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(54) **Title**: HETEROCYCLIC COMPOUNDS AND USES THEREOF

(57) **Abstract**: Compounds and pharmaceutical compositions that modulate kinase activity, including PI3 kinase activity, and compounds, pharmaceutical compositions, and methods of treatment of diseases and conditions associated with kinase activity, including PI3 kinase activity, are described herein.

HETEROCYCLIC COMPOUNDS AND USES THEREOF

[0001] This application claims priority to U.S. Provisional Application Nos. 61/509,409, filed July 19, 2011, 61/509,458, filed July 19, 2011, 61/509,474, filed July 19, 2011, and 61/562,247, filed November 21, 2011, the entireties of which are incorporated herein by reference.

BACKGROUND

[0002] The activity of cells can be regulated by external signals that stimulate or inhibit intracellular events. The process by which stimulatory or inhibitory signals are transmitted into and within a cell to elicit an intracellular response is referred to as signal transduction. Over the past decades, cascades of signal transduction events have been elucidated and found to play a central role in a variety of biological responses. Defects in various components of signal transduction pathways have been found to account for a vast number of diseases, including numerous forms of cancer, inflammatory disorders, metabolic disorders, vascular and neuronal diseases (Gaestel et al. *Current Medicinal Chemistry* (2007) 14:2214-2234).

[0003] Kinases represent a class of important signaling molecules. Kinases can generally be classified into protein kinases and lipid kinases, and certain kinases exhibit dual specificities. Protein kinases are enzymes that phosphorylate other proteins and/or themselves (*i.e.,* autophosphorylation). Protein kinases can be generally classified into three major groups based upon their substrate utilization: tyrosine kinases which predominantly phosphorylate substrates on tyrosine residues (*e.g.,* erb2, PDGF receptor, EGF receptor, VEGF receptor, src, abl), serine/threonine kinases which predominantly phosphorylate substrates on serine and/or threonine residues (*e.g.,* mTorC1, mTorC2, ATM, ATR, DNA-PK, Akt), and dual-specificity kinases which phosphorylate substrates on tyrosine, serine and/or threonine residues.

[0004] Lipid kinases are enzymes that catalyze the phosphorylation of lipids. These enzymes, and the resulting phosphorylated lipids and lipid-derived biologically active organic molecules play a role in many different physiological processes, including cell proliferation, migration, adhesion, and differentiation. Certain lipid kinases are membrane associated and they catalyze the phosphorylation of lipids contained in or associated with cell membranes. Examples of such enzymes include phosphoinositide(s) kinases (*e.g.,* PI3-kinases, PI4-Kinases), diacylglycerol kinases, and sphingosine kinases.

[0005] The phosphoinositide 3-kinases (PI3Ks) signaling pathway is one of the most highly mutated systems in human cancers. PI3K signaling is also a key factor in many other diseases in humans. PI3K signaling is involved in many disease states including allergic contact dermatitis, rheumatoid arthritis, osteoarthritis, inflammatory bowel diseases, chronic obstructive pulmonary disorder, psoriasis, multiple sclerosis, asthma, disorders related to diabetic complications, and inflammatory complications of the cardiovascular system such as acute coronary syndrome.

[0006] PI3Ks are members of a unique and conserved family of intracellular lipid kinases that phosphorylate the 3'-OH group on phosphatidylinositols or phosphoinositides. The PI3K family comprises 15 kinases with distinct substrate specificities, expression patterns, and modes of regulation. The class I PI3Ks (p110α, p110β, p110δ, and p110γ) are typically activated by tyrosine kinases or G-protein coupled receptors to generate

PIP3, which engages downstream effectors such as those in the Akt/PDK1 pathway, mTOR, the Tec family kinases, and the Rho family GTPases. The class II and III PI3Ks play a key role in intracellular trafficking through the synthesis of PI(3)P and PI(3,4)P2. The PI3Ks are protein kinases that control cell growth (mTORC1) or monitor genomic integrity (ATM, ATR, DNA-PK, and hSmg-1).

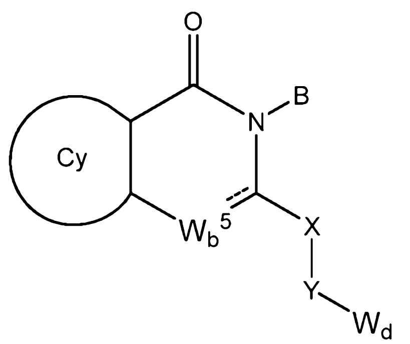
[0007] The delta (δ) isoform of class I PI3K has been implicated, in particular, in a number of diseases and biological processes. PI3K-δ is expressed primarily in hematopoietic cells including leukocytes such as T-cells, dendritic cells, neutrophils, mast cells, B-cells, and macrophages. PI3K-δ is integrally involved in mammalian immune system functions such as T-cell function, B-cell activation, mast cell activation, dendritic cell function, and neutrophil activity. Due to its integral role in immune system function, PI3K-δ is also involved in a number of diseases related to undesirable immune response such as allergic reactions, inflammatory diseases, inflammation mediated angiogenesis, rheumatoid arthritis, and auto-immune diseases such as lupus, asthma, emphysema and other respiratory diseases. Other class I PI3K involved in immune system function includes PI3K-γ, which plays a role in leukocyte signaling and has been implicated in inflammation, rheumatoid arthritis, and autoimmune diseases such as lupus.

[0008] Unlike PI3K-δ, the beta (β) isoform of class I PI3K appears to be ubiquitously expressed. PI3K-β has been implicated primarily in various types of cancer including PTEN-negative cancer (Edgar et al. *Cancer Research* (2010) 70(3):1164-1172), and HER2-overexpressing cancer such as breast cancer and ovarian cancer.

SUMMARY

[0009] Described herein are compounds capable of selectively inhibiting certain isoform(s) of class I PI3K without substantially affecting the activity of the remaining isoforms of the same class. For example, non-limiting examples of inhibitors capable of selectively inhibiting PI3K-δ and/or PI3K-γ, but without substantially affecting the activity of PI3K-β are disclosed. Such inhibitors can be effective in ameliorating disease conditions associated with PI3K-δ/γ activity.

[0010] In one aspect, provided herein are compounds are provided of Formula (I):



Formula (I)

or an enantiomer, a mixture of enantiomers, or a mixture of two or more diastereomers thereof, or its pharmaceutically acceptable forms thereof, wherein

Cy is aryl or heteroaryl substituted by 0-1 occurrences of R^3 and 0-3 occurrences of R^5;

W_b^5 is CR^8, CHR^8, or N;

R^8 is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heteroalkyl, alkoxy, amido, amino, acyl, acyloxy, sulfonamido, halo, cyano, hydroxyl, or nitro;

B is hydrogen, alkyl, amino, heteroalkyl, cycloalkyl, heterocyclyl, heterocyclylalkyl, aryl or heteroaryl, each of which is substituted with 0-4 occurrences of R^2;

each R^2 is independently alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, alkoxy, amido, amino, acyl, acyloxy, alkoxycarbonyl, sulfonamido, halo, cyano, hydroxyl, nitro, phosphate, urea or carbonate;

X is absent or is $–(CH(R^9))_z$-;

Y is absent, -O-, -S-, -S(=O)-, $-S(=O)_2$-, $-N(R^9)$-, $-C(=O)-(CHR^9)_z$-, -C(=O)-, $-N(R^9)$-C(=O)-, or $-N(R^9)$-C(=O)NH-, $-N(R^9)C(R^9)_2$-, or $-C(=O)-N(R^9)-(CHR^9)_z$;

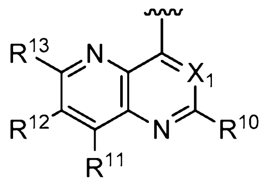
each z is independently an integer of 1, 2, 3, or 4;

wherein when W_b^5 is N, no more than one of X or Y is absent;

R^3 is alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, fluoroalkyl, heteroalkyl, alkoxy, amido, amino, acyl, acyloxy, sulfinyl, sulfonyl, sulfoxide, sulfone, sulfonamido, halo, cyano, heteroaryl, aryl, hydroxyl, or nitro; wherein each of the above substituents can be substituted with 0, 1, 2, or 3 R^{17};

each R^5 is independently alkyl, alkenyl, alkynyl, cycloalkyl, heteroalkyl, alkoxy, amido, amino, acyl, acyloxy, sulfonamido, halo, cyano, hydroxyl, or nitro;

each R^9 is independently hydrogen, alkyl, cycloalkyl, or heteroalkyl; and

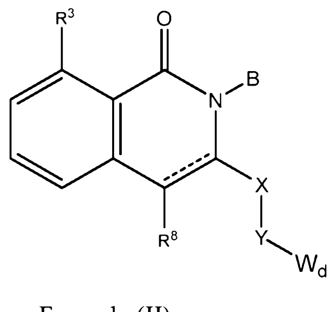
W_d is 

,

wherein X_1 is N or CR^{14};

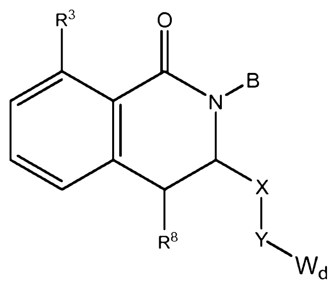
wherein R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, and R^{17} are independently hydrogen, alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, alkoxy, heterocyclyloxy, amido, amino, acyl, acyloxy, alkoxycarbonyl, sulfonamido, halo, cyano, hydroxyl, nitro, phosphate, urea, carbonate, carboxylic acid, oxo, or NR′R″ wherein R′ and R″ are taken together with nitrogen to form a cyclic moiety.

[0011] In some embodiments, the compound of Formula (I) has the structure of Formula (II):

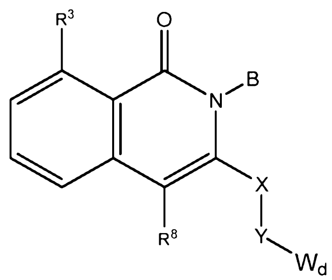


Formula (II) .

[0012] For example, the compound of Formula (II) can have a structure of Formula (IIa) or (IIb):

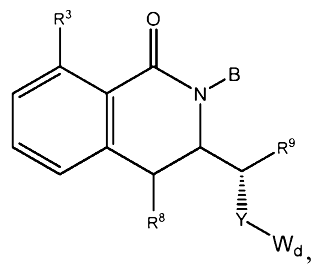


Formula (IIa) or

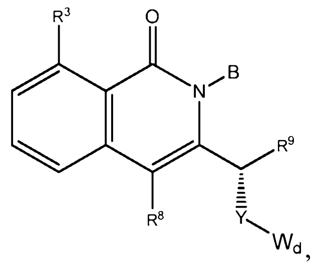


Formula (IIb) .

[0013] In other embodiments, the compound of Formula (II) has the structure of Formula (IIIa) or (IIIb):

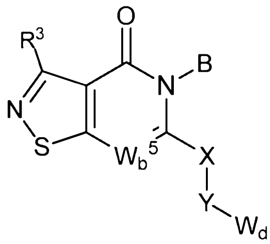


Formula (IIIa) or

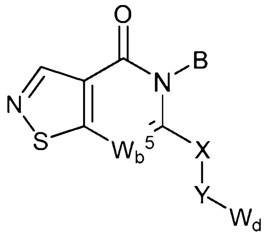


Formula (IIIb).

[0014] For example, the compound of Formula (I) has the structure of Formula (IVa) or Formula (IVb):

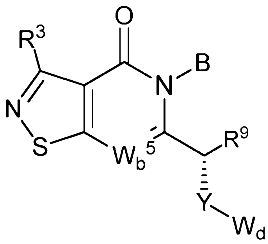


or

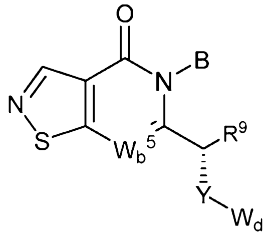


Formula (IVa) Formula (IVb).

[0015] In some embodiments, the compound of Formula (IVa) or Formula (IVb) has the structure of Formula (Va) or Formula (Vb):

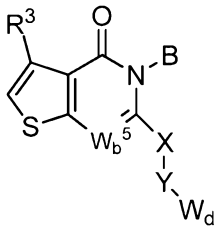


or

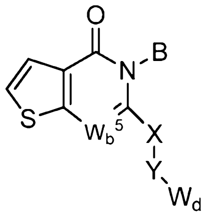


Formula (Va) Formula (Vb).

[0016] In other embodiments, the compound of Formula (I) has the structure of Formula (VIa) or Formula (VIb):

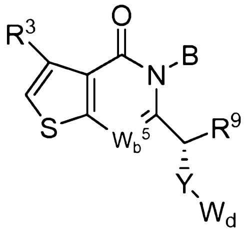


or

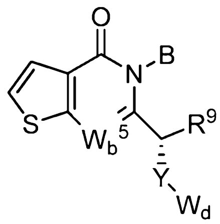


Formula (VIa) Formula (VIb).

[0017] In other embodiments, the compound of Formula (VIa) or (VIb) has the structure of Formula (VIIa) or (VIIb):

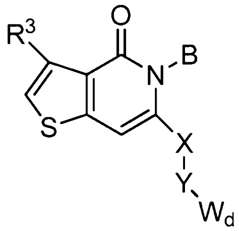


or

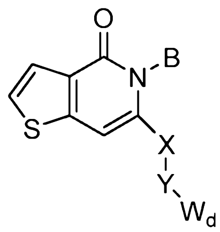


Formula (VIIa) Formula (VIIb).

[0018] In some embodiments, the compound of Formula (VIIa) or (VIIb) has the structure of Formula (VIIIa) or (VIIIb):

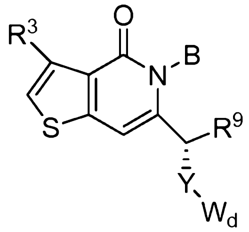


or

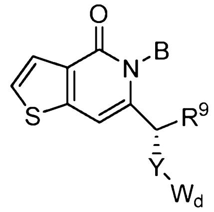


Formula (VIIIa) Formula (VIIIb).

[0019] In some embodiments, the compound of Formula (VIIa) or (VIIb) has the structure of Formula (IXa) or (IXb):

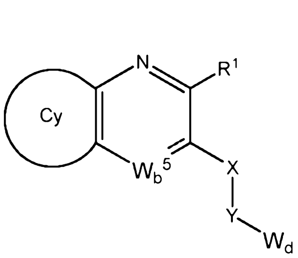


or

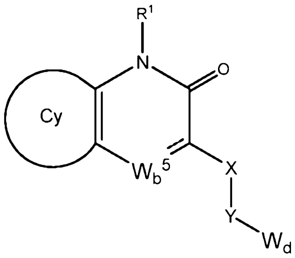


Formula (IXa) Formula (IXb).

[0020] In another aspect, provided herein are compounds of Formula (X) or (XI):



or



Formula (X) Formula (XI),

or an enantiomer, a mixture of enantiomers, or a mixture of two or more diastereomers thereof, or their pharmaceutically acceptable forms thereof, wherein:

W_b^5 is N, CHR^8, or CR^8;

R^8 is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heteroalkyl, alkoxy, amido, amino, acyl, acyloxy, sulfonamido, halo, cyano, hydroxyl, or nitro;

Cy is aryl or heteroaryl substituted by 0-1 occurrences of R^3 and 0-3 occurrences of R^5;

R^1 is –(L)-$R^{1'}$;

L is a bond, -S-, -N(R^{15})-, -C(R^{15})$_2$-, -C(=O)-, or –O-;

$R^{1'}$ is hydrogen, alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, alkoxy, heterocyclyloxy, amido, amino, acyl, acyloxy, alkoxycarbonyl, sulfonamido, halo, cyano, hydroxyl, nitro, phosphate, urea, carbonate, substituted nitrogen,or NR′R″ wherein R′ and R″ are taken together with nitrogen to form a cyclic moiety;

each R^{15} is independently hydrogen, alkyl, cycloalkyl, or heteroalkyl;

R^3 is alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, fluoroalkyl, heteroalkyl, alkoxy, amido, amino, acyl, acyloxy, sulfonamido, halo, cyano, heteroaryl, aryl, hydroxyl, or nitro; wherein each of the above substituents can be substituted with 0, 1, 2, or 3 R^{17};

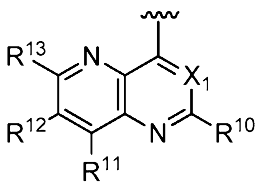
each R^5 is independently alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, alkoxy, heterocyclyloxy, amido, amino, acyl, acyloxy, alkoxycarbonyl, sulfonamido, halo, cyano, hydroxyl, nitro, phosphate, urea, carbonate, or NR′R″ wherein R′ and R″ are taken together with nitrogen to form a cyclic moiety;

X is absent or is $-(CH(R^{16}))_z-$;

Y is absent, -O-, -S-, -S(=O)-, $-S(=O)_2-$, $-N(R^{16})-$, $-C(=O)-(CHR^{16})_z-$, -C(=O)-, $-N(R^{16})-C(=O)-$, or $-N(R^{16})-C(=O)NH-$, $-N(R^{16})C(R^{16})_2-$, or $-C(=O)-N(R^{16})-(CHR^{16})_z-$;

each z is an integer of 1, 2, 3, or 4;

each R^{16} is independently hydrogen, alkyl, cycloalkyl, heterocyclyl, heteroalkyl, aryl, halo or heteroaryl; and

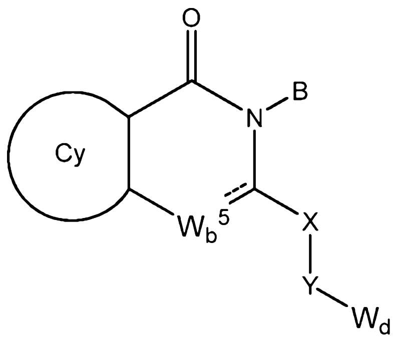
W_d is 

,

wherein X_1 is N or CR^{14};

wherein R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, and R^{17} are independently hydrogen, alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, alkoxy, heterocyclyloxy, amido, amino, acyl, acyloxy, alkoxycarbonyl, sulfonamido, halo, cyano, hydroxyl, nitro, phosphate, urea, carbonate, carboxylic acid, oxo, or NR′R″ wherein R′ and R″ are taken together with nitrogen to form a cyclic moiety.

[0021] In a first aspect, provided herein are compounds of Formula (XII):



Formula (XII)

or an enantiomer, a mixture of enantiomers, or a mixture of two or more diastereomers thereof, or its pharmaceutically acceptable forms thereof, wherein

Cy is aryl or heteroaryl substituted by 0-1 occurrences of R^3 and 0-3 occurrences of R^5;

W_b^5 is CR^8, CHR^8, or N,

R^8 is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heteroalkyl, alkoxy, amido, amino, acyl, acyloxy, sulfonamido, halo, cyano, hydroxyl, or nitro;

B is hydrogen, alkyl, amino, heteroalkyl, cycloalkyl, heterocyclyl, aryl or heteroaryl, each of which is substituted with 0-4 R^2;

R^2 is alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, alkoxy, amido, amino, acyl, acyloxy, alkoxycarbonyl, sulfonamido, halo, cyano, hydroxyl, nitro, phosphate, urea or carbonate;

X is absent or is $-(CH(R^9))_z$-;

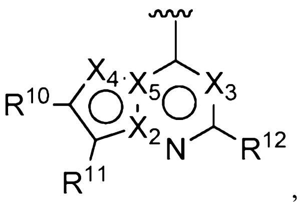
Y is absent, -O-, -S-, -S(=O)-, $-S(=O)_2-$, $-N(R^9)-$, $-C(=O)-(CHR^9)_z-$, -C(=O)-, $-N(R^9)-C(=O)-$, $-N(R^9)-C(=O)NH-$,$-N(R^9)C(R^9)_2-$, or $-C(=O)-N(R^9)-(CHR^9)_z$;

each z is independently an integer of 1, 2, 3, or 4;

R^3 is alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, haloalkyl, heteroalkyl, alkoxy, amido, amino, acyl, acyloxy, sulfinyl, sulfonyl, sulfoxide, sulfone, sulfonamido, halo, cyano, aryl, heteroaryl, hydroxyl, or nitro; wherein each of the above substituents can be substituted with 0, 1, 2, or 3 R^{17};

each R^5 is independently alkyl, alkenyl, alkynyl, cycloalkyl, heteroalkyl, alkoxy, amido, amino, acyl, acyloxy, sulfonamido, halo, cyano, hydroxyl, or nitro;

each R^9 is independently hydrogen, alkyl, cycloalkyl, or heteroalkyl; and

W_d is 

,

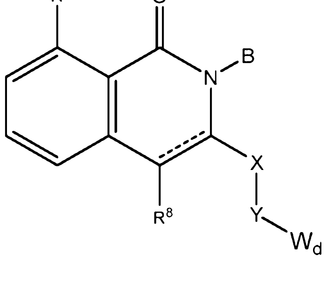
wherein one of X_5 and X_2 is N and one of X_5 and X_2 is C;

X_3 and X_4 are each independently CR^{13} or N;

X_2 and X_3 are not both N; and

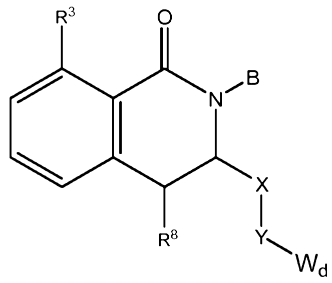
each R^{10}, R^{11}, R^{12}, R^{13}, and R^{17} is independently hydrogen, alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, alkoxy, heterocyclyloxy, amido, amino, acyl, acyloxy, alkoxycarbonyl, sulfonamido, halo, cyano, hydroxyl, nitro, phosphate, urea, carbonate, oxo, or NR′R″ wherein R′ and R″ are taken together with nitrogen to form a cyclic moiety.

[0022] In some embodiments, the compound of Formula (XII) has the structure of Formula (XIII):

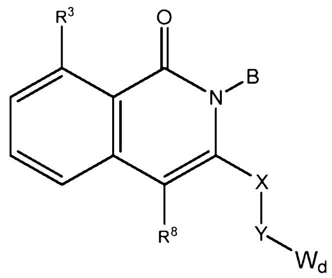


Formula (XIII) .

