25 (s, 1H), 8.17 – 8.05 (m, 1H), 7.50 (d, 1H), 6.83 (s, 1H), 5.49 (s, 2H), 5.03 – 4.37 (br, 1H), 3.86 – 3.68 (m, 2H), 3.66 – 3.58 (m, 2H), 3.22 (s, 3H), 2.07 (s, 3H), 1.96 (s, 3H). ^{19}F NMR (377 MHz, DMSO) δ -120.109, -120.134, -122.296, -122.322.

Example 43B:

[00560] LC-MS: (ES+H, m/z): $[M+H]^+ = 529.1$. 1H NMR (300 MHz, DMSO- d_6) δ 8.81 (s, 1H), 8.65 – 8.58 (m, 1H), 8.55 – 8.48 (m, 1H), 8.25 (s, 1H), 8.17 – 8.03 (m, 1H), 7.50 (d, 1H), 6.83 (s, 1H), 5.49 (s, 2H), 4.69 (br, 1H), 3.85 – 3.69 (m, 2H), 3.66 – 3.56 (m, 2H), 3.22 (s, 3H), 2.07 (s, 3H), 1.96 (s, 3H). ^{19}F NMR (377 MHz, DMSO) δ -120.104, -120.130, -122.287, -122.312.

Example 44A, 44B



Step 1: Preparation of methyl 1-{3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-5',6-dimethyl-2-oxo-[1,4'-bipyridin]-2'-yl}pyrazole-3-carboxylate:

[00561] To a stirred mixture of 2'-bromo-3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-5',6-dimethyl-[1,4'-bipyridin]-2-one (1.00 g, 2.19 mmol, 1.00 equiv) and methyl 1H-pyrazole-3-carboxylate (552 mg, 4.38 mmol, 2.00 equiv) in 1,4-dioxane (20 ml) were added CuI (83 mg, 0.43 mmol, 0.20 equiv), K_2CO_3 (605 mg, 4.38 mmol, 2.00 equiv) and N1,N2-dimethylcyclohexane-1,2-diamine (124 mg, 0.87 mmol, 0.40 equiv). The resulting mixture was stirred for 3 h at 90°C under nitrogen atmosphere. The reaction was monitored by LCMS. The mixture was allowed to cool down to room atmosphere. The residue was purified by silica gel column chromatography to afford methyl 1-{3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-5',6-dimethyl-2-oxo-[1,4'-bipyridin]-2'-yl}pyrazole-3-carboxylate (1.00 g, 90.9%) as a white solid. LC-MS: (ES+H, m/z): $[M+H]^+ = 502.1$.

Step 2: Preparation of 1-{3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-5',6-dimethyl-2-oxo-[1,4'-bipyridin]-2'-yl}pyrazole-3-carboxylic acid:

[00562] A solution of methyl 1-{3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-5',6-dimethyl-2-oxo-[1,4'-bipyridin]-2'-yl}pyrazole-3-carboxylate (1.00 g, 1.99 mmol, 1.00 equiv) and LiOH (47 mg, 1.99 mmol, 1.00 equiv) in THF (6 mL) and H₂O (6 mL) was stirred for 2 h at room temperature under nitrogen atmosphere. The reaction was monitored by LCMS. The resulting mixture was concentrated under reduced pressure to afford crude product (Li salt) 1-{3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-5',6-dimethyl-2-oxo-[1,4'-bipyridin]-2'-yl}pyrazole-3-carboxylic acid (0.90 g, 92.50%) as a white solid. LC-MS: (ES+H, m/z): [M+H]⁺=488.0.

Step 3: Preparation of 1-{3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-5',6-dimethyl-2-oxo-[1,4'-bipyridin]-2'-yl}-N-cyclopropylpyrazole-3-carboxamide:

[00563] A mixture of 1-{3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-5',6-dimethyl-2-oxo-[1,4'-bipyridin]-2'-yl}pyrazole-3-carboxylic acid (900 mg, 1.84 mmol, 1.00 equiv), HATU (2.10 g, 5.53 mmol, 3.00 equiv), DIEA (1.19 g, 9.22 mmol, 5.00 equiv) in DMF (30 mL) was stirred for 15 min, then aminocyclopropane (105 mg, 1.84 mmol, 1.00 equiv) was added and the resulting mixture was stirred for additional 2 h at 80°C. The reaction was monitored by LCMS. The reaction was poured into water (300 mL) at room temperature. The resulting mixture was extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with brine (5x300 mL), the filtrate was concentrated under reduced pressure. The residue was purified by PREP-HPLC. This resulted in 1-{3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-5',6-dimethyl-2-oxo-[1,4'-bipyridin]-2'-yl}-N-cyclopropylpyrazole-3-carboxamide (250 mg, 25.70%) as a white solid. LC-MS: (ES+H, m/z): [M+H]⁺=527.1.

Step 4: Preparation of rel-1-{3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-5',6-dimethyl-2-oxo-[1,4'-bipyridin]-2'-yl}-N-cyclopropylpyrazole-3-carboxamide and rel-1-{3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-5',6-dimethyl-2-oxo-[1,4'-bipyridin]-2'-yl}-N-cyclopropylpyrazole-3-carboxamide :

[00564] 1-{3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-5',6-dimethyl-2-oxo-[1,4'-bipyridin]-2'-yl}-N-cyclopropylpyrazole-3-carboxamide (200 mg) was separated by prep-chiral-HPLC to afford **Example 44A** (88.0 mg, ee=100.0%) and **Example 44B** (69.6 mg, ee=100.0%) as a white solid.

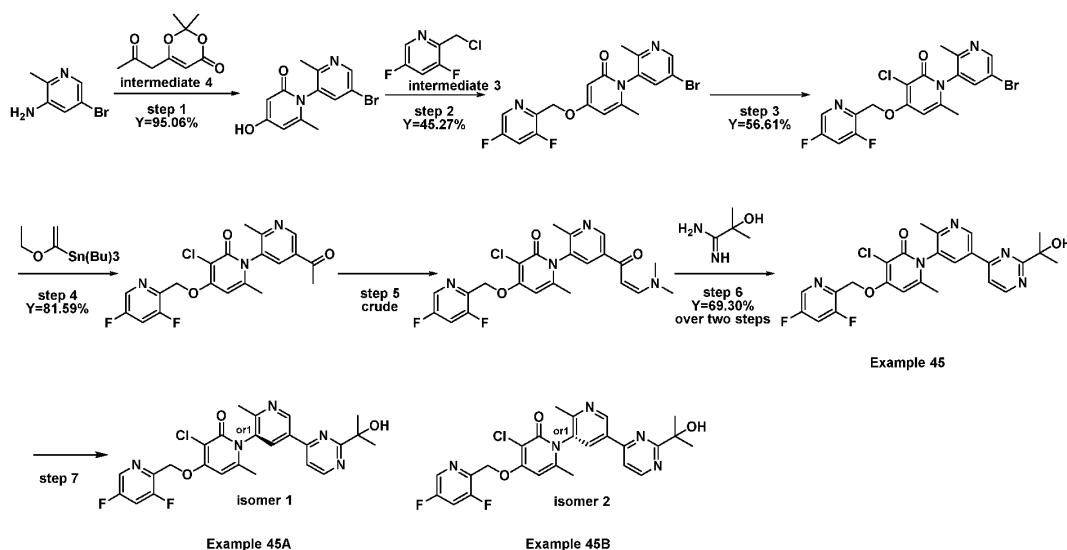
Example 44A:

[00565] LC-MS: (ES+H, m/z): [M+H]⁺=527.05. ¹H NMR (300 MHz, DMSO-d₆) δ 8.68 (d, 1H), 8.65 – 8.58 (m, 2H), 8.38 (d, 1H), 8.11 (m, 1H), 8.00 (s, 1H), 6.91 (d, 1H), 6.85 (s, 1H), 5.51 (s, 2H), 2.83 (m, 1H), 2.06 (s, 3H), 2.02 (s, 3H), 0.75 – 0.61 (m, 2H), 0.64-0.56 (m, 2H). ¹⁹F NMR (282 MHz, DMSO) δ -120.17, -120.20, -122.35, -122.37.

Example 44B:

[00566] LC-MS: (ES+H, m/z): [M+H]⁺=527.05. ¹H NMR (300 MHz, DMSO-d₆) δ 8.68 (d, 1H), 8.65 – 8.58 (m, 2H), 8.38 (d, 1H), 8.16-8.04 (m, 1H), 8.00 (s, 1H), 6.91 (d, 1H), 6.85 (s, 1H), 5.51 (s, 2H), 2.83 (m, 1H), 2.06 (s, 3H), 2.02 (s, 3H), 0.75 – 0.63 (m, 2H), 0.64-0.56 (m, 2H). ¹⁹F NMR (282 MHz, DMSO) δ -120.17, -120.20, -122.34, -122.37.

Example 45A, 45B

**Step 1: Preparation of 5'-bromo-4-hydroxy-2',6-dimethyl-[1,3'-bipyridin]-2-one:**

[00567] A solution of 5-bromo-2-methylpyridin-3-amine (10.00 g, 53.46 mmol, 1.00 equiv) and 2,2-dimethyl-6-(2-oxopropyl)-1,3-dioxin-4-one (19.70 g, 106.92 mmol, 2.00 equiv) in 1,4-dioxane (100 mL) was stirred for 2 h at 80°C under nitrogen atmosphere. To the above mixture was added H₂SO₄ (3.99 mL, 74.85 mmol, 1.40 equiv) dropwise at 0°C. The resulting mixture was stirred for another 2 h at 80°C under nitrogen atmosphere. The reaction was monitored by LCMS. The mixture was allowed to r.t. The resulting mixture was concentrated under reduced pressure. The residue was dissolved in water (50 mL) and Et₂O (100 mL). The precipitated solids were collected by filtration and washed with Et₂O (3x10 mL), to afford 5'-bromo-4-hydroxy-2',6-dimethyl-[1,3'-bipyridin]-2-one (15.00 g, 95.06%) as a white solid. LC-MS: (ES+H, m/z): [M+H]⁺=294.9.

Step 2: Preparation of 5'-bromo-4-[(3,5-difluoropyridin-2-yl)methoxy]-2',6-dimethyl-[1,3'-bipyridin]-2-one:

[00568] To a stirred solution of 5'-bromo-4-hydroxy-2',6-dimethyl-[1,3'-bipyridin]-2-one (5.40 g, 18.29 mmol, 1.00 equiv) and 2-(chloromethyl)-3,5-difluoropyridine (5.98 g, 36.59 mmol, 2.00 equiv) in DMF (100 mL) was added K₂CO₃ (10.00 g, 73.18 mmol, 4.00 equiv) and 18-Crown-6 (1.45 g, 5.48 mmol, 0.30 equiv) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 6 h at 60°C under nitrogen atmosphere. The reaction was monitored by LCMS. The mixture was allowed to r.t. The reaction was quenched with sat. NH₄Cl (aq.) at room temperature. The aqueous layer was extracted with EtOAc (3x300 mL). The residue was purified by silica gel column chromatography to afford 5'-bromo-4-[(3,5-difluoropyridin-2-yl)methoxy]-2',6-dimethyl-[1,3'-bipyridin]-2-one (4.30 g, 55.66%) as a light yellow solid. LC-MS: (ES+H, m/z): [M+H]⁺=422.0.

Step 3: Preparation of 2-propanol (3x3 mL) to afford 5'-bromo-3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-2',6-dimethyl-[1,3'-bipyridin]-2-one:

[00569] To a stirred solution of 5'-bromo-4-[(3,5-difluoropyridin-2-yl)methoxy]-2',6-dimethyl-[1,3'-bipyridin]-2-one (4.90 g, 11.60 mmol, 1.00 equiv) and NCS (1.55 g, 11.60 mmol, 1.00 equiv) in IPA (25 mL) was added 2,2-dichloroacetic acid (0.45 g, 3.48 mmol, 0.30 equiv) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 2 h at 60°C under nitrogen atmosphere. The precipitated solids were collected by filtration and washed with 2-propanol (3x3 mL) to afford 5'-bromo-3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-2',6-dimethyl-[1,3'-bipyridin]-2-one (3.00 g, 56.61%) as a white solid. LC-MS: (ES+H, m/z): [M+H]⁺ = 457.9. ¹H NMR (300 MHz, DMSO-d₆) δ 8.73 (d, 1H), 8.60 (d, 1H), 8.19 (d, J = 2.2 Hz, 1H), 8.15 – 8.02 (m, 1H), 6.80 (d, 1H), 5.48 (d, 2H), 2.15 (s, 3H), 1.96 (s, 3H).

Step 4: Preparation of 5'-acetyl-3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-2',6-dimethyl-[1,3'-bipyridin]-2-one:

[00570] To a stirred mixture of 5'-bromo-3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-2',6-dimethyl-[1,3'-bipyridin]-2-one (2.40 g, 5.25 mmol, 1.00 equiv) and tributyl(1-ethoxyethenyl)stannane (3.80 g, 10.51 mmol, 2.00 equiv) in 1,4-dioxane (10 mL) was added Pd(PPh₃)₂Cl₂ (0.74 g, 1.05 mmol, 0.20 equiv) at room temperature. The resulting mixture was stirred overnight at 120°C under nitrogen atmosphere. The mixture was allowed to cool down to r.t.. The resulting mixture was filtered, the filter cake was washed with EA (3x30 mL). The filtrate was concentrated under reduced pressure. The resulting mixture was dissolved in THF (20 mL). To the above mixture was added HCl (2 mL) dropwise at 0°C. The resulting mixture was stirred for additional 1 h at room temperature. The residue was basified to pH 9 with saturated NaHCO₃ (aq.). The resulting mixture was extracted with EtOAc (3 x 200 mL). The combined organic layers were washed with brine (1x100 mL), dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography to afford 5'-acetyl-3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-2',6-dimethyl-[1,3'-bipyridin]-2-one (1.80 g, 81.59%) as a yellow oil. LC-MS: (ES+H, m/z): [M+H]⁺ = 420.1. ¹H NMR (300 MHz, DMSO-d₆) δ 9.09 (d, 1H), 8.61 (d, 1H), 8.27 (d, 1H), 8.15 – 7.95 (m, 1H), 6.82 (s, 1H), 5.49 (d, 2H), 2.64 (s, 3H), 2.27 (s, 3H), 1.95 (s, 3H).

Step 5: Preparation of 3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-5'-[(2Z)-3-(dimethylamino)prop-2-enoyl]-2',6-dimethyl-[1,3'-bipyridin]-2-one:

[00571] Into a 250 mL round-bottom flask were added 5'-acetyl-3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-2',6-dimethyl-[1,3'-bipyridin]-2-one (1.80 g, 4.28 mmol, 1.00 equiv) and DMF-DMA (30 mL) at room temperature. The resulting mixture was stirred overnight at 80°C. The mixture was allowed to cool down to r.t.. The resulting mixture was concentrated under vacuum to afford 3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-5'-[(2Z)-3-(dimethylamino)prop-2-enoyl]-2',6-dimethyl-[1,3'-bipyridin]-2-one (crude) as a yellow solid. The crude product was used in the next step directly without further purification. LC-MS: (ES+H, m/z): [M+H]⁺ = 475.0.

Step 6: Preparation of 3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-5'-[2-(2-hydroxypropan-2-yl)pyrimidin-4-yl]-2',6-dimethyl-[1,3'-bipyridin]-2-one:

[00572] To a stirred mixture of 3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-5'-[(2Z)-3-(dimethylamino)prop-2-enoyl]-2',6-dimethyl-[1,3'-bipyridin]-2-one (1.00 g, 2.10 mmol, 1.00 equiv) and

K_2CO_3 (1.74 g, 12.63 mmol, 6.00 equiv) in 2-propanol (20 ml) were added 2-hydroxy-2-methylpropanimidamide (1.08 g, 10.53 mmol, 5.00 equiv) at room temperature under air atmosphere. The resulting mixture was stirred for 12 h at 80°C. The mixture was allowed to cool down to r.t. and then poured into water (200 mL). The resulting mixture was extracted with EtOAc (3 x 300 mL). The combined organic layers were washed with brine (300 mL), dried over anhydrous Na_2SO_4 . After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography to afford 3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-5'-[2-(2-hydroxypropan-2-yl)pyrimidin-4-yl]-2',6-dimethyl-[1,3'-bipyridin]-2-one (750 mg, 69.30%) as a yellow solid. LC-MS: (ES+H, m/z): $[M+H]^+ = 514.4$.

Step 7: Preparation of rel-3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-5'-[2-(2-hydroxypropan-2-yl)pyrimidin-4-yl]-2',6-dimethyl-[1,3'-bipyridin]-2-one and rel-3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-5'-[2-(2-hydroxypropan-2-yl)pyrimidin-4-yl]-2',6-dimethyl-[1,3'-bipyridin]-2-one :

[00573] The race-mixture (750 mg) was isolated by PREP-CHIRAL-HPLC to afford rel-3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-5'-[2-(2-hydroxypropan-2-yl)pyrimidin-4-yl]-2',6-dimethyl-[1,3'-bipyridin]-2-one (**Example 45A**: 260.7 mg, ee=100%) as a yellow solid. and rel-3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-5'-[2-(2-hydroxypropan-2-yl)pyrimidin-4-yl]-2',6-dimethyl-[1,3'-bipyridin]-2-one (**Example 45B**: 286.4 mg, ee=100%) as a yellow solid.

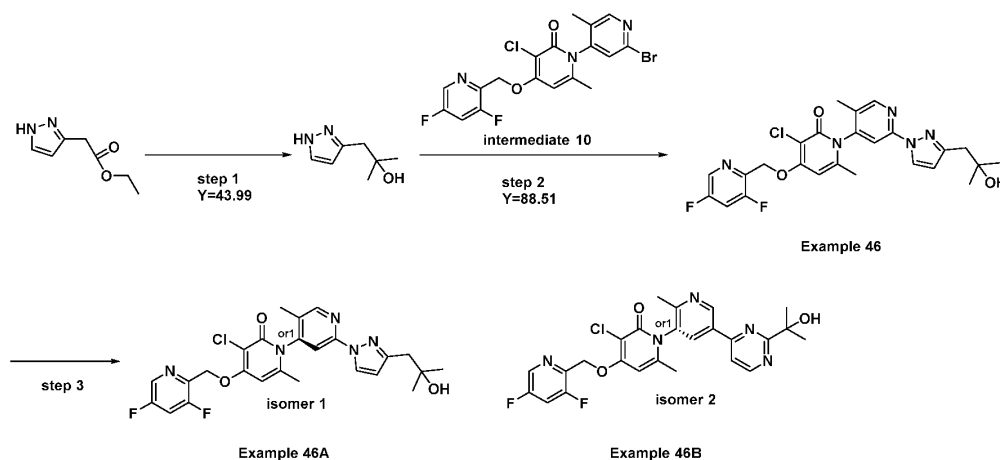
Example 45A:

[00574] LC-MS: (ES+H, m/z): $[M+H]^+ = 514.00$. 1H NMR (300 MHz, DMSO- d_6) δ 9.48 (d, 1H), 8.93 (d, 1H), 8.73 (d, 1H), 8.62 (d, 1H), 8.16 – 8.11 (m, 1H), 8.09 (s, 1H), 6.85 (d, 1H), 5.51 (d, 2H), 5.23 (s, 1H), 2.29 (s, 3H), 1.99 (s, 3H), 1.55 (s, 3H), 1.54 (s, 3H). ^{19}F NMR (282 MHz, DMSO) δ -120.14, -120.16, -122.34, -122.36.

Example 45B:

[00575] LC-MS: (ES+H, m/z): $[M+H]^+ = 514.20$. 1H NMR (300 MHz, DMSO- d_6) δ 9.48 (d, 1H), 8.93 (d, 1H), 8.73 (d, 1H), 8.62 (d, 1H), 8.15 – 8.10 (m, 1H), 8.09 (d, 1H), 6.85 (d, 1H), 5.51 (d, 2H), 5.23 (s, 1H), 2.29 (s, 3H), 1.99 (s, 3H), 1.55 (s, 3H), 1.54 (s, 3H). ^{19}F NMR (282 MHz, DMSO) δ -120.14, -120.16, -122.34, -122.36.

Example 46A, 46B



Step 1: Preparation of 2-methyl-1-(1H-pyrazol-3-yl)propan-2-ol:

[00576] To a stirred solution of ethyl 2-(1H-pyrazol-3-yl)acetate (1.50 g, 9.73 mmol, 1.00 equiv) in THF (15 mL) was added MeMgBr in THF (22.70 mL, 68.11 mmol, 7.00 equiv) dropwise at -5 °C under nitrogen atmosphere. The resulting mixture was stirred for 2 h at 0°C under nitrogen atmosphere. The reaction was monitored by LCMS. The reaction was quenched with sat. NH₄Cl (aq.) at room temperature. The resulting mixture was extracted with EtOAc (7 x 10mL). The combined organic layers were dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography to afford 2-methyl-1-(1H-pyrazol-3-yl)propan-2-ol (600 mg, 43.99%) as a yellow oil. LC-MS: (ES+H, m/z): [M+H]⁺ = 141.3.

Step 2: Preparation of 3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-2'-[3-(2-hydroxy-2-methylpropyl)pyrazol-1-yl]-5',6-dimethyl-[1,4'-bipyridin]-2-one:

[00577] To a stirred solution of 2'-bromo-3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-5',6-dimethyl-[1,4'-bipyridin]-2-one (500 mg, 1.09 mmol, 1.00 equiv), 2-methyl-1-(1H-pyrazol-3-yl)propan-2-ol (230 mg, 1.64 mmol, 1.50 equiv) and (1R,2R)-N1,N2-dimethylcyclohexane-1,2-diamine (311 mg, 2.19 mmol, 2.00 equiv) in dioxane (7 mL) were added CuI (417 mg, 2.19 mmol, 2.00 equiv) and K₂CO₃ (302 mg, 2.19 mmol, 2.00 equiv) at room temperature under nitrogen atmosphere. The resulting mixture was stirred overnight at 80°C under nitrogen atmosphere. The mixture was allowed to cool down to room temperature. The reaction was monitored by LCMS. The reaction was quenched with sat. NH₄Cl (aq.) at room temperature. The resulting mixture was extracted with EtOAc (3 x 30 mL). The combined organic layers were washed with brine (1 x 30 mL), dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography to afford 3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-2'-[3-(2-hydroxy-2-methylpropyl)pyrazol-1-yl]-5',6-dimethyl-[1,4'-bipyridin]-2-one (500 mg, 88.51%) as a white solid. LC-MS: (ES+H, m/z): [M+H]⁺ = 516.2. ¹H NMR (400 MHz, DMSO-d₆) δ 8.60 (d, 1H), 8.54 (t, 1H), 8.51 (d, 1H), 8.10 (m, 1H), 7.77 (s, 1H), 6.80 (d, 1H), 6.45 (d, 1H), 5.48 (d, 2H), 4.43 (s, 1H), 2.72 (s, 2H), 2.01 (s, 3H), 2.00 (s, 3H), 1.14 (s, 3H), 1.12 (s, 3H).

Step 3: Preparation of rel-3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-2'-[3-(2-hydroxy-2-methylpropyl)pyrazol-1-yl]-5',6-dimethyl-[1,4'-bipyridin]-2-one and rel-3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-2'-[3-(2-hydroxy-2-methylpropyl)pyrazol-1-yl]-5',6-dimethyl-[1,4'-bipyridin]-2-one :

[00578] The 3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-2'-[3-(2-hydroxy-2-methylpropyl)pyrazol-1-yl]-5',6-dimethyl-[1,4'-bipyridin]-2-one (500 mg, 0.996 mmol, 1 equiv) was isolated by PREP-HPLC to afford rel-3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-2'-[3-(2-hydroxy-2-methylpropyl)pyrazol-1-yl]-5',6-dimethyl-[1,4'-bipyridin]-2-one (**Example 46A**) (208.1 mg, 97.7% purity, ee=100%) and rel-3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-2'-[3-(2-hydroxy-2-methylpropyl)pyrazol-1-yl]-5',6-dimethyl-[1,4'-bipyridin]-2-one (**Example 46B**) (243.4 mg, 96.9% purity, ee=100%) as a white solid.

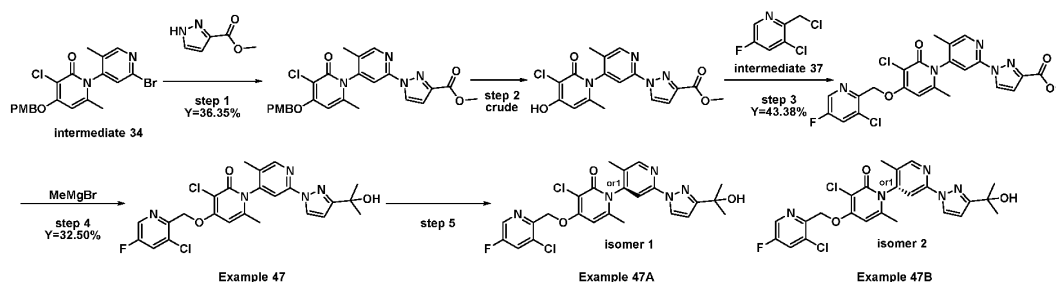
[00579] **Example 46A:** LC-MS: (ES+H, m/z): [M+H]⁺ = 516.05. ¹H NMR (400 MHz, DMSO-d₆) δ 8.60 (d, 1H), 8.54 (t, 1H), 8.51 (d, 1H), 8.10 (m, 1H), 7.77 (s, 1H), 6.80 (d, 1H), 6.45 (d, 1H), 5.48 (d, 2H), 4.43

(s, 1H), 2.72 (s, 2H), 2.01 (s, 3H), 2.00 (s, 3H), 1.14 (s, 3H), 1.12 (s, 3H). ^{19}F NMR (377 MHz, DMSO) δ -120.15, -120.17, -122.35, -122.37.

Example 46B:

[00580] LC-MS: (ES+H, m/z): $[\text{M}+\text{H}]^+ = 516.00$. ^1H NMR (400 MHz, DMSO- d_6) δ 8.60 (d, 1H), 8.54 (t, 1H), 8.51 (d, 1H), 8.10 (m, 1H), 7.77 (s, 1H), 6.80 (d, 1H), 6.45 (d, 1H), 5.48 (d, 2H), 4.43 (s, 1H), 2.72 (s, 2H), 2.01 (s, 3H), 2.00 (s, 3H), 1.14 (s, 3H), 1.12 (s, 3H). ^{19}F NMR (377 MHz, DMSO) δ -120.15, -120.16, -122.35, -122.37.

Example 47A, 47B



Step 1: Preparation of methyl 1-{3-chloro-4-[(4-methoxyphenyl)methoxy]-5',6-dimethyl-2-oxo-[1,4'-bipyridin]-2'-yl}pyrazole-3-carboxylate:

[00581] To a mixture of 2'-bromo-3-chloro-4-[(4-methoxyphenyl)methoxy]-5',6-dimethyl-2-oxo-[1,4'-bipyridin]-2-one (2.00 g, 4.44 mmol, 1.00 equiv), methyl 1H-pyrazole-3-carboxylate (673 mg, 5.33 mmol, 1.20 equiv), K_2CO_3 (1229 mg, 8.89 mmol, 2.00 equiv) and (1S,2S)-N1,N2-dimethylcyclohexane-1,2-diamine (253 mg, 1.77 mmol, 0.40 equiv) in 1,4-dioxane (20 mL) was added CuI (169 mg, 0.88 mmol, 0.20 equiv) at room temperature. The resulting mixture was stirred for 2 h at 80°C under nitrogen atmosphere. The reaction was monitored by LCMS. The mixture was allowed to cool down to room temperature. The reaction was poured into water (100 mL), then extracted with EtOAc (3 x 100 mL). The combined organic layers were dried over anhydrous Na_2SO_4 . After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography to afford methyl 1-{3-chloro-4-[(4-methoxyphenyl)methoxy]-5',6-dimethyl-2-oxo-[1,4'-bipyridin]-2'-yl}pyrazole-3-carboxylate (800 mg, 36.35%) as a white solid. LC-MS: (ES+H, m/z): $[\text{M}+\text{H}]^+ = 495.0$. ^1H NMR (400 MHz, Chloroform- d) δ 8.59 (d, 1H), 8.45 (s, 1H), 7.92 (s, 1H), 7.42 – 7.37 (m, 2H), 6.99 – 6.96 (m, 2H), 6.96 – 6.94 (m, 1H), 6.15 (s, 1H), 5.23 (s, 2H), 3.95 (s, 3H), 3.85 (s, 3H), 2.14 (s, 3H), 1.98 (s, 3H).

Step 2: Preparation of methyl 1-{3-chloro-4-hydroxy-5',6-dimethyl-2-oxo-[1,4'-bipyridin]-2'-yl}pyrazole-3-carboxylate:

[00582] To a mixture of methyl 1-{3-chloro-4-[(4-methoxyphenyl)methoxy]-5',6-dimethyl-2-oxo-[1,4'-bipyridin]-2'-yl}pyrazole-3-carboxylate (700 mg, 1.41 mmol, 1.00 equiv) in DCM (6.00 mL) was added TFA (2.00 mL) at room temperature. The resulting mixture was stirred for 1 h at room temperature under nitrogen atmosphere. The reaction was monitored by LCMS. The resulting mixture was concentrated under reduced pressure, to afford crude product methyl 1-{3-chloro-4-hydroxy-5',6-dimethyl-2-oxo-[1,4'-

bipyridin]-2'-yl}pyrazole-3-carboxylate (1 g, crude) as a yellow oil, which was used in the next step directly without further purification. LC-MS: (ES+H, m/z): [M+H]⁺ = 375.2.

Step 3: Preparation of methyl 1-{3-chloro-4-[(3-chloro-5-fluoropyridin-2-yl)methoxy]-5',6-dimethyl-2-oxo-[1,4'-bipyridin]-2'-yl}pyrazole-3-carboxylate:

[00583] To a mixture of methyl 1-{3-chloro-4-hydroxy-5',6-dimethyl-2-oxo-[1,4'-bipyridin]-2'-yl}pyrazole-3-carboxylate (1.00 g, 2.66 mmol, 1.00 equiv), K₂CO₃ (1.11 g, 8.00 mmol, 3.00 equiv) and 3-chloro-2-(chloromethyl)-5-fluoropyridine (0.96 g, 5.32 mmol, 2.00 equiv) in DMF (15.00 mL) was added 18-Crown-6 (0.35 g, 1.33 mmol, 0.50 equiv) at room temperature. The resulting mixture was stirred for 3 h at 60°C under nitrogen atmosphere. The reaction was monitored by LCMS. Desired product could be detected by LCMS. The reaction was poured into water (200 mL), extracted with EtOAc (3 x 200 mL). The combined organic layers were dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography to afford methyl 1-{3-chloro-4-[(3-chloro-5-fluoropyridin-2-yl)methoxy]-5',6-dimethyl-2-oxo-[1,4'-bipyridin]-2'-yl}pyrazole-3-carboxylate (600 mg, 43.38%) as a white solid. LC-MS: (ES+H, m/z): [M+H]⁺ = 518.1. ¹H NMR (400 MHz, Chloroform-d) δ 8.59 (d, 1H), 8.46 (s, 1H), 8.45 (s, 1H), 7.92 (s, 1H), 7.62 – 7.57 (m, 1H), 6.98 (d, 1H), 6.31 (s, 1H), 5.47 (s, 2H), 3.95 (s, 3H), 2.15 (s, 3H), 2.00 (s, 3H).