[0023] For example, the compound of Formula (XIII) can have a structure of Formula (XIIIa) or (XIIIb):

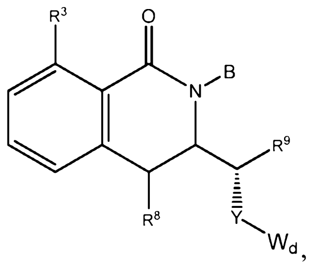


Formula (XIIIa) or

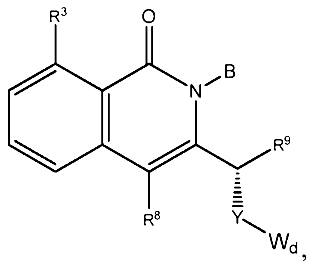


Formula (XIIIb) .

[0024] In other embodiments, the compound of Formula (XIIIa) or (XIIIb) has the structure of Formula (XIVa) or (XIVb):

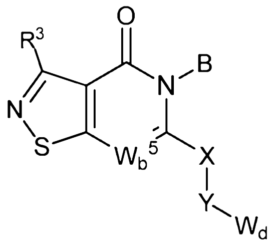
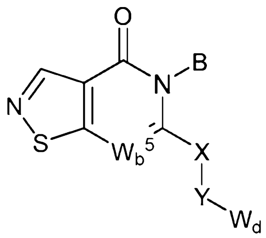


Formula (XIVa) or



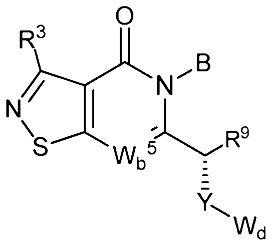
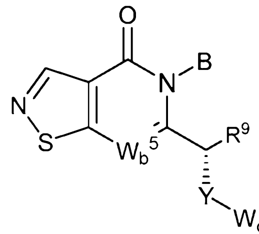
Formula (XIVb).

[0025] For example, the compound of Formula (XII) has the structure of Formula (XVa) or Formula (XVb):

 or 

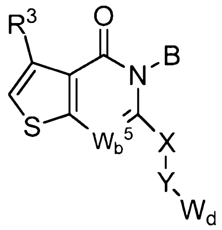
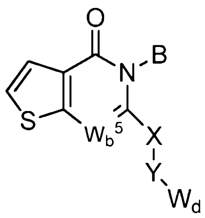
Formula (XVa) Formula (XVb).

[0026] In some embodiments, the compound of Formula (XVa) or (XVb) has the structure of Formula (XVIa) or Formula (XVIb):

 or 

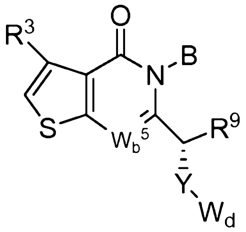
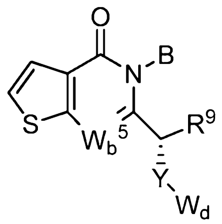
Formula (XVIa) Formula (XVIb).

[0027] In other embodiments, the compound of Formula (XII) has the structure of Formula (XVIIa) or Formula (XVIIb):

 or 

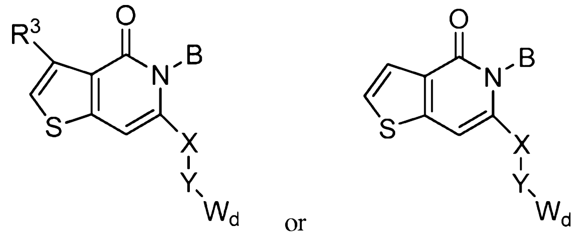
Formula (XVIIa) Formula (XVIIIb).

[0028] In other embodiments, the compound of Formula (XVIIa) or (XVIIb) has the structure of Formula (XVIIIa) or (XVIIIb):

 or 

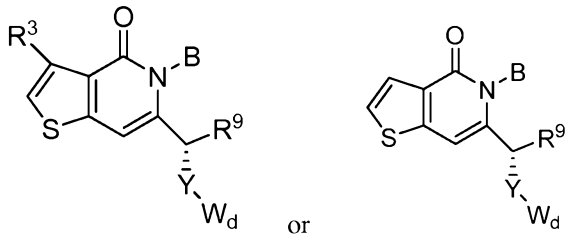
Formula (XVIIIa) Formula (XVIIIb).

[0029] In some embodiments, the compound of Formula (XVIIIa) or (XVIIIb) has the structure of Formula (XIXa) or (XIXb):



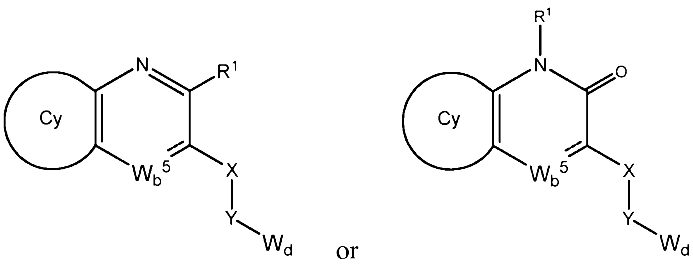
Formula (XIXa) or Formula (XIXb).

[0030] In some embodiments, the compound of Formula (XVIIIa) or (XVIIIb) has the structure of Formula (XXa) or (XXb):



Formula (XXa) or Formula (XXb).

[0031] In another aspect, provided herein is a compound of formula (XXI) or (XXII):



Formula (XXI) or Formula (XXII),

or an enantiomer, a mixture of enantiomers, or a mixture of two or more diastereomers thereof, or its pharmaceutically acceptable forms thereof, wherein:

W_b^5 is N, CHR^8 or CR^8;

R^8 is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heteroalkyl, alkoxy, amido, amino, acyl, acyloxy, sulfonamido, halo, cyano, hydroxyl, or nitro;

Cy is aryl or heteroaryl substituted by 0-1 occurrences of R^3 and 0-3 occurrences of R^5;

R^1 is –(L)-$R^{1'}$;

L is a bond, -S-, -N(R_{15})-, -C(R_{15})$_2$-, -C(=O)-, or –O-;

$R^{1'}$ is hydrogen, alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, alkoxy, heterocyclyloxy, amido, amino, acyl, acyloxy, alkoxycarbonyl, sulfonamido, halo, cyano, hydroxy, nitro, phosphate, urea, carbonate, substituted nitrogen,or NR′R″ wherein R′ and R″ are taken together with nitrogen to form a cyclic moiety;

each R^{15} is independently hydrogen, alkyl, cycloalkyl, or heteroalkyl;

R^3 is alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, haloalkyl, heteroalkyl, alkoxy, amido, amino, acyl, acyloxy, sulfinyl, sulfonyl, sulfoxide, sulfone, sulfonamido, halo, cyano, heteroaryl, aryl, hydroxyl, or nitro;

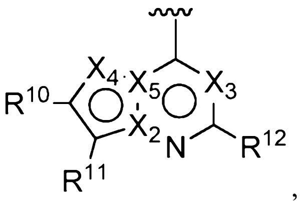
each R^5 is independently alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, alkoxy, heterocyclyloxy, amido, amino, acyl, acyloxy, alkoxycarbonyl, sulfonamido, halo, cyano, hydroxy, nitro, phosphate, urea, carbonate, oxo, or NR′R″ wherein R′ and R″ are taken together with nitrogen to form a cyclic moiety;

X is absent or is $-(CH(R^9))_z$;

Y is absent, -O-, -S-, -S(=O)-, $-S(=O)_2-$, $-N(R^9)-$, $-C(=O)-(CHR^9)_z-$, -C(=O)-, $-N(R^9)-C(=O)-$, or $-N(R^9)-C(=O)NH-$, $-N(R^9)C(R^9)_2-$, or $-C(=O)-N(R^9)-(CHR^9)_z-$;

each z is an integer of 1, 2, 3, or 4;

each R^9 is independently hydrogen, alkyl, cycloalkyl, heterocyclyl, heteroalkyl, aryl, halo or heteroaryl; and

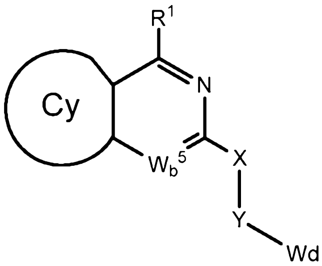
W_d is ,

wherein one of X_5 and X_2 is N and one of X_5 and X_2 is C;

wherein X_3 and X_4 are each independently selected from CR^{13} and N; and

each R^{10}, R^{11}, R^{12} and R^{13} is independently hydrogen, alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, alkoxy, heterocyclyloxy, amido, amino, acyl, acyloxy, alkoxycarbonyl, sulfonamido, halo, cyano, hydroxyl, nitro, phosphate, urea, carbonate, or NR′R″ wherein R′ and R″ are taken together with nitrogen to form a cyclic moiety.

[0032] In another aspect, provided herein is a compound of Formula (XXIII):



Formula (XXIII)

or an enantiomer, a mixture of enantiomers, or a mixture of two or more diastereomers thereof, or its pharmaceutically acceptable forms thereof, wherein

W_b^5 is N or CR^8;

R^8 is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heteroalkyl, alkoxy, amido, amino, acyl, acyloxy, sulfonamido, halo, cyano, hydroxyl, or nitro;

Cy is aryl or heteroaryl substituted by 0-1 occurrences of R^3 and 0-3 occurrences of R^5;

R^1 is –(L)-$R^{1'}$;

L is a bond, -S-, -N(R^{16})-, -C(R^{15})$_2$-, -C(=O)-, or –O-;

$R^{1'}$ is hydrogen, alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, heterocyclylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, alkoxy, heterocycloalkyloxy, amido, amino, acyl, acyloxy, alkoxycarbonyl, sulfonamido, halo, cyano, hydroxy, nitro, phosphate, urea, carbonate, substituted nitrogen,or NR′R″ wherein R′ and R″ are taken together with nitrogen to form a cyclic moiety;

R^3 is alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, haloalkyl, heteroalkyl, alkoxy, amido, amino, acyl, acyloxy, sulfinyl, sulfonyl, sulfoxide, sulfone, sulfonamido, halo, cyano, heteroaryl, aryl, hydroxyl, or nitro; wherein each of the above substituents can be substituted with 0, 1, 2, or 3 R^{17};

each R^5 is independently alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, alkoxy, heterocycloalkyloxy, amido, amino, acyl, acyloxy, alkoxycarbonyl, sulfonamido, halo, cyano, hydroxy, nitro, phosphate, urea, carbonate, or NR′R″ wherein R′ and R″ are taken together with nitrogen to form a cyclic moiety;

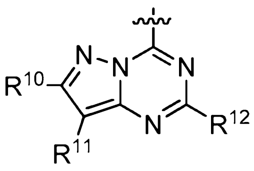
X is absent or is –(CH(R^{14}))$_z$;

Y is absent, -O-, -S-, -S(=O)-, -S(=O)$_2$-, -N(R^9)-, -C(=O)-(CHR^{14})$_z$-, -C(=O)-, -N(R^9)-C(=O)-, or -N(R^9)-C(=O)NH-,-N(R^9)C(R^{14})$_2$-, or -C(=O)-(CHR^{14})$_z$-;

each z is an integer of 1, 2, 3, or 4;

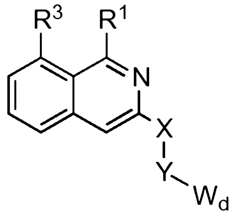
each R^9 and R^{16} is independently hydrogen, alkyl, cycloalkyl, heterocyclyl, heteroalkyl, aryl, or heteroaryl;

each R^{14} and R^{15} is independently hydrogen, alkyl, aryl, heteroaryl or halo; and

W_d is ,

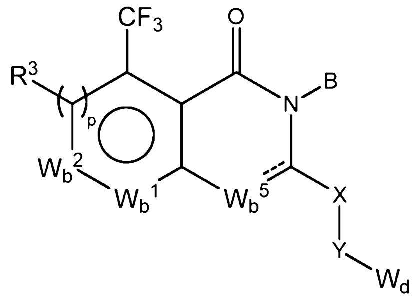
wherein R^{10}, R^{11}, R^{12}, and R^{17} are each independently hydrogen, alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, alkoxy, heterocycloalkyloxy, amido, amino, acyl, acyloxy, alkoxycarbonyl, sulfonamido, halo, cyano, hydroxy, nitro, phosphate, urea, carbonate, oxo, or NR′R″ wherein R′ and R″ are taken together with nitrogen to form a cyclic moiety.

[0033] In some embodiments, the compound of Formula (XXIII) is a compound of Formula (XXIV):



Formula (XXIV).

[0034] In one aspect, provided herein are compounds of Formula (XXV):



Formula (XXV)

or an enantiomer, a mixture of enantiomers, or a mixture of two or more diastereomers thereof, or its pharmaceutically acceptable forms thereof, wherein

W_b^1 and W_b^2 are each independently CR^3, S, O, N or NR^{13}, wherein at least one of W_b^1 and W_b^2 is CR^3, N or NR^{13};

p is 0, 1, 2 or 3;

W_b^5 is CR^8, CHR^8, or N;

R^8 is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heteroalkyl, alkoxy, amido, amino, acyl, acyloxy, sulfonamido, halo, cyano, hydroxyl, or nitro;

B is hydrogen, alkyl, amino, heteroalkyl, cycloalkyl, heterocyclyl, heterocyclylalkyl, aryl or heteroaryl, each of which is substituted with 0-4 occurrences of R^2;

X is absent or is $-(CH(R^9))_z$-;

Y is absent, -O-, -S-, -S(=O)-, -S(=O)$_2$-, -N(R^9)-, -C(=O)-(CHR^9)$_z$-, -C(=O)-, -N(R^9)-C(=O)-, or -N(R^9)-C(=O)NH-,-N(R^9)C(R^9)$_2$-, or -C(=O)-N(R^9)-(CHR^9)$_z$;

each z is independently an integer of 1, 2, 3, or 4;

wherein when W_b^5 is N, no more than one of X or Y is absent;

each R^2 is independently alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, alkoxy, amido, amino, acyl, acyloxy, alkoxycarbonyl, sulfonamido, halo, cyano, hydroxyl, nitro, phosphate, urea or carbonate;

each R^3 is independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, fluoroalkyl, heteroalkyl, alkoxy, amido, amino, acyl, acyloxy, sulfinyl, sulfonyl, sulfoxide, sulfone, sulfonamido, halo, cyano, heteroaryl, aryl, hydroxyl, or nitro;

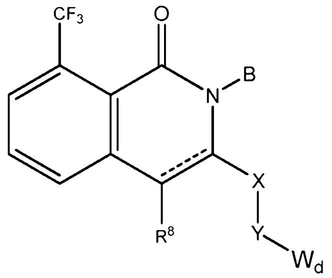
each R^9 is independently hydrogen, alkyl, cycloalkyl, heterocyclyl or heteroalkyl;

W_d is heterocyclyl, aryl, cycloalkyl, or heteroaryl which is optionally substituted with one or more R^b, R^{11} or R^{12};

wherein each R^b is independently hydrogen, halo, phosphate, urea, carbonate, alkyl, alkenyl, alkynyl, cycloalkyl, amino, heteroalkyl, or heterocyclyl; and

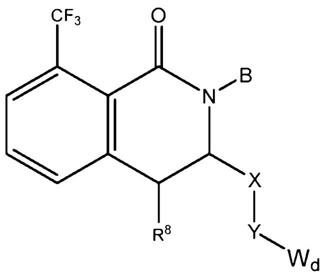
each R^{11} and R^{12} is independently hydrogen, alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, alkoxy, heterocyclyloxy, amido, amino, acyl, acyloxy, alkoxycarbonyl, sulfonamido, halo, haloalkyl, cyano, hydroxyl, nitro, phosphate, urea, carboxylic acid, carbonate, oxo, or NR′R″, wherein R′ and R″ are taken together with nitrogen to form a cyclic moiety.

[0035] In certain embodiments, the compound of Formula (XXV) has a structure of Formula (XXVI):

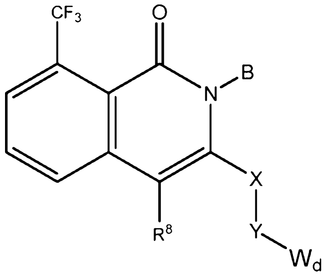


Formula (XXVI).

[0036] In some embodiments, the compound of Formula (XXVI) has a structure of Formula (XXVIa) or (XXVIb):

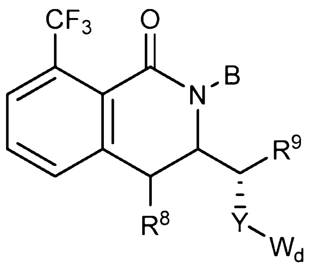


or

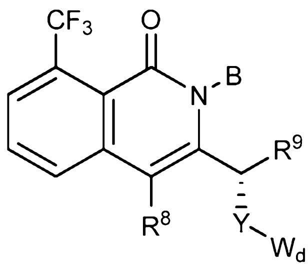


Formula (XXVIa) Formula (XXVIb).

[0037] In some embodiments, the compound of Formula (XXVI) has a structure of Formula (XXVIIa) or (XXVIIb):

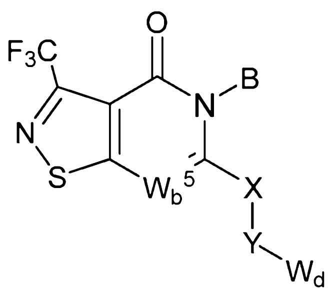


or



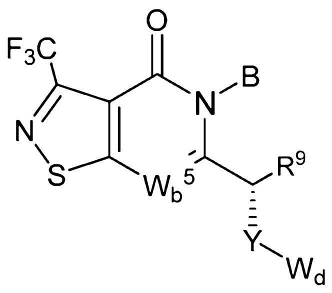
Formula (XXVIIa) Formula (XXVIIb).

[0038] In certain embodiments, the compound of Formula (XXV) has a structure of Formula (XXVIII):



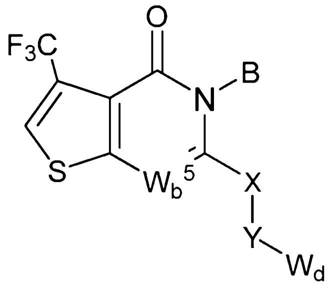
Formula (XXVIII).

[0039] In some embodiments, the compound of Formula (XXVIII) has a structure of Formula (XXIX):



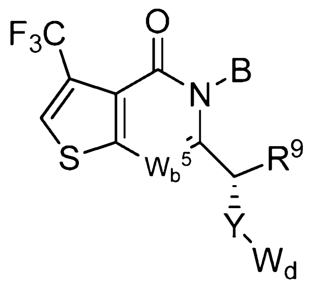
Formula (XXIX).

[0040] In certain embodiments, the compound of Formula (XXV) has a structure of Formula (XXX):



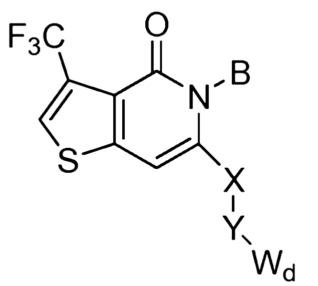
Formula (XXX).

[0041] In certain embodiments, the compound of Formula (XXX) has a structure of Formula (XXXI):



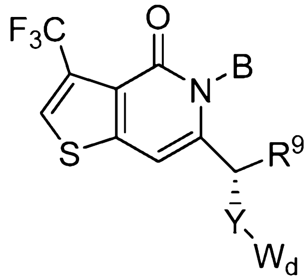
Formula (XXXI).

[0042] In certain embodiments, the compound of Formula (XXX) has a structure of Formula (XXXII):



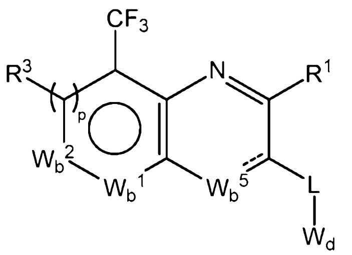
Formula (XXXII).

[0043] In some embodiments, the compound of Formula (XXXII) has a structure of Formula (XXXIII):



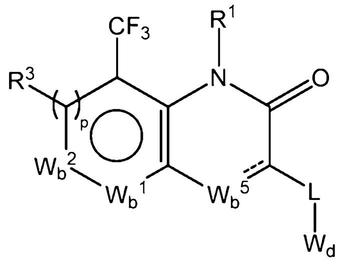
Formula (XXXIII).

[0044] In another aspect, provided herein are compounds of Formula (XXXIV) or (XXXV):



Formula (XXXIV)

or



Formula (XXXV)

or an enantiomer, a mixture of enantiomers, or a mixture of two or more diastereomers thereof, or their pharmaceutically acceptable forms thereof, wherein:

W_b^1 and W_b^2 are each independently CR^3, S, O, N or NR^{13}, wherein at least one of W_b^1 and W_b^2 is CR^3, N or NR^{13};

p is 0, 1, 2 or 3;

W_b^5 is CR^8, CHR^8, or N;

R^8 is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heteroalkyl, alkoxy, amido, amino, acyl, acyloxy, sulfonamido, halo, cyano, hydroxyl, or nitro;

R^1 is –(L)-$R^{1'}$;

L is a bond, -S-, -N(R^{15})-, -C(=O)-, or –O-;

$R^{1'}$ is hydrogen, alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, alkoxy, heterocyclyloxy, amido, amino, acyl, acyloxy, alkoxycarbonyl, sulfonamido, halo, cyano, hydroxyl, nitro, phosphate, urea, carbonate, substituted nitrogen, or NR′R″ wherein R′ and R″ are taken together with nitrogen to form a cyclic moiety;

each R^{15} is independently hydrogen, alkyl, cycloalkyl, or heteroalkyl;

X is absent or is –(CH(R^{16}))$_z$;

Y is absent, -O-, -S-, -S(=O)-, -S(=O)$_2$-, -N(R^{16})-, -C(=O)-(CHR^{16})$_z$-, -C(=O)-, -N(R^{16})-C(=O)-, or -N(R^{16})-C(=O)NH-,-N(R^{16})C(R^{16})$_2$-, or -C(=O)-N(R^{16})-(CHR^{16})$_z$-;

each z is an integer of 1, 2, 3, or 4;

each R^3 is independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, fluoroalkyl, heteroalkyl, alkoxy, amido, amino, acyl, acyloxy, sulfinyl, sulfonyl, sulfoxide, sulfone, sulfonamido, halo, cyano, heteroaryl, aryl, hydroxyl, or nitro;

each R^{13} is independently hydrogen, alkyl, cycloalkyl, heterocyclyl or heteroalkyl;

each R^{16} is independently hydrogen, alkyl, cycloalkyl, heterocyclyl, heteroalkyl, aryl, halo or heteroaryl;

W_d is heterocyclyl, aryl, cycloalkyl, or heteroaryl which is optionally substituted with one or more R^b, R^{11} or R^{12};

wherein each R^b is independently hydrogen, halo, phosphate, urea, carbonate, alkyl, alkenyl, alkynyl, cycloalkyl, amino, heteroalkyl, or heterocyclyl; and

each R^{11} and R^{12} is independently hydrogen, alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, alkoxy, heterocyclyloxy, amido, amino, acyl, acyloxy, alkoxycarbonyl, sulfonamido, halo, haloalkyl, cyano, hydroxyl, nitro, phosphate, urea, carboxylic acid, carbonate, oxo, or NR′R″, wherein R′ and R″ are taken together with nitrogen to form a cyclic moiety.