Step 4: Preparation of 3-chloro-4-[(3-chloro-5-fluoropyridin-2-yl)methoxy]-2'-[3-(2-hydroxypropan-2-yl)pyrazol-1-yl]-5',6-dimethyl-[1,4'-bipyridin]-2-one:

[00584] To a stirred solution of methyl 1-{3-chloro-4-[(3-chloro-5-fluoropyridin-2-yl)methoxy]-5',6-dimethyl-2-oxo-[1,4'-bipyridin]-2'-yl}pyrazole-3-carboxylate (400 mg, 0.77 mmol, 1.00 equiv) in THF (10 mL) was added MeMgBr (2.57 mL, 7.72 mmol, 10.00 equiv) dropwise at 0°C under nitrogen atmosphere. The resulting mixture was stirred for 1 h at 0°C under nitrogen atmosphere. The reaction was monitored by LCMS. Desired product could be detected by LCMS. The reaction was quenched with sat. NH₄Cl (aq.) (150 mL) at 0°C. The resulting mixture was extracted with EtOAc (3 x 150 mL). The combined organic layers were dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by reverse flash chromatography. The resulting mixture was concentrated under reduced pressure to afford 3-chloro-4-[(3-chloro-5-fluoropyridin-2-yl)methoxy]-2'-[3-(2-hydroxypropan-2-yl)pyrazol-1-yl]-5',6-dimethyl-[1,4'-bipyridin]-2-one (130 mg, 32.50%) as a white solid. LC-MS: (ES+H, m/z): [M+H]⁺ = 518.2.

Step 5: Preparation of rel-3-chloro-4-[(3-chloro-5-fluoropyridin-2-yl)methoxy]-2'-[3-(2-hydroxypropan-2-yl)pyrazol-1-yl]-5',6-dimethyl-[1,4'-bipyridin]-2-one and rel-3-chloro-4-[(3-chloro-5-fluoropyridin-2-yl)methoxy]-2'-[3-(2-hydroxypropan-2-yl)pyrazol-1-yl]-5',6-dimethyl-[1,4'-bipyridin]-2-one :

[00585] The racemate 3-chloro-4-[(3-chloro-5-fluoropyridin-2-yl)methoxy]-2'-[3-(2-hydroxypropan-2-yl)pyrazol-1-yl]-5',6-dimethyl-[1,4'-bipyridin]-2-one (130 mg) was separated by Prep-Chiral-HPLC to afford rel-3-chloro-4-[(3-chloro-5-fluoropyridin-2-yl)methoxy]-2'-[3-(2-hydroxypropan-2-yl)pyrazol-1-yl]-5',6-dimethyl-[1,4'-bipyridin]-2-one (**Example 47A**, 38.2 mg, ee=100.00%) as a white solid and rel-3-chloro-4-

[(3-chloro-5-fluoropyridin-2-yl)methoxy]-2'-[3-(2-hydroxypropan-2-yl)pyrazol-1-yl]-5',6-dimethyl-[1,4'-bipyridin]-2-one (**Example 47B**, 36.4 mg, ee=100.00%) as a white solid.

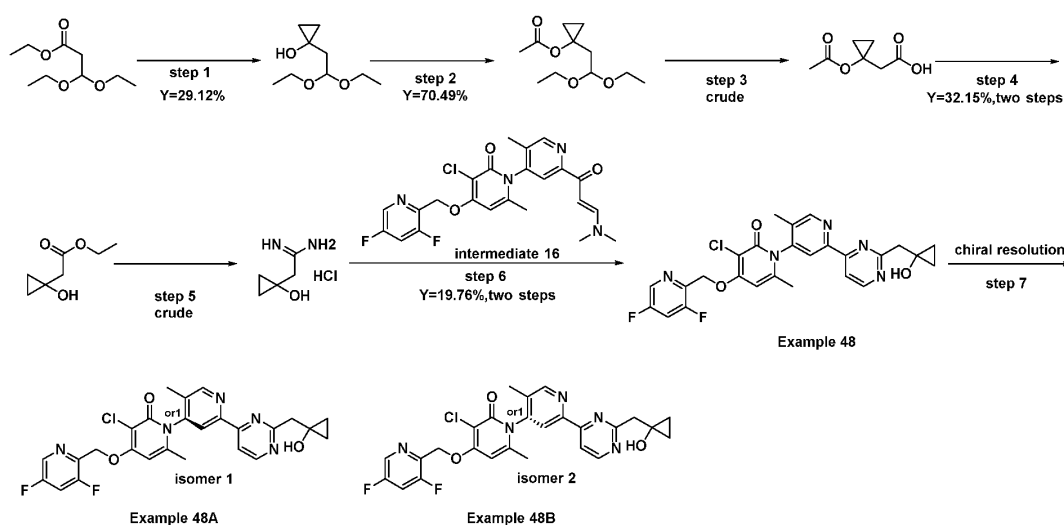
Example 47A:

[00586] LC-MS: (ES+H, m/z): $[M+H]^+ = 518.2$. ^1H NMR (400 MHz, DMSO- d_6) δ 8.68 (d, 1H), 8.54 (s, 1H), 8.51 (d, 1H), 8.29 – 8.22 (m, 1H), 7.78 (s, 1H), 6.77 (s, 1H), 6.56 (d, 1H), 5.50 (s, 2H), 5.09 (s, 1H), 2.01 (s, 3H), 1.99 (s, 3H), 1.48 (s, 6H). ^{19}F NMR (377 MHz, DMSO) δ -124.16, -124.20.

Example 47B:

[00587] LC-MS: (ES+H, m/z): $[M+H]^+ = 518.20$. ^1H NMR (400 MHz, DMSO- d_6) δ 8.68 (d, 1H), 8.54 (s, 1H), 8.51 (d, 1H), 8.30 – 8.21 (m, 1H), 7.78 (s, 1H), 6.77 (s, 1H), 6.56 (d, 1H), 5.50 (s, 2H), 5.09 (s, 1H), 2.01 (s, 3H), 1.99 (s, 3H), 1.48 (s, 6H). ^{19}F NMR (377 MHz, DMSO) δ -124.21.

Example 48A, 48B



Step 1: Preparation of 1-(2,2-diethoxyethyl)cyclopropan-1-ol:

[00588] To a stirred mixture of ethyl 3,3-diethoxypropanoate (30.00 g, 157.69 mmol, 1.00 equiv) and $\text{Ti}(\text{Oi-Pr})_4$ (67.20 g, 236.54 mmol, 1.50 equiv) in Et_2O (200 mL) and THF (50 mL) was added EtMgBr in 2-methyl-THF (2M, 233.6 mL, 630.784 mmol, 4.00 equiv) dropwise at 0°C under nitrogen atmosphere. The resulting mixture was stirred overnight at room temperature under nitrogen atmosphere. The reaction was monitored by TLC (PE/EA=7:1, R_f =0.4). The reaction was quenched by the addition of water (400 mL) at 0°C . The resulting mixture was extracted with Et_2O (2 x 500 mL), the organic phase was combined and dried over anhydrous Na_2SO_4 . After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, the pure fraction was concentrated under reduced pressure to afford 1-(2,2-diethoxyethyl)cyclopropan-1-ol (8.00 g, 29.12%) as a yellow liquid. ^1H NMR (300 MHz, Chloroform- d) δ 4.81 (t, 1H), 3.70-3.76 (m, 3H), 3.62 – 3.55 (m, 2H), 1.91 (d, 2H), 1.25 (t, 6H), 0.78 (d, 2H), 0.47 – 0.44 (m, 2H).

Step 2: Preparation of 1-(2,2-diethoxyethyl)cyclopropyl acetate:

[00589] To a stirred solution of 1-(2,2-diethoxyethyl)cyclopropan-1-ol (8.00 g, 45.91 mmol, 1.00 equiv) and DMAP (6.17 g, 50.50 mmol, 1.10 equiv) in Et₂O (100 mL) was added acetic anhydride (7.03 g, 68.87 mmol, 1.50 equiv) dropwise at 0°C under nitrogen atmosphere. The resulting mixture was stirred for 1 h at 0°C under nitrogen atmosphere. The reaction was monitored by TLC(PE/EA=10:1, R_f=0.5). The reaction was quenched with sat. NaHCO₃ (aq.) at 0°C. The aqueous layer was extracted with Et₂O (3x100 mL). The resulting mixture was concentrated under vacuum. The residue was purified by silica gel column chromatography, the pure fraction was concentrated under reduced pressure to afford 1-(2,2-diethoxyethyl)cyclopropyl acetate (7.00 g, 70.49%) as a yellow liquid. ¹H NMR (400 MHz, Chloroform-d) δ 4.71 (t, 1H), 3.63 (q, 2H), 3.52 (q, 2H), 2.08 (d, 2H), 1.98 (s, 3H), 1.20 (t, 6H), 0.89 – 0.83 (m, 2H), 0.77 – 0.74 (m, 2H).

Step 3: Preparation of [1-(acetyloxy)cyclopropyl]acetic acid:

[00590] To a stirred solution of 1-(2,2-diethoxyethyl)cyclopropyl acetate (7.00 g, 32.36 mmol, 1.00 equiv) in THF (40 mL) and H₂O (80 mL) was added oxone (8.16 g, 48.54 mmol, 1.50 equiv) in portions at room temperature. The resulting mixture was stirred overnight at room temperature. The reaction was monitored by TLC (100%EA, R_f=0.1). The resulting mixture was diluted with water (200 mL). The resulting mixture was extracted with EtOAc (5 x 200 mL). The combined organic layers were dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure to afford [1-(acetyloxy)cyclopropyl]acetic acid (6 g, crude) as a yellow oil. ¹H NMR (400 MHz, Chloroform-d) δ 2.82 (s, 2H), 2.02 (s, 3H), 1.03 – 0.97 (m, 2H), 0.90 – 0.86 (m, 2H).

Step 4: Preparation of ethyl 2-(1-hydroxycyclopropyl)acetate:

[00591] To a stirred solution of [1-(acetyloxy)cyclopropyl]acetic acid (6.00 g, 37.93 mmol, 1.00 equiv) in EtOH (200 mL) was added H₂SO₄ (60 drops) dropwise at room temperature. The resulting mixture was stirred overnight at room temperature. The reaction was monitored by TLC(PE/EA=10:1, R_f=0.5). The reaction was quenched with sat. NaHCO₃ (aq.) at room temperature. The aqueous layer was extracted with EtOAc (3x200 mL). The resulting mixture was concentrated under vacuum. The residue was purified by silica gel column chromatography, the pure fraction was concentrated under reduced pressure to afford ethyl 2-(1-hydroxycyclopropyl)acetate (1.50 g, 32.15%) as a yellow liquid. ¹H NMR (300 MHz, Chloroform-d) δ 4.22 (q, 2H), 2.60 (s, 2H), 1.32 (t, 3H), 0.88 (dd, 2H), 0.55 – 0.48 (m, 2H).

Step 5: Preparation of 2-(1-hydroxycyclopropyl)ethanimidamide hydrochloride:

[00592] To a stirred mixture of NH₄Cl (927 mg, 17.34 mmol, 5.00 equiv) in Toluene (20 mL) was added AlMe₃ (8 mL, 2 M in Toluene, 17.34 mmol, 5.00 equiv) dropwise at 0°C under nitrogen atmosphere. The resulting mixture was stirred for 10 min at 0°C under nitrogen atmosphere, and then was stirred at room temperature until no generation of gas. To the above mixture was added a solution of ethyl 2-(1-hydroxycyclopropyl)acetate (500 mg, 3.46 mmol, 1.00 equiv) in toluene dropwise at r.t. The resulting mixture was stirred overnight at 80°C. The reaction was monitored by LCMS. The mixture was allowed to cool down to room temperature. The reaction was quenched by the addition of MeOH (10 mL) at 0°C. The

resulting mixture was filtered, the filter cake was washed with MeOH (6 x 30 mL). The filtrate was concentrated under reduced pressure. The residue was dissolved in EtOH (8 mL). The resulting mixture was filtered, the filter cake was washed with EtOH (5 mL). The filtrate was concentrated under reduced pressure. This resulted in 2-(1-hydroxycyclopropyl)ethanimidamide hydrochloride (450 mg, crude) as an orange oil. ¹H NMR (300 MHz, DMSO-d₆) δ 9.01 – 8.72 (m, 4H), 5.76 (s, 1H), 2.60 (s, 2H), 0.65 (s, 4H).

Step 6: Preparation of 3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-2'-{2-[(1-hydroxycyclopropyl)methyl]pyrimidin-4-yl}-5',6-dimethyl-[1,4'-bipyridin]-2-one:

[00593] To a stirred solution of 3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-2'-[(2E)-3-(dimethylamino)prop-2-enoyl]-5',6-dimethyl-[1,4'-bipyridin]-2-one (315 mg, 0.66 mmol, 1.00 equiv) and 2-(1-hydroxycyclopropyl)ethanimidamide hydrochloride (300 mg, 1.99 mmol, 3.00 equiv) in DMF (10 mL) was added K₂CO₃ (1.84 g, 13.28 mmol, 20.00 equiv) at room temperature. The resulting mixture was stirred overnight at 60°C. The reaction was monitored by LCMS. The mixture was allowed to cool down to room temperature. The resulting mixture was diluted with water (20 mL). The aqueous layer was extracted with EtOAc (3x20 mL). The resulting mixture was concentrated under vacuum. The crude product was purified by Prep-HPLC to afford 3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-2'-{2-[(1-hydroxycyclopropyl)methyl]pyrimidin-4-yl}-5',6-dimethyl-[1,4'-bipyridin]-2-one (69.0 mg, 19.76%) as a white solid. LC-MS: (ES+H, m/z): [M+H]⁺ = 526.1. ¹H NMR (400 MHz, DMSO-d₆) δ 8.92 (d, 1H), 8.87 (s, 1H), 8.61 (d, 1H), 8.31 (s, 1H), 8.22 (d, 1H), 8.11 – 8.08 (m, 1H), 6.83 (s, 1H), 5.50 (d, 2H), 5.27 (s, 1H), 3.23 – 3.10 (m, 2H), 2.09 (s, 3H), 1.97 (s, 3H), 0.66 – 0.59 (m, 4H).

Step 7: Preparation of *rel*-3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-2'-{2-[(1-hydroxycyclopropyl)methyl]pyrimidin-4-yl}-5',6-dimethyl-[1,4'-bipyridin]-2-one and *rel*-3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-2'-{2-[(1-hydroxycyclopropyl)methyl]pyrimidin-4-yl}-5',6-dimethyl-[1,4'-bipyridin]-2-one :

[00594] The racemate (69 mg) was separated by Prep-Chiral-HPLC to afford **Example 48A** (26.0 mg, 98.7% purity, ee=100%) as a white solid and **Example 48B** (27.3 mg, 99.2% purity, ee=100%) as a white solid.

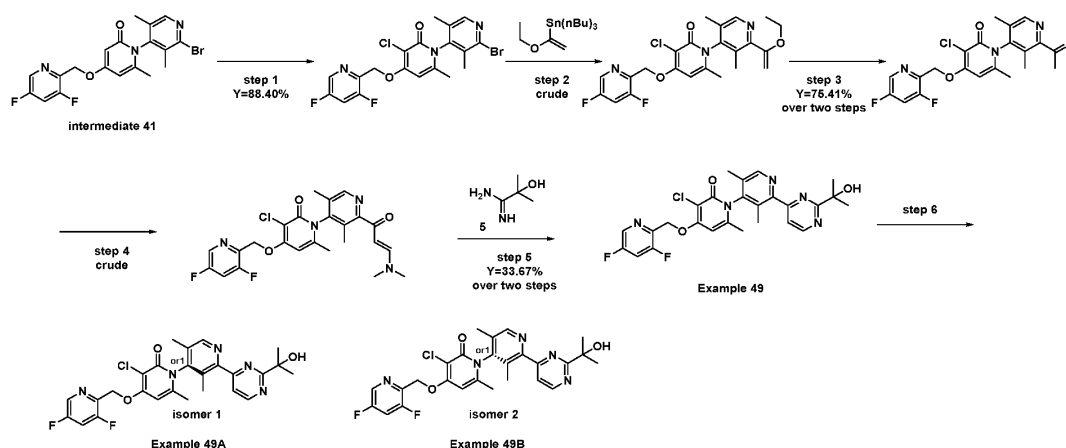
Example 48A:

[00595] LC-MS: (ES+H, m/z): [M+H]⁺ = 526.20. ¹H NMR (400 MHz, DMSO-d₆) δ 8.92 (d, 1H), 8.87 (s, 1H), 8.61 (d, 1H), 8.31 (s, 1H), 8.22 (d, 1H), 8.11 – 8.08 (m, 1H), 6.83 (s, 1H), 5.50 (d, 2H), 5.27 (s, 1H), 3.23 – 3.10 (m, 2H), 2.09 (s, 3H), 1.97 (s, 3H), 0.66 – 0.59 (m, 4H). ¹⁹F NMR (282 MHz, DMSO) δ -120.13, -120.15, -122.32, -122.35.

Example 48B:

[00596] LC-MS: (ES+H, m/z): [M+H]⁺ = 526.20. ¹H NMR (400 MHz, DMSO-d₆) δ 8.92 (d, 1H), 8.87 (s, 1H), 8.61 (d, 1H), 8.31 (s, 1H), 8.22 (d, 1H), 8.11 – 8.08 (m, 1H), 6.83 (s, 1H), 5.50 (d, 2H), 5.27 (s, 1H), 3.23 – 3.10 (m, 2H), 2.09 (s, 3H), 1.97 (s, 3H), 0.66 – 0.59 (m, 4H). ¹⁹F NMR (282 MHz, DMSO) δ -120.13, -120.15, -122.32, -122.35.

Example 49A, 49B



Step 1: Preparation of 2'-bromo-3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-3',5',6-trimethyl-[1,4'-bipyridin]-2-one:

[00597] To a stirred solution of 2'-bromo-4-[(3,5-difluoropyridin-2-yl)methoxy]-3',5',6-trimethyl-[1,4'-bipyridin]-2-one (2.60 g, 5.96 mmol, 1.00 equiv) and NCS (954 mg, 7.15 mmol, 1.20 equiv) in IPA (10 mL) was added 2,2-dichloroacetic acid (76 mg, 0.59 mmol, 0.10 equiv) dropwise at room temperature under air atmosphere. The resulting mixture was stirred for 1 h at 60°C under nitrogen atmosphere. The reaction was monitored by LCMS. The precipitated solids were collected by filtration and washed with IPA (5 mL), to afford 2'-bromo-3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-3',5',6-trimethyl-[1,4'-bipyridin]-2-one (2.48 g, 88.40%) as a white solid. LC-MS: (ES+H, m/z): [M+H]⁺ = 470.1/472.1. ¹H NMR (400 MHz, DMSO-d₆) δ 8.60 (d, 1H), 8.38 (s, 1H), 8.13 – 8.04 (m, 1H), 6.87 (d, 1H), 5.49 (d, 2H), 2.02 (s, 3H), 1.94 (s, 3H), 1.92 (s, 3H).

Step 2: Preparation of 2'-bromo-4-[(3,5-difluoropyridin-2-yl)methoxy]-3',5',6-trimethyl-[1,4'-bipyridin]-2-one:

[00598] To a stirred mixture of 2'-bromo-3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-3',5',6-trimethyl-[1,4'-bipyridin]-2-one (1.50 g, 3.18 mmol, 1.00 equiv) and tributyl(1-ethoxyethenyl)stannane (3.45 g, 9.56 mmol, 3.00 equiv) in 1,4-dioxane (5 mL) was added dichloropalladium; bis(triphenylphosphane) (223 mg, 0.31 mmol, 0.10 equiv) at room temperature under air atmosphere. The resulting mixture was stirred for 12 h at 100°C under nitrogen atmosphere. The reaction was monitored by LCMS. The mixture was allowed to cool down to r.t.. The resulting mixture was filtered, the filter cake was washed with ethyl EA (3x50 mL). The filtrate was concentrated under reduced pressure. The crude product was used in the next step directly without further purification. LC-MS: (ES+H, m/z): [M+H]⁺ = 462.2.

Step 3: Preparation of 2'-acetyl-3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-3',5',6-trimethyl-[1,4'-bipyridin]-2-one:

[00599] To a stirred solution of the above residue in THF (20 mL) were added HCl (2 mL) dropwise at 0°C under nitrogen atmosphere. The resulting mixture was stirred for 2 h at room temperature under nitrogen atmosphere. The reaction was monitored by LCMS. The residue was basified to pH 10 with

saturated Na_2CO_3 (aq.) at 0°C . The resulting mixture was extracted with EtOAc (3×100 mL). The combined organic layers were concentrated under reduced pressure. The residue was purified by silica gel column chromatography to afford 2'-acetyl-3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-3',5',6-trimethyl-[1,4'-bipyridin]-2-one (980 mg, 75.61%, over two steps) as a white solid. LC-MS: (ES+H, m/z): $[\text{M}+\text{H}]^+ = 434.2$. ^1H NMR (400 MHz, DMSO-d_6) δ 8.66 (s, 1H), 8.61 (d, 1H), 8.13 – 8.04 (m, 1H), 6.88 (d, 1H), 5.49 (d, 2H), 2.66 (s, 3H), 2.11 (s, 3H), 2.04 (s, 3H), 1.88 (s, 3H).

Step 4: Preparation of 3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-2'-[(2E)-3-(dimethylamino)prop-2-enoyl]-3',5',6-trimethyl-[1,4'-bipyridin]-2-one:

[00600] A solution of 2'-acetyl-3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-3',5',6-trimethyl-[1,4'-bipyridin]-2-one (980 mg) in DMF-DMA (5 mL) was stirred for 3 h at 100°C under nitrogen atmosphere. The reaction was monitored by LCMS. The mixture was allowed to cool down to r.t. The resulting mixture was concentrated under vacuum. The crude product was used in the next step directly without further purification. LC-MS: (ES+H, m/z): $[\text{M}+\text{H}]^+ = 489.2$.

Step 5: Preparation of 3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-2'-[2-(2-hydroxypropan-2-yl)pyrimidin-4-yl]-3',5',6-trimethyl-[1,4'-bipyridin]-2-one:

[00601] A mixture of 3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-2'-[(2E)-3-(dimethylamino)prop-2-enoyl]-3',5',6-trimethyl-[1,4'-bipyridin]-2-one (1100 mg, assumed 100% yield, 2.25 mmol, 1.00 equiv) 2-hydroxy-2-methylpropanimidamide (689 mg, 6.75 mmol, 3.00 equiv) K_2CO_3 (1500 mg, 11.25 mmol, 5.00 equiv) in propan-2-ol (10 mL) was stirred for 12 h at 80°C under nitrogen atmosphere. The reaction was monitored by LCMS. The mixture was allowed to cool down to r.t.. The resulting mixture was diluted with EA (300 mL) and washed with water (1×100 mL). The organic layer was concentrated under reduced pressure. The residue was purified by silica gel column chromatography to afford crude product. The crude product was isolated by PREP-HPLC to afford 3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-2'-[2-(2-hydroxypropan-2-yl)pyrimidin-4-yl]-3',5',6-trimethyl-[1,4'-bipyridin]-2-one (400 mg, 33.67%, over two steps) as a white solid. LC-MS: (ES+H, m/z): $[\text{M}+\text{H}]^+ = 528.0$.

Step 6: Preparation of rel-3-chloro-4-((3,5-difluoropyridin-2-yl)methoxy)-2'-(2-(2-hydroxypropan-2-yl)pyrimidin-4-yl)-3',5',6-trimethyl-2H-[1,4'-bipyridin]-2-one and rel-3-chloro-4-((3,5-difluoropyridin-2-yl)methoxy)-2'-(2-(2-hydroxypropan-2-yl)pyrimidin-4-yl)-3',5',6-trimethyl-2H-[1,4'-bipyridin]-2-one :

[00602] The racemate (190 mg) was separated by Prep-Chiral-HPLC to afford rel-3-chloro-4-((3,5-difluoropyridin-2-yl)methoxy)-2'-(2-(2-hydroxypropan-2-yl)pyrimidin-4-yl)-3',5',6-trimethyl-2H-[1,4'-bipyridin]-2-one (**Example 49A**: 66.6 mg, 96.8% purity, ee=100%) as a white solid and rel-3-chloro-4-((3,5-difluoropyridin-2-yl)methoxy)-2'-(2-(2-hydroxypropan-2-yl)pyrimidin-4-yl)-3',5',6-trimethyl-2H-[1,4'-bipyridin]-2-one (**Example 49B**: 73.0 mg, 97.9% purity, ee=99.34%) as a white solid.

Example 49A:

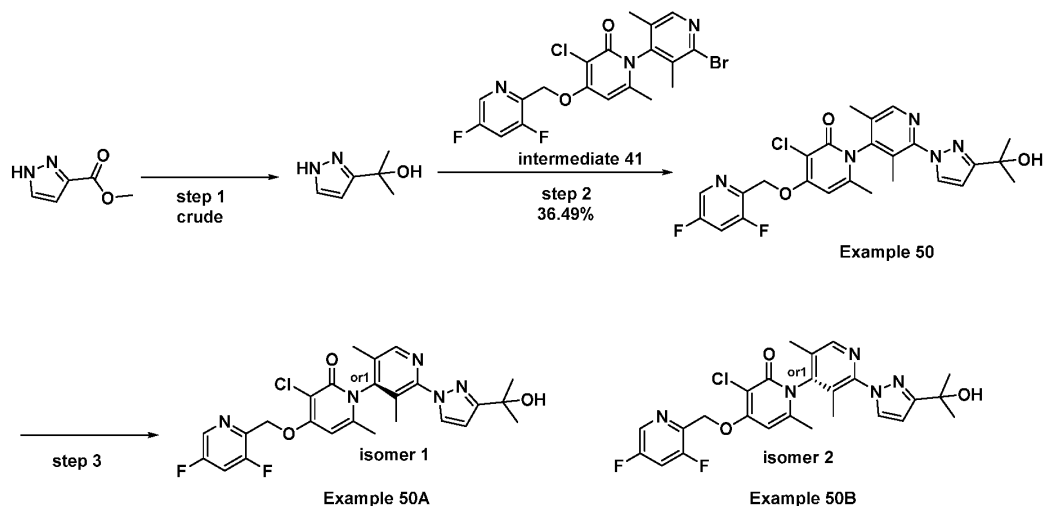
[00603] LC-MS: (ES+H, m/z): $[\text{M}+\text{H}]^+ = 528.00$. ^1H NMR (400 MHz, DMSO-d_6) δ 8.97 (d, 1H), 8.70 (s, 1H), 8.61 (d, 1H), 8.16 – 8.05 (m, 1H), 7.90 (d, 1H), 6.89 (s, 1H), 5.50 (d, 2H), 5.22 – 5.00 (m, 1H), 2.21 (s,

3H), 2.06 (s, 3H), 1.95 (s, 3H), 1.53 (s, 6H). ^{19}F NMR (377 MHz, DMSO) δ -120.13, -120.15, -122.31, -122.32.

Example 49B:

[00604] LC-MS: (ES+H, m/z): $[\text{M}+\text{H}]^+ = 528.00$. ^1H NMR (400 MHz, DMSO- d_6) δ 8.97 (d, 1H), 8.70 (s, 1H), 8.61 (d, 1H), 8.17 – 8.06 (m, 1H), 7.90 (d, 1H), 6.89 (d, 1H), 5.50 (d, 2H), 5.12 (s, 1H), 2.21 (s, 3H), 2.06 (s, 3H), 1.95 (s, 3H), 1.54 (s, 6H). ^{19}F NMR (377 MHz, DMSO) δ -120.13, -120.15, -122.30, -122.32.

Example 50A, 50B



Step 1: Preparation of 2-(1H-pyrazol-3-yl)propan-2-ol:

[00605] To a stirred solution of methyl 1H-pyrazole-3-carboxylate (5.00 g, 39.64 mmol, 1.00 equiv) in THF was added bromo(methyl)magnesium (132 mL, 3 M in 2-MeTHF, 396.46 mmol, 10.00 equiv) dropwise at 0°C under nitrogen atmosphere. The resulting mixture was stirred for 1 h at 0°C under nitrogen atmosphere. The reaction was monitored by LCMS. The reaction was quenched with sat. NH_4Cl (aq.) at 0°C. The resulting mixture was extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with brine (200 mL), dried over anhydrous Na_2SO_4 . After filtration, the filtrate was concentrated under reduced pressure. This resulted in 2-(1H-pyrazol-3-yl)propan-2-ol (3.00 g, crude) as a yellow oil. The crude product was used in the next step directly without further purification. LC-MS: (ES+H, m/z): $[\text{M}+\text{H}]^+ = 127.08$.

Step 2: Preparation of 3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-2'-[3-(2-hydroxypropan-2-yl)pyrazol-1-yl]-3',5',6-trimethyl-[1,4'-bipyridin]-2-one:

[00606] To a stirred mixture of 2'-bromo-3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-3',5',6-trimethyl-[1,4'-bipyridin]-2-one (300 mg, 0.63 mmol, 1.00 equiv) and 2-(1H-pyrazol-3-yl)propan-2-ol (160 mg, 1.27 mmol, 2.00 equiv) in dioxane (15 mL) were added K_2CO_3 (176 mg, 1.27 mmol, 2.00 equiv), CuI (242 mg, 1.27 mmol, 2.00 equiv) and (1R,2R)-1-N,2-N-dimethylcyclohexane-1,2-diamine (181 mg, 1.27 mmol, 2.00 equiv) at room temperature under nitrogen atmosphere. The resulting mixture was stirred overnight at 80°C under nitrogen atmosphere. The reaction was monitored by LCMS. The mixture was allowed to cool down to room temperature. The resulting mixture was filtered, the filter cake was washed with EtOAc (3x50 mL).

The filtrate was concentrated under reduced pressure. The residue was purified by PREP-HPLC to afford 3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-2'-[3-(2-hydroxypropan-2-yl)pyrazol-1-yl]-3',5',6-trimethyl-[1,4'-bipyridin]-2-one (120 mg, 36.49%) as a white solid. LC-MS: (ES+H, m/z): [M+H]⁺ = 516.3.

Step 3: Preparation of rel-3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-2'-[3-(2-hydroxypropan-2-yl)pyrazol-1-yl]-3',5',6-trimethyl-[1,4'-bipyridin]-2-one & rel-3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-2'-[3-(2-hydroxypropan-2-yl)pyrazol-1-yl]-3',5',6-trimethyl-[1,4'-bipyridin]-2-one :

[00607] The 3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-2'-[3-(2-hydroxypropan-2-yl)pyrazol-1-yl]-3',5',6-trimethyl-[1,4'-bipyridin]-2-one (120 mg) was separated by Prep-Chiral-HPLC to afford **Example 50A** (31.7 mg, 99.7% purity, ee=100%) and **Example 50B** (66.5 mg, 99.8% purity, ee=100%) as a white solid.

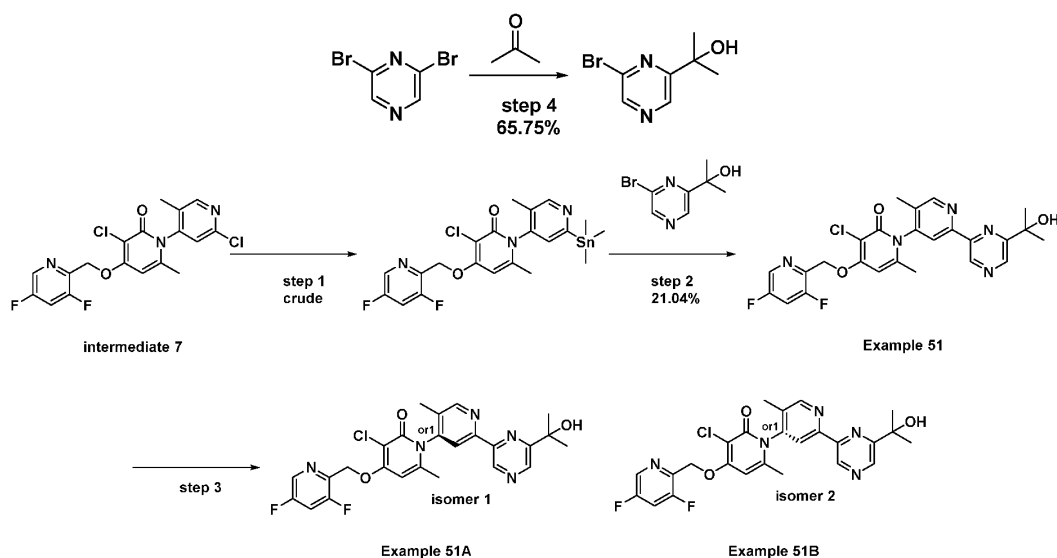
Example 50A:

[00608] LC-MS: (ES+H, m/z): [M+H]⁺ = 516.2. ¹H NMR (300 MHz, DMSO-d₆) δ 8.61 (d, 1H), 8.47 (s, 1H), 8.23 (d, 1H), 8.11 (ddd, 1H), 6.88 (d, 1H), 6.51 (d, 1H), 5.50 (d, 2H), 5.05 (s, 1H), 2.08 (s, 3H), 2.01 (s, 3H), 1.87 (s, 3H), 1.48 (s, 3H), 1.47 (s, 3H). ¹⁹F NMR (282 MHz, DMSO) δ -120.12, -120.14, -122.29, -122.32.

Example 50B:

[00609] LC-MS: (ES+H, m/z): [M+H]⁺ = 516.2. ¹H NMR (300 MHz, DMSO-d₆) δ 8.61 (d, 1H), 8.47 (s, 1H), 8.23 (d, 1H), 8.10 (ddd, 1H), 6.88 (d, 1H), 6.51 (d, 1H), 5.50 (d, 2H), 5.05 (s, 1H), 2.08 (s, 3H), 2.01 (s, 3H), 1.87 (s, 3H), 1.48 (s, 3H), 1.43 (s, 3H). ¹⁹F NMR (282 MHz, DMSO) δ -120.12, -120.14, -122.29, -122.31.

Example 51A, 51B



Step 1: Preparation of 3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-5',6-dimethyl-2'-(trimethylstannyl)-[1,4'-bipyridin]-2-one:

[00610] To a stirred solution of 2',3-dichloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-5',6-dimethyl-[1,4'-bipyridin]-2-one (1.00 g, 2.4 mmol, 1.00 equiv) and Sn_2Me_6 (3.18 g, 9.70 mmol, 4.00 equiv) in dioxane (20 mL) was added AsPh_3 (222 mg, 0.72 mmol, 0.3 equiv) and $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$ (510 mg, 0.72 mmol, 0.30equiv) at room temperature under nitrogen atmosphere. The resulting mixture was stirred overnight at 80°C under nitrogen atmosphere. The reaction was monitored by LCMS. The mixture was allowed to cool down to room temperature. The resulting mixture was diluted with EtOAc (100 mL). The resulting mixture was washed with 4 x 300 mL of KF (aq). The combined organic layers were washed with brine (100 mL), dried over anhydrous Na_2SO_4 . After filtration, the filtrate was concentrated under reduced pressure. This resulted in 3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-5',6-dimethyl-2'-(trimethylstannyl)-[1,4'-bipyridin]-2-one (1.30 g crude) as a brown solid. The crude product was used in the next step directly without further purification. LC-MS: (ES+H, m/z): $[\text{M}+\text{H}]^+ = 542.0$.

Step 2: Preparation of 3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-2'-[6-(2-hydroxypropan-2-yl)pyrazin-2-yl]-5',6-dimethyl-[1,4'-bipyridin]-2-one:

[00611] To a stirred mixture of 3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-5',6-dimethyl-2'-(trimethylstannyl)-[1,4'-bipyridin]-2-one (500 mg, 0.92 mmol, 1.00 equiv) and 2-(6-bromopyrazin-2-yl)propan-2-ol (200 mg, 0.92 mmol, 1.00 equiv) in dioxane (15 mL) were added CuI (176 mg, 0.925 mmol, 1.00 equiv) and $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$ (129 mg, 0.18 mmol, 0.20 equiv) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 3 h at 80°C under nitrogen atmosphere. The reaction was monitored by LCMS. The mixture was allowed to cool down to room temperature. The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography to afford 3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-2'-[6-(2-hydroxypropan-2-yl)pyrazin-2-yl]-5',6-dimethyl-[1,4'-bipyridin]-2-one (130 mg crude) as a yellow solid. The crude was purified by reverse flash chromatography. The pure fractions were concentrated under reduced pressure, to afford 3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-2'-[6-(2-hydroxypropan-2-yl)pyrazin-2-yl]-5',6-dimethyl-[1,4'-bipyridin]-2-one (100 mg, 21.04%) as a white solid. LC-MS: (ES+H, m/z): $[\text{M}+\text{H}]^+ = 514.2$.

Step 3: Preparation of rel-3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-2'-[6-(2-hydroxypropan-2-yl)pyrazin-2-yl]-5',6-dimethyl-[1,4'-bipyridin]-2-one & rel-3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-2'-[6-(2-hydroxypropan-2-yl)pyrazin-2-yl]-5',6-dimethyl-[1,4'-bipyridin]-2-one :

[00612] The 3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-2'-[6-(2-hydroxypropan-2-yl)pyrazin-2-yl]-5',6-dimethyl-[1,4'-bipyridin]-2-one (250 mg) was separated by prep-chiral-HPLC to afford **Example 51A** (37.0 mg, 99.6% purity, ee = 100%) and **Example 51B** (60.4 mg, = 98.0% purity, ee = 100%) as a white solid.

Example 51A:

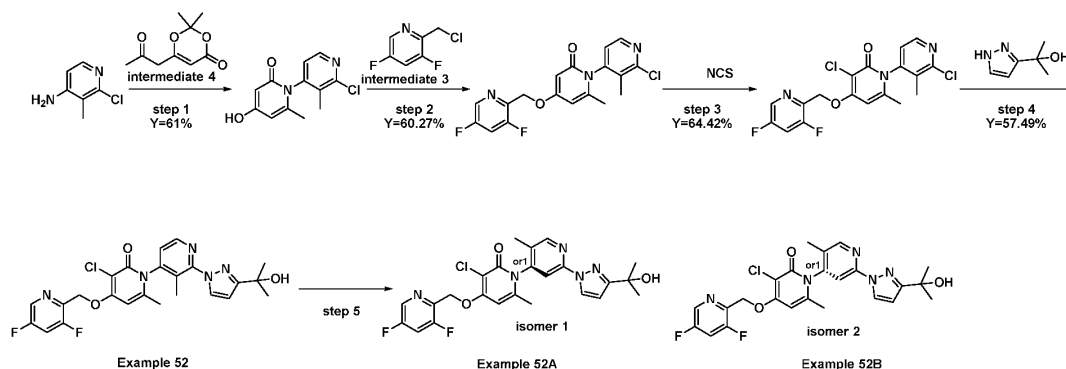
[00613] LC-MS: (ES+H, m/z): $[\text{M}+\text{H}]^+ = 514.2$. ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 9.49 (s, 1H), 9.03 (s, 1H), 8.91 (s, 1H), 8.68 (d, 1H), 8.40 (s, 1H), 8.18 (ddd, 1H), 6.90 (s, 1H), 5.60 (s, 1H), 5.53 (d, 2H), 2.16 (s, 3H), 2.05 (s, 3H), 1.61 (s, 3H), 1.60 (s, 3H). ^{19}F NMR (282 MHz, DMSO) δ -120.12, -120.15, -122.30, -122.32.

Example 51B:

[00614] LC-MS: (ES+H, m/z): [M+H]⁺=514.1. ¹H NMR (400 MHz, DMSO-d₆) δ 9.42 (s, 1H), 8.97 (s, 1H), 8.84 (s, 1H), 8.62 (d, 1H), 8.35 (s, 1H), 8.15 (ddd, 1H), 6.84 (s, 1H), 5.53 (s, 1H), 5.49 (d, 2H), 2.10 (s, 3H), 1.99 (s, 3H), 1.54 (s, 3H), 1.53 (s, 3H). ¹⁹F NMR (377 MHz, DMSO) δ -120.11, -120.13, -122.29, -122.31.

Step 4: Preparation of 2-(6-bromopyrazin-2-yl)propan-2-ol:

[00615] To a stirred solution of 2,6-dibromopyrazine (5.00 g, 21.01 mmol, 1.00 equiv) in Toluene (125 mL) was added n-BuLi (8.4 mL, 2.5 M in hexane, 21.01 mmol, 1.00 equiv) dropwise over 15 min at -78°C under nitrogen atmosphere. The resulting mixture was stirred for 30 min at -78°C under nitrogen atmosphere. To the above mixture was added acetone (1.83 g, 31.52 mmol, 1.50 equiv) dropwise over 30 min at -78°C. The resulting mixture was stirred for additional 1h at -78°C. The reaction was monitored by LCMS. The reaction was quenched by the addition of sat. NH₄Cl (aq.) (20mL) at 0°C. The resulting mixture was extracted with EtOAc (3 x 100mL). The combined organic layers were washed with brine (1x200 mL), dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography to afford 2-(6-bromopyrazin-2-yl)propan-2-ol (3.00 g, 65.75%) as a yellow oil. LC-MS: (ES+H, m/z): [M+H]⁺=217.2.

Example 52A, 52B**Step 1: Preparation of 2'-chloro-4-hydroxy-3',6-dimethyl-2H-[1,4'-bipyridin]-2-one:**

[00616] A solution of 2-chloro-3-methylpyridin-4-amine (5.00 g, 35.06 mmol, 1.00 equiv) and 2,2-dimethyl-6-(2-oxopropyl)-1,3-dioxin-4-one (9.69 g, 52.60 mmol, 1.50 equiv) in 1,4-dioxane was stirred for 3 h at 90°C under nitrogen atmosphere. The reaction was allowed to r.t. and monitored by LCMS. To the above mixture was added H₂SO₄ (3.44 g, 35.06 mmol, 1.00 equiv) dropwise at room temperature under nitrogen atmosphere. The resulting mixture was stirred for additional 1 h at 90°C under nitrogen atmosphere. The mixture was allowed to cool down to room temperature. The reaction was monitored by LCMS. The resulting mixture was concentrated then water (10 mL) was added and the slurry stirred for additional 10 minutes at room temperature. Then ether (10 mL) was added and the mixture stirred for additional 10 minutes at room temperature. The solid was collected by filtration to afford 2'-chloro-4-hydroxy-3',6-dimethyl-[1,4'-bipyridin]-2-one (5.40 g, 61.0%) as a white solid. LC-MS: (ES+H, m/z): [M+H]⁺=251.0.

Step 2: Preparation of 2'-chloro-4-((3,5-difluoropyridin-2-yl)methoxy)-3',6-dimethyl-2H-[1,4'-bipyridin]-2-one :

[00617] To a stirred mixture of 2'-chloro-4-hydroxy-3',6-dimethyl-[1,4'-bipyridin]-2-one (5.00 g, 19.94 mmol, 1.00 equiv) and 2-(chloromethyl)-3,5-difluoropyridine (13.05 g, 79.78 mmol, 4.00 equiv) in DMF (50 mL) were added K_2CO_3 (27.57 g, 199.46 mmol, 10.00 equiv) and 18-Crown-6 (2.64 g, 9.97 mmol, 0.5 equiv) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for additional 6 h at 60°C under nitrogen atmosphere. The mixture was allowed to cool down to room temperature. The reaction was monitored by LCMS. The resulting mixture was diluted with ethyl acetate (400 mL). The organic layer was washed with water (100 mL) and brine (100 mL), and then dried over Na_2SO_4 . The solution was concentrated under reduced pressure. The residue was purified by silica gel column chromatography to afford 2'-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-3',6-dimethyl-[1,4'-bipyridin]-2-one (5.22 g, 60.3%) as a white solid. LC-MS: (ES+H, m/z): $[M+H]^+ = 378.0$.

Step 3: Preparation of 2',3-dichloro-4-((3,5-difluoropyridin-2-yl)methoxy)-3',6-dimethyl-2H-[1,4'-bipyridin]-2-one:

[00618] To a stirred mixture of 2'-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-3',6-dimethyl-[1,4'-bipyridin]-2-one (5.00 g, 13.23 mmol, 1.00 equiv) and 2,2-dichloroacetic acid (0.34 g, 2.64 mmol, 0.2 equiv) in i-PrOH (15 mL) were added NCS (1.77 g, 13.23 mmol, 1.00 equiv) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 2 h at 60°C under nitrogen atmosphere. The mixture was allowed to cool down to room temperature. The reaction was monitored by LCMS. The precipitated solids were collected by filtration and washed with IPA (2x10 mL), to afford 2',3-dichloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-3',6-dimethyl-[1,4'-bipyridin]-2-one (3.82 g, 64.4%) as a white solid. LC-MS: (ES+H, m/z): $[M+H]^+ = 411.9$. 1H NMR (400 MHz, DMSO- d_6) δ 8.60 (d, 1H), 8.46 (d, 1H), 8.15 – 8.03 (m, 1H), 7.49 (d, 1H), 6.82 (s, 1H), 5.49 (d, 2H), 2.03 (s, 3H), 1.96 (s, 3H).

Step 4: Preparation of 3-chloro-4-((3,5-difluoropyridin-2-yl)methoxy)-2'-(3-(2-hydroxypropan-2-yl)-1H-pyrazol-1-yl)-3',6-dimethyl-2H-[1,4'-bipyridin]-2-one:

[00619] To a stirred mixture of 2',3-dichloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-3',6-dimethyl-[1,4'-bipyridin]-2-one (500 mg, 1.21 mmol, 1.00 equiv), 2-(1H-pyrazol-3-yl)propan-2-ol (459 mg, 3.64 mmol, 3.00 equiv) in 1,4-dioxane were added (1R,2R)-N1,N2-dimethylcyclohexane-1,2-diamine (345 mg, 0.48 mmol, 2.00 equiv), CuI (230 mg, 0.24 mmol, 1.00 equiv), K_2CO_3 (335 mg, 2.42 mmol, 2.00 equiv) and NaI (363 mg, 2.42 mmol, 2.00 equiv) at room temperature under nitrogen atmosphere. The resulting mixture was stirred overnight at 100°C under nitrogen atmosphere. The mixture was allowed to cool down to room temperature. Desired product could be detected by LCMS. The resulting mixture was diluted with EA (100 mL), then washed with water (2x50 mL) and brine (50 mL), dried over anhydrous Na_2SO_4 . After filtration, the resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography to afford 3-chloro-4-((3,5-difluoropyridin-2-yl)methoxy)-2'-(3-(2-hydroxypropan-2-yl)-1H-pyrazol-1-yl)-3',6-dimethyl-2H-[1,4'-bipyridin]-2-one (350 mg, 57.5%, crude), which was further purified by PREP-HPLC. This resulted in 3-chloro-4-[(3,5-difluoropyridin-2-

yl)methoxy]-2'-[3-(2-hydroxypropan-2-yl)pyrazol-1-yl]-3',6-dimethyl-[1,4'-bipyridin]-2-one (90 mg, 14.8%) as a white solid. LC-MS: (ES+H, m/z): $[M+H]^+ = 502.1$.

Step 5: Preparation of rel-3-chloro-4-((3,5-difluoropyridin-2-yl)methoxy)-2'-(3-(2-hydroxypropan-2-yl)-1H-pyrazol-1-yl)-3',6-dimethyl-2H-[1,4'-bipyridin]-2-one and rel-3-chloro-4-((3,5-difluoropyridin-2-yl)methoxy)-2'-(3-(2-hydroxypropan-2-yl)-1H-pyrazol-1-yl)-3',6-dimethyl-2H-[1,4'-bipyridin]-2-one

[00620] The racemate (350 mg) was separated by prep-chiral-HPLC, the pure fraction was concentrated under vacuum and was lyophilized to afford **Example 52A** (32.4 mg, 99.4% purity, ee=100%) as a white solid and **Example 52B** (32.2 mg, 99.0% purity, ee=99.6%) as a white solid.

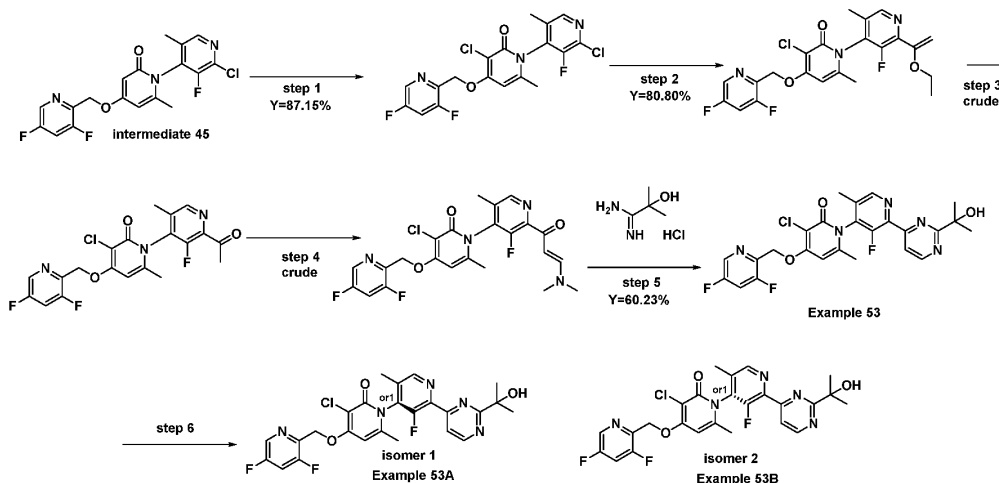
Example 52A:

[00621] LC-MS: (ES+H, m/z): $[M+H]^+ = 502.1$. ^1H NMR (400 MHz, DMSO- d_6) δ 8.60 (d, 1H), 8.53 (d, 1H), 8.28 (d, 1H), 8.12 – 8.06 (m, 1H), 7.45 (d, 1H), 6.82 (s, 1H), 6.52 (d, 1H), 5.49 (d, 2H), 5.08 (s, 1H), 2.12 (s, 3H), 1.99 (s, 3H), 1.48 (s, 3H), 1.47 (s, 3H). ^{19}F NMR (377 MHz, DMSO) δ -120.13, -120.15., -122.31, -122.33.

Example 52B:

[00622] LC-MS: (ES+H, m/z): $[M+H]^+ = 502.1$. ^1H NMR (400 MHz, DMSO- d_6) δ 8.61 (s, 1H), 8.54 (d, 1H), 8.29 (s, 1H), 8.14 – 8.05 (m, 1H), 7.48 – 7.42 (m, 1H), 6.83 (s, 1H), 6.53 (s, 1H), 5.49 (s, 2H), 5.08 (s, 1H), 2.13 (s, 3H), 2.00 (s, 3H), 1.48 (s, 3H), 1.47 (s, 3H). ^{19}F NMR (377 MHz, DMSO) δ -120.13, -120.15., -122.31, -122.33.

Example 53A, 53B



Step 1: Preparation of 2',3-dichloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-3'-fluoro-5',6-dimethyl-[1,4'-bipyridin]-2-one:

[00623] To a stirred solution of 2'-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-3'-fluoro-5',6-dimethyl-[1,4'-bipyridin]-2-one (1.90 g, 4.80 mmol, 1.00 equiv) and NCS (0.83 g, 6.21 mmol, 1.30 equiv) in DCM (40 mL) were added 2,2-dichloroacetic acid (61 mg, 0.48 mmol, 0.1 equiv) dropwise at room temperature under nitrogen atmosphere. The resulting mixture was stirred overnight at room temperature under nitrogen

atmosphere. The reaction was monitored by LCMS. The resulting mixture was poured into water (100 mL). The resulting mixture was extracted with EtOAc (3 x 50mL). The combined organic layers were washed with brine (3 x 50 mL), dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, the filtrate was concentrated under reduced pressure to afford 2',3-dichloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-3'-fluoro-5',6-dimethyl-[1,4'-bipyridin]-2-one (1.80 g, 87.15%) as a yellow solid. LC-MS: (ES+H, m/z): [M+H]⁺ = 429.8. ¹H NMR (300 MHz, DMSO-d₆) δ 8.61 (d, 1H), 8.49 (s, 1H), 8.15 – 8.03 (m, 1H), 6.90 (s, 1H), 5.52 (d, 2H), 2.08 (s, 3H), 2.03 (s, 3H).

Step 2: Preparation of 3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-2'-(1-ethoxyethenyl)-3'-fluoro-5',6-dimethyl-[1,4'-bipyridin]-2-one:

[00624] To a stirred solution of 2',3-dichloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-3'-fluoro-5',6-dimethyl-[1,4'-bipyridin]-2-one (800 mg, 1.86 mmol, 1.00 equiv) and Pd(PPh₃)₂Cl₂ (65 mg, 0.09 mmol, 0.05 equiv) in 1,4-dioxane (10 ml) was added tributyl(1-ethoxyethenyl)stannane (1.34 g, 3.72 mmol, 2.00 equiv) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 2 h at 100°C under nitrogen atmosphere. The reaction was monitored by LCMS. The mixture was allowed to cool down to room temperature. The resulting mixture was poured into water (80mL). The resulting mixture was extracted with EtOAc (3 x 100mL). The combined organic layers were washed with brine (3x10 mL), dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, the filtrate was concentrated under reduced pressure to afford 3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-2'-(1-ethoxyethenyl)-3'-fluoro-5',6-dimethyl-[1,4'-bipyridin]-2-one (700 mg, 80.80%) as a white solid. LC-MS: (ES+H, m/z): [M+H]⁺ = 466.0.

Step 3: Preparation of 2'-acetyl-3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-3'-fluoro-5',6-dimethyl-[1,4'-bipyridin]-2-one:

[00625] To a stirred solution of 3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-2'-(1-ethoxyethenyl)-3'-fluoro-5',6-dimethyl-[1,4'-bipyridin]-2-one (700 mg, 1.50 mmol, 1.00 equiv) in THF (30ml) was added conc.HCl (3 mL) at 0°C under nitrogen atmosphere. The resulting mixture was stirred for 1h at room temperature under nitrogen atmosphere. The reaction was monitored by LCMS. The resulting mixture was poured into water (100mL) at 0°C. The resulting mixture was extracted with EtOAc (3 x 100mL). The combined organic layers were washed with brine (3x10 mL), dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure to afford 2'-acetyl-3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-3'-fluoro-5',6-dimethyl-[1,4'-bipyridin]-2-one (680 mg, crude) as a white solid. LC-MS: (ES+H, m/z): [M+H]⁺ = 438.0.

Step 4: Preparation of 3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-2'-[(2E)-3-(dimethylamino)prop-2-enoyl]-3'-fluoro-5',6-dimethyl-[1,4'-bipyridin]-2-one:

[00626] Into a 40 mL sealed tube were added 2'-acetyl-3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-3'-fluoro-5',6-dimethyl-[1,4'-bipyridin]-2-one (680 mg, 1.55 mmol, 1.00 equiv) and DMF-DMA (6 mL) at room temperature. The resulting mixture was stirred for 2 h at 100°C under nitrogen atmosphere. The

reaction was monitored by LCMS. The mixture was allowed to cool down to room temperature. The resulting mixture was concentrated under reduced pressure to afford 3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-2'-[(2E)-3-(dimethylamino)prop-2-enoyl]-3'-fluoro-5',6-dimethyl-[1,4'-bipyridin]-2-one (820 mg, crude) as a brown solid. LC-MS: (ES+H, m/z): $[M+H]^+ = 493.0$.

Step 5: Preparation of 3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-3'-fluoro-2'-[2-(2-hydroxypropan-2-yl)pyrimidin-4-yl]-5',6-dimethyl-[1,4'-bipyridin]-2-one (TFA salt):

[00627] To a stirred solution of 3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-2'-[(2E)-3-(dimethylamino)prop-2-enoyl]-3'-fluoro-5',6-dimethyl-[1,4'-bipyridin]-2-one (200 mg, 0.41 mmol, 1.00 equiv) and 2-hydroxy-2-methyl-propionamide hydrochloride (282 mg, 2.03 mmol, 5.00 equiv) in DMF (4 ml) was added K_2CO_3 (168 mg, 1.22 mmol, 3.00 equiv) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 3 h at 80°C under nitrogen atmosphere. The reaction was monitored by LCMS. The resulting mixture was poured into water (80 mL). The resulting mixture was extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with brine (3x10 mL), dried over anhydrous Na_2SO_4 . After filtration, the filtrate was concentrated under reduced pressure. The crude product was purified by Prep-HPLC to afford 3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-3'-fluoro-2'-[2-(2-hydroxypropan-2-yl)pyrimidin-4-yl]-5',6-dimethyl-[1,4'-bipyridin]-2-one (TFA salt) (130 mg, 60.23%) as a brown solid. LC-MS: (ES+H, m/z): $[M+H]^+ = 532.1$.

Step 6: Preparation of rel-3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-3'-fluoro-2'-[2-(2-hydroxypropan-2-yl)pyrimidin-4-yl]-5',6-dimethyl-[1,4'-bipyridin]-2-one & rel-3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-3'-fluoro-2'-[2-(2-hydroxypropan-2-yl)pyrimidin-4-yl]-5',6-dimethyl-[1,4'-bipyridin]-2-one :

[00628] The 3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-3'-fluoro-2'-[2-(2-hydroxypropan-2-yl)pyrimidin-4-yl]-5',6-dimethyl-[1,4'-bipyridin]-2-one (TFA salt) (130 mg) was basified to pH=9 with NH_3H_2O then purified by Prep-Chiral-HPLC, the pure fraction was concentrated under pressure then lyophilized to afford (**Example 53A**) (32.7 mg, 98.0% purity, ee=100%) as a white solid and (**Example 53B**) (32.4 mg, 98.0% purity, ee=100%) as a white solid.

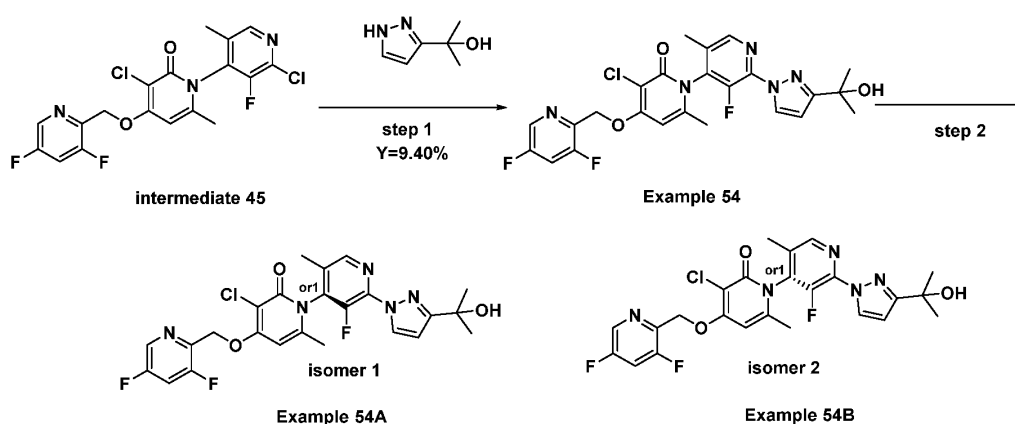
Example 53A:

LC-MS: (ES+H, m/z): $[M+H]^+ = 532.0$. 1H NMR (300 MHz, DMSO- d_6) δ 9.03 (d, 1H), 8.78 (s, 1H), 8.61 (d, 1H), 8.15-8.07 (m, 1H), 8.04 (d, 1H), 6.91 (s, 1H), 5.53 (d, 2H), 5.08 (s, 1H), 2.18 (s, 3H), 2.06 (s, 3H), 1.53 (s, 3H), 1.50 (s, 3H). ^{19}F NMR (282 MHz, DMSO) δ -120.17, -120.19, -122.35, -122.38, -132.08.

Example 53B:

LC-MS: (ES+H, m/z): $[M+H]^+ = 532.0$. 1H NMR (300 MHz, DMSO- d_6) δ 9.03 (d, 1H), 8.78 (s, 1H), 8.61 (d, 1H), 8.15-8.07 (m, 1H), 8.04 (d, 1H), 6.91 (s, 1H), 5.53 (d, 2H), 5.08 (s, 1H), 2.18 (s, 3H), 2.06 (s, 3H), 1.53 (s, 3H), 1.50 (s, 3H). ^{19}F NMR (282 MHz, DMSO) δ -120.17, -120.19, -122.35, -122.37, -132.08.

Example 54A, 54B



Step 1: Preparation of 3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-3'-fluoro-2'-[3-(2-hydroxypropan-2-yl)pyrazol-1-yl]-5',6-dimethyl-[1,4'-bipyridin]-2-one:

[00629] To a stirred mixture of 2',3-dichloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-3'-fluoro-5',6-dimethyl-[1,4'-bipyridin]-2-one (880 mg, 2.04 mmol, 1.00 equiv) and 2-(1H-pyrazol-3-yl)propan-2-ol (516 mg, 4.09 mmol, 2.00 equiv) in 1,4-dioxane (10 mL) were added (1S,2S)-N1,N2-dimethylcyclohexane-1,2-diamine (290 mg, 2.04 mmol, 1.00 equiv), CuI (38 mg, 0.20 mmol, 0.10 equiv) and K₂CO₃ (565 mg, 4.09 mmol, 2.00 equiv) at room temperature under nitrogen atmosphere. The resulting mixture was stirred overnight at 80°C under nitrogen atmosphere. The reaction was monitored by LCMS. The mixture was allowed to cool down to room temperature. The resulting mixture was diluted with water (20 mL). The resulting mixture was extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with brine (2 x 50 mL), dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, the pure fraction was concentrated under vacuum to afford the crude product. The crude product was purified by Prep-HPLC to afford 3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-3'-fluoro-2'-[3-(2-hydroxypropan-2-yl)pyrazol-1-yl]-5',6-dimethyl-[1,4'-bipyridin]-2-one (100 mg, 9.40%) as a white solid. LC-MS: (ES+H, m/z): [M+H]⁺ = 520.0.

Step 2: Preparation of rel-3-chloro-4-((3,5-difluoropyridin-2-yl)methoxy)-3'-fluoro-2'-(3-(2-hydroxypropan-2-yl)-1H-pyrazol-1-yl)-5',6-dimethyl-2H-[1,4'-bipyridin]-2-one (Example 54A) & rel-3-chloro-4-((3,5-difluoropyridin-2-yl)methoxy)-3'-fluoro-2'-(3-(2-hydroxypropan-2-yl)-1H-pyrazol-1-yl)-5',6-dimethyl-2H-[1,4'-bipyridin]-2-one (Example 54B):

[00630] The 3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-3'-fluoro-2'-[3-(2-hydroxypropan-2-yl)pyrazol-1-yl]-5',6-dimethyl-[1,4'-bipyridin]-2-one (100 mg) was separated by Prep-CHIRAL to afford **Example 54A** (25.4 mg, 99.6% purity, ee=100%) and **Example 54B** (27.6 mg, 99.7% purity, ee=98.8%) as a white solid.