[0045] In certain embodiments, a compound as disclosed herein selectively modulates phosphatidyl inositol-3 kinase (PI3 kinase) delta isoform. In certain embodiments, the compound selectively inhibits the delta isoform over the beta isoform. By way of non-limiting example, the ratio of selectivity can be greater than a factor of about 10, greater than a factor of about 50, greater than a factor of about 100, greater than a factor of about 200, greater than a factor of about 400, greater than a factor of about 600, greater than a factor of about 800, greater than a factor of about 1000, greater than a factor of about 1500, greater than a factor of about 2000, greater than a factor of about 5000, greater than a factor of about 10,000, or greater than a factor of about 20,000, where selectivity can be measured by I_{C50}, among other means. In certain embodiments, the PI3 kinase delta isoform I_{C50} activity of a compound as disclosed herein can be less than about 1000 nM, less than about 100 nM, less than about 10 nM, or less than about 1 nM.

[0046] In certain embodiments, provided herein is a composition (*e.g.*, a pharmaceutical composition) comprising a compound as described herein and a pharmaceutically acceptable excipient. In some embodiments, provided herein is a method of inhibiting a phosphatidyl inositol-3 kinase (PI3 kinase), comprising contacting the PI3 kinase with an effective amount of a compound or pharmaceutical composition as described herein. In certain embodiments, a method is provided for inhibiting a phosphatidyl inositol-3 kinase (PI3 kinase) wherein said PI3 kinase is present in a cell. The inhibition can take place in a subject suffering from a disorder selected from cancer, bone disorder, inflammatory disease, immune disease, nervous system disease (*e.g.*, a neuropsychiatric disorder), metabolic disease, respiratory disease, thrombosis, and cardiac disease. In certain embodiments, a second therapeutic agent is administered to the subject.

[0047] In certain embodiments, a method is provided of selectively inhibiting a phosphatidyl inositol-3 kinase (PI3 kinase) delta isoform over PI3 kinase beta isoform wherein the inhibition takes place in a cell. Non-limiting examples of the methods disclosed herein can comprise contacting PI3 kinase delta isoform with an effective amount of a compound or pharmaceutical composition as disclosed herein. In an embodiment, such contact can occur in a cell.

[0048] In certain embodiments, a method is provided of selectively inhibiting a phosphatidyl inositol-3 kinase (PI3 kinase) delta isoform over PI3 kinase beta isoform wherein the inhibition takes place in a subject suffering from a disorder selected from cancer, bone disorder, inflammatory disease, immune disease, nervous system disease (*e.g.*, a neuropsychiatric disorder), metabolic disease, respiratory disease, thrombosis, and cardiac disease, said method comprising administering an effective amount of a compound or pharmaceutical composition to said subject. In certain embodiments, provided herein is a method of treating a subject suffering from a disorder associated with phosphatidyl inositol-3 kinase (PI3 kinase), said method comprising selectively modulating the phosphatidyl inositol-3 kinase (PI3 kinase) delta isoform over PI3 kinase beta isoform by administering an amount of a compound or pharmaceutical composition to said subject, wherein said amount is sufficient for selective modulation of PI3 kinase delta isoform over PI3 kinase beta isoform.

[0049] In some embodiments, provided herein is a method of making a compound as described herein.

[0050] In certain embodiments, provided herein is a reaction mixture comprising a compound as described herein.

[0051] In certain embodiments, provided herein is a kit comprising a compound as described herein.

[0052] In some embodiments, a method is provided for treating a disease or disorder described herein, the method comprising administering a therapeutically effective amount of a compound or pharmaceutical composition described herein to a subject.

[0053] In some embodiments, a method is provided for treating a PI3K mediated disorder in a subject, the method comprising administering a therapeutically effective amount of a compound or pharmaceutical composition described herein to a subject.

[0054] In some embodiments, provided herein is a use of a compound or a pharmaceutical composition described herein for the treatment of a disease or disorder described herein in a subject.

[0055] In some embodiments, provided herein is a use of a compound or a pharmaceutical composition described herein for the treatment of a PI3K mediated disorder in a subject.

[0056] In some embodiments, provided herein is a use of a compound or a pharmaceutical composition described herein in the manufacture of a medicament for the treatment of a disease or disorder described herein in a subject.

[0057] In certain embodiments, provided herein is use of a compound or a pharmaceutical composition described herein in the manufacture of a medicament for the treatment of a PI3K mediated disorder in a subject.

INCORPORATION BY REFERENCE

[0058] 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. In case of conflict, the present application, including any definitions herein, will control.

DETAILED DESCRIPTION

[0059] In one embodiment, provided are heterocyclyl compounds, and pharmaceutically acceptable forms, including, but not limited to, salts, hydrates, solvates, isomers, prodrugs, and isotopically labeled derivatives thereof.

[0060] In another embodiment, provided are methods of treating and/or managing various diseases and disorders, which comprises administering to a patient a therapeutically effective amount of a compound provided herein, or a pharmaceutically acceptable form (*e.g.*, salts, hydrates, solvates, isomers, prodrugs, and isotopically labeled derivatives) thereof. Examples of diseases and disorders are described herein.

[0061] In another embodiment, provided are methods of preventing various diseases and disorders, which comprises administering to a patient in need of such prevention a prophylactically effective amount of a compound provided herein, or a pharmaceutically acceptable form (*e.g.,* salts, hydrates, solvates, isomers, prodrugs, and isotopically labeled derivatives) thereof. Examples of diseases and disorders are described herein.

[0062] In other embodiments, a compound provided herein, or a pharmaceutically acceptable form (*e.g.,* salts, hydrates, solvates, isomers, prodrugs, and isotopically labeled derivatives) thereof, is administered in combination with another drug ("second active agent") or treatment. Second active agents include small molecules and large molecules (*e.g.*, proteins and antibodies), examples of which are provided herein, as well as stem cells. Other methods or therapies that can be used in combination with the administration of compounds provided herein include, but are not limited to, surgery, blood transfusions, immunotherapy, biological therapy, radiation therapy, and other non-drug based therapies presently used to treat, prevent or manage various disorders described herein.

[0063] Also provided are pharmaceutical compositions (*e.g.,* single unit dosage forms) that can be used in the methods provided herein. In one embodiment, pharmaceutical compositions comprise a compound provided herein, or a pharmaceutically acceptable form (*e.g.*, salts, hydrates, solvates, isomers, prodrugs, and isotopically labeled derivatives) thereof, and optionally one or more second active agents.

[0064] While specific embodiments have been discussed, the specification is illustrative only and not restrictive. Many variations of this disclosure will become apparent to those skilled in the art upon review of this specification.

[0065] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as is commonly understood by one of skill in the art to which this specification pertains.

[0066] As used in the specification and claims, the singular form "a", "an" and "the" includes plural references unless the context clearly dictates otherwise.

[0067] As used herein, "agent" or "biologically active agent" or "second active agent" refers to a biological, pharmaceutical, or chemical compound or other moiety. Non-limiting examples include simple or complex organic or inorganic molecules, a peptide, a protein, an oligonucleotide, an antibody, an antibody derivative, an antibody fragment, a vitamin, a vitamin derivative, a carbohydrate, a toxin, or a chemotherapeutic compound, and metabolites thereof. Various compounds can be synthesized, for example, small molecules and oligomers *(e.g.,* oligopeptides and oligonucleotides), and synthetic organic compounds based on various core structures. In addition, various natural sources can provide compounds for screening, such as plant or animal extracts, and the like. A skilled artisan can readily recognize that there is no limit as to the structural nature of the agents of this disclosure.

[0068] The term "agonist" as used herein refers to a compound or agent having the ability to initiate or enhance a biological function of a target protein or polypeptide, such as increasing the activity or expression of the target protein or polypeptide. Accordingly, the term "agonist" is defined in the context of the biological role of the target protein or polypeptide. While some agonists herein specifically interact with (*e.g.,* bind to) the target, compounds and/or agents that initiate or enhance a biological activity of the target protein or polypeptide by interacting with other members of the signal transduction pathway of which the target polypeptide is a member are also specifically included within this definition.

[0069] The terms "antagonist" and "inhibitor" are used interchangeably, and they refer to a compound or agent having the ability to inhibit a biological function of a target protein or polypeptide, such as by inhibiting the activity or expression of the target protein or polypeptide. Accordingly, the terms "antagonist" and "inhibitor" are defined in the context of the biological role of the target protein or polypeptide. While some antagonists herein specifically interact with (*e.g.,* bind to) the target, compounds that inhibit a biological activity of the target protein or polypeptide by interacting with other members of the signal transduction pathway of which the target protein or polypeptide are also specifically included within this definition. Non-limiting examples of biological activity inhibited by an antagonist include those associated with the development, growth, or spread of a tumor, or an undesired immune response as manifested in autoimmune disease.

[0070] An "anti-cancer agent", "anti-tumor agent" or "chemotherapeutic agent" refers to any agent useful in the treatment of a neoplastic condition. One class of anti-cancer agents comprises chemotherapeutic agents. "Chemotherapy" means the administration of one or more chemotherapeutic drugs and/or other agents to a cancer patient by various methods, including intravenous, oral, intramuscular, intraperitoneal, intravesical, subcutaneous, transdermal, buccal, or inhalation or in the form of a suppository.

[0071] The term "cell proliferation" refers to a phenomenon by which the cell number has changed as a result of division. This term also encompasses cell growth by which the cell morphology has changed (*e.g.,* increased in size) consistent with a proliferative signal.

[0072] The term "co-administration," "administered in combination with," and their grammatical equivalents, as used herein, encompasses administration of two or more agents to subject so that both agents and/or their metabolites are present in the subject at the same time. Co-administration includes simultaneous administration in separate compositions, administration at different times in separate compositions, or administration in a composition in which both agents are present.

[0073] The term "effective amount" or "therapeutically effective amount" refers to that amount of a compound or pharmaceutical composition described herein that is sufficient to effect the intended application including, but not limited to, disease treatment, as illustrated below. The therapeutically effective amount can vary depending upon the intended application (*in vitro* or *in vivo),* or the subject and disease condition being treated, *e.g.,* the weight and age of the subject, the severity of the disease condition, the manner of administration and the like, which can readily be determined by one of ordinary skill in the art. The term also applies to a dose that will induce a particular response in target cells, *e.g.,* reduction of platelet adhesion and/or cell migration. The specific dose will vary depending on, for example, the particular compounds chosen, the dosing regimen to be followed, whether it is administered in combination with other agents, timing of administration, the tissue to which it is administered, and the physical delivery system in which it is carried.

[0074] As used herein, the terms “treatment”, “treating”, “palliating” and “ameliorating” are used interchangeably herein. These terms refer to an approach for obtaining beneficial or desired results including, but not limited to, therapeutic benefit and/or a prophylactic benefit. By therapeutic benefit is meant eradication or amelioration of the underlying disorder being treated. Also, a therapeutic benefit is achieved with the eradication or amelioration of one or more of the physiological symptoms associated with the underlying disorder such that an improvement is observed in the patient, notwithstanding that the patient can still be afflicted with the underlying disorder. For prophylactic benefit, the pharmaceutical compositions can be administered to a patient at risk of developing a particular disease, or to a patient reporting one or more of the physiological symptoms of a disease, even though a diagnosis of this disease may not have been made.

[0075] A “therapeutic effect,” as that term is used herein, encompasses a therapeutic benefit and/or a prophylactic benefit as described above. A prophylactic effect includes delaying or eliminating the appearance of a disease or condition, delaying or eliminating the onset of symptoms of a disease or condition, slowing, halting, or reversing the progression of a disease or condition, or any combination thereof.

[0076] “Signal transduction” is a process during which stimulatory or inhibitory signals are transmitted into and within a cell to elicit an intracellular response. A “modulator” of a signal transduction pathway refers to a *compound* which modulates the activity of one or more cellular proteins mapped to the same specific signal transduction pathway. A modulator can augment (agonist) or suppress (antagonist) the activity of a signaling molecule.

[0077] The term “*selective* inhibition” or “selectively inhibit” as applied to a biologically active agent refers to the agent’s ability to selectively reduce the target signaling activity as compared to off-target signaling activity, via direct or interact interaction with the target. For example, a compound that selectively inhibits one isoform of PI3K over another isoform of PI3K has an activity of at least 2X against a first isoform relative to the compound’s activity against the second isoform (*e.g.*, at least about 3X, 5X, 10X, 20X, 50X, or 100X).

[0078] “Radiation therapy” means exposing a patient, using routine methods and compositions known to the practitioner, to *radiation* emitters such as, but not limited to, alpha-particle emitting radionuclides (*e.g.,* actinium and thorium radionuclides), low linear energy transfer (LET) radiation emitters (*i.e.,* beta emitters), conversion electron emitters (*e.g.,* strontium-89 and samarium-153-EDTMP), or high-energy radiation, including without limitation x-rays, gamma rays, and neutrons.

[0079] “Subject” to which administration is contemplated includes, but is not limited to, humans (*i.e.*, a male or female of any age group, *e.g.*, a pediatric subject (*e.g.*, infant, child, adolescent) or adult subject (*e.g.*, young adult, middle–aged adult or senior adult)) and/or other primates (*e.g.*, cynomolgus *monkeys*, rhesus monkeys); mammals, including commercially relevant mammals such as cattle, pigs, horses, sheep, goats, cats, and/or dogs; and/or birds, including commercially relevant birds such as chickens, ducks, geese, quail, and/or turkeys.

[0080] The term "*in vivo*" refers to an event that takes place in a subject's body.

[0081] The term "*in vitro*" refers to an event that takes places outside of a subject's body. For example, an *in* vitro assay encompasses any assay conducted outside of a subject. *In vitro* assays encompass cell-based assays in which cells, alive or dead, are employed. *In vitro* assays also encompass a cell-free assay in which no intact cells are employed.

[0082] As used herein, "pharmaceutically acceptable esters" include, but are not limited to, alkyl, alkenyl, alkynyl, aryl, aralkyl, and cycloalkyl esters of acidic groups, including, but not limited to, carboxylic acids, phosphoric acids, phosphinic acids, sulfonic acids, sulfinic acids and boronic acids.

[0083] As used herein, "pharmaceutically acceptable enol ethers" include, but are not limited to, derivatives of formula -C=C(OR) where R can be selected from alkyl, alkenyl, alkynyl, aryl, aralkyl and cycloalkyl. Pharmaceutically acceptable enol esters include, but are not limited to, derivatives of formula -C=C(OC(O)R) where R can be selected from hydrogen, alkyl, alkenyl, alkynyl, aryl, aralkyl and cycloalkyl.

[0084] As used herein, a "pharmaceutically acceptable form" of a disclosed compound includes, but is not limited to, pharmaceutically acceptable salts, hydrates, solvates, isomers, prodrugs, and isotopically labeled derivatives of disclosed compounds. In one embodiment, a "pharmaceutically acceptable form" includes, but is not limited to, pharmaceutically acceptable salts, isomers, prodrugs and isotopically labeled derivatives of disclosed compounds.

[0085] In certain embodiments, the pharmaceutically acceptable form is a pharmaceutically acceptable salt. As used herein, the term "pharmaceutically acceptable salt" refers to those salts which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of subjects without undue toxicity, irritation, allergic response and the like, and are commensurate with a reasonable benefit/risk ratio. Pharmaceutically acceptable salts are well known in the art. For example, Berge *et al.* describes pharmaceutically acceptable salts in detail in *J. Pharmaceutical Sciences* (1977) 66:1–19. Pharmaceutically acceptable salts of the compounds provided herein include those derived from suitable inorganic and organic acids and bases. Examples of pharmaceutically acceptable, nontoxic acid addition salts are salts of an amino group formed with inorganic acids such as hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid and perchloric acid or with organic acids such as acetic acid, oxalic acid, maleic acid, tartaric acid, citric acid, succinic acid or malonic acid or by using other methods used in the art such as ion exchange. Other pharmaceutically acceptable salts include adipate, alginate, ascorbate, aspartate, benzenesulfonate, besylate, benzoate, bisulfate, borate, butyrate, camphorate, camphorsulfonate, citrate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, formate, fumarate, glucoheptonate, glycerophosphate, gluconate, hemisulfate, heptanoate, hexanoate, hydroiodide, 2–hydroxy–ethanesulfonate, lactobionate, lactate, laurate, lauryl sulfate, malate, maleate, malonate, methanesulfonate, 2–naphthalenesulfonate, nicotinate, nitrate, oleate, oxalate, palmitate, pamoate, pectinate, persulfate, 3–phenylpropionate, phosphate, picrate, pivalate, propionate, stearate, succinate, sulfate, tartrate, thiocyanate, p–toluenesulfonate, undecanoate, valerate salts, and the like. In some embodiments, organic acids from which salts can be derived include, for example, acetic acid, propionic acid, glycolic acid, pyruvic acid, oxalic acid, maleic acid, malonic acid, succinic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, salicylic acid, and the like.

[0086] Pharmaceutically acceptable salts derived from appropriate bases include alkali metal, alkaline earth metal, ammonium and $N^+(C_{1-4}alkyl)^4$- salts. Representative alkali or alkaline earth metal salts include sodium, lithium, potassium, calcium, magnesium, iron, zinc, copper, manganese, aluminum, and the like. Further pharmaceutically acceptable salts include, when appropriate, nontoxic ammonium, quaternary ammonium, and amine cations formed using counterions such as halide, hydroxide, carboxylate, sulfate, phosphate, nitrate, lower alkyl sulfonate and aryl sulfonate. Organic bases from which salts can be derived include, for example, primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines, basic ion exchange resins, and the like, such as isopropylamine, trimethylamine, diethylamine, triethylamine, tripropylamine, and ethanolamine. In some embodiments, the pharmaceutically acceptable base addition salt is chosen from ammonium, potassium, sodium, calcium, and magnesium salts.

[0087] In certain embodiments, the pharmaceutically acceptable form is a "solvate" (*e.g.,* a hydrate). As used herein, the term "solvate" refers to compounds that further include a stoichiometric or non-stoichiometric amount of solvent bound by non-covalent intermolecular forces. The solvate can be of a disclosed compound or a pharmaceutically acceptable salt thereof. Where the solvent is water, the solvate is a "hydrate". Pharmaceutically acceptable solvates and hydrates are complexes that, for example, can include 1 to about 100, or 1 to about 10, or one to about 2, about 3 or about 4, solvent or water molecules. It will be understood that the term "compound" as used herein encompasses the compound and solvates of the compound, as well as mixtures thereof.

[0088] In certain embodiments, the pharmaceutically acceptable form is a prodrug. As used herein, the term "prodrug" refers to compounds that are transformed *in vivo* to yield a disclosed compound or a pharmaceutically acceptable form of the compound. A prodrug can be inactive when administered to a subject, but is converted *in vivo* to an active compound, for example, by hydrolysis (*e.g.,* hydrolysis in blood). In certain cases, a prodrug has improved physical and/or delivery properties over the parent compound. Prodrugs are typically designed to enhance pharmaceutically and/or pharmacokinetically based properties associated with the parent compound. The prodrug compound often offers advantages of solubility, tissue compatibility or delayed release in a mammalian organism (*see, e.g.,* Bundgard, H., *Design of Prodrugs* (1985), pp. 7-9, 21-24 (Elsevier, Amsterdam). A discussion of prodrugs is provided in Higuchi, T., et al., "Pro-drugs as Novel Delivery Systems," *A.C.S. Symposium Series,* Vol. 14, and in *Bioreversible Carriers in Drug Design*, ed. Edward B. Roche, American Pharmaceutical Association and Pergamon Press, 1987, both of which are incorporated in full by reference herein. Exemplary advantages of a prodrug can include, but are not limited to, its physical properties, such as enhanced water solubility for parenteral administration at physiological pH compared to the parent compound, or it enhances absorption from the digestive tract, or it can enhance drug stability for long–term storage.

[0089] The term "prodrug" is also meant to include any covalently bonded carriers, which release the active compound *in vivo* when such prodrug is administered to a subject. Prodrugs of an active compound, as described herein, can be prepared by modifying functional groups present in the active compound in such a way that the modifications are cleaved, either in routine manipulation or *in vivo*, to the parent active compound. Prodrugs include compounds wherein a hydroxy, amino or mercapto group is bonded to any group that, when the prodrug of the active compound is administered to a subject, cleaves to form a free hydroxy, free amino or free mercapto group, respectively. Examples of prodrugs include, but are not limited to, acetate, formate and benzoate derivatives of an alcohol or acetamide, formamide and benzamide derivatives of an amine functional group in the active compound and the like. Other examples of prodrugs include compounds that comprise -NO, -NO_2, -ONO, or -ONO_2 moieties. Prodrugs can typically be prepared using well-known methods, such as those described in *Burger's Medicinal Chemistry and Drug Discovery*, 172-178, 949-982 (Manfred E. Wolff ed., 5th ed., 1995), and *Design of Prodrugs* (H. Bundgaard ed., Elselvier, New York, 1985).