Example 54A:

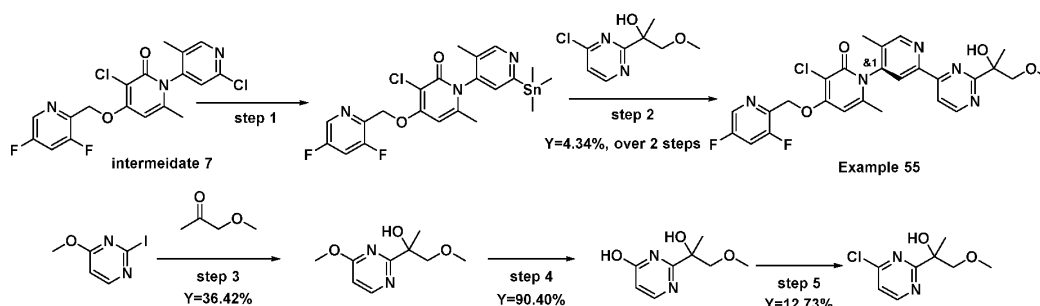
[00631] LC-MS: (ES+H, m/z): [M+H]⁺ = 520.1. ¹H NMR (300 MHz, DMSO-d₆) δ 8.61 (d, 1H), 8.50 (s, 1H), 8.36 (d, 1H), 8.30-8.11 (m, 1H), 6.90 (s, 1H), 6.59 (d, 1H), 5.53 (s, 2H), 5.11 (s, 1H), 2.11 (s, 3H), 2.07

(s, 3 H), 1.47 (s, 3H), 1.43 (s, 3H). ^{19}F NMR (282 MHz, DMSO) δ -120.18, -120.21, -122.35, -122.38, -138.00.

Example 54B:

[00632] LC-MS: (ES+H, m/z): $[\text{M}+\text{H}]^+ = 520.1$. ^1H NMR (300 MHz, DMSO- d_6) δ 8.61 (d, 1H), 8.49 (s, 1H), 8.35 (d, 1H), 8.15 – 8.04 (m, 1H), 6.90 (s, 1H), 6.59 (d, 1H), 5.53 (s, 2H), 5.11 (s, 1H), 2.11 (s, 3H), 2.07 (s, 3 H), 1.47 (s, 3H), 1.43 (s, 3H). ^{19}F NMR (282 MHz, DMSO) δ -120.18, -120.21, -122.35, -122.38 - 137.99.

Example 55



Step 1: Preparation of 3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-5',6-dimethyl-2'-(trimethylstannyl)-[1,4'-bipyridin]-2-one:

[00633] A solution of 2',3-dichloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-5',6-dimethyl-[1,4'-bipyridin]-2-one (2.00 g, 4.85 mmol, 1.00 equiv) and Sn_2Me_6 (6.36 g, 19.41 mmol, 4.00 equiv) in dioxane (20 mL) was added AsPh_3 (0.74 g, 2.43 mmol, 0.50 equiv), $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$ (0.68 g, 0.97 mmol, 0.20 equiv) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 2 h at 80°C under nitrogen atmosphere. Desired product was detected by LCMS, the mixture was allowed to cool down to room temperature. The resulting mixture was diluted with ethyl acetate (50 mL). The resulting mixture was washed with 5x20 mL of sat. KF aq. The combined organic layers were washed with brine (50 mL), dried over anhydrous Na_2SO_4 . After filtration, the filtrate was concentrated under reduced pressure to afford 3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-5',6-dimethyl-2'-(trimethylstannyl)-[1,4'-bipyridin]-2-one (3.00 g, crude) as a brown semi-solid. LC-MS: (ES+H, m/z): $[\text{M}+\text{H}]^+ = 541.9$.

Step 2: Preparation of 3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-2'-[2-(2-hydroxy-1-methoxypropan-2-yl)pyrimidin-4-yl]-5',6-dimethyl-[1,4'-bipyridin]-2-one:

[00634] To a stirred mixture of 3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-5',6-dimethyl-2'-(trimethylstannyl)-[1,4'-bipyridin]-2-one (1.60 g, 2.96 mmol, 1.00 equiv) and 2-(4-chloropyrimidin-2-yl)-1-methoxypropan-2-ol (299.89 mg, 1.48 mmol, 0.50 equiv) in dioxane (10 mL) were added $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$ (623.24 mg, 0.89 mmol, 0.30 equiv) and CuI (563.69 mg, 2.96 mmol, 1.00 equiv) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 2 h at 100°C under nitrogen atmosphere. Desired product was detected by LCMS. The mixture was allowed to cool down to room temperature. The resulting mixture was diluted with water (50 mL). The resulting mixture was extracted with EtOAc (3 x 50 mL). The

combined organic layers were washed with brine (2 x 50 mL), dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography to afford the crude product (200 mg) as a yellow oil, which was further purified by HP-Flash to afford 3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-2'-[2-(2-hydroxy-1-methoxypropan-2-yl)pyrimidin-4-yl]-5',6-dimethyl-[1,4'-bipyridin]-2-one (60.8 mg, 4.34%, racemate) as a white solid. LC-MS: (ES+H, m/z): [M+H]⁺=544.15. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.98 (d, 1H), 8.86 (s, 1H), 8.75 (s, 0.5H), 8.70 (s, 0.5H), 8.61 (d, 1H), 8.26 (d, 1H), 8.15 – 8.05 (m, 1H), 6.85 (s, 1H), 5.50 (s, 2H), 5.35 (s, 0.5H), 5.31 (s, 0.5H), 3.78 – 3.55 (m, 2H), 3.18 (s, 1.5H), 3.16 (s, 1.5H), 2.11 (s, 3H), 1.99 (d, 3H), 1.48 (s, 1.5H), 1.47 (s, 1.5H). ¹⁹F NMR (377 MHz, DMSO) δ -120.13, -120.15, -122.31, -122.33.

Step 3: Preparation of 2-methoxy-1-(4-methyl-methoxy-2-(4-methoxypyrimidin-2-yl)propan-2-ol

[00635] A solution of 2-iodo-4-methoxypyrimidine (17.00 g, 72.03 mmol, 1.00 equiv) in toluene (400 mL) was treated with *i*-PrMgCl (1.3 mol/L in THF, 46.82 mL, 93.64 mmol, 1.30 equiv) for 0.5 h at 0°C under nitrogen atmosphere. LCMS showed the reactant was consumed completely and a new peak was detected. Then 1-methoxypropan-2-one (9.52 g, 108.05 mmol, 1.50 equiv) was added to the above solution and the mixture reaction was stirred at 0°C for 2 h. LCMS showed the desired MS was found. The reaction was quenched by the addition of sat. NH₄Cl (aq.) (200 mL) at room temperature. The resulting mixture was extracted with EtOAc (2 x 200 mL). The combined organic layers were washed with brine (100 mL), dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by reverse flash chromatography. This resulted in 2-methoxy-1-(4-methyl-methoxy-2-(4-methoxypyrimidin-2-yl)propan-2-ol (5.20 g, 36.42%) as a yellow oil. LC-MS: (ES+H, m/z): [M+H]⁺=199.2. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.51 (d, 1H), 6.82 (d, 1H), 4.99 (s, 1H), 3.95 (s, 3H), 3.66 – 3.55 (m, 2H), 3.19 (s, 3H), 1.42 (s, 3H).

Step 4: Preparation of 2-methoxy-1-(4-methyl-methoxy-2-(4-methoxypyrimidin-2-yl)propan-2-ol

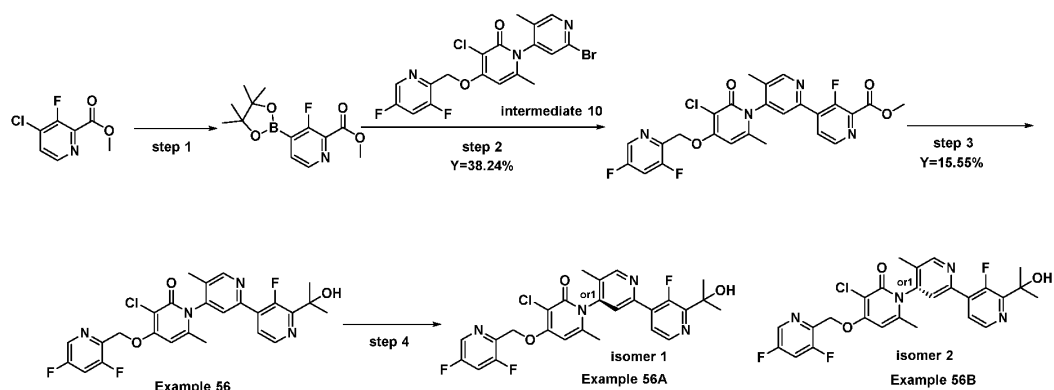
[00636] Into a 500 mL round-bottom flask were added 1-methoxy-2-(4-methoxypyrimidin-2-yl)propan-2-ol (5.00 g, 25.22 mmol, 1.00 equiv) and (ethylsulfanyl)sodium (25.46 g, 302.69 mmol, 12.00 equiv) in DMF (300 mL) at room temperature. The resulting mixture was stirred overnight at 100°C under nitrogen atmosphere. LCMS showed the reactant was consumed completely desired MS was found. The mixture was allowed to cool down to r.t. and the reaction was acidified to pH 6 with HCl (4M in dioxane), the resulting mixture was concentrated under reduced pressure. Then the residue was dissolved in ACN (100 mL) and filtrated, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography to afford 2-(2-hydroxy-1-methoxypropan-2-yl)pyrimidin-4-ol (4.20 g, 90.40%) as a yellow solid. LC-MS: (ES+H, m/z): [M+H]⁺=185.2.

Step 5: Preparation of 2-(4-chloropyrimidin-2-yl)-1-methoxypropan-2-ol

[00637] To a solution of 2-(2-hydroxy-1-methoxypropan-2-yl)pyrimidin-4-ol (2.50 g, 13.57 mmol, 1.00 equiv) in DCE (20 mL) was added POCl₃ (3.80 mL, 40.72 mmol, 3.00 equiv) dropwise at 0°C. The resulting mixture was stirred for 2 h at 50°C under nitrogen atmosphere. Desired product was detected by LCMS. The mixture was allowed to cool down to r.t. and concentrated under reduced pressure. The residue was purified

by silica gel column chromatography to afford 2-(4-chloropyrimidin-2-yl)-1-methoxypropan-2-ol (350 mg, 12.73%) as a yellow oil. LC-MS: (ES+H, m/z): $[M+H]^+ = 203.2$. ^1H NMR (300 MHz, DMSO- d_6) δ 8.86 (d, 1H), 7.68 (d, 1H), 5.32 (s, 1H), 3.69 (s, 2H), 3.26 (s, 3H), 1.52 (s, 3H).

Example 56A, 56B



Step 1&2: Preparation of methyl 4-{3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-6-methyl-2-oxopyridin-1-yl}-3'-fluoro-5-methyl-[2,4'-bipyridine]-2'-carboxylate:

[00638] To a stirred solution of methyl 4-chloro-3-fluoropyridine-2-carboxylate (3 g, 15.825 mmol, 1 equiv) and 4,4,5,5-tetramethyl-2-(tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (16.07 g, 63.300 mmol, 4 equiv) in 1,4-dioxane (200 mL) were added AcOK (4.66 g, 47.475 mmol, 3 equiv) and XPhos Palladacycl Gen.4 (113.48 mg, 0.132 mmol, 0.05 equiv) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 1 h at 80°C under nitrogen atmosphere. The reaction was monitored by LCMS. The mixture was allowed to cool down to room temperature. The resulting mixture was used in the next step directly without further purification. LC-MS: (ES+H, m/z): $[M+H]^+ = 200.0$.

[00639] To the above mixture were added 2'-bromo-3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-5',6-dimethyl-[1,4'-bipyridin]-2-one (1.8 g, 3.942 mmol, 1 equiv), K_2CO_3 (1.63 g, 11.826 mmol, 3 equiv), $\text{Pd}(\text{PPh}_3)_4$ (455.07 mg, 0.394 mmol, 0.1 equiv) and H_2O (50 mL) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 1.5 h at 80°C under nitrogen atmosphere. The reaction was monitored by LCMS. The mixture was allowed to cool down to room temperature. The resulting mixture was poured into water (500 mL). The resulting mixture was extracted with EtOAc (3 x 500mL). The combined organic layers were washed with brine (3 x 500 mL), dried over anhydrous Na_2SO_4 . After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, the pure fraction was concentrated under pressure to afford methyl 4-{3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-6-methyl-2-oxopyridin-1-yl}-3'-fluoro-5-methyl-[2,4'-bipyridine]-2'-carboxylate (800 mg, 38.23%) as a brown solid. LC-MS: (ES+H, m/z): $[M+H]^+ = 531.2$. ^1H NMR (400 MHz, DMSO- d_6) δ 8.90 (s, 1H), 8.65 (d, 1H), 8.60 (d, 1H), 8.21 (t, 1H), 8.11 – 8.07 (m, 1H), 7.95 (s, 1H), 6.81 (s, 1H), 5.49 (d, 2H), 3.93 (s, 3H), 2.10 (s, 3H), 1.98 (s, 3H).

Step 3: Preparation of 3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-1-[3'-fluoro-2'-(2-hydroxypropan-2-yl)-5-methyl-[2,4'-bipyridin]-4-yl]-6-methylpyridin-2-one:

[00640] To a stirred solution of methyl 4-{3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-6-methyl-2-oxopyridin-1-yl}-3'-fluoro-5-methyl-[2,4'-bipyridine]-2'-carboxylate (450 mg, 0.84 mmol, 1.00 equiv) in THF (20 mL) was added CH₃MgBr (1.70 mL, 5.08 mmol, 6.00 equiv, 3.4 M in 2-MeTHF) dropwise at 0°C under nitrogen atmosphere. The resulting mixture was stirred for 1 h at 0°C under nitrogen atmosphere. The reaction was monitored by LCMS. The reaction was quenched with sat. NH₄Cl (aq.) (50 mL) at 0°C. The resulting mixture was extracted with EtOAc (3 x 30 mL). The combined organic layers were washed with brine (3x20 mL), dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by Prep-TLC (EA) to afford crude product, which was further purified by Prep-HPLC, the pure fraction was concentrated under pressure to afford 3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-1-[3'-fluoro-2'-(2-hydroxypropan-2-yl)-5-methyl-[2,4'-bipyridin]-4-yl]-6-methylpyridin-2-one (70 mg, 15.55%) as a white solid. LC-MS: (ES+H, m/z): [M+H]⁺ = 531.1.

Step 4: Preparation of rel-3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-1-[3'-fluoro-2'-(2-hydroxypropan-2-yl)-5-methyl-[2,4'-bipyridin]-4-yl]-6-methylpyridin-2-one & rel-3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-1-[3'-fluoro-2'-(2-hydroxypropan-2-yl)-5-methyl-[2,4'-bipyridin]-4-yl]-6-methylpyridin-2-one :

[00641] The crude product (70 mg) was separated by Prep-Chiral-HPLC, the pure fraction was concentrated under reduced pressure and lyophilized to afford 3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-1-[3'-fluoro-2'-(2-hydroxypropan-2-yl)-5-methyl-[2,4'-bipyridin]-4-yl]-6-methylpyridin-2-one (**Example 56A**, 21.8 mg, 36.33%, ee=100%) as a white solid and 3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-1-[3'-fluoro-2'-(2-hydroxypropan-2-yl)-5-methyl-[2,4'-bipyridin]-4-yl]-6-methylpyridin-2-one (**Example 56B**, 18.6 mg, 31.00%, ee=100%) as a white solid.

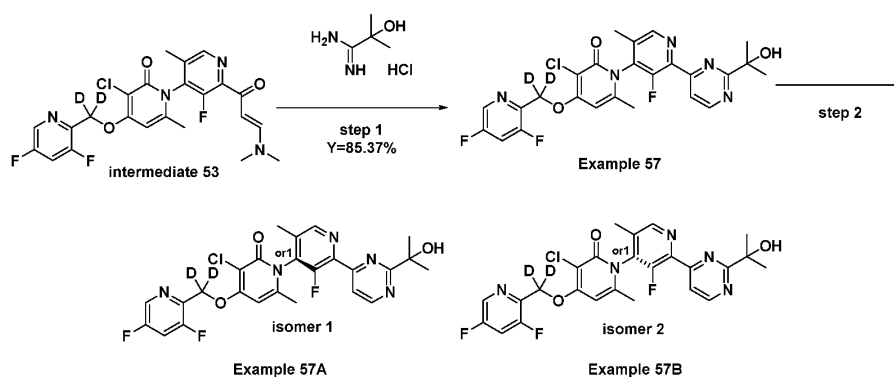
Example 56A:

[00642] LC-MS: (ES+H, m/z): [M+H]⁺ = 531.25. ¹H NMR (300 MHz, DMSO-d₆) δ 8.88 (s, 1H), 8.61 (d, 1H), 8.48 (d, 1H), 8.19 – 8.05 (m, 1H), 7.96 – 7.81 (m, 2H), 6.82 (s, 1H), 5.55 – 5.45 (m, 2H), 5.37 (s, 1H), 2.10 (s, 3H), 1.99 (s, 3H), 1.56 (s, 6H). ¹⁹F NMR (282 MHz, DMSO) δ -120.158, -120.177, -122.350, -122.368, -125.910.

Example 56B:

[00643] LC-MS: (ES+H, m/z): [M+H]⁺ = 531.25. ¹H NMR (300 MHz, DMSO-d₆) δ 8.88 (s, 1H), 8.61 (d, 1H), 8.48 (d, 1H), 8.19 – 8.05 (m, 1H), 7.96 – 7.81 (m, 2H), 6.82 (s, 1H), 5.55 – 5.45 (m, 2H), 5.37 (s, 1H), 2.10 (s, 3H), 1.99 (s, 3H), 1.56 (s, 6H). ¹⁹F NMR (282 MHz, DMSO) δ -120.140, -120.159, -122.310, -122.330, -125.923.

Example 57A, 57B



Step 1: Preparation of 3-chloro-4-[(3,5-difluoropyridin-2-yl)(2H2)methoxy]-3'-fluoro-2'-[2-(2-hydroxypropan-2-yl)pyrimidin-4-yl]-5',6-dimethyl-[1,4'-bipyridin]-2-one:

[00644] To a stirred solution of 3-chloro-4-[(3,5-difluoropyridin-2-yl)(2H2)methoxy]-2'-[(2E)-3-(dimethylamino)prop-2-en-2-yl]-3'-fluoro-5',6-dimethyl-[1,4'-bipyridin]-2-one (0.76 g, 1.53 mmol, 1.00 equiv) and 2-hydroxy-2-methylpropanimidamide hydrochloride (1.06 g, 7.68 mmol, 5.00 equiv) in *i*-PrOH (10 mL) were added K_2CO_3 (1.06 g, 7.68 mmol, 5.00 equiv) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 2 h at 80°C under nitrogen atmosphere. Desired product could be detected by LCMS. The resulting mixture was filtered, the filter cake was washed with *i*-PrOH (3x3 mL). The filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography. This resulted in 3-chloro-4-[(3,5-difluoropyridin-2-yl)(2H2)methoxy]-3'-fluoro-2'-[2-(2-hydroxypropan-2-yl)pyrimidin-4-yl]-5',6-dimethyl-[1,4'-bipyridin]-2-one (700 mg, 85.37%) as a yellow solid. LC-MS: (ES+H, m/z): $[M+H]^+ = 534.1$.

Step 2: Preparation of rel-3-chloro-4-[(3,5-difluoropyridin-2-yl)(2H2)methoxy]-3'-fluoro-2'-[2-(2-hydroxypropan-2-yl)pyrimidin-4-yl]-5',6-dimethyl-[1,4'-bipyridin]-2-one & rel-3-chloro-4-[(3,5-difluoropyridin-2-yl)(2H2)methoxy]-3'-fluoro-2'-[2-(2-hydroxypropan-2-yl)pyrimidin-4-yl]-5',6-dimethyl-[1,4'-bipyridin]-2-one :

[00645] The rac-mixture (550 mg) was separated by Prep-Chiral HPLC to afford rel-3-chloro-4-[(3,5-difluoropyridin-2-yl)(2H2)methoxy]-3'-fluoro-2'-[2-(2-hydroxypropan-2-yl)pyrimidin-4-yl]-5',6-dimethyl-[1,4'-bipyridin]-2-one (**Example 57A**, 170.1 mg, 98.7% purity, 96.4% deuterium purity, ee=100%) & rel-3-chloro-4-[(3,5-difluoropyridin-2-yl)(2H2)methoxy]-3'-fluoro-2'-[2-(2-hydroxypropan-2-yl)pyrimidin-4-yl]-5',6-dimethyl-[1,4'-bipyridin]-2-one (**Example 57B** 194.9 mg, 98.8% purity, 96.5% deuterium purity, ee=98.6%)

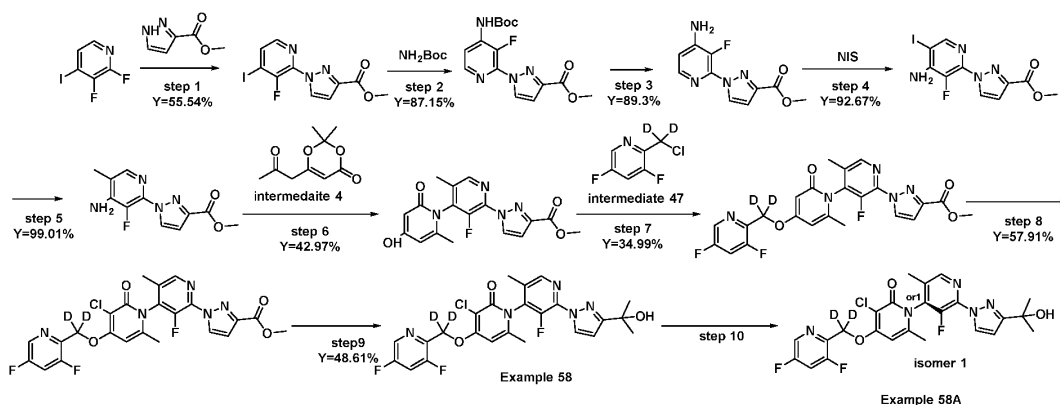
Example 57A:

[00646] LC-MS: (ES+H, m/z): $[M+H]^+ = 534.00$. 1H NMR (300 MHz, DMSO- d_6) δ 9.03 (d, 1H), 8.78 (d, 1H), 8.61 (d, 1H), 8.15 – 8.07 (m, 1H), 8.04 (d, 1H), 6.91 (d, 1H), 5.09 (s, 1H), 2.18 (s, 3H), 2.06 (s, 3H), 1.53 (s, 6H). ^{19}F NMR (282 MHz, DMSO) δ -120.25, -120.28, -122.32, -122.34, -132.08.

Example 57B:

[00647] LC-MS: (ES+H, m/z): $[M+H]^+ = 534.1$. ^1H NMR (300 MHz, DMSO- d_6) δ 9.03 (d, 1H), 8.78 (d, 1H), 8.61 (d, 1H), 8.15 – 8.06 (m, 1H), 8.04 (d1H), 6.91 (d, 1H), 5.09 (s, 1H), 2.18 (s, 3H), 2.06 (s, 3H), 1.53 (s, 6H). ^{19}F NMR (282 MHz, DMSO) δ -120.25, -120.27, -122.31, -122.34, -132.07.

Example 58A



Step 1: Preparation of methyl 1-(3-fluoro-4-iodopyridin-2-yl)pyrazole-3-carboxylate:

[00648] A mixture of 2,3-difluoro-4-iodopyridine (50.00 g, 207.49 mmol, 1.00 equiv), methyl 1H-pyrazole-3-carboxylate (23.53 g, 186.74 mmol, 0.90 equiv) and Cs_2CO_3 (67.60 g, 207.49 mmol, 1.00 equiv) in DMF (500 mL) was stirred for 2 h at 100°C under nitrogen atmosphere. The reaction was monitored by LCMS. The mixture was allowed to cool down to room temperature. The resulting mixture was filtered, the filter cake was washed with EtOAc (3 x 300 mL). The filtrate was concentrated under reduced pressure. The residue was purified by trituration with water (1000 mL). The precipitated solids were collected by filtration and washed with Et₂O (3x100 mL). This resulted in methyl 1-(3-fluoro-4-iodopyridin-2-yl) pyrazole-3-carboxylate (40.00g, 55.54%) as a white solid. LC-MS: (ES+H, m/z): $[M+H]^+ = 348.0$. ^1H NMR (300 MHz, DMSO- d_6) δ 8.51 (d, $J = 2.7$, 1H), 8.13 – 8.00 (m, 2H), 7.03 (d, $J = 2.7$ Hz, 1H), 3.87 (s, 3H).

Step 2: Preparation of methyl 1-{4-[(tert-butoxycarbonyl) amino]-3-fluoropyridin-2-yl} pyrazole-3-carboxylate:

[00649] To a stirred mixture of methyl 1-(3-fluoro-4-iodopyridin-2-yl) pyrazole-3-carboxylate (50.00 g, 144.06 mmol, 1.00 equiv) and tert-butyl carbamate (33.75 g, 288.12 mmol, 2.00 equiv) in dioxane (200 mL) were added CsF (65.65 g, 432.18 mmol, 3.00 equiv), XantPhos (8.33 g, 14.41 mmol, 0.10 equiv) and $\text{Pd}_2(\text{dba})_3$ (6.59 g, 7.20 mmol, 0.05 equiv) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 2 h at 100°C under nitrogen atmosphere. The reaction was monitored by LCMS. The mixture was allowed to cool down to room temperature. The resulting mixture was filtered, the filter cake was washed with EtOAc (3x400 mL). The filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography to afford methyl 1-{4-[(tert-butoxycarbonyl) amino]-3-fluoropyridin-2-yl} pyrazole-3-carboxylate (42.2 g, 87.15%) as a yellow solid. LC-MS: (ES+H, m/z): $[M+H]^+ = 337.15$.

Step 3: Preparation of methyl 1-(4-amino-3-fluoropyridin-2-yl) pyrazole-3-carboxylate:

[00650] A solution of methyl 1-{4-[(tert-butoxycarbonyl) amino]-3-fluoropyridin-2-yl} pyrazole-3-carboxylate (50 g, 148.67 mmol, 1.00 equiv) in DCM (500 mL) was treated with TFA (250 mL) for 1h at room temperature under nitrogen atmosphere. The reaction was monitored by LCMS. The resulting mixture was concentrated under reduced pressure. The resulting mixture was diluted with DCM (250mL). The mixture was basified to pH 9 with saturated NaHCO_3 (aq.). The resulting mixture was extracted with CH_2Cl_2 (3 x 250mL). The combined organic layers were washed with brine (1x1000 mL), dried over anhydrous Na_2SO_4 . After filtration, the filtrate was concentrated under reduced pressure, to afford methyl 1-(4-amino-3-fluoropyridin-2-yl) pyrazole-3-carboxylate (31.36 g, 89.30%) as a white solid. LC-MS: (ES+ H, m/z): $[\text{M}+\text{H}]^+ = 237.1$

Step 4: Preparation of [1-(4-amino-3-fluoro-5-iodopiperidin-2-yl) pyrazolidin-3-yl]

(methoxy)methanol:

[00651] A solution of methyl 1-(4-amino-3-fluoropyridin-2-yl) pyrazole-3-carboxylate (40.00g, 169.34 mmol, 1.00 equiv), NIS (45.70 g, 203.21 mmol, 1.20 equiv) and $\text{TsOH}\cdot\text{H}_2\text{O}$ (1.61 g, 8.47 mmol, 0.05 equiv) in MeCN (250 mL) was stirred for 2h at 60°C under nitrogen atmosphere. The reaction was monitored by LCMS. The mixture was allowed to cool down to room temperature. The resulting mixture was diluted with ethyl acetate (500 mL). The combined organic layers were washed with brine (3x500mL), dried over anhydrous Na_2SO_4 to afford [1-(4-amino-3-fluoro-5-iodopiperidin-2-yl) pyrazolidin-3-yl] (methoxy)methanol (58.7 g, 92.67%) as a yellow solid. LC-MS: (ES+H, m/z): $[\text{M}+\text{H}]^+ = 362.90$. ^1H NMR (300 MHz, DMSO-d_6) δ 8.40 (d, $J = 2.6$ Hz, 1H), 8.24 (s, 1H), 6.99 (d, $J = 2.6$ Hz, 1H), 6.78 (s, 2H), 3.86 (s, 3H).

Step 5: Preparation of methyl 1-(4-amino-3-fluoro-5-methylpyridin-2-yl) pyrazole-3-carboxylate:

[00652] A mixture of methyl 1-(4-amino-3-fluoro-5-iodopyridin-2-yl) pyrazole-3-carboxylate (25.00 g, 69.04 mmol, 1.00 equiv), $\text{Pd}(\text{dppf})\text{Cl}_2$ (5.01 g, 6.90 mmol, 0.10 equiv), Cs_2CO_3 (67.49 g, 207.12 mmol, 3.00 equiv) and trimethyl-1,3,5,2,4,6-trioxatriborinane (87.05 g, 345.20 mmol, 5.00 equiv, 50 wt%) in dioxane (400 mL) was stirred for 2 h at 100°C under nitrogen atmosphere. The reaction was monitored by LCMS. The mixture was allowed to cool down to room temperature. The resulting mixture was filtered, the filter cake was washed with ethyl acetate (3x1000mL). The filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography to afford methyl 1-(4-amino-3-fluoro-5-methylpyridin-2-yl) pyrazole-3-carboxylate (17.10 g, 99.01%) as a light-yellow solid. LC-MS: (ES+H, m/z): $[\text{M}+\text{H}]^+ = 251.2$.

Step 6: Preparation of methyl 1-{3'-fluoro-4-hydroxy-2,5'-dimethyl-6-oxo-[1,4'-bipyridin]-2'-yl} pyrazole-3-carboxylate:

[00653] To a solution of methyl 1-(4-amino-3-fluoro-5-methylpyridin-2-yl) pyrazole-3-carboxylate (25.00g, 99.91 mmol, 1.00 equiv) and 2,2-dimethyl-6-(2-oxopropyl)-1,3-dioxin-4-one (36.78 g, 199.82 mmol, 2.00 equiv) in dioxane (260 mL) was added $\text{Ti}(\text{Oi-Pr})_4$ (2.84 g, 9.99 mmol, 0.10 equiv), the resulting mixture was stirred for 1 h at 90°C under nitrogen atmosphere. The reaction was monitored by LCMS. The mixture was allowed to cool down to room temperature. The mixture was followed by the addition of H_2SO_4

(9.79 g, 99.91 mmol, 1.00 equiv) dropwise at room temperature. The resulting mixture was stirred for 1h at 90°C under nitrogen atmosphere. The reaction was monitored by LCMS. The mixture was allowed to cool down to room temperature. The resulting mixture was concentrated under reduced pressure. The residue was purified by trituration with water (200 mL) and Et₂O (100 mL). The precipitated solids were collected by filtration and washed with Et₂O (3x100 mL), to afford methyl 1-{3'-fluoro-4-hydroxy-2,5'-dimethyl-6-oxo-[1,4'-bipyridin]-2'-yl} pyrazole-3-carboxylate (15.38 g, 42.97%) as a brown solid. LC-MS: (ES+H, m/z): [M+H]⁺ = 359.0.

Step 7: Preparation of methyl 1-{4-[(3,5-difluoropyridin-2-yl) (2H2) methoxy]-3'-fluoro-2,5'-dimethyl-6-oxo-[1,4'-bipyridin]-2'-yl} pyrazole-3-carboxylate:

[00654] To a stirred mixture of methyl 1-(3-fluoro-5-methylpyridin-2-yl) pyrazole-3-carboxylate (10.00 g, 42.51 mmol, 1.00 equiv) and 2-[chloro(2H2) methyl]-3,5-difluoropyridine (10.52 g, 63.77 mmol, 1.50 equiv) in DMF (100 mL) were added Cs₂CO₃ (41.56 g, 127.53 mmol, 3.00 equiv) and 18-Crown-6 (1.12 g, 4.25 mmol, 0.10 equiv) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 2 h at 70°C under nitrogen atmosphere. The reaction was monitored by LCMS. The mixture was allowed to cool down to room temperature. The resulting mixture was diluted with EtOAc (500 mL). The organic layers were washed with water (5 x 500 mL), dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography to afford methyl 1-{4-[(3,5-difluoropyridin-2-yl) (2H2) methoxy]-3'-fluoro-2,5'-dimethyl-6-oxo-[1,4'-bipyridin]-2'-yl} pyrazole-3-carboxylate (7.25 g, 34.99%) as a white solid. LC-MS: (ES+H, m/z): [M+H]⁺ = 488.15.