[0090] For example, if a disclosed compound or a pharmaceutically acceptable form of the compound contains a carboxylic acid functional group, a prodrug can comprise a pharmaceutically acceptable ester formed by the replacement of the hydrogen atom of the acid group with a group such as (C_1-C_8)alkyl, (C_2-C_{12})alkanoyloxymethyl, 1-(alkanoyloxy)ethyl having from 4 to 9 carbon atoms, 1-methyl-1-(alkanoyloxy)-ethyl having from 5 to 10 carbon atoms, alkoxycarbonyloxymethyl having from 3 to 6 carbon atoms, 1-(alkoxycarbonyloxy)ethyl having from 4 to 7 carbon atoms, 1-methyl-1-(alkoxycarbonyloxy)ethyl having from 5 to 8 carbon atoms, N-(alkoxycarbonyl)aminomethyl having from 3 to 9 carbon atoms, 1-(N-(alkoxycarbonyl)amino)ethyl having from 4 to 10 carbon atoms, 3-phthalidyl, 4-crotonolactonyl, gamma-butyrolacton-4-yl, di-N,N-(C_1-C_2)alkylamino(C_2-C_3)alkyl (such as β-dimethylaminoethyl), carbamoyl-(C_1-C_2)alkyl, N,N-di(C_1-C_2)alkylcarbamoyl-(C_1-C_2)alkyl and piperidino-, pyrrolidino- or morpholino(C_2-C_3)alkyl.

[0091] Similarly, if a disclosed compound or a pharmaceutically acceptable form of the compound contains an alcohol functional group, a prodrug can be formed by the replacement of the hydrogen atom of the alcohol group with a group such as (C_1-C_6)alkanoyloxymethyl, 1-((C_1-C_6)alkanoyloxy)ethyl, 1-methyl-1-((C_1-C_6)alkanoyloxy)ethyl (C_1-C_6)alkoxycarbonyloxymethyl, N-(C_1-C_6)alkoxycarbonylaminomethyl, succinoyl, (C_1-C_6)alkanoyl, α-amino(C_1-C_4)alkanoyl, arylacyl and α-aminoacyl, or α-aminoacyl-α-aminoacyl, where each α-aminoacyl group is independently selected from the naturally occurring L-amino acids, $P(O)(OH)_2$, -$P(O)(O(C_1$-$C_6)alkyl)_2$ or glycosyl (the radical resulting from the removal of a hydroxyl group of the hemiacetal form of a carbohydrate).

[0092] If a disclosed compound or a pharmaceutically acceptable form of the compound incorporates an amine functional group, a prodrug can be formed by the replacement of a hydrogen atom in the amine group with a group such as R-carbonyl, RO-carbonyl, NRR′-carbonyl where R and R′ are each independently (C_1-C_{10})alkyl, (C_3-C_7)cycloalkyl, benzyl, a natural α-aminoacyl or natural α-aminoacyl-natural α-aminoacyl, —C(OH)C(O)OY^1 wherein Y^1 is H, (C_1-C_6)alkyl or benzyl, -C(OY^2)Y^3 wherein Y^2 is (C_1-C_4) alkyl and Y^3 is (C_1-C_6)alkyl, carboxy(C_1-C_6)alkyl, amino(C_1-C_4)alkyl or mono-N— or di-N,N—(C_1-C_6)alkylaminoalkyl, —C(Y^4)Y^5 wherein Y^4 is H or methyl and Y^5 is mono-N— or di-N,N—(C_1-C_6)alkylamino, morpholino, piperidin-1-yl or pyrrolidin-1-yl.

[0093] In certain embodiments, the pharmaceutically acceptable form is an isomer. "Isomers" are different compounds that have the same molecular formula. "Stereoisomers" are isomers that differ only in the way the atoms are arranged in space. As used herein, the term "isomer" includes any and all geometric isomers and stereoisomers. For example, "isomers" include geometric double bond cis– and trans–isomers, also termed E– and

Z– isomers; R– and S–enantiomers; diastereomers, (d)–isomers and (l)–isomers, racemic mixtures thereof; and other mixtures thereof, as falling within the scope of this disclosure.

[0094] Geometric isomers can be represented by the symbol $\overline{\text{- - - - - -}}$ which denotes a bond that can be a single, double or triple bond as described herein. Provided herein are various geometric isomers and mixtures thereof resulting from the arrangement of substituents around a carbon-carbon double bond or arrangement of substituents around a carbocyclic ring. Substituents around a carbon-carbon double bond are designated as being in the "*Z*" or "*E*" configuration wherein the terms "*Z*" and "*E*" are used in accordance with IUPAC standards. Unless otherwise specified, structures depicting double bonds encompass both the "*E*" and "*Z*" isomers.

[0095] Substituents around a carbon-carbon double bond alternatively can be referred to as "cis" or "trans," where "cis" represents substituents on the same side of the double bond and "trans" represents substituents on opposite sides of the double bond. The arrangement of substituents around a carbocyclic ring can also be designated as "cis" or "trans." The term "cis" represents substituents on the same side of the plane of the ring, and the term "trans" represents substituents on opposite sides of the plane of the ring. Mixtures of compounds wherein the substituents are disposed on both the same and opposite sides of plane of the ring are designated "cis/trans."

[0096] "Enantiomers" are a pair of stereoisomers that are non-superimposable mirror images of each other. A mixture of a pair of enantiomers in any proportion can be known as a "racemic" mixture. The term "(±)" is used to designate a racemic mixture where appropriate. "Diastereoisomers" are stereoisomers that have at least two asymmetric atoms, but which are not mirror-images of each other. The absolute stereochemistry is specified according to the Cahn-Ingold-Prelog R-S system. When a compound is an enantiomer, the stereochemistry at each chiral carbon can be specified by either R or S. Resolved compounds whose absolute configuration is unknown can be designated (+) or (-) depending on the direction (dextro- or levorotatory) which they rotate plane polarized light at the wavelength of the sodium D line. Certain of the compounds described herein contain one or more asymmetric centers and can thus give rise to enantiomers, diastereomers, and other stereoisomeric forms that can be defined, in terms of absolute stereochemistry at each asymmetric atom, as (R)- or (S)-. The present chemical entities, pharmaceutical compositions and methods are meant to include all such possible isomers, including racemic mixtures, optically substantially pure forms and intermediate mixtures. Optically active (R)- and (S)- isomers can be prepared, for example, using chiral synthons or chiral reagents, or resolved using conventional techniques.

[0097] The "enantiomeric excess" or "% enantiomeric excess" of a composition can be calculated using the equation shown below. In the example shown below, a composition contains 90% of one enantiomer, *e.g.,* the S enantiomer, and 10% of the other enantiomer, *e.g.,* the R enantiomer.

$$ee = (90\text{-}10)/100 = 80\%.$$

[0098] Thus, a composition containing 90% of one enantiomer and 10% of the other enantiomer is said to have an enantiomeric excess of 80%. Some compositions described herein contain an enantiomeric excess of at least about 50%, about 75%, about 90%, about 95%, or about 99% of the S enantiomer. In other words, the compositions contain an enantiomeric excess of the S enantiomer over the R enantiomer. In other embodiments, some compositions described herein contain an enantiomeric excess of at least about 50%, about 75%, about 90%, about 95%, or about 99% of the R enantiomer. In other words, the compositions contain an enantiomeric excess of the R enantiomer over the S enantiomer.

[0099] For instance, an isomer/enantiomer can, in some embodiments, be provided substantially free of the corresponding enantiomer, and can also be referred to as “optically enriched,” “enantiomerically enriched,” “enantiomerically pure” and “non-racemic,” as used interchangeably herein. These terms refer to compositions in which the percent by weight of one enantiomer is greater than the amount of that one enantiomer in a control mixture of the racemic composition (*e.g.,* greater than 1:1 by weight). For example, an enantiomerically enriched preparation of the S enantiomer, means a preparation of the compound having greater than about 50% by weight of the S enantiomer relative to the R enantiomer, such as at least about 75% by weight, further such as at least about 80% by weight. In some embodiments, the enrichment can be much greater than about 80% by weight, providing a “substantially enantiomerically enriched,” “substantially enantiomerically pure” or a "substantially non-racemic" preparation, which refers to preparations of compositions which have at least about 85% by weight of one enantiomer relative to other enantiomer, such as at least about 90% by weight, and further such as at least about 95% by weight. In certain embodiments, the compound provided herein is made up of at least about 90% by weight of one enantiomer. In other embodiments, the compound is made up of at least about 95%, about 98%, or about 99% by weight of one enantiomer.

[00100] In some embodiments, the compound is a racemic mixture of (S)- and (R)- isomers. In other embodiments, provided herein is a mixture of compounds wherein individual compounds of the mixture exist predominately in an (S)- or (R)- isomeric configuration. For example, the compound mixture has an (S)-enantiomeric excess of greater than about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, about 95%, about 96%, about 97%, about 98%, about 99%, about 99.5%, or more. In other embodiments, the compound mixture has an (S)-enantiomeric excess of greater than about 55% to about 99.5%, greater than about about 60% to about 99.5%, greater than about 65% to about 99.5%, greater than about 70% to about 99.5%, greater than about 75% to about 99.5%, greater than about 80% to about 99.5%, greater than about 85% to about 99.5%, greater than about 90% to about 99.5%, greater than about 95% to about 99.5%, greater than about 96% to about 99.5%, greater than about 97% to about 99.5%, greater than about 98% to greater than about 99.5%, greater than about 99% to about 99.5%, or more.

[00101] In other embodiments, the compound mixture has an (R)-enantiomeric purity of greater than about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, about 95%, about 96%, about 97%, about 98%, about 99%, about 99.5% or more. In some other embodiments, the compound mixture has an (R)-enantiomeric excess of greater than about 55% to about 99.5%, greater than about about 60% to about 99.5%, greater than about 65% to about 99.5%, greater than about 70% to about 99.5%, greater than about 75% to about 99.5%, greater than about 80% to about 99.5%, greater than about 85% to about 99.5%, greater than about 90% to about 99.5%, greater than about 95% to about 99.5%, greater than about 96% to about 99.5%, greater than about 97% to about 99.5%, greater than about 98% to greater than about 99.5%, greater than about 99% to about 99.5% or more.

[00102] In other embodiments, the compound mixture contains identical chemical entities except for their stereochemical orientations, namely (S)- or (R)- isomers. For example, if a compound disclosed herein has -CH(R)- unit, and R is not hydrogen, then the -CH(R)- is in an (S)- or (R)- stereochemical orientation for each of the identical chemical entities. In some embodiments, the mixture of identical chemical entities is a racemic mixture of (S)- and (R)- isomers. In another embodiment, the mixture of the identical chemical entities (except for their stereochemical orientations), contain predominately (S)-isomers or predominately (R)- isomers. For example, the (S)- isomers in the mixture of identical chemical entities are present at about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, about 95%, about 96%, about 97%, about 98%, about 99%, about 99.5% ,or more, relative to the (R)- isomers. In some embodiments, the (S)- isomers in the mixture of identical chemical entities are present at an (S)-enantiomeric excess of greater than about 55% to about 99.5%, greater than about about 60% to about 99.5%, greater than about 65% to about 99.5%, greater than about 70% to about 99.5%, greater than about 75% to about 99.5%, greater than about 80% to about 99.5%, greater than about 85% to about 99.5%, greater than about 90% to about 99.5%, greater than about 95% to about 99.5%, greater than about 96% to about 99.5%, greater than about 97% to about 99.5%, greater than about 98% to greater than about 99.5%, greater than about 99% to about 99.5% or more.

[00103] In another embodiment, the (R)- isomers in the mixture of identical chemical entities (except for their stereochemical orientations), are present at about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, about 95%, about 96%, about 97%, about 98%, about 99%, about 99.5%, or more, relative to the (S)- isomers. In some embodiments, the (R)- isomers in the mixture of identical chemical entities (except for their stereochemical orientations), are present at a (R)- enantiomeric excess greater than about 55% to about 99.5%, greater than about about 60% to about 99.5%, greater than about 65% to about 99.5%, greater than about 70% to about 99.5%, greater than about 75% to about 99.5%, greater than about 80% to about 99.5%, greater than about 85% to about 99.5%, greater than about 90% to about 99.5%, greater than about 95% to about 99.5%, greater than about 96% to about 99.5%, greater than about 97% to about 99.5%, greater than about 98% to greater than about 99.5%, greater than about 99% to about 99.5%, or more.

[00104] Enantiomers can be isolated from racemic mixtures by any method known to those skilled in the art, including chiral high pressure liquid chromatography (HPLC), the formation and crystallization of chiral salts, or prepared by asymmetric syntheses. *See,* for example, *Enantiomers, Racemates and Resolutions* (Jacques, Ed., Wiley Interscience, New York, 1981); Wilen et al., *Tetrahedron* 33:2725 (1977); *Stereochemistry of Carbon Compounds* (E.L. Eliel, Ed., McGraw–Hill, NY, 1962); and *Tables of Resolving Agents and Optical Resolutions* p. 268 (E.L. Eliel, Ed., Univ. of Notre Dame Press, Notre Dame, IN 1972).

[00105] In certain embodiments, the pharmaceutically acceptable form is a tautomer. As used herein, the term "tautomer" is a type of isomer that includes two or more interconvertable compounds resulting from at least one formal migration of a hydrogen atom and at least one change in valency (*e.g.,* a single bond to a double bond, a triple bond to a single bond, or vice versa). "Tautomerization" includes prototropic or proton-shift tautomerization, which is considered a subset of acid-base chemistry. "Prototropic tautomerization" or "proton-shift tautomerization" involves the migration of a proton accompanied by changes in bond order. The exact ratio of the

tautomers depends on several factors, including temperature, solvent, and pH. Where tautomerization is possible (*e.g.,* in solution), a chemical equilibrium of tautomers can be reached. Tautomerizations (*i.e.,* the reaction providing a tautomeric pair) can be catalyzed by acid or base, or can occur without the action or presence of an external agent. Exemplary tautomerizations include, but are not limited to, keto–to–enol; amide–to–imide; lactam–to–lactim; enamine–to–imine; and enamine–to–(a different) enamine tautomerizations. A specific example of keto-enol tautomerization is the interconversion of pentane-2,4-dione and 4-hydroxypent-3-en-2-one tautomers. Another example of tautomerization is phenol-keto tautomerization. A specific example of phenol-keto tautomerization is the interconversion of pyridin-4-ol and pyridin-4(1H)-one tautomers.

[00106] Unless otherwise stated, structures depicted herein are also meant to include compounds which differ only in the presence of one or more isotopically enriched atoms. For example, compounds having the present structures except for the replacement of a hydrogen by a deuterium or tritium, or the replacement of a carbon by ^{13}C- or ^{14}C-enriched carbon are within the scope of this disclosure.

[00107] The disclosure also embraces isotopically labeled compounds which are identical to those recited herein, except 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 disclosed compounds include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorus, fluorine and chlorine, such as ^{2}H, ^{3}H, ^{13}C, ^{14}C, ^{15}N, ^{18}O, ^{17}O, ^{31}P, ^{32}P, ^{35}S, ^{18}F, and ^{36}Cl, respectively. Certain isotopically-labeled disclosed compounds (*e.g.,* those labeled with ^{3}H and ^{14}C) are useful in compound and/or substrate tissue distribution assays. Tritiated (*i.e.,* ^{3}H) and carbon-14 (*i.e.,* ^{14}C) isotopes can allow for ease of preparation and detectability. Further, substitution with heavier isotopes such as deuterium (*i.e.,* ^{2}H) can afford certain therapeutic advantages resulting from greater metabolic stability (*e.g.*, increased in vivo half-life or reduced dosage requirements). Isotopically labeled disclosed compounds can generally be prepared by substituting an isotopically labeled reagent for a non-isotopically labeled reagent. In some embodiments, provided herein are compounds that can also contain unnatural proportions of atomic isotopes at one or more of atoms that constitute such compounds. All isotopic variations of the compounds as disclosed herein, whether radioactive or not, are encompassed within the scope of the present disclosure.

[00108] "Pharmaceutically acceptable carrier" or "pharmaceutically acceptable excipient" includes any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents and the like. The use of such media and agents for pharmaceutically active substances is well known in the art. Except insofar as any conventional media or agent is incompatible with the active ingredient, its use in the therapeutic compositions as disclosed herein is contemplated. Supplementary active ingredients can also be incorporated into the pharmaceutical compositions.

[00109] Definitions of specific functional groups and chemical terms are described in more detail below. The chemical elements are identified in accordance with the Periodic Table of the Elements, CAS version, Handbook of Chemistry and Physics, 75th ed., inside cover, and specific functional groups are generally defined as described therein. Additionally, general principles of organic chemistry, as well as specific functional moieties and reactivity, are described in *Organic Chemistry*, Thomas Sorrell, University Science Books, Sausalito, 1999; Smith

and March *March's Advanced Organic Chemistry*, 5th ed., John Wiley & Sons, Inc., New York, 2001; Larock, *Comprehensive Organic Transformations*, VCH Publishers, Inc., New York, 1989; and Carruthers, Some *Modern Methods of Organic Synthesis*, 3rd ed., Cambridge University Press, Cambridge, 1987.

[00110] When a range of values is listed, it is intended to encompass each value and sub–range within the range. For example "C_{1-6} alkyl" is intended to encompass, C_1, C_2, C_3, C_4, C_5, C_6, C_{1-6}, C_{1-5}, C_{1-4}, C_{1-3}, C_{1-2}, C_{2-6}, C_{2-5}, C_{2-4}, C_{2-3}, C_{3-6}, C_{3-5}, C_{3-4}, C_{4-6}, C_{4-5}, and C_{5-6} alkyl.

[00111] "Alkyl" refers to a straight or branched hydrocarbon chain radical consisting solely of carbon and hydrogen atoms, containing no unsaturation, having from one to ten carbon atoms (*e.g.*, C_1-C_{10} alkyl). Whenever it appears herein, a numerical range such as "1 to 10" refers to each integer in the given range; *e.g.*, "1 to 10 carbon atoms" means that the alkyl group can consist of 1 carbon atom, 2 carbon atoms, 3 carbon atoms, etc., up to and including 10 carbon atoms, although the present definition also covers the occurrence of the term "alkyl" where no numerical range is designated. In some embodiments, it is a C_1-C_6 alkyl group. In some embodiments, alkyl groups have 1 to 10, 1 to 6, or 1 to 3 carbon atoms. Representative saturated straight chain alkyls include, but are not limited to, -methyl, -ethyl, -n-propyl, -n-butyl, -n-pentyl, and -n-hexyl; while saturated branched alkyls include, but are not limited to, -isopropyl, -sec-butyl, -isobutyl, -tert-butyl, -isopentyl, 2-methylbutyl, 3-methylbutyl, 2-methylpentyl, 3-methylpentyl, 4-methylpentyl, 2-methylhexyl, 3-methylhexyl, 4-methylhexyl, 5-methylhexyl, 2,3-dimethylbutyl, and the like. The alkyl is attached to the parent molecule by a single bond. Unless stated otherwise in the specification, an alkyl group is optionally substituted by one or more of substituents which independently include: acyl, alkyl, alkenyl, alkynyl, alkoxy, alkylaryl, cycloalkyl, aralkyl, aryl, aryloxy, amino, amido, amidino, imino, azide, carbonate, carbamate, carbonyl, heteroalkyl, heteroaryl, heteroarylalkyl, heterocycloalkyl, hydroxy, cyano, halo, haloalkoxy, haloalkyl, ester, ether, mercapto, thio, alkylthio, arylthio, thiocarbonyl, nitro, oxo, phosphate, phosphonate, phosphinate, silyl, sulfinyl, sulfonyl, sulfonamidyl, sulfoxyl, sulfonate, urea, $-Si(R^a)_3$-, $-OR^a$, $-SR^a$, $-OC(O)-R^a$, $-N(R^a)_2$, $-C(O)R^a$, $-C(O)OR^a$, $-OC(O)N(R^a)_2$, $-C(O)N(R^a)_2$, $-N(R^a)C(O)OR^a$, $-N(R^a)C(O)R^a$, $-N(R^a)C(O)N(R^a)_2$,$-N(R^a)C(NR^a)N(R^a)_2$, $-N(R^a)S(O)_tR^a$ (where t is 1 or 2), $-S(O)_tOR^a$ (where t is 1 or 2), $-S(O)_tN(R^a)_2$ (where t is 1 or 2), or $–O-P(=O)(OR^a)_2$ where each R^a is independently hydrogen, alkyl, haloalkyl, carbocyclyl, carbocyclylalkyl, aryl, aralkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl or heteroarylalkyl, and each of these moieties can be optionally substituted as defined herein.

[00112] "Perhaloalkyl" refers to an alkyl group in which all of the hydrogen atoms have been replaced with a halogen selected from fluoro, chloro, bromo, and iodo. In some embodiments, all of the hydrogen atoms are each replaced with fluoro. In some embodiments, all of the hydrogen atoms are each replaced with chloro. Examples of perhaloalkyl groups include $–CF_3$, $–CF_2CF_3$, $–CF_2CF_2CF_3$, $–CCl_3$, $–CFCl_2$, $–CF_2Cl$ and the like.

[00113] "Alkyl-cycloalkyl" refers to an -(alkyl)cycloalkyl radical where alkyl and cycloalkyl are as disclosed herein and which are optionally substituted by one or more of the substituents described as suitable substituents for alkyl and cycloalkyl respectively. The "alkyl-cycloalkyl" is bonded to the parent molecular structure through the alkyl group. The terms "alkenyl-cycloalkyl" and "alkynyl-cycloalkyl" mirror the above description of "alkyl-cycloalkyl" wherein the term "alkyl" is replaced with "alkenyl" or "alkynyl" respectively, and "alkenyl" or "alkynyl" are as described herein.

[00114] "Alkylaryl" refers to an -(alkyl)aryl radical where aryl and alkyl are as disclosed herein and which are optionally substituted by one or more of the substituents described as suitable substituents for aryl and alkyl respectively. The "alkylaryl" is bonded to the parent molecular structure through the alkyl group. The terms "-(alkenyl)aryl" and "-(alkynyl)aryl" mirror the above description of "-(alkyl)aryl" wherein the term "alkyl" is replaced with "alkenyl" or "alkynyl" respectively, and "alkenyl" or "alkynyl" are as described herein.

[00115] "Alkyl-heteroaryl" refers to an -(alkyl)heteroaryl radical where heteroaryl and alkyl are as disclosed herein and which are optionally substituted by one or more of the substituents described as suitable substituents for heteroaryl and alkyl respectively. The "alkyl-heteroaryl" is bonded to the parent molecular structure through the alkyl group. The terms "-(alkenyl)heteroaryl" and "-(alkynyl)heteroaryl" mirror the above description of "-(alkyl)heteroaryl" wherein the term "alkyl" is replaced with "alkenyl" or "alkynyl" respectively, and "alkenyl" or "alkynyl" are as described herein.