Step 8: Preparation of 3-chloro-4-[(3,5-difluoropyridin-2-yl) (2H2) methoxy]-2'-[(2E)-3-(dimethylamino) prop-2-enoyl]-3'-fluoro-5',6-dimethyl-[1,4'-bipyridin]-2-one:

[00655] A mixture of methyl 1-{4-[(3,5-difluoropyridin-2-yl)(2H2)methoxy]-3'-fluoro-2,5'-dimethyl-6-oxo-[1,4'-bipyridin]-2'-yl}pyrazole-3-carboxylate (10.00 g, 20.52 mmol, 1.00 equiv), NCS (3.56 g, 26.68 mmol, 1.30 equiv) and 2,2-dichloroacetic acid (0.26 g, 2.05 mmol, 0.10 equiv) in i-PrOH (100 mL) was stirred for 1h at 60°C under nitrogen atmosphere. The reaction was monitored by LCMS. The mixture was allowed to cool down to room temperature. The resulting mixture was diluted with EtOAc (200 mL). The resulting mixture was washed with 3x200 mL of water. The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography to afford methyl 1-{3-chloro-4-[(3,5-difluoropyridin-2-yl) (2H2) methoxy]-3'-fluoro-5',6-dimethyl-2-oxo-[1,4'-bipyridin]-2'-yl} pyrazole-3-carboxylate (6.20g, 57.91%) as a white solid. LC-MS: (ES+H, m/z): [M+H]⁺ = 522.2.

Step 9: Preparation of 3-chloro-4-[(3,5-difluoropyridin-2-yl) (2H2) methoxy]-3'-fluoro-2'-[3-(2-hydroxypropan-2-yl) pyrazol-1-yl]-5',6-dimethyl-[1,4'-bipyridin]-2-one:

[00656] To a stirred solution of methyl 1-{3-chloro-4-[(3,5-difluoropyridin-2-yl) (2H2) methoxy]-3'-fluoro-5',6-dimethyl-2-oxo-[1,4'-bipyridin]-2'-yl} pyrazole-3-carboxylate (5.00g, 9.58 mmol, 1.00 equiv) in THF (50 mL) was added CH₃MgBr (31.93 mL, 95.80 mmol, 10.00 equiv (3M in THF)) dropwise at 0°C under nitrogen atmosphere. The resulting mixture was stirred for 2h at 0°C under nitrogen atmosphere.

Desired product could be detected by LCMS. The mixture was allowed to cool down to 0°C. The reaction was quenched by the addition of sat. NH₄Cl (aq.) (150 mL) at 0°C. The resulting mixture was extracted with EtOAc (4 x 300 mL). The combined organic layers were washed with brine (300 mL), dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography the filtrate was concentrated under reduced pressure to afford 3-chloro-4-[(3,5-difluoropyridin-2-yl) (2H2) methoxy]-3'-fluoro-2'-[3-(2-hydroxypropan-2-yl) pyrazol-1-yl]-5',6-dimethyl-[1,4'-bipyridin]-2-one (2.43 g, 48.61%) as a white solid. LC-MS: (ES+H, m/z): [M+H]⁺ = 522.1.

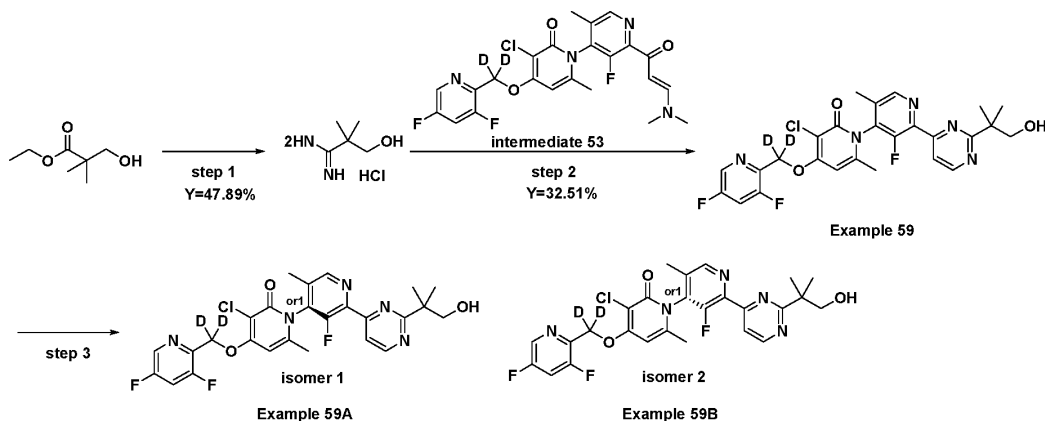
Step 10: Preparation of (Example 58A) rel-3-chloro-4-[(3,5-difluoropyridin-2-yl)(2H2)methoxy]-3'-fluoro-2'-[3-(2-hydroxypropan-2-yl)pyrazol-1-yl]-5',6-dimethyl-[1,4'-bipyridin]-2-one:

[00657] The rac-mixture (17.50 g) was separated by Prep-Chiral SFC to afford rel-3-chloro-4-[(3,5-difluoropyridin-2-yl) (2H2) methoxy]-3'-fluoro-2'-[3-(2-hydroxypropan-2-yl)pyrazol-1-yl]-5',6-dimethyl-[1,4'-bipyridin]-2-one (**Example 58A**, 6.49 g, ee=100%).

Example 58A:

[00658] LC-MS: (ES+H, m/z): [M+H]⁺ = 522.15. ¹H NMR (400 MHz, DMSO-d₆) δ 8.61 (d, *J* = 2.3 Hz, 1H), 8.50 (s, 1H), 8.37 (d, *J* = 2.6 Hz, 1H), 8.15 – 8.06 (m, 1H), 6.91 (s, 1H), 6.60 (d, *J* = 2.6 Hz, 1H), 5.13 (s, 1H), 2.09 (d, *J* = 16.1 Hz, 6H), 1.48 (s, 6H). ¹⁹F NMR (377 MHz, DMSO) δ -120.25, -120.27, -122.29, -122.31, -137.97.

Example 59A, 59B



Step 1: Preparation of 3-hydroxy-2,2-dimethylpropanimidamide hydrochloride:

[00659] To a stirred mixture of NH₄Cl (7.32 g, 136.81 mmol, 5.00 equiv) in Toluene (20 mL) was added AlMe₃ (9.86 g, 136.81 mmol, 5.00 equiv) dropwise at 0°C under nitrogen atmosphere. The resulting mixture was stirred for 10 min at 0°C under nitrogen atmosphere, then the mixture was warmed to r.t. until no generation of gas. To the above mixture was added a solution of ethyl 3-hydroxy-2,2-dimethylpropanoate (4.00 g, 27.36 mmol, 1.00 equiv) in Tol dropwise at r.t. The resulting mixture was stirred overnight at 80°C. The reaction was monitored by LCMS. The reaction was quenched by the addition of MeOH (50 mL) at 0°C. The resulting mixture was filtered, the filter cake was washed with MeOH (300 mL). The filtrate was concentrated under reduced pressure. The residue was dissolved in EtOH (20 mL). The resulting mixture was filtered, the filter cake was washed with EtOH (5 mL). The filtrate was concentrated under reduced

pressure. This resulted in 3-hydroxy-2,2-dimethylpropanimidamide hydrochloride (2 g, 47.89%) as a white solid. ¹H NMR (300 MHz, DMSO-*d*₆) δ 9.01 (s, 2H), 8.61 (s, 2H), 5.41 (t, 1H), 3.46 (d, 2H), 1.15 (s, 6H).

Step 2: Preparation of 3-chloro-4-((3,5-difluoropyridin-2-yl)methoxy-d2)-3'-fluoro-2'-(2-(1-hydroxy-2-methylpropan-2-yl)pyrimidin-4-yl)-5',6-dimethyl-2H-[1,4'-bipyridin]-2-one:

[00660] A solution of (E)-3-chloro-4-((3,5-difluoropyridin-2-yl)methoxy-d2)-2'-(3-(dimethylamino)acryloyl)-3'-fluoro-5',6-dimethyl-2H-[1,4'-bipyridin]-2-one (500 mg, 1.01 mmol, 1.00 equiv) in DMF (20 mL) was added 3-hydroxy-2,2-dimethylpropanimidamide hydrochloride (1.17 g, 10.10 mmol, 10.00 equiv) and K₂CO₃ (1.40 g, 10.10 mmol, 10.00 equiv). The resulting mixture was stirred for 2 h at 80°C under nitrogen atmosphere. The reaction was monitored by LCMS. Desired product could be detected by LCMS. The mixture was allowed to cool down to room temperature. The resulting mixture was poured into water (20 mL) and extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (2x10 mL), dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The crude residue (500 mg) was purified by HP-Flash to afford the crude product (280 mg) which was further purified by PREP-HPLC to afford 3-chloro-4-((3,5-difluoropyridin-2-yl)methoxy-d2)-3'-fluoro-2'-(2-(1-hydroxy-2-methylpropan-2-yl)pyrimidin-4-yl)-5',6-dimethyl-2H-[1,4'-bipyridin]-2-one (180 mg, 32.51%) as a yellow solid. LC-MS: (ES+H, m/z): [M+H]⁺ = 548.2.

Step 3: Preparation of rel-3-chloro-4-((3,5-difluoropyridin-2-yl)methoxy-d2)-3'-fluoro-2'-(2-(1-hydroxy-2-methylpropan-2-yl)pyrimidin-4-yl)-5',6-dimethyl-2H-[1,4'-bipyridin]-2-one & rel-3-chloro-4-((3,5-difluoropyridin-2-yl)methoxy-d2)-3'-fluoro-2'-(2-(1-hydroxy-2-methylpropan-2-yl)pyrimidin-4-yl)-5',6-dimethyl-2H-[1,4'-bipyridin]-2-one :

[00661] The racemate (180 mg) was separated by Prep-CHIRAL-HPLC to afford **Example 59A** (66.6 mg, 99.1% purity, 95.1% deuterium purity, ee=97.7%) as a white solid and **Example 59B** (62.0 mg, 99.3% purity, 95.5% deuterium purity, ee=98.3%).

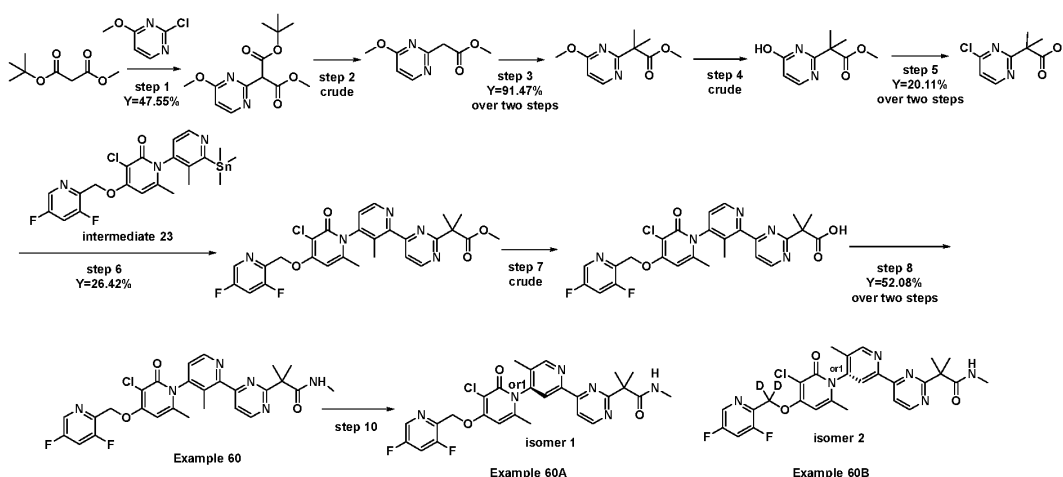
Example 59A:

[00662] LC-MS: (ES+H, m/z): [M+H]⁺ = 548.1. ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.97 (d, 1H), 8.77 (s, 1H), 8.62 (d, 1H), 8.17 – 8.06 (m, 1H), 7.97 (d, 1H), 6.91 (s, 1H), 4.58 (t, 1H), 3.69 (d, 2H), 2.17 (s, 3H), 2.05 (s, 3H), 1.32 (s, 6H). ¹⁹F NMR (282 MHz, DMSO) δ -120.25, -120.27, -122.33, -122.35, -132.33.

Example 59B:

[00663] LC-MS: (ES+H, m/z): [M+H]⁺ = 548.1. ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.97 (d, 1H), 8.77 (d, 1H), 8.62 (d, 1H), 8.17 – 8.04 (m, 1H), 7.97 (d, 1H), 6.91 (d, 1H), 4.58 (t, 1H), 3.69 (d, 2H), 2.17 (s, 3H), 2.05 (s, 3H), 1.32 (s, 6H). ¹⁹F NMR (282 MHz, DMSO) δ -120.25, -120.28, -122.33, -122.35, -132.33.

Example 60A, 60B



Step 1: Preparation of 1-tert-butyl 3-methyl 2-(4-methoxypyrimidin-2-yl)propanedioate:

[00664] To a stirred solution of 1-tert-butyl 3-methyl propanedioate (33.74 g, 193.69 mmol, 4.00 equiv) in DMF (70 mL) was added NaH (6.97 g, 290.53 mmol, 6.00 equiv) in portions at 0°C. The resulting mixture was stirred for 30 min at room temperature under nitrogen atmosphere. To the above mixture was added 2-chloro-4-methoxypyrimidine (7.00 g, 48.42 mmol, 1.00 equiv). The resulting mixture was stirred overnight at 80°C under nitrogen atmosphere. The reaction was monitored by LCMS. The reaction was quenched by the addition of sat. NH_4Cl (aq.) (100 mL) at 0°C. The resulting mixture was extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with brine (200 mL), dried over anhydrous Na_2SO_4 . After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography to afford 1-tert-butyl 3-methyl 2-(4-methoxypyrimidin-2-yl) propanedioate (6.50 g, 47.55%) as a yellow liquid. LC-MS: (ES+H, m/z): $[\text{M}+\text{H}]^+ = 283.1$. ^1H NMR (400 MHz, DMSO-d_6) δ 8.51 (d, 1H), 6.91 (d, 1H), 4.96 (s, 1H), 3.89 (s, 3H), 3.70 (s, 3H), 1.42 (s, 9H).

Step 2: Preparation of methyl 2-(4-methoxypyrimidin-2-yl) acetate:

[00665] To a stirred mixture of 1-tert-butyl 3-methyl 2-(4-methoxypyrimidin-2-yl) propanedioate (6.5 g, 23.02 mmol, 1 equiv) in DCM (60 mL) was added TFA (30 mL) dropwise at room temperature. The resulting mixture was stirred for 1 h at room temperature. The reaction was monitored by LCMS. The resulting mixture was concentrated under reduced pressure to afford methyl 2-(4-methoxypyrimidin-2-yl) acetate (4.5 g, crude) as a yellow liquid. LC-MS: (ES+H, m/z): $[\text{M}+\text{H}]^+ = 183.1$. ^1H NMR (300 MHz, DMSO-d_6) δ 8.47 (d, 1H), 6.85 (d, 1H), 3.90 (s, 3H), 3.89 (s, 2H), 3.65 (s, 3H).

Step 3: Preparation of methyl 2-(4-methoxypyrimidin-2-yl)-2-methylpropanoate:

[00666] To a stirred mixture of methyl 2-(4-methoxypyrimidin-2-yl) acetate (4.41 g, assumed 100% yield, 24.20 mmol, 1.00 equiv) in THF (50 mL) was added LiHMDS (26.62 mL, 26.62 mmol, 1.10 equiv) dropwise at -78°C under nitrogen atmosphere. The resulting mixture was stirred for 30 min at -78°C under nitrogen atmosphere. To the above mixture was added CH_3I (3.78 g, 26.62 mmol, 1.10 equiv) dropwise at -78°C under nitrogen atmosphere. The resulting mixture was stirred for additional 1 h at room temperature. Then to the above mixture was added LiHMDS (26.62 mL, 26.62 mmol, 1.10 equiv) dropwise at -78°C. The

resulting mixture was stirred for 30 min at -78°C under nitrogen atmosphere. To the above mixture was added CH₃I (3.78 g, 26.62 mmol, 1.10 equiv) dropwise at -78°C under nitrogen atmosphere. The resulting mixture was stirred for additional 1h at room temperature. The reaction was monitored by LCMS. The reaction was quenched with sat. NH₄Cl (aq.) at 0°C. The resulting mixture was extracted with EtOAc (3 x 200 mL). The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure to afford methyl 2-(4-methoxypyrimidin-2-yl)-2-methylpropanoate (4.75 g, 91.47%) as a yellow liquid. LC-MS: (ES+H, m/z): [M+H]⁺ = 211.05. ¹H NMR (300 MHz, DMSO-d₆) δ 8.47 (d, 1H), 6.86 (d, 1H), 3.89 (s, 3H), 3.61 (s, 3H), 1.52 (s, 6H).

Step 4: Preparation of methyl 2-(4-hydroxypyrimidin-2-yl)-2-methylpropanoate:

[00667] A mixture of methyl 2-(4-methoxypyrimidin-2-yl)-2-methylpropanoate (4.75 g, 22.59 mmol, 1.00 equiv) and TMSI (18.08 g, 90.37 mmol, 4.00 equiv) in ACN (50 mL) was stirred overnight at 80°C. The reaction was monitored by LCMS. The resulting mixture was concentrated under reduced pressure to afford methyl 2-(4-hydroxypyrimidin-2-yl)-2-methylpropanoate (8.24 g, crude) as a brown solid. LC-MS: (ES+H, m/z): [M+H]⁺ = 197.1.

Step 6: Preparation of methyl 2-(4-{3-chloro-4-[(3,5-difluoropyridin-2-yl) methoxy]-3',6-dimethyl-2-oxo-[1,4'-bipyridin]-2'-yl} pyrimidin-2-yl)-2-methylpropanoate:

[00668] To a stirred solution of 3-chloro-4-[(3,5-difluoropyridin-2-yl) methoxy]-3',6-dimethyl-2-(trimethylstannyl)-[1,4'-bipyridin]-2-one (920 mg, assumed 100% yield, 1.70 mmol, 1.00 equiv), methyl 2-(4-chloropyrimidin-2-yl)-2-methylpropanoate (365 mg, 1.70 mmol, 1.00 equiv) in 1,4-dioxane (15 ml) were added Pd(PPh₃)₂Cl₂ (238 mg, 0.34 mmol, 0.20 equiv) and CuI (324 mg, 1.70 mmol, 1.00 equiv). The resulting mixture was stirred for 2 h at 120°C under nitrogen atmosphere. The reaction was monitored by LCMS. Desired product could be detected by LCMS. The mixture was allowed to cool down to room temperature. The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography to afford crude product. The crude product was purified by reverse phase flash to afford methyl 2-(4-{3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-3',6-dimethyl-2-oxo-[1,4'-bipyridin]-2'-yl} pyrimidin-2-yl)-2-methylpropanoate (250 mg, 26.42%, over two steps) as a yellow oil. LC-MS: (ES+H, m/z): [M+H]⁺ = 556.1. ¹H NMR (400 MHz, DMSO-d₆) δ 8.98 (d, 1H), 8.77 (d, 1H), 8.60 (d, 1H), 8.14-8.04 (m, 1H), 7.94 (d, 1H), 7.58 (d, 1H), 6.83 (s, 1H), 5.49 (d, 2H), 3.59 (s, 3H), 2.16 (s, 3H), 1.96 (s, 3H), 1.59 (s, 6H).

Step 8: Preparation of 2-(4-{3-chloro-4-[(3,5-difluoropyridin-2-yl) methoxy]-3',6-dimethyl-2-oxo-[1,4'-bipyridin]-2'-yl} pyrimidin-2-yl)-2-methylpropanoic acid:

[00669] To a stirred solution methyl 2-(4-{3-chloro-4-[(3,5-difluoropyridin-2-yl) methoxy]-3',6-dimethyl-2-oxo-[1,4'-bipyridin]-2'-yl} pyrimidin-2-yl)-2-methylpropanoate (300 mg, 0.54 mmol, 1.00 equiv) in THF (6 mL) was added a solution of LiOH (26 mg, 1.08 mmol, 2.00 equiv) in H₂O (3 mL) dropwise at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 2 h at 80°C under nitrogen atmosphere. The reaction was monitored by LCMS. Desired product could be detected by LCMS. The mixture was allowed to cool down to room temperature. The resulting mixture was concentrated under

reduced pressure. The resulting mixture (300 mg) was used in the next step directly without further purification. LC-MS: (ES+H, m/z): [M+H]⁺ = 542.3.

Step 9: Preparation of 2-(4-{3-chloro-4-[(3,5-difluoropyridin-2-yl) methoxy]-3',6-dimethyl-2-oxo-[1,4'-bipyridin]-2'-yl} pyrimidin-2-yl)-N,2-dimethylpropanamide:

[00670] To a stirred solution of 2-(4-{3-chloro-4-[(3,5-difluoropyridin-2-yl) methoxy]-3',6-dimethyl-2-oxo-[1,4'-bipyridin]-2'-yl} pyrimidin-2-yl)-2-methylpropanoic acid (292 mg, assumed 100% yield, 0.55 mmol, 1.00 equiv) in ACN (3 mL) were added Methylamine (0.8 mL, 2M in THF) and NMI (454 mg, 5.540mmol, 10.00 equiv) and TCFH (776 mg, 2.77mmol, 5.00 equiv) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 1 h at room temperature under nitrogen atmosphere. The reaction was monitored by LCMS. The resulting mixture was diluted with EA (50 mL), then washed with water (2 x 50 mL) and brine (50 mL), the organic layer was concentrated to afford crude product (300 mg), which was further purified by Prep-HPLC to afford 2-(4-{3-chloro-4-[(3,5-difluoropyridin-2-yl) methoxy]-3',6-dimethyl-2-oxo-[1,4'-bipyridin]-2'-yl} pyrimidin-2-yl)-N,2-dimethylpropanamide (160 mg, 52.08%, over two steps) as a white solid. LC-MS: (ES+H, m/z): [M+H]⁺ = 555.3.

Step 10: Preparation of rel-2-(4-(3-chloro-4-((3,5-difluoropyridin-2-yl)methoxy)-3',6-dimethyl-2-oxo-2H-[1,4'-bipyridin]-2'-yl)pyrimidin-2-yl)-N,2-dimethylpropanamide and rel-2-(4-(3-chloro-4-((3,5-difluoropyridin-2-yl)methoxy)-3',6-dimethyl-2-oxo-2H-[1,4'-bipyridin]-2'-yl)pyrimidin-2-yl)-N,2-dimethylpropanamide :

[00671] The racemate (160 mg) was separated by PREP-CHIRAL-HPLC to afford rel-2-(4-(3-chloro-4-((3,5-difluoropyridin-2-yl)methoxy)-3',6-dimethyl-2-oxo-2H-[1,4'-bipyridin]-2'-yl)pyrimidin-2-yl)-N,2-dimethylpropanamide (**Example 60A**: 44.2 mg, 99.6% purity, ee=100%) as a white solid and rel-2-(4-(3-chloro-4-((3,5-difluoropyridin-2-yl)methoxy)-3',6-dimethyl-2-oxo-2H-[1,4'-bipyridin]-2'-yl)pyrimidin-2-yl)-N,2-dimethylpropanamide (**Example 60B**: 42.6 mg, 99.2% purity, ee=100%) as a white solid.

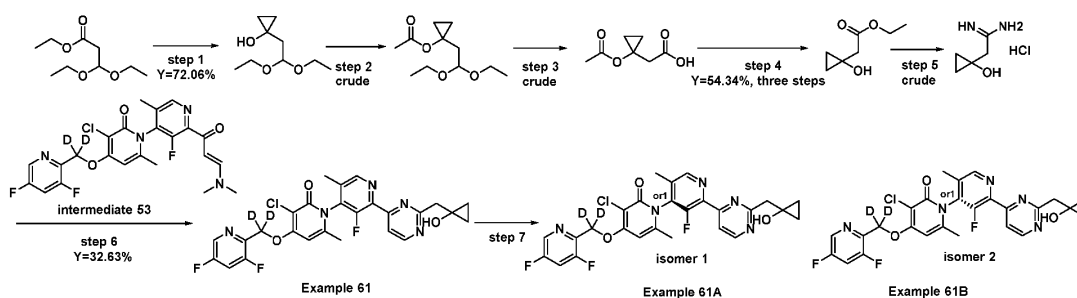
Examples 60A:

[00672] LC-MS: (ES+H, m/z): [M+H]⁺ = 555.1. ¹H NMR (400 MHz, DMSO-d₆) δ 8.95 (d, 1H), 8.77 (d, 1H), 8.61 (d, 1H), 8.15 – 8.05 (m, 1H), 7.91 (d, 1H), 7.57 (d, 1H), 7.41 (q, 1H), 6.83 (s, 1H), 5.49 (d, 2H), 2.54 (d, 3H), 2.19 (s, 3H), 1.96 (s, 3H), 1.54 (s, 3H), 1.54 (s, 3H). ¹⁹F NMR (377 MHz, DMSO) δ -120.14, -120.16, -122.34, -122.36.

Example 60B:

[00673] LC-MS: (ES+H, m/z): [M+H]⁺ = 555.1. ¹H NMR (400 MHz, DMSO-d₆) δ 8.95 (d, 1H), 8.77 (d, 1H), 8.61 (d, 1H), 8.14 – 8.05 (m, 1H), 7.91 (d, 1H), 7.57 (d, 1H), 7.41 (q, 1H), 6.83 (s, 1H), 5.49 (d, 2H), 2.55 (d, 3H), 2.19 (s, 3H), 1.96 (s, 3H), 1.54 (s, 3H), 1.54 (s, 3H). ¹⁹F NMR (377 MHz, DMSO) δ -120.14, -120.16, -122.34, -122.36.

Example 61A, 61B



Step 1: Preparation of 1-(2,2-diethoxyethyl)cyclopropan-1-ol:

[00674] To a stirred mixture of ethyl 3,3-diethoxypropanoate (10.00 g, 52.56 mmol, 1.00 equiv) and $\text{Ti}(\text{O}i\text{-Pr})_4$ (22.41 g, 78.84 mmol, 1.50 equiv) in Et_2O (80 mL) and THF (20 mL) was added EtMgBr in 2-methyl-THF (3.4 M, 61 mL, 210.26 mmol, 4.00 equiv) dropwise at 0°C under nitrogen atmosphere. The resulting mixture was stirred overnight at room temperature under nitrogen atmosphere. The reaction was monitored by TLC (PE/EA=5:1, R_f =0.3). The reaction was quenched by the addition of water (100 mL) at 0°C . The resulting mixture was extracted with Et_2O (3x100 mL), the organic phase was combined and dried over anhydrous Na_2SO_4 . After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, the pure fraction was concentrated under reduced pressure to afford 1-(2,2-diethoxyethyl)cyclopropan-1-ol (6.60 g, 72.06%) as a yellow liquid. ^1H NMR (300 MHz, Chloroform- d) δ 4.82 (t, 1H), 3.79 – 3.70 (m, 3H), 3.59-3.55 (m, 2H), 1.91 (d, 2H), 1.28 – 1.23 (m, 6H), 0.81 – 0.76 (m, 2H), 0.49 – 0.44 (m, 2H).

Step 2: Preparation of 1-(2,2-diethoxyethyl)cyclopropyl acetate:

[00675] To a stirred solution of 1-(2,2-diethoxyethyl)cyclopropan-1-ol (6.60 g, 37.87 mmol, 1.00 equiv) and DMAP (5.09 g, 41.66 mmol, 1.10 equiv) in Et_2O (60 mL) was added acetic anhydride (5.80 g, 56.81 mmol, 1.50 equiv) dropwise at 0°C under nitrogen atmosphere. The resulting mixture was stirred for 1 h at 0°C under nitrogen atmosphere. The reaction was monitored by TLC (PE/EA=5:1, R_f =0.4). The reaction was quenched with sat. NaHCO_3 (aq.) at 0°C . The aqueous layer was extracted with Et_2O (3x100 mL). The resulting mixture was concentrated under vacuum. The residue was purified by silica gel column chromatography, the pure fraction was concentrated under reduced pressure to afford 1-(2,2-diethoxyethyl)cyclopropyl acetate (7.00 g, crude) as a yellow liquid. ^1H NMR (400 MHz, Chloroform- d) δ 4.71 (t, 1H), 3.63-3.59 (m, 2H), 3.51-3.47 (m, 2H), 2.08 (d, 2H), 1.98 (s, 3H), 1.20 (t, 6H), 0.85-0.81 (m, 2H), 0.78 – 0.73 (m, 2H).

Step 3: Preparation of [1-(acetyloxy)cyclopropyl]acetic acid:

[00676] To a stirred solution of 1-(2,2-diethoxyethyl)cyclopropyl acetate (7.00 g, 32.36 mmol, 1.00 equiv) in THF (25 mL) and H_2O (50 mL) was added oxone (12.23 g, 72.75 mmol, 1.50 equiv) in portions at room temperature. The resulting mixture was stirred overnight at room temperature. The reaction was monitored by TLC (100%EA, R_f =0.1). The resulting mixture was diluted with water (100 mL). The resulting mixture was extracted with EtOAc (5 x 100 mL). The combined organic layers were dried over anhydrous Na_2SO_4 . After filtration, the filtrate was concentrated under reduced pressure to afford [1-

(acetyloxy)cyclopropyl]acetic acid (5.00 g, crude) as a yellow oil. ¹H NMR (300 MHz, Chloroform-d) δ 2.85 (s, 2H), 2.04 (s, 3H), 1.06 – 0.99 (m, 2H), 0.93 – 0.90 (m, 2H).

Step 4: Preparation of ethyl 2-(1-hydroxycyclopropyl)acetate:

[00677] To a stirred solution of [1-(acetyloxy)cyclopropyl]acetic acid (4.00 g, 25.29 mmol, 1.00 equiv) in EtOH (50 mL) was added H₂SO₄ (40 drops) dropwise at room temperature. The resulting mixture was stirred overnight at room temperature. The reaction was monitored by TLC(PE/EA=10:1, R_f=0.5). The reaction was quenched with sat. NaHCO₃ (aq.) at room temperature. The aqueous layer was extracted with EtOAc (3x100 mL). The resulting mixture was concentrated under vacuum. The residue was purified by silica gel column chromatography, the pure fraction was concentrated under reduced pressure to afford ethyl 2-(1-hydroxycyclopropyl)acetate (2.50 g, 53.43%) as a yellow liquid. ¹H NMR (400 MHz, Chloroform-d) δ 4.21 (q, 2H), 2.58 (s, 2H), 1.29 (t, 3H), 0.89 – 0.85 (m, 2H), 0.53 – 0.47 (m, 2H).