[00116] "Alkyl-heterocyclyl" refers to an –(alkyl)heterocycyl radical where alkyl and heterocyclyl are as disclosed herein and which are optionally substituted by one or more of the substituents described as suitable substituents for heterocyclyl and alkyl respectively. The "alkyl-heterocyclyl" is bonded to the parent molecular structure through the alkyl group. The terms "-(alkenyl)heterocyclyl" and "-(alkynyl)heterocyclyl" mirror the above description of "-(alkyl)heterocyclyl" wherein the term "alkyl" is replaced with "alkenyl" or "alkynyl" respectively, and "alkenyl" or "alkynyl" are as described herein.

[00117] "Alkenyl" refers to a straight or branched hydrocarbon chain radical group consisting solely of carbon and hydrogen atoms, containing at least one double bond, and having from two to ten carbon atoms (*i.e.*, C_2-C_{10} alkenyl). Whenever it appears herein, a numerical range such as "2 to 10" refers to each integer in the given range; *e.g.*, "2 to 10 carbon atoms" means that the alkenyl group can consist of 2 carbon atoms, 3 carbon atoms, etc., up to and including 10 carbon atoms. In certain embodiments, an alkenyl comprises two to eight carbon atoms. In other embodiments, an alkenyl comprises two to five carbon atoms (*e.g.*, C_2-C_5 alkenyl). The alkenyl is attached to the parent molecular structure by a single bond, for example, ethenyl (*i.e.*, vinyl), prop-1-enyl (*i.e.*, allyl), but-1-enyl, pent-1-enyl, penta-1,4-dienyl, and the like. The one or more carbon–carbon double bonds can be internal (such as in 2–butenyl) or terminal (such as in 1–butenyl). Examples of C_{2-4} alkenyl groups include ethenyl (C_2), 1–propenyl (C_3), 2–propenyl (C_3), 1–butenyl (C_4), 2–butenyl (C_4), butadienyl (C_4) and the like. Examples of C_{2-6} alkenyl groups include the aforementioned C_{2-4} alkenyl groups as well as pentenyl (C_5), pentadienyl (C_5), hexenyl (C_6) and the like. Additional examples of alkenyl include heptenyl (C_7), octenyl (C_8), octatrienyl (C_8) and the like. Unless stated otherwise in the specification, an alkenyl group is optionally substituted by one or more substituents which independently include: acyl, alkyl, alkenyl, alkynyl, alkoxy, alkylaryl, cycloalkyl, aralkyl, aryl, aryloxy, amino, amido, amidino, imino, azide, carbonate, carbamate, carbonyl, heteroalkyl, heteroaryl, heteroarylalkyl, heterocycloalkyl, hydroxy, cyano, halo, haloalkoxy, haloalkyl, ester, ether, mercapto, thio, alkylthio, arylthio, thiocarbonyl, nitro, oxo, phosphate, phosphonate, phosphinate, silyl, sulfinyl, sulfonyl, sulfonamidyl, sulfoxyl, sulfonate, urea, $-Si(R^a)_3$-, $-OR^a$, $-SR^a$, $-OC(O)-R^a$, $-N(R^a)_2$, $-C(O)R^a$, $-C(O)OR^a$, $-OC(O)N(R^a)_2$, $-C(O)N(R^a)_2$, $-N(R^a)C(O)OR^a$, $-N(R^a)C(O)R^a$, - $N(R^a)C(O)N(R^a)_2$, $N(R^a)C(NR^a)N(R^a)_2$, $-N(R^a)S(O)_tR^a$ (where t is 1 or 2), $-S(O)_tOR^a$ (where t is 1 or 2), $-S(O)_tN(R^a)_2$ (where t is 1 or 2), or $–O-P(=O)(OR^a)_2$ where each R^a is independently

hydrogen, alkyl, haloalkyl, carbocyclyl, carbocyclylalkyl, aryl, aralkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl or heteroarylalkyl, and each of these moieties can be optionally substituted as defined herein.

[00118] "Alkynyl" refers to a straight or branched hydrocarbon chain radical group consisting solely of carbon and hydrogen atoms, containing at least one triple bond, having from two to ten carbon atoms (*i.e.,* C_2-C_{10} alkynyl). Whenever it appears herein, a numerical range such as "2 to 10" refers to each integer in the given range; *e.g.,* "2 to 10 carbon atoms" means that the alkynyl group can consist of 2 carbon atoms, 3 carbon atoms, etc., up to and including 10 carbon atoms. In certain embodiments, an alkynyl comprises two to eight carbon atoms. In other embodiments, an alkynyl has two to five carbon atoms (*e.g.,* C_2-C_5 alkynyl). The alkynyl is attached to the parent molecular structure by a single bond, for example, ethynyl, propynyl, butynyl, pentynyl, hexynyl, and the like. Unless stated otherwise in the specification, an alkynyl group is optionally substituted by one or more substituents which independently include: acyl, alkyl, alkenyl, alkynyl, alkoxy, alkylaryl, cycloalkyl, aralkyl, aryl, aryloxy, amino, amido, amidino, imino, azide, carbonate, carbamate, carbonyl, heteroalkyl, heteroaryl, heteroarylalkyl, heterocycloalkyl, hydroxy, cyano, halo, haloalkoxy, haloalkyl, ester, ether, mercapto, thio, alkylthio, arylthio, thiocarbonyl, nitro, oxo, phosphate, phosphonate, phosphinate, silyl, sulfinyl, sulfonyl, sulfonamidyl, sulfoxyl, sulfonate, urea, $-Si(R^a)_3$-, $-OR^a$, $-SR^a$, $-OC(O)-R^a$, $-N(R^a)_2$, $-C(O)R^a$, $-C(O)OR^a$, $-OC(O)N(R^a)_2$, $-C(O)N(R^a)_2$, $-N(R^a)C(O)OR^a$, $-N(R^a)C(O)R^a$, - $N(R^a)C(O)N(R^a)_2$, $N(R^a)C(NR^a)N(R^a)_2$, $-N(R^a)S(O)_tR^a$ (where t is 1 or 2), $-S(O)_tOR^a$ (where t is 1 or 2), $-S(O)_tN(R^a)_2$ (where t is 1 or 2), or $-O-P(=O)(OR^a)_2$ where each R^a is independently hydrogen, alkyl, haloalkyl, carbocyclyl, carbocyclylalkyl, aryl, aralkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl or heteroarylalkyl, and each of these moieties can be optionally substituted as defined herein.

[00119] The term "alkoxy" refers to the group -O-alkyl, including from 1 to 10 carbon atoms of a straight, branched, cyclic configuration and combinations thereof, attached to the parent molecular structure through an oxygen. Examples include methoxy, ethoxy, propoxy, isopropoxy, cyclopropyloxy, cyclohexyloxy and the like. "Lower alkoxy" refers to alkoxy groups containing one to six carbons. In some embodiments, C_1-C_4 alkoxy is an alkoxy group which encompasses both straight and branched chain alkyls of from 1 to 4 carbon atoms. Unless stated otherwise in the specification, an alkoxy group is optionally substituted by one or more substituents which independently include: acyl, alkyl, alkenyl, alkynyl, alkoxy, alkylaryl, cycloalkyl, aralkyl, aryl, aryloxy, amino, amido, amidino, imino, azide, carbonate, carbamate, carbonyl, heteroalkyl, heteroaryl, heteroarylalkyl, heterocycloalkyl, hydroxy, cyano, halo, haloalkoxy, haloalkyl, ester, ether, mercapto, thio, alkylthio, arylthio, thiocarbonyl, nitro, oxo, phosphate, phosphonate, phosphinate, silyl, sulfinyl, sulfonyl, sulfonamidyl, sulfoxyl, sulfonate, urea, $-Si(R^a)_3$-, $-OR^a$, $-SR^a$, $-OC(O)-R^a$, $-N(R^a)_2$, $-C(O)R^a$, $-C(O)OR^a$, $-OC(O)N(R^a)_2$, $-C(O)N(R^a)_2$, $-N(R^a)C(O)OR^a$, $-N(R^a)C(O)R^a$, - $N(R^a)C(O)N(R^a)_2$, $N(R^a)C(NR^a)N(R^a)_2$, $-N(R^a)S(O)_tR^a$ (where t is 1 or 2), $-S(O)_tOR^a$ (where t is 1 or 2), $-S(O)_tN(R^a)_2$ (where t is 1 or 2), or $-O-P(=O)(OR^a)_2$ where each R^a is independently hydrogen, alkyl, haloalkyl, carbocyclyl, carbocyclylalkyl, aryl, aralkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl or heteroarylalkyl, and each of these moieties can be optionally substituted as defined herein. The terms "alkenoxy" and "alkynoxy" mirror the above description of "alkoxy" wherein the prefix "alk" is replaced with "alken" or "alkyn" respectively, and the parent "alkenyl" or "alkynyl" terms are as described herein.

[00120] The term "alkoxycarbonyl" refers to a group of the formula (alkoxy)(C=O)- attached to the parent molecular structure through the carbonyl carbon having from 1 to 10 carbon atoms. Thus a C_1-C_6 alkoxycarbonyl group is an alkoxy group having from 1 to 6 carbon atoms attached through its oxygen to a carbonyl linker. The C_1-C_6 designation does not include the carbonyl carbon in the atom count. "Lower alkoxycarbonyl" refers to an alkoxycarbonyl group wherein the alkyl portion of the alkoxy group is a lower alkyl group. In some embodiments, C_1-C_4 alkoxy is an alkoxy group which encompasses both straight and branched chain alkoxy groups of from 1 to 4 carbon atoms. Unless stated otherwise in the specification, an alkoxycarbonyl group is optionally substituted by one or more substituents which independently include: acyl, alkyl, alkenyl, alkynyl, alkoxy, alkylaryl, cycloalkyl, aralkyl, aryl, aryloxy, amino, amido, amidino, imino, azide, carbonate, carbamate, carbonyl, heteroalkyl, heteroaryl, heteroarylalkyl, heterocycloalkyl, hydroxy, cyano, halo, haloalkoxy, haloalkyl, ester, ether, mercapto, thio, alkylthio, arylthio, thiocarbonyl, nitro, oxo, phosphate, phosphonate, phosphinate, silyl, sulfinyl, sulfonyl, sulfonamidyl, sulfoxyl, sulfonate, urea, $-Si(R^a)_3$-, $-OR^a$, $-SR^a$, $-OC(O)-R^a$, $-N(R^a)_2$, $-C(O)R^a$, $-C(O)OR^a$, $-OC(O)N(R^a)_2$, $-C(O)N(R^a)_2$, $-N(R^a)C(O)OR^a$, $-N(R^a)C(O)R^a$, - $N(R^a)C(O)N(R^a)_2$, $N(R^a)C(NR^a)N(R^a)_2$, $-N(R^a)S(O)_tR^a$ (where t is 1 or 2), $-S(O)_tOR^a$ (where t is 1 or 2), $-S(O)_tN(R^a)_2$ (where t is 1 or 2), or $-O-P(=O)(OR^a)_2$ where each R^a is independently hydrogen, alkyl, haloalkyl, carbocyclyl, carbocyclylalkyl, aryl, aralkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl or heteroarylalkyl, and each of these moieties can be optionally substituted as defined herein. The terms "alkenoxycarbonyl" and "alkynoxycarbonyl" mirror the above description of "alkoxycarbonyl" wherein the prefix "alk" is replaced with "alken" or "alkyn" respectively, and the parent "alkenyl" or "alkynyl" terms are as described herein.

[00121] "Acyl" refers to R-C(O)- groups such as, but not limited to, (alkyl)-C(O)-, (alkenyl)-C(O)-, (alkynyl)-C(O)-, (aryl)-C(O)-, (cycloalkyl)-C(O)-, (heteroaryl)-C(O)-, (heteroalkyl)-C(O)-, and (heterocycloalkyl)-C(O)-, wherein the group is attached to the parent molecular structure through the carbonyl functionality. In some embodiments, it is a C_1-C_{10} acyl radical which refers to the total number of chain or ring atoms of the, for example, alkyl, alkenyl, alkynyl, aryl, cyclohexyl, heteroaryl or heterocycloalkyl portion plus the carbonyl carbon of acyl. For example, a C_4-acyl has three other ring or chain atoms plus carbonyl. If the R radical is heteroaryl or heterocycloalkyl, the hetero ring or chain atoms contribute to the total number of chain or ring atoms. Unless stated otherwise in the specification, the "R" of an acyloxy group can be optionally substituted by one or more substituents which independently include: acyl, alkyl, alkenyl, alkynyl, alkoxy, alkylaryl, cycloalkyl, aralkyl, aryl, aryloxy, amino, amido, amidino, imino, azide, carbonate, carbamate, carbonyl, heteroalkyl, heteroaryl, heteroarylalkyl, heterocycloalkyl, hydroxy, cyano, halo, haloalkoxy, haloalkyl, ester, ether, mercapto, thio, alkylthio, arylthio, thiocarbonyl, nitro, oxo, phosphate, phosphonate, phosphinate, silyl, sulfinyl, sulfonyl, sulfonamidyl, sulfoxyl, sulfonate, urea, $-Si(R^a)_3$-, $-OR^a$, $-SR^a$, $-OC(O)-R^a$, $-N(R^a)_2$, $-C(O)R^a$, $-C(O)OR^a$, $-OC(O)N(R^a)_2$, $-C(O)N(R^a)_2$, $-N(R^a)C(O)OR^a$, $-N(R^a)C(O)R^a$, - $N(R^a)C(O)N(R^a)_2$, $N(R^a)C(NR^a)N(R^a)_2$, $-N(R^a)S(O)_tR^a$ (where t is 1 or 2), $-S(O)_tOR^a$ (where t is 1 or 2), $-S(O)_tN(R^a)_2$ (where t is 1 or 2), or $-O-P(=O)(OR^a)_2$ where each R^a is independently hydrogen, alkyl, haloalkyl, carbocyclyl, carbocyclylalkyl, aryl, aralkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl or heteroarylalkyl, and each of these moieties can be optionally substituted as defined herein.

[00122] "Acyloxy" refers to a R(C=O)O- radical wherein "R" can be alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, aryl, cyclohexyl, heteroaryl or heterocycloalkyl, which are as described herein. The acyloxy group is attached to the parent molecular structure through the oxygen functionality. In some embodiments, an acyloxy group is a C_1-C_4 acyloxy radical which refers to the total number of chain or ring atoms of the alkyl, alkenyl, alkynyl, aryl, cyclohexyl, heteroaryl or heterocycloalkyl portion of the acyloxy group plus the carbonyl carbon of acyl, *i.e.,* a C_4-acyloxy has three other ring or chain atoms plus carbonyl. If the R radical is heteroaryl or heterocycloalkyl, the hetero ring or chain atoms contribute to the total number of chain or ring atoms. Unless stated otherwise in the specification, the "R" of an acyloxy group is optionally substituted by one or more substituents which independently include: acyl, alkyl, alkenyl, alkynyl, alkoxy, alkylaryl, cycloalkyl, aralkyl, aryl, aryloxy, amino, amido, amidino, imino, azide, carbonate, carbamate, carbonyl, heteroalkyl, heteroaryl, heteroarylalkyl, heterocycloalkyl, hydroxy, cyano, halo, haloalkoxy, haloalkyl, ester, ether, mercapto, thio, alkylthio, arylthio, thiocarbonyl, nitro, oxo, phosphate, phosphonate, phosphinate, silyl, sulfinyl, sulfonyl, sulfonamidyl, sulfoxyl, sulfonate, urea, -Si(R^a)$_3$-, -OR^a, -SR^a, -OC(O)-R^a, -N(R^a)$_2$, -C(O)R^a, -C(O)OR^a, -OC(O)N(R^a)$_2$, -C(O)N(R^a)$_2$, -N(R^a)C(O)OR^a, -N(R^a)C(O)R^a, - N(R^a)C(O)N(R^a)$_2$, N(R^a)C(NR^a)N(R^a)$_2$, -N(R^a)S(O)$_t$$R^a$ (where t is 1 or 2), -S(O)$_t$OR^a (where t is 1 or 2), -S(O)$_t$N(R^a)$_2$ (where t is 1 or 2), or –O-P(=O)(OR^a)$_2$ where each R^a is independently hydrogen, alkyl, haloalkyl, carbocyclyl, carbocyclylalkyl, aryl, aralkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl or heteroarylalkyl and each of these moieties can be optionally substituted as defined herein.

[00123] "Amino" or "amine" refers to a -N(R^b)$_2$, -N(R^b)R^b-, or –R^bN(R^b)R^b- radical group, where each R^b is independently selected from hydrogen, alkyl, alkenyl, alkynyl, haloalkyl, heteroalkyl (bonded through a chain carbon), cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocycloalkyl (bonded through a ring carbon), heterocycloalkylalkyl, heteroaryl (bonded through a ring carbon) or heteroarylalkyl, unless stated otherwise in the specification, each of which moiety can itself be optionally substituted as described herein. When a -N(R^b)$_2$ group has two R^b other than hydrogen, they can be combined with the nitrogen atom to form a 3-, 4-, 5-, 6-, or 7-membered ring. For example, -N(R^b)$_2$ is meant to include, but not be limited to, 1-pyrrolidinyl and 4-morpholinyl. Unless stated otherwise in the specification, an amino group is optionally substituted by one or more substituents which independently include: acyl, alkyl, alkenyl, alkynyl, alkoxy, alkylaryl, cycloalkyl, aralkyl, aryl, aryloxy, amino, amido, amidino, imino, azide, carbonate, carbamate, carbonyl, heteroalkyl, heteroaryl, heteroarylalkyl, heterocycloalkyl, hydroxy, cyano, halo, haloalkoxy, haloalkyl, ester, ether, mercapto, thio, alkylthio, arylthio, thiocarbonyl, nitro, oxo, phosphate, phosphonate, phosphinate, silyl, sulfinyl, sulfonyl, sulfonamidyl, sulfoxyl, sulfonate, urea, -Si(R^a)$_3$-, -OR^a, -SR^a, -OC(O)-R^a, -N(R^a)$_2$, -C(O)R^a, -C(O)OR^a, -OC(O)N(R^a)$_2$, -C(O)N(R^a)$_2$, -N(R^a)C(O)OR^a, -N(R^a)C(O)R^a, - N(R^a)C(O)N(R^a)$_2$, N(R^a)C(NR^a)N(R^a)$_2$, -N(R^a)S(O)$_t$$R^a$ (where t is 1 or 2), -S(O)$_t$OR^a (where t is 1 or 2), -S(O)$_t$N(R^a)$_2$ (where t is 1 or 2), or –O-P(=O)(OR^a)$_2$ where each R^a is independently hydrogen, alkyl, haloalkyl, carbocyclyl, carbocyclylalkyl, aryl, aralkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl or heteroarylalkyl, and each of these moieties can be optionally substituted as defined herein.

[00124] The terms "amine" and "amino" also refer to N-oxides of the groups -N^+(H)(R^a)O^-, and -N^+(R^a)(R^a)O-, R^a as described above, where the N-oxide is bonded to the parent molecular structure through

the N atom. N-oxides can be prepared by treatment of the corresponding amino group with, for example, hydrogen peroxide or m-chloroperoxybenzoic acid. The person skilled in the art is familiar with reaction conditions for carrying out the N-oxidation.

[00125] "Amide" or "amido" refers to a chemical moiety with formula $-C(O)N(R^b)_2$ or $-NR^bC(O)R^b$, where R^b is independently selected from hydrogen, alkyl, alkenyl, alkynyl, haloalkyl, heteroalkyl (bonded through a chain carbon), cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocycloalkyl (bonded through a ring carbon), heterocycloalkylalkyl, heteroaryl (bonded through a ring carbon) or heteroarylalkyl, unless stated otherwise in the specification, each of which moiety can itself be optionally substituted as described herein. In some embodiments, this radical is a C_1-C_4 amido or amide radical, which includes the amide carbonyl in the total number of carbons in the radical. When a $-C(O)N(R^b)_2$ has two R^b other than hydrogen, they can be combined with the nitrogen atom to form a 3-, 4-, 5-, 6-, or 7-membered ring. For example, $N(R^b)_2$ portion of a $-C(O)N(R^b)_2$ radical is meant to include, but not be limited to, 1-pyrrolidinyl and 4-morpholinyl. Unless stated otherwise in the specification, an amido R^b group is optionally substituted by one or more substituents which independently include: acyl, alkyl, alkenyl, alkynyl, alkoxy, alkylaryl, cycloalkyl, aralkyl, aryl, aryloxy, amino, amido, amidino, imino, azide, carbonate, carbamate, carbonyl, heteroalkyl, heteroaryl, heteroarylalkyl, heterocycloalkyl, hydroxy, cyano, halo, haloalkoxy, haloalkyl, ester, ether, mercapto, thio, alkylthio, arylthio, thiocarbonyl, nitro, oxo, phosphate, phosphonate, phosphinate, silyl, sulfinyl, sulfonyl, sulfonamidyl, sulfoxyl, sulfonate, urea, $-Si(R^a)_3$-, $-OR^a$, $-SR^a$, $-OC(O)-R^a$, $-N(R^a)_2$, $-C(O)R^a$, $-C(O)OR^a$, $-OC(O)N(R^a)_2$, $-C(O)N(R^a)_2$, $-N(R^a)C(O)OR^a$, $-N(R^a)C(O)R^a$, $-N(R^a)C(O)N(R^a)_2$, $N(R^a)C(NR^a)N(R^a)_2$, $-N(R^a)S(O)_tR^a$ (where t is 1 or 2), $-S(O)_tOR^a$ (where t is 1 or 2), $-S(O)_tN(R^a)_2$ (where t is 1 or 2), or $-O-P(=O)(OR^a)_2$ where each R^a is independently hydrogen, alkyl, haloalkyl, carbocyclyl, carbocyclylalkyl, aryl, aralkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl or heteroarylalkyl, and each of these moieties can be optionally substituted as defined herein.

[00126] The term "amide" or "amido" is inclusive of an amino acid or a peptide molecule. Any amine, hydroxy, or carboxyl side chain on the compounds described herein can be transformed into an amide group. The procedures and specific groups to make such amides are known to those of skill in the art and can readily be found in reference sources such as Greene and Wuts, *Protective Groups in Organic Synthesis*, 3rd Ed., John Wiley & Sons, New York, NY, 1999, which is incorporated herein by reference in its entirety.

[00127] "Amidino" refers to both the $-C(=NR^b)N(R^b)_2$ and $-N(R^b)-C(=NR^b)$- radicals, where each R^b is independently selected from hydrogen, alkyl, alkenyl, alkynyl, haloalkyl, heteroalkyl (bonded through a chain carbon), cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocycloalkyl (bonded through a ring carbon), heterocycloalkylalkyl, heteroaryl (bonded through a ring carbon) or heteroarylalkyl, unless stated otherwise in the specification, each of which moiety can itself be optionally substituted as described herein.

[00128] "Aromatic" or "aryl" refers to a radical with six to ten ring atoms (*e.g.*, C_6-C_{10} aromatic or C_6-C_{10} aryl) which has at least one ring having a conjugated pi electron system which is carbocyclic (*e.g.*, phenyl, fluorenyl, and naphthyl). For example, bivalent radicals formed from substituted benzene derivatives and having the free valences at ring atoms are named as substituted phenylene radicals. In other embodiments, bivalent radicals derived from univalent polycyclic hydrocarbon radicals whose names end in "-yl" by removal of one hydrogen atom

from the carbon atom with the free valence are named by adding "-idene" to the name of the corresponding univalent radical, *e.g.*, a naphthyl group with two points of attachment is termed naphthylidene. Whenever it appears herein, a numerical range such as "6 to 10 aryl" refers to each integer in the given range; *e.g.*, "6 to 10 ring atoms" means that the aryl group can consist of 6 ring atoms, 7 ring atoms, etc., up to and including 10 ring atoms. The term includes monocyclic or fused-ring polycyclic (*i.e.*, rings which share adjacent pairs of ring atoms) groups. Unless stated otherwise in the specification, an aryl moiety can be optionally substituted by one or more substituents which independently include: acyl, alkyl, alkenyl, alkynyl, alkoxy, alkylaryl, cycloalkyl, aralkyl, aryl, aryloxy, amino, amido, amidino, imino, azide, carbonate, carbamate, carbonyl, heteroalkyl, heteroaryl, heteroarylalkyl, heterocycloalkyl, hydroxy, cyano, halo, haloalkoxy, haloalkyl, ester, ether, mercapto, thio, alkylthio, arylthio, thiocarbonyl, nitro, oxo, phosphate, phosphonate, phosphinate, silyl, sulfinyl, sulfonyl, sulfonamidyl, sulfoxyl, sulfonate, urea, $-Si(R^a)_3$-, $-OR^a$, $-SR^a$, $-OC(O)-R^a$, $-N(R^a)_2$, $-C(O)R^a$, $-C(O)OR^a$, $-OC(O)N(R^a)_2$, $-C(O)N(R^a)_2$, $-N(R^a)C(O)OR^a$, $-N(R^a)C(O)R^a$, - $N(R^a)C(O)N(R^a)_2$, $N(R^a)C(NR^a)N(R^a)_2$, $-N(R^a)S(O)_tR^a$ (where t is 1 or 2), $-S(O)_tOR^a$ (where t is 1 or 2), $-S(O)_tN(R^a)_2$ (where t is 1 or 2), or $-O-P(=O)(OR^a)_2$ where each R^a is independently hydrogen, alkyl, haloalkyl, carbocyclyl, carbocyclylalkyl, aryl, aralkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl or heteroarylalkyl, and each of these moieties can be optionally substituted as defined herein.

[00129] "Aralkyl" or "arylalkyl" refers to an (aryl)alkyl- radical where aryl and alkyl are as disclosed herein and which are optionally substituted by one or more of the substituents described as suitable substituents for aryl and alkyl respectively. The "aralkyl/arylalkyl" is bonded to the parent molecular structure through the alkyl group. The terms "aralkenyl/arylalkenyl" and "aralkynyl/arylalkynyl" mirror the above description of "aralkyl/arylalkyl" wherein the "alkyl" is replaced with "alkenyl" or "alkynyl" respectively, and the "alkenyl" or "alkynyl" terms are as described herein.

[00130] "Azide" refers to a $-N_3$ radical.

[00131] "Carbamate" refers to any of the following radicals: $-O-(C=O)-N(R^b)$-, $-O-(C=O)-N(R^b)_2$, $-N(R^b)-(C=O)-O$-, and $-N(R^b)-(C=O)-OR^b$, wherein each R^b is independnently selected from alkyl, alkenyl, alkynyl, haloalkyl, heteroalkyl (bonded through a chain carbon), cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocycloalkyl (bonded through a ring carbon), heterocycloalkylalkyl, heteroaryl (bonded through a ring carbon) or heteroarylalkyl, unless stated otherwise in the specification, each of which moiety can itself be optionally substituted as described herein.

[00132] "Carbonate" refers to a –O-(C=O)-O- radical.

[00133] "Carbonyl" refers to a –(C=O)- radical.

[00134] "Carboxaldehyde" refers to a –(C=O)H radical.

[00135] "Carboxyl" refers to a –(C=O)OH radical.

[00136] "Cyano" refers to a –CN radical.

[00137] "Cycloalkyl" and "carbocyclyl" each refer to a monocyclic or polycyclic radical that contains only carbon and hydrogen, and can be saturated or partially unsaturated. Partially unsaturated cycloalkyl groups can be termed "cycloalkenyl" if the carbocycle contains at least one double bond, or "cycloalkynyl" if the carbocycle contains at least one triple bond. Cycloalkyl groups include groups having from 3 to 10 ring atoms (*i.e.*, C_3-C_{10}

cycloalkyl). Whenever it appears herein, a numerical range such as "3 to 10" refers to each integer in the given range; *e.g.,* "3 to 10 carbon atoms" means that the cycloalkyl group can consist of 3 carbon atoms, 4 carbon atoms, 5 carbon atoms, etc., up to and including 10 carbon atoms. The term "cycloalkyl" also includes bridged and spiro-fused cyclic structures containing no heteroatoms. The term also includes monocyclic or fused-ring polycyclic (*i.e.,* rings which share adjacent pairs of ring atoms) groups. In some embodiments, it is a C_3-C_8 cycloalkyl radical. In some embodiments, it is a C_3-C_5 cycloalkyl radical. Illustrative examples of cycloalkyl groups include, but are not limited to the following moieties: C_{3-6} carbocyclyl groups include, without limitation, cyclopropyl (C_3), cyclobutyl (C_4), cyclopentyl (C_5), cyclopentenyl (C_5), cyclohexyl (C_6), cyclohexenyl (C_6), cyclohexadienyl (C_6) and the like. Examples of C_{3-8} carbocyclyl groups include the aforementioned C_{3-6} carbocyclyl groups as well as cycloheptyl (C_7), cycloheptadienyl (C_7), cycloheptatrienyl (C_7), cyclooctyl (C_8), bicyclo[2.2.1]heptanyl, bicyclo[2.2.2]octanyl, and the like. Examples of C_{3-10} carbocyclyl groups include the aforementioned C_{3-8} carbocyclyl groups as well as octahydro–1*H*–indenyl, decahydronaphthalenyl, spiro[4.5]decanyl and the like. Unless stated otherwise in the specification, a cycloalkyl group is optionally substituted by one or more substituents which independently include: acyl, alkyl, alkenyl, alkynyl, alkoxy, alkylaryl, cycloalkyl, aralkyl, aryl, aryloxy, amino, amido, amidino, imino, azide, carbonate, carbamate, carbonyl, heteroalkyl, heteroaryl, heteroarylalkyl, heterocycloalkyl, hydroxy, cyano, halo, haloalkoxy, haloalkyl, ester, ether, mercapto, thio, alkylthio, arylthio, thiocarbonyl, nitro, oxo, phosphate, phosphonate, phosphinate, silyl, sulfinyl, sulfonyl, sulfonamidyl, sulfoxyl, sulfonate, urea, $-Si(R^a)_3$-, $-OR^a$, $-SR^a$, $-OC(O)-R^a$, $-N(R^a)_2$, $-C(O)R^a$, $-C(O)OR^a$, $-OC(O)N(R^a)_2$, $-C(O)N(R^a)_2$, $-N(R^a)C(O)OR^a$, $-N(R^a)C(O)R^a$, -$N(R^a)C(O)N(R^a)_2$, $N(R^a)C(NR^a)N(R^a)_2$, $-N(R^a)S(O)_tR^a$ (where t is 1 or 2), $-S(O)_tOR^a$ (where t is 1 or 2), $-S(O)_tN(R^a)_2$ (where t is 1 or 2), or $–O-P(=O)(OR^a)_2$ where each R^a is independently hydrogen, alkyl, haloalkyl, carbocyclyl, carbocyclylalkyl, aryl, aralkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl or heteroarylalkyl, and each of these moieties can be optionally substituted as defined herein.

[00138] "Cycloalkyl-alkyl" refers to a –(cycloalkyl)alkyl radical where cycloalkyl and alkyl are as disclosed herein and which are optionally substituted by one or more of the substituents described as suitable substituents for cycloalkyl and alkyl respectively. The "cycloalkyl-alkyl" is bonded to the parent molecular structure through the cycloalkyl group. The terms "cycloalkyl-alkenyl" and "cycloalkyl-alkynyl" mirror the above description of "cycloalkyl-alkyl" wherein the term "alkyl" is replaced with "alkenyl" or "alkynyl" respectively, and "alkenyl" or "alkynyl" are as described herein.

[00139] "Cycloalkyl-heterocycloalkyl" refers to a –(cycloalkyl)heterocycylalkyl radical where cycloalkyl and heterocycloalkyl are as disclosed herein and which are optionally substituted by one or more of the substituents described as suitable substituents for heterocycloalkyl and cycloalkyl respectively. The "cycloalkyl-heterocycloalkyl" is bonded to the parent molecular structure through the cycloalkyl group.

[00140] "Cycloalkyl-heteroaryl" refers to a –(cycloalkyl)heteroaryl radical where cycloalkyl and heteroaryl are as disclosed herein and which are optionally substituted by one or more of the substituents described as suitable substituents for heteroaryl and cycloalkyl respectively. The "cycloalkyl-heteroaryl" is bonded to the parent molecular structure through the cycloalkyl group.

[00141] As used herein, a "covalent bond" or "direct bond" refers to a single bond joining two groups.

[00142] "Ester" refers to a radical of formula –COOR, where R is selected from alkyl, alkenyl, alkynyl, haloalkyl, heteroalkyl (bonded through a chain carbon), cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocycloalkyl (bonded through a ring carbon), heterocycloalkylalkyl, heteroaryl (bonded through a ring carbon) or heteroarylalkyl. Any amine, hydroxy, or carboxyl side chain on the compounds described herein can be esterified. The procedures and specific groups to make such esters are known to those of skill in the art and can readily be found in reference sources such as Greene and Wuts, *Protective Groups in Organic Synthesis*, 3rd Ed., John Wiley & Sons, New York, NY, 1999, which is incorporated herein by reference in its entirety. Unless stated otherwise in the specification, an ester group can be optionally substituted by one or more substituents which independently include: acyl, alkyl, alkenyl, alkynyl, alkoxy, alkylaryl, cycloalkyl, aralkyl, aryl, aryloxy, amino, amido, amidino, imino, azide, carbonate, carbamate, carbonyl, heteroalkyl, heteroaryl, heteroarylalkyl, heterocycloalkyl, hydroxy, cyano, halo, haloalkoxy, haloalkyl, ester, ether, mercapto, thio, alkylthio, arylthio, thiocarbonyl, nitro, oxo, phosphate, phosphonate, phosphinate, silyl, sulfinyl, sulfonyl, sulfonamidyl, sulfoxyl, sulfonate, urea, $-Si(R^a)_3$-, $-OR^a$, $-SR^a$, $-OC(O)-R^a$, $-N(R^a)_2$, $-C(O)R^a$, $-C(O)OR^a$, $-OC(O)N(R^a)_2$, $-C(O)N(R^a)_2$, $-N(R^a)C(O)OR^a$, $-N(R^a)C(O)R^a$, $-N(R^a)C(O)N(R^a)_2$, $N(R^a)C(NR^a)N(R^a)_2$, $-N(R^a)S(O)_tR^a$ (where t is 1 or 2), $-S(O)_tOR^a$ (where t is 1 or 2), $-S(O)_tN(R^a)_2$ (where t is 1 or 2), or $-O-P(=O)(OR^a)_2$ where each R^a is independently hydrogen, alkyl, haloalkyl, carbocyclyl, carbocyclylalkyl, aryl, aralkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl or heteroarylalkyl, and each of these moieties can be optionally substituted as defined herein.

[00143] "Ether" refers to a $-R^b-O-R^b-$ radical where each R^b is independently selected from hydrogen, alkyl, alkenyl, alkynyl, haloalkyl, heteroalkyl (bonded through a chain carbon), cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocycloalkyl (bonded through a ring carbon), heterocycloalkylalkyl, heteroaryl (bonded through a ring carbon) or heteroarylalkyl, unless stated otherwise in the specification, each of which moiety can itself be optionally substituted as described herein.

[00144] "Halo", "halide", or, alternatively, "halogen" means fluoro, chloro, bromo or iodo. The terms "haloalkyl," "haloalkenyl," "haloalkynyl" and "haloalkoxy" include alkyl, alkenyl, alkynyl and alkoxy structures that are substituted with one or more halo groups or with combinations thereof. For example, the terms "fluoroalkyl" and "fluoroalkoxy" include haloalkyl and haloalkoxy groups, respectively, in which the halo is fluorine, such as, but not limited to, trifluoromethyl, difluoromethyl, 2,2,2-trifluoroethyl, 1-fluoromethyl-2-fluoroethyl, and the like. Each of the alkyl, alkenyl, alkynyl and alkoxy groups are as defined herein and can be optionally further substituted as defined herein.

[00145] "Heteroalkyl", "heteroalkenyl" and "heteroalkynyl" include alkyl, alkenyl and alkynyl radicals, respectively, which have one or more skeletal chain atoms selected from an atom other than carbon, *e.g.*, oxygen, nitrogen, sulfur, phosphorus or combinations thereof. A numerical range can be given, *e.g.*, C_1-C_4 heteroalkyl which refers to the chain length in total, which in this example is 4 atoms long. For example, a $-CH_2OCH_2CH_3$ radical is referred to as a "C_4" heteroalkyl, which includes the heteroatom center in the atom chain length description. Connection to the parent molecular strucuture can be through either a heteroatom or a carbon in the heteroalkyl chain. For example, an N-containing heteroalkyl moiety refers to a group in which at least one of the skeletal atoms is a nitrogen atom. One or more heteroatom(s) in the heteroalkyl radical can be optionally oxidized. One or more

nitrogen atoms, if present, can also be optionally quaternized. For example, heteroalkyl also includes skeletal chains substituted with one or more nitrogen oxide (-O-) substituents. Exemplary heteroalkyl groups include, without limitation, ethers such as methoxyethanyl ($-CH_2CH_2OCH_3$), ethoxymethanyl ($-CH_2OCH_2CH_3$), (methoxymethoxy)ethanyl ($-CH_2CH_2OCH_2OCH_3$), (methoxymethoxy)methanyl ($-CH_2OCH_2OCH_3$) and (methoxyethoxy)methanyl ($-CH_2OCH_2$ CH_2OCH_3) and the like; amines such as $-CH_2CH_2NHCH_3$, $-CH_2CH_2N(CH_3)_2$, $-CH_2NHCH_2CH_3$, $-CH_2N(CH_2CH_3)(CH_3)$ and the like. Heteroalkyl, heteroalkenyl, and heteroalkynyl groups can each be optionally substituted by one or more substituents which independently include: acyl, alkyl, alkenyl, alkynyl, alkoxy, alkylaryl, cycloalkyl, aralkyl, aryl, aryloxy, amino, amido, amidino, imino, azide, carbonate, carbamate, carbonyl, heteroalkyl, heteroaryl, heteroarylalkyl, heterocycloalkyl, hydroxy, cyano, halo, haloalkoxy, haloalkyl, ester, ether, mercapto, thio, alkylthio, arylthio, thiocarbonyl, nitro, oxo, phosphate, phosphonate, phosphinate, silyl, sulfinyl, sulfonyl, sulfonamidyl, sulfoxyl, sulfonate, urea, $-Si(R^a)_3$-, $-OR^a$, $-SR^a$, $-OC(O)-R^a$, $-N(R^a)_2$, $-C(O)R^a$, $-C(O)OR^a$, $-OC(O)N(R^a)_2$, $-C(O)N(R^a)_2$, $-N(R^a)C(O)OR^a$, $-N(R^a)C(O)R^a$, $-N(R^a)C(O)N(R^a)_2$, $N(R^a)C(NR^a)N(R^a)_2$, $-N(R^a)S(O)_tR^a$ (where t is 1 or 2), $-S(O)_tOR^a$ (where t is 1 or 2), $-S(O)_tN(R^a)_2$ (where t is 1 or 2), or $-O-P(=O)(OR^a)_2$ where each R^a is independently hydrogen, alkyl, haloalkyl, carbocyclyl, carbocyclylalkyl, aryl, aralkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl or heteroarylalkyl, and each of these moieties can be optionally substituted as defined herein.

[00146] "Heteroalkyl-aryl" refers to a -(heteroalkyl)aryl radical where heteroalkyl and aryl are as disclosed herein and which are optionally substituted by one or more of the substituents described as suitable substituents for heteroalkyl and aryl respectively. The "heteroalkyl-aryl" is bonded to the parent molecular structure through an atom of the heteroalkyl group.

[00147] "Heteroalkyl-heteroaryl" refers to a -(heteroalkyl)heteroaryl radical where heteroalkyl and heteroaryl are as disclosed herein and which are optionally substituted by one or more of the substituents described as suitable substituents for heteroalkyl and heteroaryl respectively. The "heteroalkyl-heteroaryl" is bonded to the parent molecular structure through an atom of the heteroalkyl group.

[00148] "Heteroalkyl-heterocycloalkyl" refers to a -(heteroalkyl)heterocycloalkyl radical where heteroalkyl and heterocycloalkyl are as disclosed herein and which are optionally substituted by one or more of the substituents described as suitable substituents for heteroalkyl and heterocycloalkyl respectively. The "heteroalkyl-heterocycloalkyl" is bonded to the parent molecular structure through an atom of the heteroalkyl group.

[00149] "Heteroalkyl-cycloalkyl" refers to a -(heteroalkyl)cycloalkyl radical where heteroalkyl and cycloalkyl are as disclosed herein and which are optionally substituted by one or more of the substituents described as suitable substituents for heteroalkyl and cycloalkyl respectively. The "heteroalkyl-cycloalkyl" is bonded to the parent molecular structure through an atom of the heteroalkyl group.

[00150] "Heteroaryl" or, alternatively, "heteroaromatic" refers to a refers to a radical of a 5–18 membered monocyclic or polycyclic (*e.g.*, bicyclic or tricyclic) aromatic ring system (*e.g.*, having 6, 10 or 14 π electrons shared in a cyclic array) having ring carbon atoms and 1–6 ring heteroatoms provided in the aromatic ring system, wherein each heteroatom is independently selected from nitrogen, oxygen, phosphorous and sulfur ("5–18 membered heteroaryl"). Heteroaryl polycyclic ring systems can include one or more heteroatoms in one or both

rings. Whenever it appears herein, a numerical range such as "5 to 18" refers to each integer in the given range; *e.g.*, "5 to 18 ring atoms" means that the heteroaryl group can consist of 5 ring atoms, 6 ring atoms, etc., up to and including 18 ring atoms. For example, bivalent radicals derived from univalent heteroaryl radicals whose names end in "-yl" by removal of one hydrogen atom from the atom with the free valence are named by adding "-idene" to the name of the corresponding univalent radical, *e.g.*, a pyridyl group with two points of attachment is a pyridylidene.

[00151] For example, an N-containing "heteroaromatic" or "heteroaryl" moiety refers to an aromatic group in which at least one of the skeletal atoms of the ring is a nitrogen atom. One or more heteroatom(s) in the heteroaryl radical can be optionally oxidized. One or more nitrogen atoms, if present, can also be optionally quaternized. Heteroaryl also includes ring systems substituted with one or more nitrogen oxide (-O-) substituents, such as pyridinyl N-oxides. The heteroaryl is attached to the parent molecular structure through any atom of the ring(s).

[00152] "Heteroaryl" also includes ring systems wherein the heteroaryl ring, as defined above, is fused with one or more aryl groups wherein the point of attachment to the parent molecular structure is either on the aryl or on the heteroaryl ring, or wherein the heteroaryl ring, as defined above, is fused with one or more cycloalkyl or heterocycyl groups wherein the point of attachment to the parent molecular structure is on the heteroaryl ring. For polycyclic heteroaryl groups wherein one ring does not contain a heteroatom (*e.g.*, indolyl, quinolinyl, carbazolyl and the like), the point of attachment to the parent molecular structure can be on either ring, *i.e.*, either the ring bearing a heteroatom (*e.g.*, 2–indolyl) or the ring that does not contain a heteroatom (*e.g.*, 5–indolyl). In some embodiments, a heteroaryl group is a 5–10 membered aromatic ring system having ring carbon atoms and 1–4 ring heteroatoms provided in the aromatic ring system, wherein each heteroatom is independently selected from nitrogen, oxygen, phosphorous, and sulfur ("5–10 membered heteroaryl"). In some embodiments, a heteroaryl group is a 5–8 membered aromatic ring system having ring carbon atoms and 1–4 ring heteroatoms provided in the aromatic ring system, wherein each heteroatom is independently selected from nitrogen, oxygen, phosphorous, and sulfur ("5–8 membered heteroaryl"). In some embodiments, a heteroaryl group is a 5–6 membered aromatic ring system having ring carbon atoms and 1–4 ring heteroatoms provided in the aromatic ring system, wherein each heteroatom is independently selected from nitrogen, oxygen, phosphorous, and sulfur ("5–6 membered heteroaryl"). In some embodiments, the 5–6 membered heteroaryl has 1–3 ring heteroatoms selected from nitrogen, oxygen, phosphorous, and sulfur. In some embodiments, the 5–6 membered heteroaryl has 1–2 ring heteroatoms selected from nitrogen, oxygen, phosphorous, and sulfur. In some embodiments, the 5–6 membered heteroaryl has 1 ring heteroatom selected from nitrogen, oxygen, phosphorous, and sulfur.