Step 5: Preparation of 2-(1-hydroxycyclopropyl)ethanimidamide hydrochloride:

[00678] To a stirred mixture of NH₄Cl (4.64 g, 86.70 mmol, 5.00 equiv) in Toluene (50 mL) was added AlMe₃ (43 mL, 2 M in Toluene, 86.70 mmol, 5.00 equiv) dropwise at 0°C under nitrogen atmosphere. The resulting mixture was stirred for 10 min at 0°C under nitrogen atmosphere, and then was stirred at room temperature until no generation of gas. To the above mixture was added a solution of ethyl 2-(1-hydroxycyclopropyl)acetate (2.50 g, 17.34 mmol, 1.00 equiv) in toluene dropwise at r.t. The resulting mixture was stirred overnight at 80°C. The reaction was monitored by LCMS. The mixture was allowed to cool down to room temperature. The reaction was quenched by the addition of MeOH (30 mL) at 0°C. The resulting mixture was filtered, the filter cake was washed with MeOH (6 x 50 mL). The filtrate was concentrated under reduced pressure. The residue was dissolved in EtOH (50 mL). The resulting mixture was filtered, the filter cake was washed with EtOH (20 mL). The filtrate was concentrated under reduced pressure. This resulted in 2-(1-hydroxycyclopropyl)ethanimidamide hydrochloride (2.4 g, crude) as an orange oil. ¹H NMR (300 MHz, DMSO-d₆) δ 8.98 – 8.72 (m, 4H), 5.80 (s, 1H), 2.62 (s, 2H), 0.67 (s, 4H).

Step 6: Preparation of 3-chloro-4-((3,5-difluoropyridin-2-yl)methoxy-d2)-3'-fluoro-2'-(2-((1-hydroxycyclopropyl)methyl)pyrimidin-4-yl)-5',6-dimethyl-2H-[1,4'-bipyridin]-2-one:

[00679] To a stirred solution of 3-chloro-4-[(3,5-difluoropyridin-2-yl)(2H2)methoxy]-2'-[(2E)-3-(dimethylamino)prop-2-enoyl]-3'-fluoro-5',6-dimethyl-[1,4'-bipyridin]-2-one (500 mg, 1.01 mmol, 1.00 equiv) and 2-(1-hydroxycyclopropyl)ethanimidamide hydrochloride (1.52 g, 10.10 mmol, 10.00 equiv) in DMF (5 mL) was added K₂CO₃ (2.79 g, 20.20 mmol, 20.00 equiv) at room temperature. The resulting mixture was stirred overnight at 60°C. The reaction was monitored by LCMS. The mixture was allowed to cool down to room temperature. The resulting mixture was diluted with water (20 mL). The aqueous layer was extracted with EtOAc (3x20 mL). The resulting mixture was concentrated under vacuum. The crude product was purified twice by Prep-HPLC to afford 3-chloro-4-((3,5-difluoropyridin-2-yl)methoxy-d2)-3'-fluoro-2'-(2-((1-hydroxycyclopropyl)methyl)pyrimidin-4-yl)-5',6-dimethyl-2H-[1,4'-bipyridin]-2-one (180 mg, 32.63%) as a yellow solid. LC-MS: (ES+H, m/z): [M+H]⁺=546.3.

Step7: Preparation of *rel*-3-chloro-4-((3,5-difluoropyridin-2-yl)methoxy-d2)-3'-fluoro-2'-(2-((1-hydroxycyclopropyl)methyl)pyrimidin-4-yl)-5',6-dimethyl-2H-[1,4'-bipyridin]-2-one and *rel*-3-chloro-4-((3,5-difluoropyridin-2-yl)methoxy-d2)-3'-fluoro-2'-(2-((1-hydroxycyclopropyl)methyl)pyrimidin-4-yl)-5',6-dimethyl-2H-[1,4'-bipyridin]-2-one :

[00680] The racemate (180 mg) was separated by Prep-Chiral-HPLC, the pure fraction was concentrated under reduced pressure and lyophilized to afford **Example 61A** (62.1 mg, 98.9% purity, 95.3% deuterium purity, ee=100%) as a yellow solid and **Example 61B** (65.6 mg, 99.3% purity, 95.3% deuterium purity, ee=100%) as a white solid.

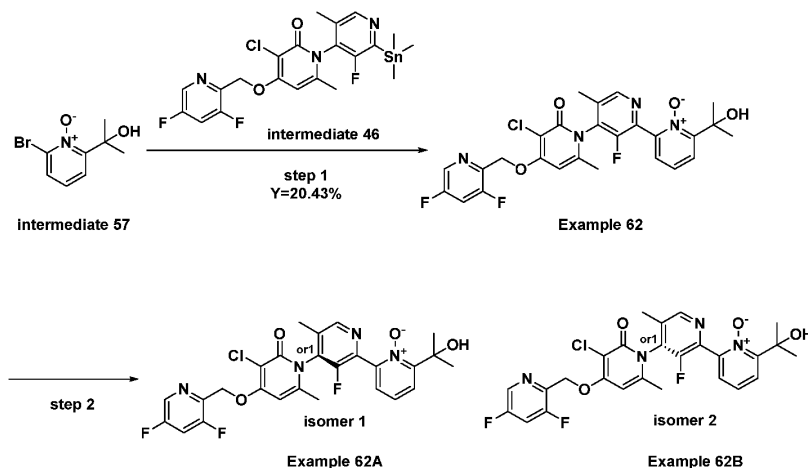
Example 61A:

[00681] LC-MS: (ES+H, m/z): [M+H]⁺=546.3. ¹H NMR (400 MHz, DMSO-d₆) δ 8.95 (d, 1H), 8.77 (s, 1H), 8.61 (d, 1H), 8.16 – 8.05 (m, 1H), 8.00 (d, 1H), 6.90 (s, 1H), 5.33 (s, 1H), 3.26 – 3.07 (m, 2H), 2.17 (s, 3H), 2.05 (s, 3H), 0.59 (s, 4H). ¹⁹F NMR (377 MHz, DMSO) δ -120.25, -120.27, -122.33, -122.34, -132.52.

Example 61B:

LC-MS: (ES+H, m/z): [M+H]⁺=546.3. ¹H NMR (400 MHz, DMSO-d₆) δ 8.95 (d, 1H), 8.77 (s, 1H), 8.61 (d, 1H), 8.14 – 8.07 (m, 1H), 8.00 (d, 1H), 6.90 (d, 1H), 5.33 (s, 1H), 3.23 – 3.08 (m, 2H), 2.17 (s, 3H), 2.05 (s, 3H), 0.59 (s, 4H). ¹⁹F NMR (377 MHz, DMSO) δ -120.24, -120.26, -122.32, -122.34, -132.51.

Example 62A, 62B



Step 1: Preparation of 4'-{3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-6-methyl-2-oxopyridin-1-yl}-3'-fluoro-6-(2-hydroxypropan-2-yl)-5'-methyl-[2,2'-bipyridin]-1-ium-1-olate:

[00682] To the reaction solution of 3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-3'-fluoro-5',6-dimethyl-2'-(trimethylstannyl)-[1,4'-bipyridin]-2-one (assumed 100% yield, 1.00 g, 1.79 mmol, 1.00 equiv) was added 2-bromo-6-(2-hydroxypropan-2-yl)pyridin-1-ium-1-olate (0.83 g, 3.58 mmol, 2.00 equiv), CuI (0.34 g, 1.79 mmol, 1.00 equiv) and Pd(PPh₃)₂Cl₂ (0.25 g, 0.35 mmol, 0.20 equiv), the mixture was stirred for 2 h at 80°C under nitrogen atmosphere. The reaction was monitored by LCMS. The reaction was monitored by LCMS. The mixture was allowed to r.t.. The residue was dissolved in EtOAc (200 mL). The resulting mixture was washed with sat. NaHCO₃ (aq.) (2x100 mL). The combined organic layers were

concentrated under reduced pressure. The residue was purified by silica gel column chromatography to afford crude product (400 mg). The crude product was isolated by PREP-HPLC to afford 4'-{3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-6-methyl-2-oxopyridin-1-yl}-3'-fluoro-6-(2-hydroxypropan-2-yl)-5'-methyl-[2,2'-bipyridin]-1-ium-1-olate (200 mg, 20.43%) as a white solid. LC-MS: (ES+H, m/z): [M+H]⁺ = 547.2. ¹H NMR (400 MHz, DMSO-d₆) δ 8.70 (d, 1H), 8.60 (d, 1H), 8.14 – 8.04 (m, 1H), 7.82 (dd, 1H), 7.75 (dd, 1H), 7.60 (t, 1H), 6.89 (d, 1H), 6.62 (s, 1H), 5.52 (d, 2H), 2.17 (s, 3H), 2.06 (s, 3H), 1.60 (s, 6H).

Step 2: Preparation of rel-3-chloro-4-((3,5-difluoropyridin-2-yl)methoxy)-3'-fluoro-6''-(2-hydroxypropan-2-yl)-5',6-dimethyl-2-oxo-2H-[1,4':2',2''-terpyridine] 1''-oxide and rel-3-chloro-4-((3,5-difluoropyridin-2-yl)methoxy)-3'-fluoro-6''-(2-hydroxypropan-2-yl)-5',6-dimethyl-2-oxo-2H-[1,4':2',2''-terpyridine] 1''-oxide :

[00683] The racemate (250 mg) was separated by Prep-HPLC to afford rel-3-chloro-4-((3,5-difluoropyridin-2-yl)methoxy)-3'-fluoro-6''-(2-hydroxypropan-2-yl)-5',6-dimethyl-2-oxo-2H-[1,4':2',2''-terpyridine] 1''-oxide (**Example 62A**: 78.2 mg, 98.1% purity, ee=100%) as a white solid and rel-3-chloro-4-((3,5-difluoropyridin-2-yl)methoxy)-3'-fluoro-6''-(2-hydroxypropan-2-yl)-5',6-dimethyl-2-oxo-2H-[1,4':2',2''-terpyridine] 1''-oxide (**Example 62B**: 78.6 mg, 98.7% purity, ee=98.7%) as a white solid.

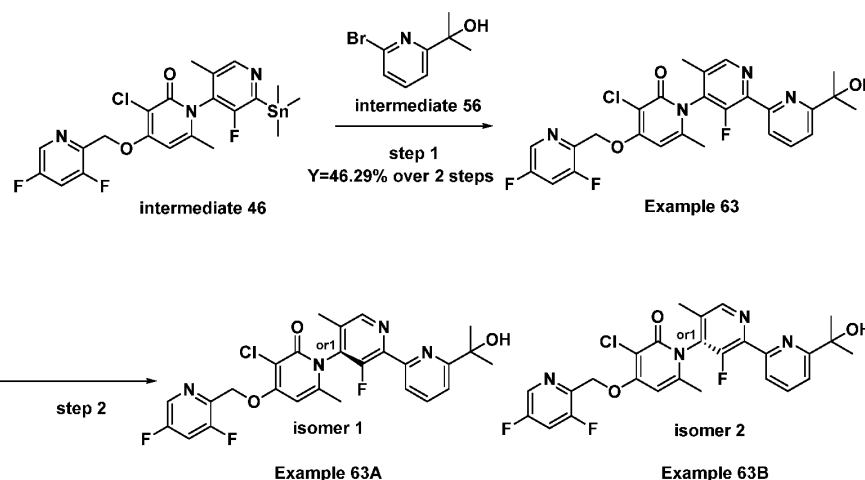
Example 62A:

[00684] LC-MS: (ES+H, m/z): [M+H]⁺ = 547.1. ¹H NMR (400 MHz, DMSO-d₆) δ 8.69 (d, 1H), 8.60 (d, 1H), 8.18 – 8.01 (m, 1H), 7.82 (dd, 1H), 7.75 (dd, 1H), 7.60 (t, 1H), 6.88 (d, 1H), 6.61 (s, 1H), 5.51 (d, 2H), 2.17 (s, 3H), 2.05 (s, 3H), 1.60 (s, 6H). ¹⁹F NMR (377 MHz, DMSO) δ -120.19, -120.21, -122.37, -122.39, -128.08.

Example 62B:

[00685] LC-MS: (ES+H, m/z): [M+H]⁺ = 547.1. ¹H NMR (400 MHz, DMSO-d₆) δ 8.69 (d, 1H), 8.60 (d, 1H), 8.13 – 8.05 (m, 1H), 7.82 (dd, 1H), 7.75 (dd, 1H), 7.60 (t, 1H), 6.88 (d, 1H), 6.61 (s, 1H), 5.51 (d, 2H), 2.17 (s, 3H), 2.05 (s, 3H), 1.60 (s, 6H). ¹⁹F NMR (377 MHz, DMSO) δ -120.19, -120.21, -122.37, -122.39, -128.08.

Example 63A, 63B



Step 1: Preparation of 3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-1-[3-fluoro-6'-(2-hydroxypropan-2-yl)-5-methyl-[2,2'-bipyridin]-4-yl]-6-methylpyridin-2-one:

[00686] To the above mixture of step 3 was added 2-(6-bromopyridin-2-yl)propan-2-ol (754.34 mg, 3.49 mmol, 3.00 equiv), Pd(PPh₃)₂Cl₂ (163.36 mg, 0.23 mmol, 0.20 equiv) and CuI (221.62 mg, 1.16 mmol, 1.00 equiv) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 1 h at 80°C under nitrogen atmosphere. The reaction was monitored by LCMS. The mixture was allowed to cool down to room temperature. The resulting mixture was diluted with water (50 mL). The resulting mixture was extracted with EtOAc (3 x100 mL). The combined organic layers were washed with brine (3x100 mL), dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The crude product was purified by Prep-HPLC to afford 3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-1-[3-fluoro-6'-(2-hydroxypropan-2-yl)-5-methyl-[2,2'-bipyridin]-4-yl]-6-methylpyridin-2-one (286.00 mg, 46.29%) as a white solid. LC-MS: (ES+H, m/z): [M+H]⁺ = 531.00. ¹H NMR (300 MHz, DMSO-d₆) δ 8.69 (d, 1H), 8.61 (d, 1H), 8.15 – 8.05 (m, 1H), 8.01 – 7.90 (m, 2H), 7.75 (dd, 1H), 6.89 (s, 1H), 5.52 (d, 2H), 5.31 (s, 1H), 2.14 (s, 3H), 2.05 (s, 3H), 1.46 (s, 6H).

Step 2: Preparation of rel-3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-1-[3-fluoro-6'-(2-hydroxypropan-2-yl)-5-methyl-[2,2'-bipyridin]-4-yl]-6-methylpyridin-2-one & rel-3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-1-[3-fluoro-6'-(2-hydroxypropan-2-yl)-5-methyl-[2,2'-bipyridin]-4-yl]-6-methylpyridin-2-one :

[00687] The rac-mixture (286.00 mg) was separated by Prep-Chiral HPLC to afford rel-3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-1-[3-fluoro-6'-(2-hydroxypropan-2-yl)-5-methyl-[2,2'-bipyridin]-4-yl]-6-methylpyridin-2-one (**Example 63A**, 65.1 mg, 99.2% purity, ee=99.9%) & rel-3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-1-[3-fluoro-6'-(2-hydroxypropan-2-yl)-5-methyl-[2,2'-bipyridin]-4-yl]-6-methylpyridin-2-one (**Example 63B**, 59.0 mg, 99.6% purity, ee=99.9%)

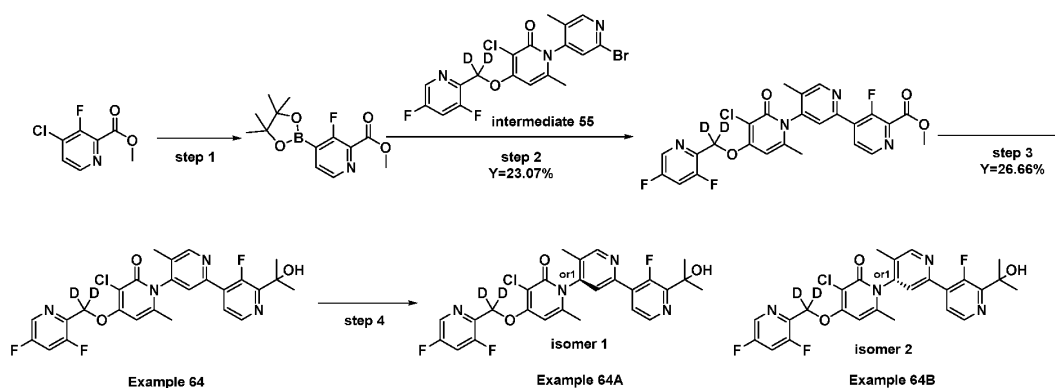
Example 63A:

[00688] LC-MS: (ES+H, m/z): [M+H]⁺ = 531.1. ¹H NMR (300 MHz, DMSO-d₆) δ 8.69 (d, 1H), 8.61 (d, 1H), 8.18 – 8.04 (m, 1H), 8.02 – 7.88 (m, 2H), 7.75 (dd, 1H), 6.89 (s, 1H), 5.52 (d, 2H), 5.30 (s, 1H), 2.13 (s, 3H), 2.04 (s, 3H), 1.46 (s, 6H). ¹⁹F NMR (282 MHz, DMSO) δ -120.17, -120.20, -122.36, -122.39, -134.43.

Example 63B:

[00689] LC-MS: (ES+H, m/z): [M+H]⁺ = 531.05. ¹H NMR (300 MHz, DMSO-d₆) δ 8.69 (d, 1H), 8.61 (d, 1H), 8.18 – 8.04 (m, 1H), 8.01 – 7.87 (m, 2H), 7.75 (dd, 1H), 6.89 (d, 1H), 5.52 (d, 2H), 5.30 (s, 1H), 2.13 (s, 3H), 2.04 (s, 3H), 1.46 (s, 6H). ¹⁹F NMR (282 MHz, DMSO) δ -120.17, -120.19, -122.36, -122.39, -134.42.

Example 64A, 64B



Step 1: Preparation of methyl 3-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine-2-carboxylate:

[00690] To a stirred mixture of methyl 4-chloro-3-fluoropyridine-2-carboxylate (2.00 g, 10.55 mmol, 1.00 equiv), bis(pinacolato)diboron (13.40 g, 52.75 mmol, 5.00 equiv) in dioxane (10 mL) were added AcOK (3.11 g, 31.65 mmol, 3.00 equiv) and XPhos Pd G3 (446 mg, 0.52 mmol, 0.05 equiv) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for additional 1.5 h at 80 °C. The mixture was allowed to cool down to room temperature. Desired product could be detected by LCMS. The resulting mixture was used in the next step directly without further purification. LC-MS: (ES+H, m/z): [M+H]⁺ =200.1 (boronic acid).

Step 2: Preparation of methyl 4-{3-chloro-4-[(3-chloro-5-fluoropyridin-2-yl)(2H2)methoxy]-5',6-dimethyl-2-oxo-[1,4'-bipyridin]-2'-yl}-3-oxopyrazine-2-carboxylate:

[00691] To the above mixture were added bis(2'-bromo-3-chloro-4-[(3,5-difluoropyridin-2-yl)(2H2)methoxy]-5',6-dimethyl-[1,4'-bipyridin]-2-one) (1.96 g, 2.13 mmol, 0.60 equiv), K₂CO₃ (1.48 g, 10.67 mmol, 3.00 equiv), Pd(dppf)Cl₂ (520 mg, 0.71 mmol, 0.20 equiv) and H₂O (2.5 mL) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 1.5 h at 80°C under nitrogen atmosphere. The reaction was monitored by LCMS. The mixture was allowed to cool down to room temperature. The resulting mixture was poured into water (50 mL). The resulting mixture was extracted with EtOAc (3 x 50mL). The combined organic layers were dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, the pure fraction was concentrated under pressure to afford methyl 4-{3-chloro-4-[(3-chloro-5-fluoropyridin-2-yl)(2H2)methoxy]-5',6-dimethyl-2-oxo-[1,4'-bipyridin]-2'-yl}-3-oxopyrazine-2-carboxylate (450 mg, 23.07%) as a white solid. LC-MS: (ES+H, m/z): [M+H]⁺ =533.0. ¹H NMR (300 MHz, DMSO-d₆) δ 8.91 (s, 1H), 8.66 (d, 1H), 8.61 (d, 1H), 8.22 (t, 1H), 8.10 – 8.07 (m, 1H), 7.97 (s, 1H), 6.82 (s, 1H), 3.93 (s, 3H), 2.11 (s, 3H), 1.99 (s, 3H).

Step 3: Preparation of 3-chloro-4-[(3,5-difluoropyridin-2-yl)(2H2)methoxy]-1-[3'-fluoro-2'-(2-hydroxypropan-2-yl)-5-methyl-[2,4'-bipyridin]-4-yl]-6-methylpyridin-2-one:

[00692] To a stirred mixture of methyl 4-{3-chloro-4-[(3,5-difluoropyridin-2-yl)(2H2)methoxy]-6-methyl-2-oxopyridin-1-yl}-3'-fluoro-5-methyl-[2,4'-bipyridine]-2'-carboxylate (450 mg, 0.84 mmol, 1.00 equiv) and

LiCl (35 mg, 0.844 mmol, 1 equiv) in THF (40 mL) was added CH₃MgI (4 mL, 8.00 mmol, 21.32 equiv, 2.0 M in ethyl ether) dropwise at 0°C under nitrogen atmosphere. The resulting mixture was stirred for 1 h at 0°C under nitrogen atmosphere. The reaction was monitored by LCMS. The reaction was quenched with saturated NH₄Cl (aq., 50 mL) at 0°C. The resulting mixture was extracted with EtOAc (3 x 30mL). The combined organic layers were dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, the pure fraction was concentrated under pressure to afford crude product, which was further purified by Prep-HPLC, the pure fraction was concentrated under pressure to afford 3-chloro-4-[(3,5-difluoropyridin-2-yl)(2H2)methoxy]-1-[3'-fluoro-2'-(2-hydroxypropan-2-yl)-5-methyl-[2,4'-bipyridin]-4-yl]-6-methylpyridin-2-one (120 mg, 26.66%) as a white solid. LC-MS: (ES+H, m/z): [M+H]⁺=533.1. ¹H NMR (300 MHz, DMSO-d₆) δ 8.88 (s, 1H), 8.61 (d, 1H), 8.48 (d, 1H), 8.14 – 8.07 (m, 1H), 7.91 – 7.88 (m, 2H), 6.82 (s, 1H), 5.37 (s, 1H), 2.10 (s, 3H), 2.00 (s, 3H), 1.56 (s, 6H).

Step 4: Preparation of rel-3-chloro-4-[(3,5-difluoropyridin-2-yl)(2H2)methoxy]-1-[3'-fluoro-2'-(2-hydroxypropan-2-yl)-5-methyl-[2,4'-bipyridin]-4-yl]-6-methylpyridin-2-one & rel-3-chloro-4-[(3,5-difluoropyridin-2-yl)(2H2)methoxy]-1-[3'-fluoro-2'-(2-hydroxypropan-2-yl)-5-methyl-[2,4'-bipyridin]-4-yl]-6-methylpyridin-2-one :

[00693] The racemate (120 mg) was separated by Prep-Chiral-HPLC, the pure fraction was concentrated under reduced pressure and lyophilized to afford **Example 64A** (39.3 mg, 97.6% purity, 97.3% deuterium purity, ee=100%) and **Example 64B** (39.5 mg, 98.4% purity, 97.9% deuterium purity, ee=100%) as a white solid.

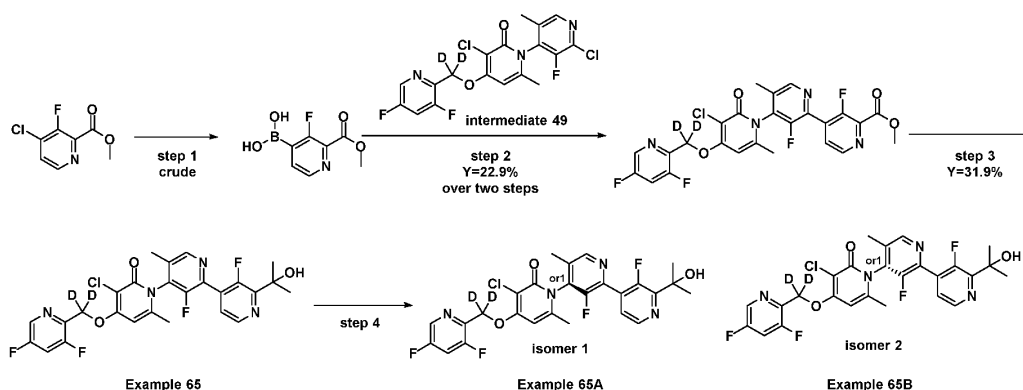
Example 64A:

[00694] LC-MS: (ES+H, m/z): [M+H]⁺=533.20. ¹H NMR (400 MHz, DMSO-d₆) δ 8.88 (s, 1H), 8.60 (d, 1H), 8.47 (d, 1H), 8.12 – 8.07 (m, 1H), 7.90 – 7.88 (m, 2H), 6.81 (s, 1H), 5.37 (s, 1H), 2.09 (s, 3H), 1.98 (s, 3H), 1.56 (s, 6H). ¹⁹F NMR (377 MHz, DMSO) δ -120.25, -120.27, -122.33, -122.35, -125.91.

Example 64B:

[00695] LC-MS: (ES+H, m/z): [M+H]⁺=533.25. ¹H NMR (400 MHz, DMSO-d₆) δ 8.88 (s, 1H), 8.60 (d, 1H), 8.47 (d, 1H), 8.12 – 8.07 (m, 1H), 7.90 – 7.88 (m, 2H), 6.81 (s, 1H), 5.37 (s, 1H), 2.09 (s, 3H), 1.98 (s, 3H), 1.56 (s, 6H). ¹⁹F NMR (377 MHz, DMSO) δ -120.25, -120.27, -122.33, -122.35, -125.91.

Example 65A, 65B



Step 1: Preparation of 3-fluoro-2-(methoxycarbonyl)pyridin-4-ylboronic acid:

[00696] To a stirred mixture of methyl 4-chloro-3-fluoropyridine-2-carboxylate (1.50 g, 7.91 mmol, 1.00 equiv) and bis(pinacolato)diboron (10.05 g, 39.56 mmol, 5.00 equiv) in dioxane (30 mL) were added potassium acetate (2.33 g, 23.73 mmol, 3.00 equiv) and XPhos Pd G3 (0.33 g, 0.39 mmol, 0.05 equiv) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 1.5 h at 80°C under nitrogen atmosphere. The mixture was allowed to cool down to room temperature. The reaction was monitored by LCMS. The crude product mixture was used in the next step directly without further purification. LC-MS: (ES+H, m/z): [M+H]⁺=200.0.

Step 2: Preparation of methyl 4-{3-chloro-4-[(3,5-difluoropyridin-2-yl)(2H2)methoxy]-6-methyl-2-oxopyridin-1-yl}-3,3'-difluoro-5-methyl-[2,4'-bipyridine]-2'-carboxylate:

[00697] To the above mixture were added bis(2'-bromo-3-chloro-4-[(3,5-difluoropyridin-2-yl)(2H2)methoxy]-5',6-dimethyl-[1,4'-bipyridin]-2-one) (1.71 g, 1.87 mmol, 0.70 equiv), K₂CO₃ (1.11 g, 8.01 mmol, 3.00 equiv), Pd(dppf)Cl₂ (0.39 g, 0.53 mmol, 0.20 equiv), dioxane (30 mL) and H₂O (3 mL) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for additional 1.5 h at 80°C. The mixture was allowed to cool down to room temperature. The reaction was monitored by LCMS. The resulting mixture was poured into water (200 mL). The resulting mixture was filtered, the filter cake was washed with EtOAc (3 x 200 mL). The combined organic layers were washed with brine (200 mL). The filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography to afford methyl 4-{3-chloro-4-[(3,5-difluoropyridin-2-yl)(2H2)methoxy]-6-methyl-2-oxopyridin-1-yl}-3,3'-difluoro-5-methyl-[2,4'-bipyridine]-2'-carboxylate (1.00 g, 22.9%) as a yellow solid. LC-MS: (ES+H, m/z): [M+H]⁺=551.1.

Step 3: Preparation of 3-chloro-1-[3,3'-difluoro-2'-(2-hydroxypropan-2-yl)-5-methyl-[2,4'-bipyridin]-4-yl]-4-[(3,5-difluoropyridin-2-yl)(2H2)methoxy]-6-methylpyridin-2-one:

[00698] To a stirred solution of methyl 4-{3-chloro-4-[(3-fluoropyridin-2-yl)(2H2)methoxy]-6-methyl-2-oxopyridin-1-yl}-3,3'-difluoro-5-methyl-[2,4'-bipyridine]-2'-carboxylate (850 mg, 1.59 mmol, 1.00 equiv) in THF (80 mL) was added CH₃MgBr (5.32 mL, 15.95 mmol, 10.00 equiv, 3 M in 2-MeTHF) dropwise at 0°C under nitrogen atmosphere. The resulting mixture was stirred for 1.5 h at 0°C under nitrogen atmosphere. The reaction was monitored by LCMS. The reaction was quenched with sat.

NH₄Cl (aq., 20 ml) at 0°C. The resulting mixture was extracted with EtOAc (3 x 80ml). The combined organic layers were washed with brine (3 x 80 mL), dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography to afford crude product, which was further purified by Prep-HPLC, the pure fraction was concentrated under pressure to afford 3-chloro-1-[3,3'-difluoro-2'-(2-hydroxypropan-2-yl)-5-methyl-[2,4'-bipyridin]-4-yl]-4-[(3,5-difluoropyridin-2-yl)(2H2)methoxy]-6-methylpyridin-2-one (280 mg, 85% purity, 31.9% yield) as a white solid. LC-MS: (ES+H, m/z): [M+H]⁺ = 551.1. ¹H NMR (400 MHz, DMSO-d₆) δ 8.79 (s, 1H), 8.61 (d, 1H), 8.53 (d, 1H), 8.12-8.10 (m, 1H), 7.68 (t, 1H), 6.92 (s, 1H), 5.39 (s, 1H), 2.19 (s, 3H), 2.07 (s, 3H), 1.56 (s, 6H).

Step 4: Preparation of rel-3-chloro-1-[3,3'-difluoro-2'-(2-hydroxypropan-2-yl)-5-methyl-[2,4'-bipyridin]-4-yl]-4-[(3,5-difluoropyridin-2-yl)(2H2)methoxy]-6-methylpyridin-2-one & rel-3-chloro-1-[3,3'-difluoro-2'-(2-hydroxypropan-2-yl)-5-methyl-[2,4'-bipyridin]-4-yl]-4-[(3,5-difluoropyridin-2-yl)(2H2)methoxy]-6-methylpyridin-2-one :

[00699] The racemate (270 mg) was separated by Prep-Chiral-HPLC, the pure fraction was concentrated under reduced pressure and lyophilized to afford **Example 65A** 61.8 mg, 99.9% purity, ee=100%, 96.4% deuterium purity) as a white solid and **Example 65B** (53.1 mg, 99.8% purity, ee=99.3%, 96.6% deuterium purity) as a white solid.

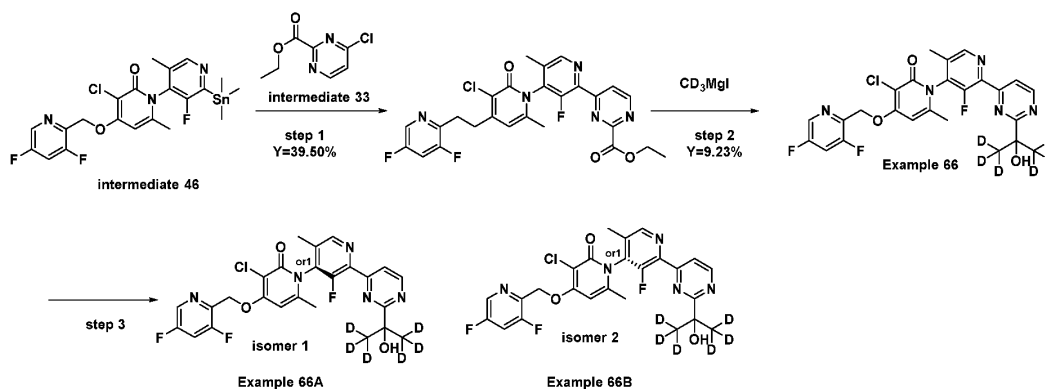
Example 65A:

[00700] LC-MS: (ES+H, m/z): [M+H]⁺ = 551.3. ¹H NMR (300 MHz, DMSO-d₆) δ 8.79 (s, 1H), 8.61 (d, 1H), 8.53 (d, 1H), 8.13-8.06 (m, 1H), 7.68 (t, 1H), 6.94 (s, 1H), 5.38 (s, 1H), 2.18 (s, 3H), 2.06 (s, 3H), 1.55 (s, 6H). ¹⁹F NMR (282 MHz, DMSO) δ -120.216, -120.284, -122.313, -122.350, -123.233, -123.343, -132.080, -132.190.

Example 65B:

[00701] LC-MS: (ES+H, m/z): [M+H]⁺ = 551.3. ¹H NMR (300 MHz, DMSO-d₆) δ 8.79 (s, 1H), 8.60 (d, 1H), 8.53 (d, 1H), 8.12-8.06 (m, 1H), 7.68 (t, 1H), 6.91 (s, 1H), 5.38 (s, 1H), 2.18 (s, 3H), 2.06 (s, 3H), 1.55 (s, 6H). ¹⁹F NMR (282 MHz, DMSO) δ -120.211, -120.279, -122.305, -122.343, -123.230, -123.340, -132.074, -132.185

Example 66A, 66B



Step 1: Preparation of ethyl 4-(3-chloro-4-(2-(3,5-difluoropyridin-2-yl)ethyl)-3'-fluoro-5',6-dimethyl-2-oxo-2H-[1,4'-bipyridin]-2'-yl)pyrimidine-2-carboxylate:

[00702] To 3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-3'-fluoro-5',6-dimethyl-2'-(trimethylstannyl)-[1,4'-bipyridin]-2-one (1 g crude) was added ethyl 4-chloropyrimidine-2-carboxylate (1302 mg, 6.98 mmol, 3.00 equiv), Pd(PPh₃)₂Cl₂ (326 mg, 0.46 mmol, 0.20 equiv) and CuI (443 mg, 2.32 mmol, 1.00 equiv) at room temperature. The resulting mixture was stirred for 2 h at 80°C under nitrogen atmosphere. The reaction was monitored by LCMS. The mixture was allowed to cool down to room temperature. The resulting mixture was diluted with water (50 mL). The resulting mixture was extracted with EtOAc (3 x 100 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography to afford ethyl 4-(3-chloro-4-(2-(3,5-difluoropyridin-2-yl)ethyl)-3'-fluoro-5',6-dimethyl-2-oxo-2H-[1,4'-bipyridin]-2'-yl)pyrimidine-2-carboxylate (500 mg, 39.50%, over two steps) as a yellow solid. LC-MS: (ES+H, m/z): [M+H]⁺ = 546.1.

Step 2: Preparation of 3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-3'-fluoro-2'-(2-[2-hydroxy(1,1,1,3,3,3-2H6)propan-2-yl]pyrimidin-4-yl)-5',6-dimethyl-[1,4'-bipyridin]-2-one:

[00703] To a stirred solution of ethyl 4-{3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-3'-fluoro-5',6-dimethyl-2-oxo-[1,4'-bipyridin]-2'-yl}pyrimidine-2-carboxylate (550 mg, 1.00 mmol, 1.00 equiv) and LiCl (85 mg, 2.01 mmol, 2.00 equiv) in THF (8 mL) was added iodo((2H3)methyl)magnesium (3.02 mL, 3.00 mmol, 3 equiv, 1 M) dropwise at -10°C under nitrogen atmosphere. The resulting mixture was stirred for 30 min at -10°C under nitrogen atmosphere. The reaction was monitored by LCMS. The reaction was quenched with sat. NH₄Cl (aq.) at -10°C. The resulting mixture was extracted with EtOAc (3 x 50 mL). The combined organic layers were dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The crude product was isolated by PREP-HPLC to afford 3-chloro-4-[(3,5-difluoropyridin-2-yl)methoxy]-3'-fluoro-2'-(2-[2-hydroxy(1,1,1,3,3,3-2H6)propan-2-yl]pyrimidin-4-yl)-5',6-dimethyl-[1,4'-bipyridin]-2-one (50 mg, 9.23%). LC-MS: (ES+H, m/z): [M+H]⁺ = 538.2.

Step 3: Preparation of rel-3-chloro-4-((3,5-difluoropyridin-2-yl)methoxy)-3'-fluoro-2'-(2-(2-hydroxypropan-2-yl-1,1,1,3,3,3-d6)pyrimidin-4-yl)-5',6-dimethyl-2H-[1,4'-bipyridin]-2-one & rel-3-chloro-4-((3,5-difluoropyridin-2-yl)methoxy)-3'-fluoro-2'-(2-(2-hydroxypropan-2-yl-1,1,1,3,3,3-d6)pyrimidin-4-yl)-5',6-dimethyl-2H-[1,4'-bipyridin]-2-one :

[00704] The rac-mixture (50 mg) was separated by Prep-Chiral HPLC to afford rel-3-chloro-4-((3,5-difluoropyridin-2-yl)methoxy)-3'-fluoro-2'-(2-(2-hydroxypropan-2-yl-1,1,1,3,3,3-d6)pyrimidin-4-yl)-5',6-dimethyl-2H-[1,4'-bipyridin]-2-one (**Example 66A**: 22.6 mg, 99.7% purity, ee=100%) as a white solid and rel-3-chloro-4-((3,5-difluoropyridin-2-yl)methoxy)-3'-fluoro-2'-(2-(2-hydroxypropan-2-yl-1,1,1,3,3,3-d6)pyrimidin-4-yl)-5',6-dimethyl-2H-[1,4'-bipyridin]-2-one (**Example 66B**: 21.2 mg, 99.6% purity, ee=100%) as a white solid.

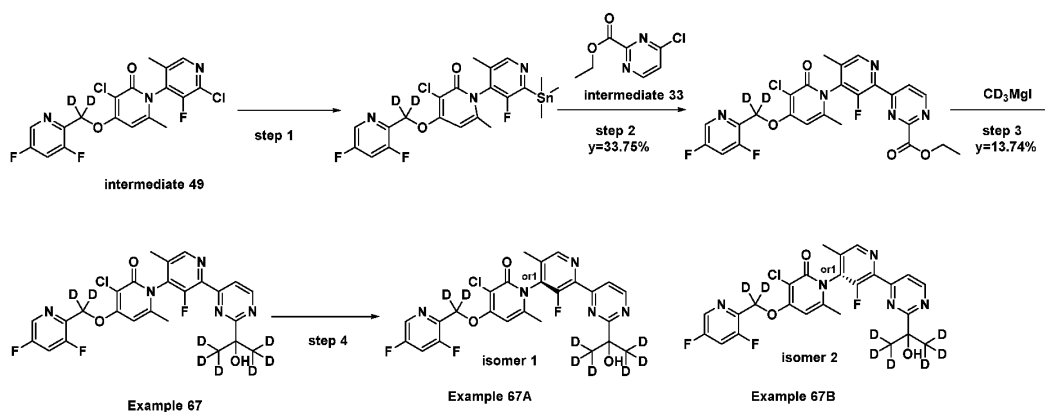
Example 66A:

[00705] LC-MS: (ES+H, m/z): $[M+H]^+ = 538.2$. ^1H NMR (400 MHz, DMSO- d_6) δ 9.02 (d, 1H), 8.78 (s, 1H), 8.61 (d, 1H), 8.15 – 8.06 (m, 1H), 8.04 (d, 1H), 6.90 (s, 1H), 5.53 (d, 2H), 5.06 (d, 1H), 2.18 (s, 3H), 2.05 (s, 3H). ^{19}F NMR (377 MHz, DMSO) δ -120.17, -120.19, -122.35, -122.36, -132.09.

Example 66B:

[00706] LC-MS: (ES+H, m/z): $[M+H]^+ = 538.2$. ^1H NMR (400 MHz, DMSO- d_6) δ 9.02 (d, 1H), 8.78 (s, 1H), 8.61 (d, 1H), 8.15 – 8.06 (m, 1H), 8.04 (d, 1H), 6.90 (s, 1H), 5.52 (d, 2H), 5.05 (d, 1H), 2.18 (s, 3H), 2.05 (s, 3H). ^{19}F NMR (377 MHz, DMSO) δ -120.17, -120.19, -122.36, -122.38, -132.09.

Example 67A, 67B



Step 1: Preparation of 3-chloro-4-((3,5-difluoropyridin-2-yl)methoxy-d2)-3'-fluoro-5',6-dimethyl-2'-(trimethylstannyl)-2H-[1,4'-bipyridin]-2-one:

[00707] To a stirred mixture of 2',3-dichloro-4-[(3,5-difluoropyridin-2-yl)(2H2)methoxy]-3'-fluoro-5',6-dimethyl-[1,4'-bipyridin]-2-one (2.00g, 4.62 mmol, 1.00 equiv) and $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$ (649 mg, 0.92 mmol, 0.20 equiv) in THF (20 mL) were added AsPh_3 (283 mg, 0.92 mmol, 0.20 equiv) and Sn_2Me_6 (3.02 g, 9.25 mmol, 2.00 equiv) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 2 h at 80°C under nitrogen atmosphere. The reaction was monitored by LCMS. Desired product could be detected by LCMS. The resulting mixture was used in the next step directly without further purification. LC-MS: (ES+H, m/z): $[M+H]^+ = 562.1$.

Step 2: Preparation of ethyl 4-(3-chloro-4-((3,5-difluoropyridin-2-yl)methoxy-d2)-3'-fluoro-5',6-dimethyl-2-oxo-2H-[1,4'-bipyridin]-2'-yl)pyrimidine-2-carboxylate:

[00708] To a stirred mixture of 3-chloro-4-[(3,5-difluoropyridin-2-yl)(2H2)methoxy]-3'-fluoro-5',6-dimethyl-2'-(trimethylstannyl)-[1,4'-bipyridin]-2-one hydrofluoride (2.70 g, 4.65 mmol, 1.00 equiv) and ethyl 4-chloropyrimidine-2-carboxylate (1.73 g, 9.30 mmol, 2.00 equiv) in THF (20 mL) were added $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$ (652 mg, 0.93 mmol, 0.20 equiv) and CuI (885 mg, 4.65 mmol, 1.00 equiv) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 2 h at 80°C under nitrogen atmosphere. The reaction was monitored by LCMS. The resulting mixture was cooled down to r.t. and poured into 20 mL of water. The resulting mixture was extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (50 mL), dried over anhydrous Na_2SO_4 . After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography to

afford ethyl 4-(3-chloro-4-((3,5-difluoropyridin-2-yl)methoxy-d2)-3'-fluoro-5',6-dimethyl-2-oxo-2H-[1,4'-bipyridin]-2'-yl)pyrimidine-2-carboxylate (860 mg, 33.75%) as a white solid. LC-MS: (ES+H, m/z): [M+H]⁺=548.1. ¹H NMR (300 MHz, Chloroform-d) δ 9.08 (d, 1H), 8.70 – 8.63 (m, 1H), 8.42 (d, 1H), 8.20 (dd, 1H), 7.35 – 7.33 (m, 1H), 6.47 (d, 1H), 4.56 (q, 2H), 2.26 (s, 3H), 2.07 (s, 3H), 1.49 (t, 3H).

Step 3: Preparation of 3-chloro-4-((3,5-difluoropyridin-2-yl)methoxy-d2)-3'-fluoro-2'-(2-(2-hydroxypropan-2-yl-1,1,1,3,3,3-d6)pyrimidin-4-yl)-5',6-dimethyl-2H-[1,4'-bipyridin]-2-one:

[00709] To a stirred mixture of ethyl 4-{3-chloro-4-[(3,5-difluoropyridin-2-yl)(2H2)methoxy]-3'-fluoro-5',6-dimethyl-2-oxo-[1,4'-bipyridin]-2'-yl}pyrimidine-2-carboxylate (480 mg, 0.87 mmol, 1.00 equiv) in THF was added iodo((2H3)methyl)magnesium (9 mL, 8.76 mmol, 10.00 equiv) dropwise at 0°C under nitrogen atmosphere. The resulting mixture was stirred for 1 h at 0°C under nitrogen atmosphere. The reaction was monitored by LCMS. Desired product could be detected by LCMS. The reaction was quenched with sat. NH₄Cl (aq.) at 0°C. The resulting mixture was extracted with EtOAc (3 x20 mL). The combined organic layers were washed with brine (50 mL), dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography to afford the crude product. The crude product was purified by Prep-HPLC to afford 3-chloro-4-((3,5-difluoropyridin-2-yl)methoxy-d2)-3'-fluoro-2'-(2-(2-hydroxypropan-2-yl-1,1,1,3,3,3-d6)pyrimidin-4-yl)-5',6-dimethyl-2H-[1,4'-bipyridin]-2-one (65 mg, 13.74%) as a white solid. LC-MS: (ES+H, m/z): [M+H]⁺=540.2.

Step 4: Preparation of rel-3-chloro-4-((3,5-difluoropyridin-2-yl)methoxy-d2)-3'-fluoro-2'-(2-(2-hydroxypropan-2-yl-1,1,1,3,3,3-d6)pyrimidin-4-yl)-5',6-dimethyl-2H-[1,4'-bipyridin]-2-one & rel-3-chloro-4-((3,5-difluoropyridin-2-yl)methoxy-d2)-3'-fluoro-2'-(2-(2-hydroxypropan-2-yl-1,1,1,3,3,3-d6)pyrimidin-4-yl)-5',6-dimethyl-2H-[1,4'-bipyridin]-2-one :

The racemate (65 mg) was separated by prep-chiral-HPLC to afford **Example 67A** (9.7 mg, 97.4% purity, 98.9% deuterium purity, ee=97.44%) and **Example 67B** (8.8 mg, 98.4% purity, 98.6% deuterium purity, ee=97.02%) as a white solid.

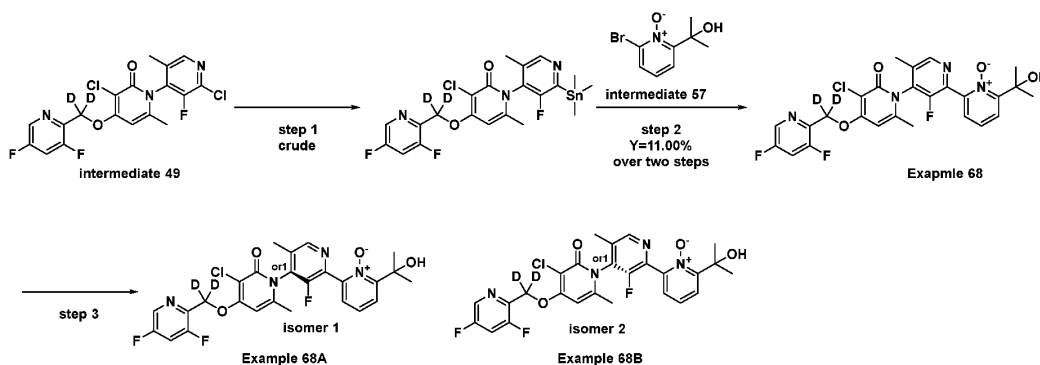
Example 67A:

[00710] LC-MS: (ES+H, m/z): [M+H]⁺=540.10. ¹H NMR (300 MHz, DMSO-d₆) δ 9.03 (d, 1H), 8.77 (s, 1H), 8.61 (d, 1H), 8.13-8.02 (m, 2H), 6.90 (s, 1H), 5.04 (s, 1H), 2.17 (s, 3H), 2.05 (s, 3H). ¹⁹F NMR (282 MHz, DMSO) δ -119.61, -119.66, -120.85, -120.87, -132.49.

Example 67B:

[00711] LC-MS: (ES+H, m/z): [M+H]⁺=540.2. ¹H NMR (300 MHz, DMSO-d₆) δ 9.03 (d, 1H), 8.77 (s, 1H), 8.61 (d, 1H), 8.13-8.03 (m, 2H), 6.90 (s, 1H), 5.05 (s, 1H), 2.17 (s, 3H), 2.05 (s, 3H). ¹⁹F NMR (282 MHz, DMSO) δ -120.23, -120.25, -122.32, -122.34, -132.06.

Example 68A, 68B



Step 1: Preparation of 3-chloro-4-[(3,5-difluoropyridin-2-yl) (2H2) methoxy]-3'-fluoro-5',6-dimethyl-2'-(trimethylstannyl)-[1,4'-bipyridin]-2-one:

[00712] A mixture of 2',3-dichloro-4-[(3,5-difluoropyridin-2-yl) (2H2) methoxy]-3'-fluoro-5',6-dimethyl-[1,4'-bipyridin]-2-one (1.00 g, 2.31 mmol, 1.00 equiv), Sn_2Me_6 (1.51 g, 4.62 mmol, 2.00 equiv), $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$ (0.32 g, 0.46 mmol, 0.20 equiv), AsPh_3 (0.14 g, 0.46 mmol, 0.20 equiv) in dioxane (10 mL) was stirred for 2 h at 80°C under nitrogen atmosphere. The reaction was monitored by LCMS. The resulting mixture was used in the next step directly without further purification. LC-MS: (ES+H, m/z): $[\text{M}+\text{H}]^+ = 562.1$.

Step 2: Preparation of 4'-{3-chloro-4-[(3,5-difluoropyridin-2-yl) (2H2) methoxy]-6-methyl-2-oxopyridin-1-yl}-3'-fluoro-6-(2-hydroxypropan-2-yl)-5'-methyl-[2,2'-bipyridin]-1-ium-1-olate:

[00713] To the above mixture of step 1 was added 2-bromo-6-(2-hydroxypropan-2-yl) pyridin-1-ium-1-olate (0.83 g, 3.58 mmol, 2.00 equiv), CuI (0.34 g, 1.79 mmol, 1.00 equiv) and $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$ (0.25 g, 0.35 mmol, 0.20 equiv). the mixture was stirred for 2 h at 80°C under nitrogen atmosphere. The reaction was monitored by LCMS. The mixture was allowed to r.t. and then diluted with EtOAc (200 mL). The resulting mixture was washed with sat. NaHCO_3 (aq.) (2x 100 mL). The organic layer was concentrated under reduced pressure. The residue was purified by silica gel column chromatography to afford crude product. The crude product was isolated by PREP-HPLC to afford 4'-{3-chloro-4-[(3,5-difluoropyridin-2-yl) (2H2) methoxy]-6-methyl-2-oxopyridin-1-yl}-3'-fluoro-6-(2-hydroxypropan-2-yl)-5'-methyl-[2,2'-bipyridin]-1-ium-1-olate (140 mg, 11.00 %). LC-MS: (ES+H, m/z): $[\text{M}+\text{H}]^+ = 549.2$. ^1H NMR (300 MHz, Chloroform-d) δ 8.53 (s, 1H), 8.36 (d, 1H), 7.56 (dd, 1H), 7.49 – 7.39 (m, 2H), 7.34 – 7.26 (m, 1H), 6.46 (d, 1H), 2.20 (s, 3H), 2.10 (s, 3H), 1.67 (s, 3H), 1.63 (s, 3H).

Step 3: Preparation of rel-4'-{3-chloro-4-[(3,5-difluoropyridin-2-yl) (2H2) methoxy]-6-methyl-2-oxopyridin-1-yl}-3'-fluoro-6-(2-hydroxypropan-2-yl)-5'-methyl-[2,2'-bipyridin]-1-ium-1-olate & rel-4'-{3-chloro-4-[(3,5-difluoropyridin-2-yl) (2H2) methoxy]-6-methyl-2-oxopyridin-1-yl}-3'-fluoro-6-(2-hydroxypropan-2-yl)-5'-methyl-[2,2'-bipyridin]-1-ium-1-olate :

[00714] The rac-mixture (140 mg) was separated by Prep-Chiral HPLC to afford rel-4'-{3-chloro-4-[(3,5-difluoropyridin-2-yl) (2H2) methoxy]-6-methyl-2-oxopyridin-1-yl}-3'-fluoro-6-(2-hydroxypropan-2-yl)-5'-methyl-[2,2'-bipyridin]-1-ium-1-olate (**Example 68A**: 40.8 mg, 99.0% purity, ee=100.0%) as a white solid and rel-4'-{3-chloro-4-[(3,5-difluoropyridin-2-yl) (2H2) methoxy]-6-methyl-2-oxopyridin-1-yl}-3'-fluoro-6-

(2-hydroxypropan-2-yl)-5'-methyl-[2,2'-bipyridin]-1-ium-1-olate (**Example 68B**: 40.3 mg, 98.2% purity, ee=100.0%) as a white solid.

Example 68A:

[00715] LC-MS: (ES+H, m/z): $[M+H]^+ = 549.25$. 1H NMR (300 MHz, DMSO- d_6) δ 8.70 (s, 1H), 8.61 (d, 1H), 8.14 – 8.04 (m, 1H), 7.83 (dd, 1H), 7.75 (dd, 1H), 7.60 (t, 1H), 6.89 (d, 1H), 6.62 (s, 1H), 2.17 (s, 3H), 2.06 (s, 3H), 1.61 (s, 3H), 1.59 (s, 3H). ^{19}F NMR (282 MHz, DMSO) δ -120.27, -120.29, -122.33, -122.36, -128.07.

Example 68B:

[00716] LC-MS: (ES+H, m/z): $[M+H]^+ = 549.20$. 1H NMR (300 MHz, DMSO- d_6) δ 8.70 (s, 1H), 8.61 (d, 1H), 8.17 – 8.01 (m, 1H), 7.83 (dd, 1H), 7.75 (dd, 1H), 7.60 (t, 1H), 6.89 (d, 1H), 6.62 (s, 1H), 2.17 (s, 3H), 2.06 (s, 3H), 1.61 (s, 3H), 1.59 (s, 3H). ^{19}F NMR (282 MHz, DMSO) δ -120.27, -120.29, -122.33, -122.36, -128.07.

Biological Examples:

Protein expression and purification

[00717] Expression vectors of the recombinant MK2 and PRAK kinases were constructed by cloning of the codon optimized gene sequences of MK2 (Uniprot ID P49137, amino acid fragment F46-H400), or PRAK (Uniprot ID Q8IW41, amino acid fragment M1-Q471) into pGEX-4T1 (GE) for over expression of these kinases with N-terminal GST-tag. Protein expression was carried out in *E. coli* BL21 by growing the hosts in TB medium, induction of protein expression with 0.5 mM IPTG at approximate 0.8 OD₆₀₀, and incubation of the cultures at 18°C for 14-20 hours afterwards. The harvested cells were resuspended in 100 ml of Lysis buffer (50 mM Tris-HCl, pH 8.0, 500 mM NaCl, 1 mM DTT, 5% glycerol, and 1 mM PMSF) per gram of wet cell mass and homogenized at 4°C in a microfluidizer (ATS, Suzhou, China) at 14,000 psi pressure, 3 passes. The cell lysates were clarified by centrifugation and the supernatants containing the GST-fusion proteins were purified by affinity chromatography using GSH-Sepharose (GE) gravity flow columns pre-equilibrated in Buffer A (50 mM Tris-HCl, pH 8.0, 500 mM NaCl, 1 mM DTT, and 5% glycerol). After thorough washing of the columns with Buffer A, the bound GST-proteins were eluted by Buffer B (50 mM Tris, pH 8.0, 500 mM NaCl, 1 mM DTT, 5 % glycerol, 10 mM glutathione), followed by size-exclusion purification on Superdex 200 column equilibrated in Buffer A. The purified proteins were concentrated to approximately 1 mg/ml and stored at -80°C.

Biochemical Assay

[00718] This study evaluates the inhibitory potency of invention compound on p38/MK2 pathway vs p38/PRAK pathway. More specially the compound concentration (IC₅₀) was determined that inhibited half of the maximal activation of MK2 or PRAK by p38. MK2 activation study was set up without or with a serial of 10-point 1:3 dilution of invention compound at top dose of 1 or 10 μ M, and PRAK activation study was set up without or with a serial of 10-point 1:3 dilution of invention compound at top dose of 300 μ M.

The MK2 and PRAK activity were determined by the phosphorylation level of HSP27 peptide conjugated with FITC.

[00719] A typical assay was conducted in 20μL volume including 60 pM active p38α (Carna, cat# 04-152), 10μM ATP, 1μM FITC-HSP27 peptide (Sangon, Cat# P22354), and 1 nM inactive MK2, or PRAK in 1X reaction buffer (20mM HEPES, pH7.5, 10mM MgCl₂, 1mM DTT, 0.01% Triton X-100, 0.01% BSA). After 2h incubation of the reaction mixture with various concentration of invention compound (200nL), 60 μL 1X IMAP solution Mixture (Molecular Devices, Cat# R8127) was added to the reaction mixture and incubated for another half hour. The signal was then read by Synergy™ Neo2 Multi-Mode *Microplate Reader* with filter setting (Ex/Em=485nm/FITC FP-P pol 528nm & FITC FP-S pol 528nm)

[00720] The signal was then normalized to vehicle control and fitted in Xfit to generate IC₅₀. The selectivity of MK2 over PRAK was calculated by the formular Selectivity= IC₅₀ of PRAK/ IC₅₀ of MK2.

[00721] The data from the above assays is found in table 2.

TABLE 2

Ex. number	p38a/MK2 (10 μM) Enzyme pIC ₅₀	p38a/MK2 (1 μM) Enzyme pIC ₅₀	p38a/PRAK Enzyme pIC ₅₀
1	5.2		<3.5
2	7.5		5.4
3	7.7		5.3
3A		8	5.4
3B	<5.0		<3.5
4	7.8		5.1
4A		8.8	5.4
4B	6.1		<3.5
5	7.8		5.5
5A	8.2		5.6
5B	5.7		<3.5
6	7.5		4.9
6A	7.6		5
6B		8.3	5
6C	5.5		<3.5
6D	5.6		<3.5
7	6.3		4.2
8	<5.0		<3.5
9A		8.4	5.5
10	5.8		5.3
14	7.7		4.7
15	5.4		3.8
16	7.4		4.8
17	5.6		4.4
18A	6.8		4.6
18B	<5.0		<3.5
18C	<5.0		<3.5
18D	7.1		5.5
19A	6.6		5.3
19B	<5.0		<3.5
20A	5.7		5.3

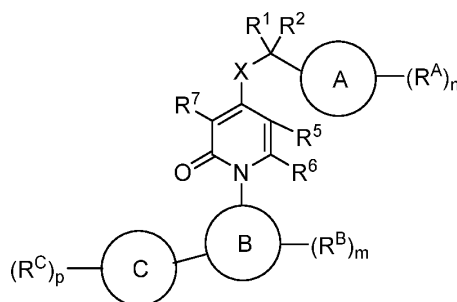
Ex. number	p38a/MK2 (10 μ M) Enzyme pIC ₅₀	p38a/MK2 (1 μ M) Enzyme pIC ₅₀	p38a/PRAK Enzyme pIC ₅₀
20B	<5.0		<3.5
21A	<5.0		<3.5
21B		8.5	5.7
22A	7.5		4.8
22B	<5.0		<3.5
23A		8.5	4.9
23B	<5.0		<3.5
24A		8.8	5.2
24B	5.8		<3.5
25A	7.5		5.5
25B	5.5		<3.5
26A		7.9	5.7
26B	5.8		<3.5
27A	7.2		3.9
27B	5.3		<3.5
28A	5.4		<3.5
28B	<5.0		<3.5
29A		8.1	4.9
29B	<5.0		<3.5
30	6.2		4.6
31A	5.7		5.5
31B	<5.0		<3.5
32A		7.7	5.2
32B	6		<3.5
32C	7.2		5.2
32D	5.9		<3.5
33A		7.6	5.3
33B	6.5		4.3
34A		7.7	5
34B	7.9		5.2
34C	5.7		<3.5
34D	5.5		<3.5
35A		7.3	5
35B		7.8	5.3
35C		<6.0	<3.5
35D		<6.0	<3.5
36A		8.3	5.3
36B		8.2	4.8
36C		<6.0	<3.5
36D		<6.0	<3.5
37A		8.3	5.6
37B		<6.0	<3.5
38A		7	4.5
38B		<6.0	<3.5
39A		8	4.9
39B		<6.0	<3.5
40A		6.9	4.8
40B		<6.0	<3.5
41A		8.3	5.5
41B		<6.0	<3.5
42A		6.3	5.2
42B		<6.0	<3.5

Ex. number	p38a/MK2 (10 μ M) Enzyme pIC ₅₀	p38a/MK2 (1 μ M) Enzyme pIC ₅₀	p38a/PRAK Enzyme pIC ₅₀
43A		7.9	5.6
43B		<6.0	<3.5
44A		7.6	5.2
44B		<6.0	<3.5
45A		<6.0	<3.5
45B		6.3	4.4
46A		7.8	5.6
46B		<6.0	<3.5
47A		8.7	5.3
47B		<6.0	<3.5
48A		8.3	5.7
48B		<6.0	<3.5
49A		8.2	5.5
49B		<6.0	<3.5
50A		7.9	5
50B		<6.0	<3.5
51A		7.1	5.3
51B		<6.0	<3.5
52A		<6.0	<3.5
52B		7.8	4.6
53A		<6.0	<3.5
53B		9.9	6.1
54A		<6.0	<3.5
54B		9.2	5.8
55		7.2	5
56A		8.7	5.8
56B		<6.0	<3.5
57A		8.9	6.1
57B		<8.0	3.9
58A		8.9	6
58B		<6.0	<3.5
59A		<6.0	<3.5
59B		9	6.5
60A		<7.0	<3.5
60B		7.6	4.7
61A		<7.0	3.8
61B		8.5	6.2
62A		8.8	6.1
62B		<7.0	<3.5
63A		<7.0	<3.5
63B		9.5	6.5
64A		8.7	5.7
64B		<7.0	<3.5
65A		8.4	6.7
65B		<7.0	4.1
66A		<7.0	<3.5
66B		8.2	6
67A		8.8	6.5
67B		7.1	4.5
68A		<7.0	<3.5
68B		9.7	6.4

CLAIMS

WHAT IS CLAIMED IS:

1. A compound of Formula (II), or a pharmaceutically acceptable salt, solvate, N-oxide, or stereoisomer thereof:



Formula (II),

wherein:

Ring A is phenyl or heteroaryl;

each R^A is independently hydrogen, deuterium, halogen, -CN, -NO₂, -OH, -OR^a, -OC(=O)R^a, -OC(=O)OR^b, -OC(=O)NR^cR^d, -SH, -SR^a, -S(=O)R^a, -S(=O)₂R^a, -S(=O)₂NR^cR^d, -NR^cR^d, -NR^bC(=O)NR^cR^d, -NR^bC(=O)R^a, -NR^bC(=O)OR^b, -NR^bS(=O)₂R^a, -C(=O)R^a, -C(=O)OR^b, -C(=O)NR^cR^d, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein the alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is optionally and independently substituted with one or more R^{Aa} ;

or two R^A on the same atom are taken together to form an oxo;

each R^{Aa} is independently deuterium, halogen, -CN, -NO₂, -OH, -OR^a, -OC(=O)R^a, -OC(=O)OR^b, -OC(=O)NR^cR^d, -SH, -SR^a, -S(=O)R^a, -S(=O)₂R^a, -S(=O)₂NR^cR^d, -NR^cR^d, -NR^bC(=O)NR^cR^d, -NR^bC(=O)R^a, -NR^bC(=O)OR^b, -NR^bS(=O)₂R^a, -C(=O)R^a, -C(=O)C(=O)R^a, -C(=O)OR^b, -C(=O)NR^cR^d, -C(=O)C(=O)NR^cR^d, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

or two R^{Aa} on the same atom are taken together to form an oxo;

n is 0-4;