[00153] Examples of heteroaryls include, but are not limited to, azepinyl, acridinyl, benzimidazolyl, benzindolyl, 1,3-benzodioxolyl, benzofuranyl, benzooxazolyl, benzo[d]thiazolyl, benzothiadiazolyl, benzo[*b*][1,4]dioxepinyl, benzo[b][1,4]oxazinyl, 1,4-benzodioxanyl, benzonaphthofuranyl, benzoxazolyl, benzodioxolyl, benzodioxinyl, benzoxazolyl, benzopyranyl, benzopyranonyl, benzofuranyl, benzofuranonyl, benzofurazanyl, benzothiazolyl, benzothienyl (benzothiophenyl), benzothieno[3,2-d]pyrimidinyl, benzotriazolyl, benzo[4,6]imidazo[1,2-a]pyridinyl, carbazolyl, cinnolinyl, cyclopenta[d]pyrimidinyl, 6,7-dihydro-5H-cyclopenta[4,5]thieno[2,3-d]pyrimidinyl, 5,6-dihydrobenzo[h]quinazolinyl,

5,6-dihydrobenzo[h]cinnolinyl, 6,7-dihydro-5H-benzo[6,7]cyclohepta[1,2-c]pyridazinyl, dibenzofuranyl, dibenzothiophenyl, furanyl, furazanyl, furanonyl, furo[3,2-c]pyridinyl, 5,6,7,8,9,10-hexahydrocycloocta[d]pyrimidinyl, 5,6,7,8,9,10-hexahydrocycloocta[d]pyridazinyl, 5,6,7,8,9,10-hexahydrocycloocta[d]pyridinyl,isothiazolyl, imidazolyl, indazolyl, indolyl, indazolyl, isoindolyl, indolinyl, isoindolinyl, isoquinolyl, indolizinyl, isoxazolyl, 5,8-methano-5,6,7,8-tetrahydroquinazolinyl, naphthyridinyl, 1,6-naphthyridinonyl, oxadiazolyl, 2-oxoazepinyl, oxazolyl, oxiranyl, 5,6,6a,7,8,9,10,10a-octahydrobenzo[h]quinazolinyl, 1-phenyl-1*H*-pyrrolyl, phenazinyl, phenothiazinyl, phenoxazinyl, phthalazinyl, pteridinyl, purinyl, pyranyl, pyrrolyl, pyrazolyl, pyrazolo[3,4-d]pyrimidinyl, pyridinyl, pyrido[3,2-d]pyrimidinyl, pyrido[3,4-d]pyrimidinyl, pyrazinyl, pyrimidinyl, pyridazinyl, pyrrolyl, quinazolinyl, quinoxalinyl, quinolinyl, isoquinolinyl, tetrahydroquinolinyl, 5,6,7,8-tetrahydroquinazolinyl, 5,6,7,8-tetrahydrobenzo[4,5]thieno[2,3-d]pyrimidinyl,
6,7,8,9-tetrahydro-5H-cyclohepta[4,5]thieno[2,3-d]pyrimidinyl, 5,6,7,8-tetrahydropyrido[4,5-c]pyridazinyl, thiazolyl, thiadiazolyl, thiapyranyl, triazolyl, tetrazolyl, triazinyl, thieno[2,3-d]pyrimidinyl, thieno[3,2-d]pyrimidinyl, thieno[2,3-c]pridinyl, and thiophenyl (*i.e.,* thienyl). Unless stated otherwise in the specification, a heteroaryl moiety is optionally substituted by one or more substituents which independently include: acyl, alkyl, alkenyl, alkynyl, alkoxy, alkylaryl, cycloalkyl, aralkyl, aryl, aryloxy, amino, amido, amidino, imino, azide, carbonate, carbamate, carbonyl, heteroalkyl, heteroaryl, heteroarylalkyl, heterocycloalkyl, hydroxy, cyano, halo, haloalkoxy, haloalkyl, ester, ether, mercapto, thio, alkylthio, arylthio, thiocarbonyl, nitro, oxo, phosphate, phosphonate, phosphinate, silyl, sulfinyl, sulfonyl, sulfonamidyl, sulfoxyl, sulfonate, urea, $-Si(R^a)_3$-, $-OR^a$, $-SR^a$, $-OC(O)-R^a$, $-N(R^a)_2$, $-C(O)R^a$, $-C(O)OR^a$, $-OC(O)N(R^a)_2$, $-C(O)N(R^a)_2$, $-N(R^a)C(O)OR^a$, $-N(R^a)C(O)R^a$, $-N(R^a)C(O)N(R^a)_2$, $N(R^a)C(NR^a)N(R^a)_2$, $-N(R^a)S(O)_tR^a$ (where t is 1 or 2), $-S(O)_tOR^a$ (where t is 1 or 2), $-S(O)_tN(R^a)_2$ (where t is 1 or 2), or $–O-P(=O)(OR^a)_2$ where each R^a is independently hydrogen, alkyl, haloalkyl, carbocyclyl, carbocyclylalkyl, aryl, aralkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl or heteroarylalkyl and each of these moieties can be optionally substituted as defined herein.

[00154] "Heteroaryl-alkyl" refers to a -(heteroaryl)alkyl radical where heteroaryl and alkyl are as disclosed herein and which are optionally substituted by one or more of the substituents described as suitable substituents for heteroaryl and alkyl respectively. The "heteroaryl-alkyl" is bonded to the parent molecular structure through any atom of the heteroaryl group.

[00155] "Heteroaryl-heterocycloalkyl" refers to an -(heteroaryl)heterocycloalkyl radical where heteroaryl and heterocycloalkyl are as disclosed herein and which are optionally substituted by one or more of the substituents described as suitable substituents for heteroaryl and heterocycloalkyl respectively. The "heteroaryl-heterocycloalkyl" is bonded to the parent molecular structure through an atom of the heteroaryl group.

[00156] "Heteroaryl-cycloalkyl" refers to an -(heteroaryl)cycloalkyl radical where heteroaryl and cycloalkyl are as disclosed herein and which are optionally substituted by one or more of the substituents described as suitable substituents for heteroaryl and cycloalkyl respectively. The "heteroaryl-cycloalkyl" is bonded to the parent molecular structure through a carbon atom of the heteroaryl group.

[00157] "Heterocyclyl", "heterocycloalkyl" or 'heterocarbocyclyl" each refer to any 3- to 18-membered non-aromatic radical monocyclic or polycyclic moiety comprising at least one heteroatom selected from nitrogen, oxygen, phosphorous and sulfur. A heterocyclyl group can be a monocyclic, bicyclic, tricyclic or tetracyclic ring system, wherein the polycyclic ring systems can be a fused, bridged or spiro ring system. Heterocyclyl polycyclic ring systems can include one or more heteroatoms in one or both rings. A heterocyclyl group can be saturated or partially unsaturated. Partially unsaturated heterocycloalkyl groups can be termed "heterocycloalkenyl" if the heterocyclyl contains at least one double bond, or "heterocycloalkynyl" if the heterocyclyl contains at least one triple bond. Whenever it appears herein, a numerical range such as "5 to 18" refers to each integer in the given range; *e.g.,* "5 to 18 ring atoms" means that the heterocyclyl group can consist of 5 ring atoms, 6 ring atoms, etc., up to and including 18 ring atoms. For example, bivalent radicals derived from univalent heterocyclyl radicals whose names end in "-yl" by removal of one hydrogen atom from the atom with the free valence are named by adding "-idene" to the name of the corresponding univalent radical, *e.g.,* a piperidine group with two points of attachment is a piperidylidene.

[00158] An N-containing heterocyclyl moiety refers to an non-aromatic group in which at least one of the ring atoms is a nitrogen atom. The heteroatom(s) in the heterocyclyl radical can be optionally oxidized. One or more nitrogen atoms, if present, can be optionally quaternized. Heterocyclyl also includes ring systems substituted with one or more nitrogen oxide (-O-) substituents, such as piperidinyl N-oxides. The heterocyclyl is attached to the parent molecular structure through any atom of any of the ring(s).

[00159] "Heterocyclyl" also includes ring systems wherein the heterocycyl ring, as defined above, is fused with one or more carbocycyl groups wherein the point of attachment is either on the carbocycyl or heterocyclyl ring, or ring systems wherein the heterocyclyl ring, as defined above, is fused with one or more aryl or heteroaryl groups, wherein the point of attachment to the parent molecular structure is on the heterocyclyl ring. In some embodiments, a heterocyclyl group is a 3–10 membered non–aromatic ring system having ring carbon atoms and 1–4 ring heteroatoms, wherein each heteroatom is independently selected from nitrogen, oxygen, phosphorous and sulfur ("3–10 membered heterocyclyl"). In some embodiments, a heterocyclyl group is a 5–8 membered non–aromatic ring system having ring carbon atoms and 1–4 ring heteroatoms, wherein each heteroatom is independently selected from nitrogen, oxygen, phosphorous and sulfur ("5–8 membered heterocyclyl"). In some embodiments, a heterocyclyl group is a 5–6 membered non–aromatic ring system having ring carbon atoms and 1–4 ring heteroatoms, wherein each heteroatom is independently selected from nitrogen, oxygen, phosphorous and sulfur ("5–6 membered heterocyclyl"). In some embodiments, the 5–6 membered heterocyclyl has 1–3 ring heteroatoms selected from nitrogen, oxygen phosphorous and sulfur. In some embodiments, the 5–6 membered heterocyclyl has 1–2 ring heteroatoms selected from nitrogen, oxygen, phosphorous and sulfur. In some embodiments, the 5–6 membered heterocyclyl has 1 ring heteroatom selected from nitrogen, oxygen, phosphorous and sulfur.

[00160] Exemplary 3–membered heterocyclyls containing 1 heteroatom include, without limitation, azirdinyl, oxiranyl, thiorenyl. Exemplary 4–membered heterocyclyls containing 1 heteroatom include, without limitation, azetidinyl, oxetanyl and thietanyl. Exemplary 5–membered heterocyclyls containing 1 heteroatom include, without limitation, tetrahydrofuranyl, dihydrofuranyl, tetrahydrothiophenyl, dihydrothiophenyl,

pyrrolidinyl, dihydropyrrolyl and pyrrolyl–2,5–dione. Exemplary 5–membered heterocyclyls containing 2 heteroatoms include, without limitation, dioxolanyl, oxathiolanyl and dithiolanyl. Exemplary 5–membered heterocyclyls containing 3 heteroatoms include, without limitation, triazolinyl, oxadiazolinyl, and thiadiazolinyl. Exemplary 6–membered heterocyclyl groups containing 1 heteroatom include, without limitation, piperidinyl, tetrahydropyranyl, dihydropyridinyl, and thianyl. Exemplary 6–membered heterocyclyl groups containing 2 heteroatoms include, without limitation, piperazinyl, morpholinyl, dithianyl, dioxanyl, and triazinanyl. Exemplary 7–membered heterocyclyl groups containing 1 heteroatom include, without limitation, azepanyl, oxepanyl and thiepanyl. Exemplary 8–membered heterocyclyl groups containing 1 heteroatom include, without limitation, azocanyl, oxecanyl and thiocanyl. Exemplary bicyclic heterocyclyl groups include, without limitation, indolinyl, isoindolinyl, dihydrobenzofuranyl, dihydrobenzothienyl, tetrahydrobenzothienyl, tetrahydrobenzofuranyl, tetrahydroindolyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, decahydroquinolinyl, decahydroisoquinolinyl, octahydrochromenyl, octahydroisochromenyl, decahydronaphthyridinyl, decahydro–1,8–naphthyridinyl, octahydropyrrolo[3,2–b]pyrrole, indolinyl, phthalimidyl, naphthalimidyl, chromanyl, chromenyl, 1H–benzo[e][1,4]diazepinyl, 1,4,5,7–tetrahydropyrano[3,4–b]pyrrolyl, 5,6–dihydro–4H–furo[3,2–b]pyrrolyl, 6,7–dihydro–5H–furo[3,2–b]pyranyl, 5,7–dihydro–4H–thieno[2,3–c]pyranyl, 2,3–dihydro–1H–pyrrolo[2,3–b]pyridinyl, 2,3–dihydrofuro[2,3–b]pyridinyl, 4,5,6,7–tetrahydro–1H–pyrrolo[2,3–b]pyridinyl, 4,5,6,7–tetrahydrofuro[3,2–c]pyridinyl, 4,5,6,7–tetrahydrothieno[3,2–b]pyridinyl, 1,2,3,4–tetrahydro–1,6–naphthyridinyl, and the like.

[00161] Unless stated otherwise, heterocyclyl moieties are optionally substituted by one or more substituents which independently include: acyl, alkyl, alkenyl, alkynyl, alkoxy, alkylaryl, cycloalkyl, aralkyl, aryl, aryloxy, amino, amido, amidino, imino, azide, carbonate, carbamate, carbonyl, heteroalkyl, heteroaryl, heteroarylalkyl, heterocycloalkyl, hydroxy, cyano, halo, haloalkoxy, haloalkyl, ester, ether, mercapto, thio, alkylthio, arylthio, thiocarbonyl, nitro, oxo, phosphate, phosphonate, phosphinate, silyl, sulfinyl, sulfonyl, sulfonamidyl, sulfoxyl, sulfonate, urea, $-Si(R^a)_3-$, $-OR^a$, $-SR^a$, $-OC(O)-R^a$, $-N(R^a)_2$, $-C(O)R^a$, $-C(O)OR^a$, $-OC(O)N(R^a)_2$, $-C(O)N(R^a)_2$, $-N(R^a)C(O)OR^a$, $-N(R^a)C(O)R^a$, $-N(R^a)C(O)N(R^a)_2$, $N(R^a)C(NR^a)N(R^a)_2$, $-N(R^a)S(O)_tR^a$ (where t is 1 or 2), $-S(O)_tOR^a$ (where t is 1 or 2), $-S(O)_tN(R^a)_2$ (where t is 1 or 2), or $-O-P(=O)(OR^a)_2$ where each R^a is independently hydrogen, alkyl, haloalkyl, carbocyclyl, carbocyclylalkyl, aryl, aralkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl or heteroarylalkyl and each of these moieties can be optionally substituted as defined herein.

[00162] "Heterocyclyl-alkyl" refers to a -(heterocyclyl)alkyl radical where heterocyclyl and alkyl are as disclosed herein and which are optionally substituted by one or more of the substituents described as suitable substituents for heterocyclyl and alkyl respectively. The "heterocyclyl-alkyl" is bonded to the parent molecular structure through any atom of the heterocyclyl group. The terms "heterocyclyl-alkenyl" and "heterocyclyl-alkynyl" mirror the above description of "heterocyclyl-alkyl" wherein the term "alkyl" is replaced with "alkenyl" or "alkynyl" respectively, and "alkenyl" or "alkynyl" are as described herein.

[00163] "Imino" refers to the "$-(C=N)-R^b$" radical where R^b is selected from hydrogen, alkyl, alkenyl, alkynyl, haloalkyl, heteroalkyl (bonded through a chain carbon), cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocycloalkyl (bonded through a ring carbon), heterocycloalkylalkyl, heteroaryl (bonded through a ring carbon)

or heteroarylalkyl, unless stated otherwise in the specification, each of which moiety can itself be optionally substituted as described herein.

[00164] "Moiety" refers to a specific segment or functional group of a molecule. Chemical moieties are often recognized chemical entities embedded in or appended to a molecule.

[00165] "Nitro" refers to the $-NO_2$ radical.

[00166] "Oxa" refers to the -O- radical.

[00167] "Oxo" refers to the =O radical.

[00168] "Phosphate" refers to a $-O\text{-}P(=O)(OR^b)_2$ radical, where each R^b is independently selected from hydrogen, alkyl, alkenyl, alkynyl, haloalkyl, heteroalkyl (bonded through a chain carbon), cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocycloalkyl (bonded through a ring carbon), heterocycloalkylalkyl, heteroaryl (bonded through a ring carbon) or heteroarylalkyl, unless stated otherwise in the specification, each of which moiety can itself be optionally substituted as described herein. In some embodiments, when R^a is hydrogen and depending on the pH, the hydrogen can be replaced by an appropriately charged counter ion.

[00169] "Phosphonate" refers to a $-O\text{-}P(=O)(R^b)(OR^b)$ radical, where each R^b is independently selected from hydrogen, alkyl, alkenyl, alkynyl, haloalkyl, heteroalkyl (bonded through a chain carbon), cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocycloalkyl (bonded through a ring carbon), heterocycloalkylalkyl, heteroaryl (bonded through a ring carbon) or heteroarylalkyl, unless stated otherwise in the specification, each of which moiety can itself be optionally substituted as described herein. In some embodiments, when R^a is hydrogen and depending on the pH, the hydrogen can be replaced by an appropriately charged counter ion.

[00170] "Phosphinate" refers to a $-P(=O)(R^b)(OR^b)$ radical, where each R^b is independently selected from hydrogen, alkyl, alkenyl, alkynyl, haloalkyl, heteroalkyl (bonded through a chain carbon), cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocycloalkyl (bonded through a ring carbon), heterocycloalkylalkyl, heteroaryl (bonded through a ring carbon) or heteroarylalkyl, unless stated otherwise in the specification, each of which moiety can itself be optionally substituted as described herein. In some embodiments, when R^a is hydrogen and depending on the pH, the hydrogen can be replaced by an appropriately charged counter ion.

[00171] A "leaving group or atom" is any group or atom that will, under the reaction conditions, cleave from the starting material, thus promoting reaction at a specified site. Suitable non-limiting examples of such groups unless otherwise specified include halogen atoms, mesyloxy, p-nitrobenzensulphonyloxy, trifluoromethyloxy, and tosyloxy groups.

[00172] "Protecting group" has the meaning conventionally associated with it in organic synthesis, *i.e.,* a group that selectively blocks one or more reactive sites in a multifunctional compound such that a chemical reaction can be carried out selectively on another unprotected reactive site and such that the group can readily be removed after the selective reaction is complete. A variety of protecting groups are disclosed, for example, in T.H. Greene and P. G. M. Wuts, *Protective Groups in Organic Synthesis*, Third Edition, John Wiley & Sons, New York (1999), incorporated herein by reference in its entirety. For example, a hydroxy protected form is where at least one of the hydroxy groups present in a compound is protected with a hydroxy protecting group. Likewise, amines and other reactive groups can similarly be protected.

[00173] As used herein, the terms "substituted" or "substitution" mean that at least one hydrogen present on a group atom (*e.g.*, a carbon or nitrogen atom) is replaced with a permissible substituent, *e.g.*, a substituent which upon substitution for the hydrogen results in a stable compound, *e.g.*, a compound which does not spontaneously undergo transformation such as by rearrangement, cyclization, elimination, or other reaction. Unless otherwise indicated, a "substituted" group can have a substituent at one or more substitutable positions of the group, and when more than one position in any given structure is substituted, the substituent is either the same or different at each position. Substituents include one or more group(s) individually and independently selected from acyl, alkyl, alkenyl, alkynyl, alkoxy, alkylaryl, cycloalkyl, aralkyl, aryl, aryloxy, amino, amido, azide, carbonate, carbonyl, heteroalkyl, heteroaryl, heteroarylalkyl, heterocycloalkyl, hydroxy, cyano, halo, haloalkoxy, haloalkyl, ester, mercapto, thio, alkylthio, arylthio, thiocarbonyl, nitro, oxo, phosphate, phosphonate, phosphinate, silyl, sulfinyl, sulfonyl, sulfonamidyl, sulfoxyl, sulfonate, urea, $-Si(R^a)_3$, $-OR^a$, $-SR^a$, $-OC(O)-R^a$, $-N(R^a)_2$, $-C(O)R^a$, $-C(O)OR^a$, $-OC(O)N(R^a)_2$, $-C(O)N(R^a)_2$, $-N(R^a)C(O)OR^a$, $-N(R^a)C(O)R^a$, - $N(R^a)C(O)N(R^a)_2$, $N(R^a)C(NR^a)N(R^a)_2$, $-N(R^a)S(O)_tR^a$ (where t is 1 or 2), $-S(O)_tOR^a$ (where t is 1 or 2), $-S(O)_tN(R^a)_2$ (where t is 1 or 2),–$O-P(=O)(OR^a)_2$, where each R^a is independently hydrogen, alkyl, haloalkyl, carbocyclyl, carbocyclylalkyl, aryl, aralkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl or heteroarylalkyl and each of these moieties can be optionally substituted as defined herein. For example, a cycloalkyl substituent can have a halide substituted at one ormore ring carbons, and the like. The protecting groups that can form the protective derivatives of the above substituents are known to those of skill in the art and can be found in references such as Greene and Wuts, above.

[00174] "Silyl" refers to a $-Si(R^b)_3$ radical where each R^b is independently selected from alkyl, alkenyl, alkynyl, haloalkyl, heteroalkyl (bonded through a chain carbon), cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocycloalkyl (bonded through a ring carbon), heterocycloalkylalkyl, heteroaryl (bonded through a ring carbon) or heteroarylalkyl, unless stated otherwise in the specification, each of which moiety can itself be optionally substituted as described herein.

[00175] "Sulfanyl", "sulfide", and "thio" each refer to the radical $-S-R^b$, wherein R^b is selected from alkyl, alkenyl, alkynyl, haloalkyl, heteroalkyl (bonded through a chain carbon), cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocycloalkyl (bonded through a ring carbon), heterocycloalkylalkyl, heteroaryl (bonded through a ring carbon) or heteroarylalkyl, unless stated otherwise in the specification, each of which moiety can itself be optionally substituted as described herein. For instance, an "alkylthio" refers to the "alkyl-S-" radical, and "arylthio" refers to the "aryl-S-" radical, each of which are bound to the parent molecular group through the S atom. The terms "sulfide", "thiol", "mercapto", and "mercaptan" can also each refer to the group $-R^bSH$.

[00176] "Sulfinyl" or "sulfoxide" refers to the $-S(O)-R^b$ radical, wherein for "sulfinyl", R^b is H and for "sulfoxide", R^b is selected from alkyl, alkenyl, alkynyl, haloalkyl, heteroalkyl (bonded through a chain carbon), cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocycloalkyl (bonded through a ring carbon), heterocycloalkylalkyl, heteroaryl (bonded through a ring carbon) or heteroarylalkyl, unless stated otherwise in the specification, each of which moiety can itself be optionally substituted as described herein.

[00177] "Sulfonyl" or "sulfone" refers to the $-S(O_2)-R^b$ radical, wherein R^b is selected from hydrogen, alkyl, alkenyl, alkynyl, haloalkyl, heteroalkyl (bonded through a chain carbon), cycloalkyl, cycloalkylalkyl, aryl,

aralkyl, heterocycloalkyl (bonded through a ring carbon), heterocycloalkylalkyl, heteroaryl (bonded through a ring carbon) or heteroarylalkyl, unless stated otherwise in the specification, each of which moiety can itself be optionally substituted as described herein.