R^1 and R^2 are independently hydrogen, deuterium, halogen, -CN, -NO₂, -OH, -OR^a, -NR^cR^d, -C(=O)R^a, -C(=O)OR^b, -C(=O)NR^cR^d, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, or heterocycloalkyl;

or R^1 and R^2 are taken together to form an oxo;

or R^1 and R^2 are taken together to form a cycloalkyl or heterocycloalkyl; wherein the cycloalkyl and heterocycloalkyl is optionally substituted with deuterium, halogen, -CN, -OH, -OCH₃, -NH₂, -NHCH₃, -

$N(CH_3)_2$, $-C(=O)CH_3$, $-C(=O)OH$, $-C(=O)OCH_3$, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_1 - C_6 deuteroalkyl, C_1 - C_6 hydroxyalkyl, C_1 - C_6 aminoalkyl, or C_1 - C_6 heteroalkyl;

X is $-C(R^3)_2$ -, $-NR^4$ -, $-O$ -, or $-S$ -;

each R^3 are independently hydrogen, deuterium, halogen, $-CN$, $-NO_2$, $-OH$, $-OR^a$, $-NR^cR^d$, $-C(=O)R^a$, $-C(=O)OR^b$, $-C(=O)NR^cR^d$, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_1 - C_6 deuteroalkyl, C_1 - C_6 hydroxyalkyl, C_1 - C_6 aminoalkyl, C_1 - C_6 heteroalkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, cycloalkyl, or heterocycloalkyl;

or two R^3 are taken together to form an oxo;

R^4 is hydrogen, $-C(=O)R^a$, $-C(=O)OR^b$, $-C(=O)NR^cR^d$, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_1 - C_6 deuteroalkyl, C_1 - C_6 hydroxyalkyl, C_1 - C_6 aminoalkyl, C_1 - C_6 heteroalkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, cycloalkyl, or heterocycloalkyl;

R^5 is hydrogen, deuterium, halogen, $-CN$, $-NO_2$, $-OH$, $-OR^a$, $-NR^cR^d$, $-C(=O)R^a$, $-C(=O)OR^b$, $-C(=O)NR^cR^d$, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_1 - C_6 deuteroalkyl, C_1 - C_6 hydroxyalkyl, C_1 - C_6 aminoalkyl, C_1 - C_6 heteroalkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, cycloalkyl, or heterocycloalkyl;

R^6 is hydrogen, deuterium, halogen, $-CN$, $-NO_2$, $-OH$, $-OR^a$, $-NR^cR^d$, $-C(=O)R^a$, $-C(=O)OR^b$, $-C(=O)NR^cR^d$, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_1 - C_6 deuteroalkyl, C_1 - C_6 hydroxyalkyl, C_1 - C_6 aminoalkyl, C_1 - C_6 heteroalkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, cycloalkyl, or heterocycloalkyl;

R^7 is hydrogen, deuterium, halogen, $-CN$, $-NO_2$, $-OH$, $-OR^a$, $-NR^cR^d$, $-C(=O)R^a$, $-C(=O)OR^b$, $-C(=O)NR^cR^d$, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_1 - C_6 deuteroalkyl, C_1 - C_6 hydroxyalkyl, C_1 - C_6 aminoalkyl, C_1 - C_6 heteroalkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, cycloalkyl, or heterocycloalkyl;

Ring B is heterocycloalkyl or heteroaryl;

each R^B is independently hydrogen, deuterium, halogen, $-CN$, $-NO_2$, $-OH$, $-OR^a$, $-OC(=O)R^a$, $-OC(=O)OR^b$, $-OC(=O)NR^cR^d$, $-SH$, $-SR^a$, $-S(=O)R^a$, $-S(=O)_2R^a$, $-S(=O)_2NR^cR^d$, $-NR^cR^d$, $-NR^bC(=O)NR^cR^d$, $-NR^bC(=O)R^a$, $-NR^bC(=O)OR^b$, $-NR^bS(=O)_2R^a$, $-C(=O)R^a$, $-C(=O)OR^b$, $-C(=O)NR^cR^d$, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_1 - C_6 deuteroalkyl, C_1 - C_6 hydroxyalkyl, C_1 - C_6 aminoalkyl, C_1 - C_6 heteroalkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein the alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is optionally and independently substituted with one or more R^{Ba} ;

or two R^B on the same atom are taken together to form an oxo;

each R^{Ba} is independently deuterium, halogen, $-CN$, $-NO_2$, $-OH$, $-OR^a$, $-OC(=O)R^a$, $-OC(=O)OR^b$, $-OC(=O)NR^cR^d$, $-SH$, $-SR^a$, $-S(=O)R^a$, $-S(=O)_2R^a$, $-S(=O)_2NR^cR^d$, $-NR^cR^d$, $-NR^bC(=O)NR^cR^d$, $-NR^bC(=O)R^a$, $-NR^bC(=O)OR^b$, $-NR^bS(=O)_2R^a$, $-C(=O)R^a$, $-C(=O)C(=O)R^a$, $-C(=O)OR^b$, $-C(=O)NR^cR^d$, $-C(=O)C(=O)NR^cR^d$, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_1 - C_6 deuteroalkyl, C_1 - C_6 hydroxyalkyl, C_1 - C_6 aminoalkyl, C_1 - C_6 heteroalkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

or two R^{Ba} on the same atom are taken together to form an oxo;

m is 0-4;

Ring C is 5-membered heteroaryl;

each R^C is independently hydrogen, deuterium, halogen, -CN, -NO₂, -OH, -OR^a, -OC(=O)R^a, -OC(=O)OR^b, -OC(=O)NR^cR^d, -SH, -SR^a, -S(=O)R^a, -S(=O)₂R^a, -S(=O)₂NR^cR^d, -S(=O)(=NR^b)R^a, -SiR^cR^dOR^b, -NR^cR^d, -NR^bC(=O)NR^cR^d, -NR^bC(=O)R^a, -NR^bC(=O)OR^b, -NR^bS(=O)₂R^a, -C(=O)R^a, -C(=O)OR^b, -C(=O)NR^cR^d, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, (C₁-C₆alkyl)cycloalkyl, (C₁-C₆alkyl)heterocycloalkyl, (C₁-C₆alkyl)aryl, or (C₁-C₆alkyl)heteroaryl; wherein the alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is optionally and independently substituted with one or more R^{Ca};

each R^{Ca} is independently deuterium, halogen, -CN, -NO₂, -OH, -OR^a, -OC(=O)R^a, -OC(=O)OR^b, -OC(=O)NR^cR^d, -SH, -SR^a, -S(=O)R^a, -S(=O)₂R^a, -S(=O)₂NR^cR^d, -NR^cR^d, -NR^bC(=O)NR^cR^d, -NR^bC(=O)R^a, -NR^bC(=O)OR^b, -NR^bS(=O)₂R^a, -C(=O)R^a, -C(=O)C(=O)R^a, -C(=O)OR^b, -C(=O)NR^cR^d, -C(=O)C(=O)NR^cR^d, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

or two R^{Ca} on the same atom are taken together to form an oxo;

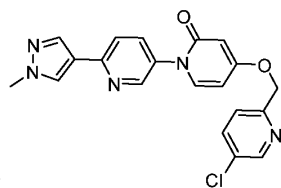
p is 0-4;

each R^a is independently C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, C₁-C₆alkyl(cycloalkyl), C₁-C₆alkyl(heterocycloalkyl), C₁-C₆alkyl(aryl), or C₁-C₆alkyl(heteroaryl); wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more oxo, deuterium, halogen, -CN, -OH, -OCH₃, -S(=O)CH₃, -S(=O)₂CH₃, -S(=O)₂NH₂, -S(=O)₂NHCH₃, -S(=O)₂N(CH₃)₂, -NH₂, -NHCH₃, -N(CH₃)₂, -C(=O)CH₃, -C(=O)OH, -C(=O)OCH₃, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, or C₁-C₆heteroalkyl;

each R^b is independently hydrogen, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, C₁-C₆alkyl(cycloalkyl), C₁-C₆alkyl(heterocycloalkyl), C₁-C₆alkyl(aryl), or C₁-C₆alkyl(heteroaryl); wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more oxo, deuterium, halogen, -CN, -OH, -OCH₃, -S(=O)CH₃, -S(=O)₂CH₃, -S(=O)₂NH₂, -S(=O)₂NHCH₃, -S(=O)₂N(CH₃)₂, -NH₂, -NHCH₃, -N(CH₃)₂, -C(=O)CH₃, -C(=O)OH, -C(=O)OCH₃, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, or C₁-C₆heteroalkyl; and

each R^c and R^d are independently hydrogen, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, C₁-C₆alkyl(cycloalkyl), C₁-C₆alkyl(heterocycloalkyl), C₁-C₆alkyl(aryl), or C₁-C₆alkyl(heteroaryl); wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more oxo,

deuterium, halogen, -CN, -OH, -OCH₃, -S(=O)CH₃, -S(=O)₂CH₃, -S(=O)₂NH₂, -S(=O)₂NHCH₃, -S(=O)₂N(CH₃)₂, -NH₂, -NHCH₃, -N(CH₃)₂, -C(=O)CH₃, -C(=O)OH, -C(=O)OCH₃, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, or C₁-C₆heteroalkyl; or R^c and R^d are taken together with the atom to which they are attached to form a heterocycloalkyl optionally substituted with one or more oxo, deuterium, halogen, -CN, -OH, -OCH₃, -S(=O)CH₃, -S(=O)₂CH₃, -S(=O)₂NH₂, -S(=O)₂NHCH₃, -S(=O)₂N(CH₃)₂, -NH₂, -NHCH₃, -N(CH₃)₂, -C(=O)CH₃, -C(=O)OH, -C(=O)OCH₃, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, or C₁-C₆heteroalkyl;

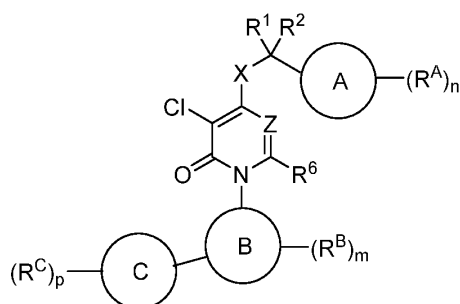


provided that the compound is not

2. The compound of claim 1, or a pharmaceutically acceptable salt, solvate, N-oxide, or stereoisomer thereof, wherein Ring A is heteroaryl.
3. The compound of claim 1, or a pharmaceutically acceptable salt, solvate, N-oxide, or stereoisomer thereof, wherein Ring A is pyridyl.
4. The compound of claim 1, or a pharmaceutically acceptable salt, solvate, N-oxide, or stereoisomer thereof, wherein Ring A is phenyl.
5. The compound of any one of claims 1-4, or a pharmaceutically acceptable salt, solvate, N-oxide, or stereoisomer thereof, wherein each R^A is independently halogen.
6. The compound of any one of claims 1-5, or a pharmaceutically acceptable salt, solvate, N-oxide, or stereoisomer thereof, wherein n is 1 or 2.
7. The compound of any one of claims 1-6, or a pharmaceutically acceptable salt, solvate, N-oxide, or stereoisomer thereof, wherein R¹ and R² are hydrogen or deuterium.
8. The compound of any one of claims 1-7, or a pharmaceutically acceptable salt, solvate, N-oxide, or stereoisomer thereof, wherein X is -O-.
9. The compound of any one of claims 1-8, or a pharmaceutically acceptable salt, solvate, N-oxide, or stereoisomer thereof, wherein R⁵ is hydrogen, deuterium, halogen, -CN, -OH, -OR^a, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkynyl, or cycloalkyl.
10. The compound of any one of claims 1-9, or a pharmaceutically acceptable salt, solvate, N-oxide, or stereoisomer thereof, wherein R⁵ is hydrogen, deuterium, halogen, -CN, or C₁-C₆alkyl.
11. The compound of any one of claims 1-10, or a pharmaceutically acceptable salt, solvate, N-oxide, or stereoisomer thereof, wherein R⁶ is hydrogen, deuterium, halogen, -CN, -OH, -OR^a, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkynyl, or cycloalkyl.

12. The compound of any one of claims 1-11, or a pharmaceutically acceptable salt, solvate, N-oxide, or stereoisomer thereof, wherein R⁶ is hydrogen, deuterium, halogen, -CN, or C₁-C₆alkyl.
13. The compound of any one of claims 1-12, or a pharmaceutically acceptable salt, solvate, N-oxide, or stereoisomer thereof, wherein R⁷ is hydrogen, deuterium, halogen, -CN, -OH, -OR^a, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkynyl, or cycloalkyl.
14. The compound of any one of claims 1-13, or a pharmaceutically acceptable salt, solvate, N-oxide, or stereoisomer thereof, wherein R⁷ is hydrogen, deuterium, halogen, -CN, or C₁-C₆alkyl.
15. The compound of any one of claims 1-14, or a pharmaceutically acceptable salt, solvate, N-oxide, or stereoisomer thereof, wherein Ring B is pyridinyl.
16. The compound of any one of claims 1-15, or a pharmaceutically acceptable salt, solvate, N-oxide, or stereoisomer thereof, wherein each R^B is independently hydrogen, deuterium, halogen, -CN, -OH, -OR^a, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkynyl, or cycloalkyl.
17. The compound of any one of claims 1-16, or a pharmaceutically acceptable salt, solvate, N-oxide, or stereoisomer thereof, wherein each R^B is independently halogen or C₁-C₆alkyl.
18. The compound of any one of claims 1-17, or a pharmaceutically acceptable salt, solvate, N-oxide, or stereoisomer thereof, wherein each R^B is independently C₁-C₆alkyl.
19. The compound of any one of claims 1-18, or a pharmaceutically acceptable salt, solvate, N-oxide, or stereoisomer thereof, wherein m is 1 or 2.
20. The compound of any one of claims 1-19, or a pharmaceutically acceptable salt, solvate, N-oxide, or stereoisomer thereof, wherein Ring C is thiazolyl, pyrazolyl, imidazolyl, oxazolyl, thiadiazole, or triazolyl.
21. The compound of any one of claims 1-20, or a pharmaceutically acceptable salt, solvate, N-oxide, or stereoisomer thereof, wherein Ring C is thiazolyl.
22. The compound of any one of claims 1-20, or a pharmaceutically acceptable salt, solvate, N-oxide, or stereoisomer thereof, wherein Ring C is pyrazolyl.
23. The compound of any one of claims 1-20, or a pharmaceutically acceptable salt, solvate, N-oxide, or stereoisomer thereof, wherein Ring C is imidazolyl.
24. The compound of any one of claims 1-20, or a pharmaceutically acceptable salt, solvate, N-oxide, or stereoisomer thereof, wherein Ring C is thiadiazole.
25. The compound of any one of claims 1-20, or a pharmaceutically acceptable salt, solvate, N-oxide, or stereoisomer thereof, wherein Ring C is triazolyl.
26. The compound of any one of claims 1-25, or a pharmaceutically acceptable salt, solvate, N-oxide, or stereoisomer thereof, wherein each R^C is independently hydrogen, deuterium, halogen, -CN, -OH, -OR^a, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, or C₁-C₆heteroalkyl.

27. The compound of any one of claims 1-26, or a pharmaceutically acceptable salt, solvate, N-oxide, or stereoisomer thereof, wherein each R^C is independently C_1 - C_6 hydroxyalkyl.
28. The compound of any one of claims 1-27, or a pharmaceutically acceptable salt, solvate, N-oxide, or stereoisomer thereof, wherein p is 1 or 2.
29. A compound of Formula (I), or a pharmaceutically acceptable salt, solvate, N-oxide, or stereoisomer thereof:



Formula (I),

wherein:

Ring A is phenyl or heteroaryl;

each R^A is independently hydrogen, deuterium, halogen, -CN, -NO₂, -OH, -OR^a, -OC(=O)R^a, -OC(=O)OR^b, -OC(=O)NR^cR^d, -SH, -SR^a, -S(=O)R^a, -S(=O)₂R^a, -S(=O)₂NR^cR^d, -NR^cR^d, -NR^bC(=O)NR^cR^d, -NR^bC(=O)R^a, -NR^bC(=O)OR^b, -NR^bS(=O)₂R^a, -C(=O)R^a, -C(=O)OR^b, -C(=O)NR^cR^d, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_1 - C_6 deuteroalkyl, C_1 - C_6 hydroxyalkyl, C_1 - C_6 aminoalkyl, C_1 - C_6 heteroalkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein the alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is optionally and independently substituted with one or more R^{Aa} ;

or two R^A on the same atom are taken together to form an oxo;

each R^{Aa} is independently deuterium, halogen, -CN, -NO₂, -OH, -OR^a, -OC(=O)R^a, -OC(=O)OR^b, -OC(=O)NR^cR^d, -SH, -SR^a, -S(=O)R^a, -S(=O)₂R^a, -S(=O)₂NR^cR^d, -NR^cR^d, -NR^bC(=O)NR^cR^d, -NR^bC(=O)R^a, -NR^bC(=O)OR^b, -NR^bS(=O)₂R^a, -C(=O)R^a, -C(=O)C(=O)R^a, -C(=O)OR^b, -C(=O)NR^cR^d, -C(=O)C(=O)NR^cR^d, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_1 - C_6 deuteroalkyl, C_1 - C_6 hydroxyalkyl, C_1 - C_6 aminoalkyl, C_1 - C_6 heteroalkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

or two R^{Aa} on the same atom are taken together to form an oxo;

n is 0-4;

R^1 and R^2 are independently hydrogen, deuterium, halogen, -CN, -NO₂, -OH, -OR^a, -NR^cR^d, -C(=O)R^a, -C(=O)OR^b, -C(=O)NR^cR^d, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_1 - C_6 deuteroalkyl, C_1 - C_6 hydroxyalkyl, C_1 - C_6 aminoalkyl, C_1 - C_6 heteroalkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, cycloalkyl, or heterocycloalkyl;

or R^1 and R^2 are taken together to form an oxo;

or R^1 and R^2 are taken together to form a cycloalkyl or heterocycloalkyl; wherein the cycloalkyl and heterocycloalkyl is optionally substituted with deuterium, halogen, -CN, -OH, -OCH₃, -NH₂, -NHCH₃, -N(CH₃)₂, -C(=O)CH₃, -C(=O)OH, -C(=O)OCH₃, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, or C₁-C₆heteroalkyl;

X is -C(R³)₂-, -NR⁴-, -O-, or -S-;

each R³ are independently hydrogen, deuterium, halogen, -CN, -NO₂, -OH, -OR^a, -NR^cR^d, -C(=O)R^a, -C(=O)OR^b, -C(=O)NR^cR^d, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, or heterocycloalkyl;

or two R³ are taken together to form an oxo;

R⁴ is hydrogen, -C(=O)R^a, -C(=O)OR^b, -C(=O)NR^cR^d, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, or heterocycloalkyl;

Z is N or CR⁵;

R⁵ is hydrogen, deuterium, halogen, -CN, -NO₂, -OH, -OR^a, -NR^cR^d, -C(=O)R^a, -C(=O)OR^b, -C(=O)NR^cR^d, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, or heterocycloalkyl;

R⁶ is hydrogen, deuterium, halogen, -CN, -NO₂, -OH, -OR^a, -NR^cR^d, -C(=O)R^a, -C(=O)OR^b, -C(=O)NR^cR^d, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, or heterocycloalkyl;

Ring B is cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

each R^B is independently hydrogen, deuterium, halogen, -CN, -NO₂, -OH, -OR^a, -OC(=O)R^a, -OC(=O)OR^b, -OC(=O)NR^cR^d, -SH, -SR^a, -S(=O)R^a, -S(=O)₂R^a, -S(=O)₂NR^cR^d, -NR^cR^d, -NR^bC(=O)NR^cR^d, -NR^bC(=O)R^a, -NR^bC(=O)OR^b, -NR^bS(=O)₂R^a, -C(=O)R^a, -C(=O)OR^b, -C(=O)NR^cR^d, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein the alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is optionally and independently substituted with one or more R^{Ba};

or two R^B on the same atom are taken together to form an oxo;

each R^{Ba} is independently deuterium, halogen, -CN, -NO₂, -OH, -OR^a, -OC(=O)R^a, -OC(=O)OR^b, -OC(=O)NR^cR^d, -SH, -SR^a, -S(=O)R^a, -S(=O)₂R^a, -S(=O)₂NR^cR^d, -NR^cR^d, -NR^bC(=O)NR^cR^d, -NR^bC(=O)R^a, -NR^bC(=O)OR^b, -NR^bS(=O)₂R^a, -C(=O)R^a, -C(=O)C(=O)R^a, -C(=O)OR^b, -C(=O)NR^cR^d, -C(=O)C(=O)NR^cR^d, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

or two R^{Ba} on the same atom are taken together to form an oxo;

m is 0-4;

Ring C is heterocycloalkyl or heteroaryl;

each R^C is independently hydrogen, deuterium, halogen, -CN, -NO₂, -OH, -OR^a, -OC(=O)R^a, -OC(=O)OR^b, -OC(=O)NR^cR^d, -SH, -SR^a, -S(=O)R^a, -S(=O)₂R^a, -S(=O)₂NR^cR^d, -S(=O)(=NR^b)R^a, -SiR^cR^dOR^b, -NR^cR^d, -NR^bC(=O)NR^cR^d, -NR^bC(=O)R^a, -NR^bC(=O)OR^b, -NR^bS(=O)₂R^a, -C(=O)R^a, -C(=O)OR^b, -C(=O)NR^cR^d, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, (C₁-C₆alkyl)cycloalkyl, (C₁-C₆alkyl)heterocycloalkyl, (C₁-C₆alkyl)aryl, or (C₁-C₆alkyl)heteroaryl; wherein the alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is optionally and independently substituted with one or more R^{Ca};

or two R^C on the same atom are taken together to form an oxo;

each R^{Ca} is independently deuterium, halogen, -CN, -NO₂, -OH, -OR^a, -OC(=O)R^a, -OC(=O)OR^b, -OC(=O)NR^cR^d, -SH, -SR^a, -S(=O)R^a, -S(=O)₂R^a, -S(=O)₂NR^cR^d, -NR^cR^d, -NR^bC(=O)NR^cR^d, -NR^bC(=O)R^a, -NR^bC(=O)OR^b, -NR^bS(=O)₂R^a, -C(=O)R^a, -C(=O)C(=O)R^a, -C(=O)OR^b, -C(=O)NR^cR^d, -C(=O)C(=O)NR^cR^d, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

or two R^{Ca} on the same atom are taken together to form an oxo;

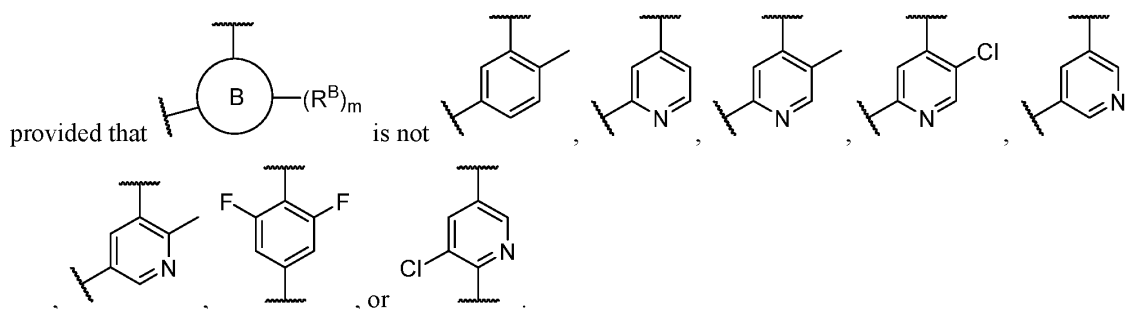
p is 0-4;

each R^a is independently C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, C₁-C₆alkyl(cycloalkyl), C₁-C₆alkyl(heterocycloalkyl), C₁-C₆alkyl(aryl), or C₁-C₆alkyl(heteroaryl); wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more oxo, deuterium, halogen, -CN, -OH, -OCH₃, -S(=O)CH₃, -S(=O)₂CH₃, -S(=O)₂NH₂, -S(=O)₂NHCH₃, -S(=O)₂N(CH₃)₂, -NH₂, -NHCH₃, -N(CH₃)₂, -C(=O)CH₃, -C(=O)OH, -C(=O)OCH₃, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, or C₁-C₆heteroalkyl;

each R^b is independently hydrogen, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, C₁-C₆alkyl(cycloalkyl), C₁-C₆alkyl(heterocycloalkyl), C₁-C₆alkyl(aryl), or C₁-C₆alkyl(heteroaryl); wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more oxo, deuterium, halogen, -CN, -OH, -OCH₃, -S(=O)CH₃, -S(=O)₂CH₃, -S(=O)₂NH₂, -S(=O)₂NHCH₃, -S(=O)₂N(CH₃)₂, -NH₂, -NHCH₃, -N(CH₃)₂, -C(=O)CH₃, -C(=O)OH, -C(=O)OCH₃, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, or C₁-C₆heteroalkyl; and

each R^c and R^d are independently hydrogen, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, C₁-C₆alkyl(cycloalkyl), C₁-C₆alkyl(heterocycloalkyl), C₁-C₆alkyl(aryl), or C₁-C₆alkyl(heteroaryl); wherein each alkyl, alkenyl, alkynyl, cycloalkyl,

heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more oxo, deuterium, halogen, -CN, -OH, -OCH₃, -S(=O)CH₃, -S(=O)₂CH₃, -S(=O)₂NH₂, -S(=O)₂NHCH₃, -S(=O)₂N(CH₃)₂, -NH₂, -NHCH₃, -N(CH₃)₂, -C(=O)CH₃, -C(=O)OH, -C(=O)OCH₃, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, or C₁-C₆heteroalkyl; or R^c and R^d are taken together with the atom to which they are attached to form a heterocycloalkyl optionally substituted with one or more oxo, deuterium, halogen, -CN, -OH, -OCH₃, -S(=O)CH₃, -S(=O)₂CH₃, -S(=O)₂NH₂, -S(=O)₂NHCH₃, -S(=O)₂N(CH₃)₂, -NH₂, -NHCH₃, -N(CH₃)₂, -C(=O)CH₃, -C(=O)OH, -C(=O)OCH₃, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, or C₁-C₆heteroalkyl;



30. The compound of claim 29, or a pharmaceutically acceptable salt, solvate, N-oxide, or stereoisomer thereof, wherein Ring A is heteroaryl.
31. The compound of claim 29, or a pharmaceutically acceptable salt, solvate, N-oxide, or stereoisomer thereof, wherein Ring A is pyridyl.
32. The compound of any one of claims 26-31, or a pharmaceutically acceptable salt, solvate, N-oxide, or stereoisomer thereof, wherein each R^A is independently halogen.
33. The compound of any one of claims 26-32, or a pharmaceutically acceptable salt, solvate, N-oxide, or stereoisomer thereof, wherein n is 1 or 2.
34. The compound of any one of claims 26-33, or a pharmaceutically acceptable salt, solvate, N-oxide, or stereoisomer thereof, wherein R¹ and R² are hydrogen or deuterium.
35. The compound of any one of claims 26-34, or a pharmaceutically acceptable salt, solvate, N-oxide, or stereoisomer thereof, wherein X is -O-.
36. The compound of any one of claims 26-35, or a pharmaceutically acceptable salt, solvate, N-oxide, or stereoisomer thereof, wherein R⁵ is hydrogen, deuterium, halogen, -CN, -OH, -OR^a, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkynyl, or cycloalkyl.
37. The compound of any one of claims 26-36, or a pharmaceutically acceptable salt, solvate, N-oxide, or stereoisomer thereof, wherein R⁵ is hydrogen, deuterium, halogen, -CN, or C₁-C₆alkyl.
38. The compound of any one of claims 26-37, or a pharmaceutically acceptable salt, solvate, N-oxide, or stereoisomer thereof, wherein R⁶ is hydrogen, deuterium, halogen, -CN, -OH, -OR^a, C₁-C₆alkyl,

C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkynyl, or cycloalkyl.

39. The compound of any one of claims 26-38, or a pharmaceutically acceptable salt, solvate, N-oxide, or stereoisomer thereof, wherein R⁶ is hydrogen, deuterium, halogen, -CN, or C₁-C₆alkyl.
40. The compound of any one of claims 26-39, or a pharmaceutically acceptable salt, solvate, N-oxide, or stereoisomer thereof, wherein Ring B is 6-membered heteroaryl.
41. The compound of any one of claims 26-40, or a pharmaceutically acceptable salt, solvate, N-oxide, or stereoisomer thereof, wherein Ring B is pyridinyl.
42. The compound of any one of claims 26-41, or a pharmaceutically acceptable salt, solvate, N-oxide, or stereoisomer thereof, wherein each R^B is independently deuterium, halogen, -CN, -OH, -OR^a, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₂-C₆alkynyl, or cycloalkyl.
43. The compound of any one of claims 26-42, or a pharmaceutically acceptable salt, solvate, N-oxide, or stereoisomer thereof, wherein each R^B is independently halogen or C₁-C₆alkyl.
44. The compound of any one of claims 26-43, or a pharmaceutically acceptable salt, solvate, N-oxide, or stereoisomer thereof, wherein m is 1 or 2.
45. The compound of any one of claims 26-39, or a pharmaceutically acceptable salt, solvate, N-oxide,

[illegible]

46. The compound of any one of claims 26-39 or 45, or a pharmaceutically acceptable salt, solvate, N-

oxide, or stereoisomer thereof, wherein



is

47. The compound of any one of claims 26-46, or a pharmaceutically acceptable salt, solvate, N-oxide, or stereoisomer thereof, wherein Ring C is a 5- or 6-membered heteroaryl.

48. The compound of any one of claims 26-47, or a pharmaceutically acceptable salt, solvate, N-oxide, or stereoisomer thereof, wherein Ring C is a pyrimidinyl.
49. The compound of any one of claims 26-48, or a pharmaceutically acceptable salt, solvate, N-oxide, or stereoisomer thereof, wherein each R^C is independently hydrogen, deuterium, halogen, -CN, -OH, -OR^a, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆deuteroalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, or C₁-C₆heteroalkyl.
50. The compound of any one of claims 26-49, or a pharmaceutically acceptable salt, solvate, N-oxide, or stereoisomer thereof, wherein each R^C is independently C₁-C₆hydroxyalkyl.
51. The compound of any one of claims 26-50, or a pharmaceutically acceptable salt, solvate, N-oxide, or stereoisomer thereof, wherein p is 1 or 2.
52. A compound selected from a compound found in table 1 or the specification, or a pharmaceutically acceptable salt, solvate, N-oxide, or stereoisomer thereof.
53. A pharmaceutical composition comprising a therapeutically effective amount of a compound of any one of claims 1-52, or a pharmaceutically acceptable salt, solvate, N-oxide, or stereoisomer thereof, and a pharmaceutically acceptable excipient.
54. A method for treating a condition comprising administering to a subject in need thereof a therapeutically effective amount of a compound of any one of claims 1-52, or a pharmaceutically acceptable salt, solvate, N-oxide, or stereoisomer thereof, wherein the condition is selected from the group consisting of an autoimmune disorder, a chronic inflammatory disorder, an acute inflammatory disorder, an auto-inflammatory disorder, a fibrotic disorder, a metabolic disorder, a neoplastic disorder, and a cardiovascular or a cerebrovascular disorder.
55. A method of treating a p38 MAP kinase-mediated disease in a subject in need thereof comprising administering to the subject a therapeutically effective amount of a compound of any one of claims 1-52, or a pharmaceutically acceptable salt, solvate, N-oxide, or stereoisomer thereof.
56. A method of treating a MK2-mediated disease in a subject in need thereof comprising administering to the subject a therapeutically effective amount of a compound of any one of claims 1-52, or a pharmaceutically acceptable salt, solvate, N-oxide, or stereoisomer thereof.