[00178] "Sulfonamidyl" or "sulfonamido" refers to the following radicals: $-S(=O)_2-N(R^b)_2$, $-N(R^b)-S(=O)_2-R^b$, $-S(=O)_2-N(R^b)-$, or $-N(R^b)-S(=O)_2-$, where each R^b is independently selected from hydrogen, alkyl, alkenyl, alkynyl, haloalkyl, heteroalkyl (bonded through a chain carbon), cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocycloalkyl (bonded through a ring carbon), heterocycloalkylalkyl, heteroaryl (bonded through a ring carbon) or heteroarylalkyl, unless stated otherwise in the specification, each of which moiety can itself be optionally substituted as described herein. The R^b groups in $-S(=O)_2-N(R^b)_2$ can be taken together with the nitrogen to which they are attached to form a 4-, 5-, 6-, or 7-membered heterocyclyl ring. In some embodiments, the term designates a C_1-C_4 sulfonamido, wherein each R^b in the sulfonamido contains 1 carbon, 2 carbons, 3 carbons, or 4 carbons total.

[00179] "Sulfoxyl" or "sulfoxide" refers to a $-S(=O)_2OH$ radical.

[00180] "Sulfonate" refers to a $-S(=O)_2-OR^b$ radical, wherein R^b is selected from alkyl, alkenyl, alkynyl, haloalkyl, heteroalkyl (bonded through a chain carbon), cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocycloalkyl (bonded through a ring carbon), heterocycloalkylalkyl, heteroaryl (bonded through a ring carbon) or heteroarylalkyl, unless stated otherwise in the specification, each of which moiety can itself be optionally substituted as described herein.

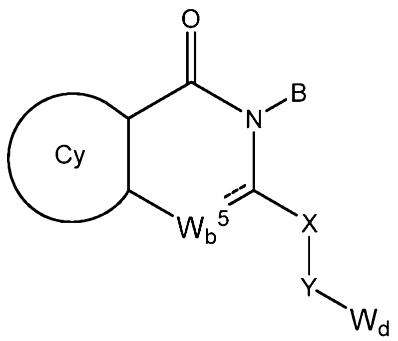
[00181] "Thiocarbonyl" refers to a –(C=S)- radical.

[00182] "Urea" refers to a $-N(R^b)-(C=O)-N(R^b)_2$ or $-N(R^b)-(C=O)-N(R^b)-$ radical, where each R^b is independently selected from alkyl, alkenyl, alkynyl, haloalkyl, heteroalkyl (bonded through a chain carbon), cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocycloalkyl (bonded through a ring carbon), heterocycloalkylalkyl, heteroaryl (bonded through a ring carbon) or heteroarylalkyl, unless stated otherwise in the specification, each of which moiety can itself be optionally substituted as described herein.

[00183] Where substituent groups are specified by their conventional chemical formulae, written from left to right, they equally encompass the chemically identical substituents that would result from writing the structure from right to left, *e.g.*, $-CH_2O-$ is equivalent to $-OCH_2-$.

Compounds

[00184] In one aspect, provided herein are compounds of Formula (I):



Formula (I)

or an enantiomer, a mixture of enantiomers, or a mixture of two or more diastereomers thereof, or its pharmaceutically acceptable forms thereof, wherein

Cy is aryl or heteroaryl substituted by 0-1 occurrences of R^3 and 0-3 occurrences of R^5;

W_b^5 is CR^8, CHR^8, or N,

R^8 is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heteroalkyl, alkoxy, amido, amino, acyl, acyloxy, sulfonamido, halo, cyano, hydroxyl, or nitro;

B is hydrogen, alkyl, amino, heteroalkyl, cycloalkyl, heterocyclyl, heterocyclylalkyl, aryl or heteroaryl, each of which is substituted with 0-4 occurrences of R^2;

each R^2 is independently alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, alkoxy, amido, amino, acyl, acyloxy, alkoxycarbonyl, sulfonamido, halo, cyano, hydroxyl, nitro, phosphate, urea or carbonate;

X is absent or is $-(CH(R^9))_z-$;

Y is absent, -O-, -S-, -S(=O)-, $-S(=O)_2-$, $-N(R^9)-$, $-C(=O)-(CHR^9)_z-$, -C(=O)-, $-N(R^9)-C(=O)-$, or $-N(R^9)-C(=O)NH-$, $-N(R^9)C(R^9)_2-$, or $-C(=O)-N(R^9)-(CHR^9)_z$;

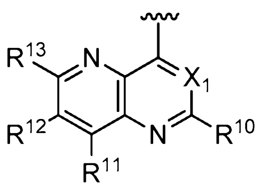
each z is independently an integer of 1, 2, 3, or 4;

wherein when W_b^5 is N, no more than one of X or Y is absent;

R^3 is alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, fluoroalkyl, heteroalkyl, alkoxy, amido, amino, acyl, acyloxy, sulfinyl, sulfonyl, sulfoxide, sulfone, sulfonamido, halo, cyano, heteroaryl, aryl, hydroxyl, or nitro; wherein each of the above substituents can be substituted with 0, 1, 2, or 3 R^{17};

each R^5 is independently alkyl, alkenyl, alkynyl, cycloalkyl, heteroalkyl, alkoxy, amido, amino, acyl, acyloxy, sulfonamido, halo, cyano, hydroxyl, or nitro;

each R^9 is independently hydrogen, alkyl, cycloalkyl, or heteroalkyl; and

W_d is 

,

wherein X_1 is N or CR^{14};

wherein R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, and R^{17} are independently hydrogen, alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, alkoxy, heterocyclyloxy, amido, amino, acyl, acyloxy, alkoxycarbonyl, sulfonamido, halo, cyano, hydroxyl, nitro, phosphate, urea, carbonate, carboxylic acid, oxo, or NR′R″ wherein R′ and R″ are taken together with nitrogen to form a cyclic moiety.

[00185] In certain embodiments, W_b^5 is CR^8. In some embodiments, R^8 is hydrogen.

[00186] In certain embodiments, Cy is aryl or heteroaryl substituted with 0-1 occurrences of R^3 and 0-3 occurrences of R^5. In some embodiments, Cy is aryl or heteroaryl substituted with 0 occurrences of R^3 and 0-3 occurrences of R^5. In some embodiments, Cy is aryl (*e.g.*, phenyl) substituted with 0-1 occurrences of R^3 and 0-3 occurrences of R^5. In some embodiments, Cy is phenyl substituted with 0-1 occurrences of R^3 and 0-3 occurrences of R^5. In some embodiments, Cy is phenyl substituted with 0 occurrences of R^3 and 0 occurrences of R^5. In some

embodiments, Cy is phenyl substituted with 1 occurrence of R^3 and 0 occurrences of R^5. In some embodiments, R^3 is alkyl (*e.g.*, methyl). In some embodiments, R^3 is halo (*e.g.*, chloro or fluoro). In some embodiments, R^3 is heteroaryl (*e.g.*, 1-methyl-4-pyrazolyl, 2-methyl-5-pyrimidyl, 2-methoxy-5-pyrimidyl, 2-amino-5-pyrimidyl, 2-amino-5-pyridyl, 2,3-dimethyl-5-pyridyl, 3-methoxy-5-pyridyl, 5-pyrimidyl, 5-methyl-3-pyridyl, 2-methyl-4-pyridyl, 2-methyl-4-pyridazinyl, 2-methoxy-5-pyrimidyl or 1,3-dimethyl-4-pyrazolyl).

[00187] In some embodiments, In some embodiments, Cy is phenyl substituted with 1 occurrence of R^3 and 1 occurrence of R^5. In some embodiments, R^3 is halo (*e.g.*, chloro or fluoro) and R^5 is halo (*e.g.*, chloro or fluoro).

[00188] In certain embodiments, Cy is heteroaryl substituted with 0-1 occurrences of R^3 and 0-3 occurrences of R^5. In some embodiments, Cy is 5-membered heteroaryl (*e.g.*, thiophenyl or isothiazolyl) substituted with 0-1 occurrences of R^3 and 0-3 occurrences of R^5. In some embodiments, Cy is thiophenyl substituted with 0 occurrences of R^3 and 1 occurrence of R^5. In some embodiments, Cy is thiophenyl substituted with 0-1 occurrence of R^3 and 0 occurrence of R^5. In some embodiments, Cy is thiophenyl substituted with 1 occurrence of R^3 and 0 occurrence of R^5. In some embodiments, Cy is isothiazolyl substituted with 0 occurrences of R^3 and 1 occurrence of R^5. In some embodiments, Cy is isothiazolyl substituted with 0-1 occurrence of R^3 and 0 occurrence of R^5. In some embodiments, Cy is isothiazolyl substituted with 1 occurrence of R^3 and 0 occurrence of R^5. In some embodiments, Cy is 6-membered heteroaryl (*e.g.*, pyridinyl).

[00189] In certain embodiments, B is hydrogen.

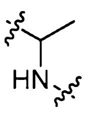
[00190] In certain embodiments, B is aryl (*e.g.*, 6-membered aryl) substituted with 0-4 occurrences of R^2. In some embodiments, B is phenyl substituted ith 0-4 occurrences of R^2. In some embodiments, B is phenyl substituted with 0 occurrences of R^2. In some embodiments, B is phenyl substituted with 1 occurrence of R^2. In some embodiments, R^2 is halo (*e.g.*, fluoro).

[00191] In certain embodiments, B is cycloalkyl (*e.g.*, cyclopropyl) substituted with 0-4 occurrences of R^2. In some embodiments, B is cyclopropyl substituted with 0-4 occurrences of R^2. In some embodiments, B is cyclopropyl substituted with 0 occurrences of R^2.

[00192] In certain embodiments, B is alkyl (*e.g.*, methyl) substituted with 0-4 occurrences of R^2. In some embodiments, B is alkyl (*e.g.*, methyl) substituted with 0 occurrences of R^2.

[00193] In some embodiments, X is $-(CH(R^9))_z$-. In some embodiments, z is 1. In some embodiments, R^9 is C_{1-10} alkyl (*e.g.*, methyl).

[00194] In some embodiments, is absent, -O-, -NH(R^9)-, or -S(=O)$_2$-. In certain embodiments, Y is absent. In some embodiments, Y is $-N(R^9)$-. In some embodiments, R^9 is hydrogen.

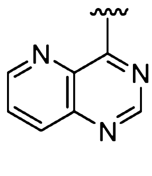
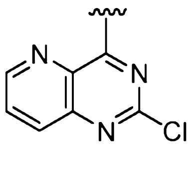
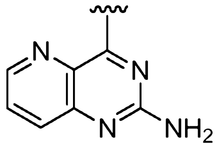
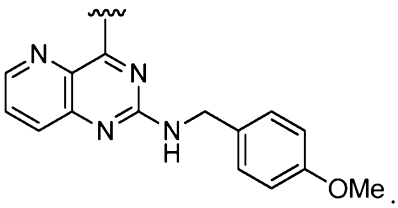
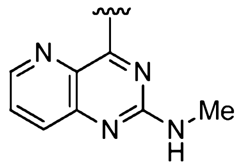
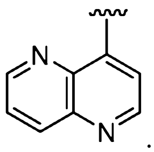
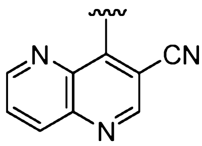
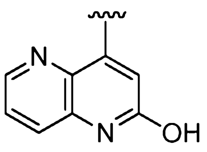
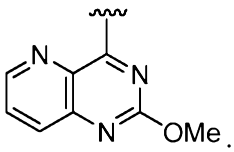
[00195] In certain embodiments, X-Y is 

. In some embodiments, X-Y is -CH_2-N(CH_3). In some embodiments, X-Y is (S)-CH(CH_3)-NH-. In some embodiments, X-Y is (R)-CH(CH_3)-NH-.

[00196] In certain embodiments, X^1 is N. In some embodiments, X^1 is CR^{14}. In some embodiments, R^{14} is hydrogen. In some embodiments, R^{14} is cyano.

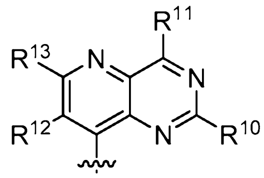
[00197] In certan embodiments, R^{10} is hydrogen. In some embodiments, R^{10} is halo (*e.g.*, chloro). In some embodiments, R^{10} is amino. Non-limiting examples include alkylamino groups, such as methylamino, ethylamino, propylamino, isopropylamino, butylamino, isobutylamino, pentylamino, isopentylamino, and hexylamino. In some embodiments, R^{10} is methylamino. In some embodiments, R^{10} is benzylamino, including optionally substituted benzylamino. In some embodiments, R^{10} is hydroxyl.

[00198] In certain embodiments, R^{11} is hydrogen. In some embodiments, R^{12} is hydrogen. In some embodiments, R^{13} is hydrogen. In some embodiments, R^{11}, R^{12} and R^{13} are hydrogen.

[00199] In certain embodiments, W_d is . In some embodiments, W_d is . In some embodiments, W_d is . In some embodiments, W_d is . In some embodiments, W_d is . In some embodiments, W_d is . In some embodiments, W_d is . In some embodiments, W_d is . In some embodiments, W_d is .

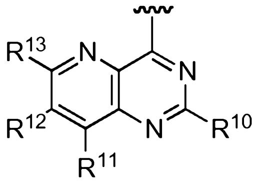
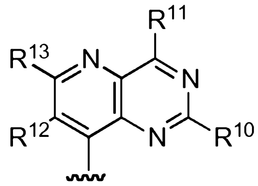
[00200] In some embodiments, Cy is aryl substituted with 0-1 occurrences of R^3 and 0-3 occurrences of R^5. For example, Cy is phenyl substituted with 1 occurrence of R^3 and 0 occurrences of R^5.

[00201] In other embodiments, Cy is heteroaryl substituted with 0-1 occurrences of R^3 and 0-3 occurrences of R^5. For example, Cy is heteroaryl substituted with 0-1 occurrences of R^3 and 0-3 occurrences of R^5. In some embodiments, Cy is 5-membered heteroaryl substituted with 0-1 occurrences of R^3 and 0-3 occurrences of R^5. In some embodiments, Cy is thiophenyl substituted with 0 occurrences of R^3 and 1 occurrence of R^5. In some embodiments, Cy is thiophenyl substituted with 0-1 occurrence of R^3 and 0 occurrence of R^5. In some embodiments, Cy is thiophenyl substituted with 1 occurrence of R^3 and 0 occurrence of R^5. In some embodiments, Cy is isothiazolyl substituted with 0 occurrences of R^3 and 1 occurrence of R^5. In some embodiments, Cy is isothiazolyl substituted with 0-1 occurrence of R^3 and 0 occurrence of R^5. In some embodiments, Cy is isothiazolyl substituted with 1 occurrence of R^3 and 0 occurrence of R^5. In other embodiments, Cy is 6-membered heteroaryl.

[00202] In some embodiments of compounds of Formula (I), W_d is .

[00203] In other embodiments of compounds of Formula (I), X is $-(CH(R^9))_z-$. For example, z is 1.

[00204]

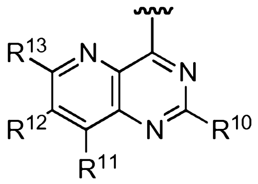
[00205] In various embodiments, W_d is  or , wherein R^{10}, R^{11}, R^{12}, and R^{13} are independently hydrogen, alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, alkoxy, heterocyclyloxy, amido, amino, acyl, acyloxy, alkoxycarbonyl, sulfonamido, halo, cyano, hydroxyl, nitro, phosphate, urea, carbonate, or NR′R″ wherein R′ and R″ are taken together with nitrogen to form a cyclic moiety.

[00206] In some embodiments of the compound of Formula (I), at least one of R^{10}, R^{11}, R^{12} and R^{13} is hydrogen, cyano, halo, unsubstituted or substituted alkyl, unsubstituted or substituted alkynyl, or unsubstituted or substituted alkenyl. In some embodiments, at least one of R^{10}, R^{11}, R^{12} and R^{13} is unsubstituted or substituted aryl. In some embodiments, at least one of R^{10}, R^{11}, R^{12} and R^{13} is unsubstituted or substituted heteroaryl, which includes but is not limited to heteroaryl having a five membered ring, heteroaryl having a six membered ring, heteroaryl with at least one nitrogen ring atom, heteroaryl with two nitrogen ring atoms, monocylic heteroaryl, and bicylic heteroaryl. In some embodiments, at least one of R^{10}, R^{11}, R^{12} and R^{13} is unsubstituted or substituted heterocyclyl, which includes but is not limited to heterocyclyl with one nitrogen ring atom, heterocyclyl with one oxygen ring atom, heterocyclyl with one sulfur ring atom, 5 membered heterocyclyl, 6 membered heterocyclyl, saturated heterocyclyl, unsaturated heterocyclyl, heterocyclyl having an unsaturated moiety connected to the heterocyclyl ring, heterocyclyl substituted by oxo, and heterocyclyl substituted by two oxo. In some embodiments, at least one of R^{10}, R^{11}, R^{12} and R^{13} is unsubstituted or substituted cycloalkyl, including, but not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, or cycloalkyl each of which can be substituted by one oxo; or cycloalkyl having an unsaturated moiety connected to the cycloalkyl ring. In some embodiments, at least one of R^{10}, R^{11}, R^{12} and R^{13} is unsubstituted or substituted amido, carboxylic acid, unsubstituted or substituted acyloxy, unsubstituted or substituted alkoxycarbonyl, unsubstituted or substituted acyl, or unsubstituted or substituted sulfonamido. In some embodiments, R^{10}, R^{11}, R^{12}, and R^{13} are independently selected from hydrogen, alkyl, heteroalkyl, alkenyl, alkynyl, alkoxy, amido, amino, acyl, acyloxy, alkoxycarbonyl, sulfonamido, halo, cyano, and hydroxyl. In some embodiments, R^{10}, R^{11}, R^{12}, and R^{13} are independently selected from hydrogen, amino, and chloro. In some embodiments, R^{10} is selected from amino and chloro.

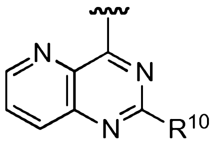
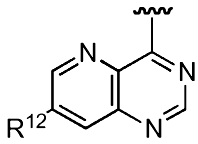
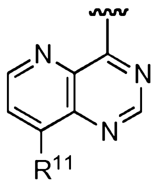
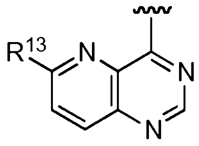
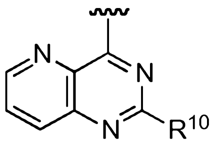
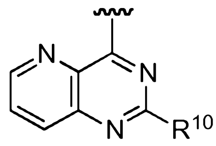
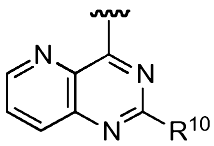
[00207] In some embodiments, when at least one of R^{10}, R^{11}, R^{12} and R^{13} is alkyl, alkynyl, alkenyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, alkoxycarbonyl, amido, acyloxy, acyl, or sulfonamido, it is substituted with one or more of alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, alkoxy, amido, amino, acyl,

acyloxy, alkoxycarbonyl, sulfonamido, halo, cyano, hydroxyl or nitro, each of which alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, alkoxy, amido, amino, acyl, acyloxy, alkoxycarbonyl, or sulfonamido can itself be substituted.

[00208] In some embodiments of compounds of Formula (I), W_d is:

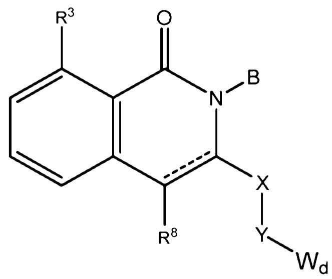

.

[00209] In some embodiments of compounds of Formula (I), W_d is a structure selected from :

, , , or . In some embodiments, W_d is  and R^{10} is hydrogen, amino or halo. For example, W_d is  and R^{10} is Cl-. In another instance, W_d is  and R^{10} is hydrogen.

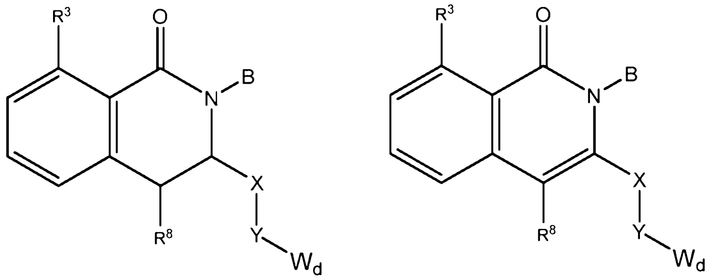
[00210] In some embodiments, Cy is aryl substituted with 0-1 occurrences of R^3 and 0-3 occurrences of R^5. For example, Cy is phenyl substituted with 1 occurrence of R^3 and 0 occurrences of R^5. In other embodiments, Cy is heteroaryl substituted with 0-1 occurrences of R^3 and 0-3 occurrences of R^5. Cy can be, for example, pyridinyl, pyridazinyl, thiophenyl, furanyl, pyrrolyl, thiazolyl, or isothiazolyl. In some embodiments, Cy is 5-membered heteroaryl substituted with 0-1 occurrences of R^3 and 0-3 occurrences of R^5. In other embodiments, Cy is 6-membered heteroaryl substituted with 0-1 occurrences of R^3 and 0-3 occurrences of R^5. In some embodiments, Cy is aryl, thiophenyl, or isothiazolyl. In some embodiments, Cy is thiophenyl substituted with 0 occurrences of R^3 and 1 occurrence of R^5. In some embodiments, Cy is thiophenyl substituted with 0-1 occurrence of R^3 and 0 occurrence of R^5. In some embodiments, Cy is thiophenyl substituted with 1 occurrence of R^3 and 0 occurrence of R^5. In some embodiments, Cy is isothiazolyl substituted with 0 occurrences of R^3 and 1 occurrence of R^5. In some embodiments, Cy is isothiazolyl substituted with 0-1 occurrence of R^3 and 0 occurrence of R^5. In some embodiments, Cy is isothiazolyl substituted with 1 occurrence of R^3 and 0 occurrence of R^5.

[00211] In some embodiments, the compound of Formula (I) has a structure of Formula (II):



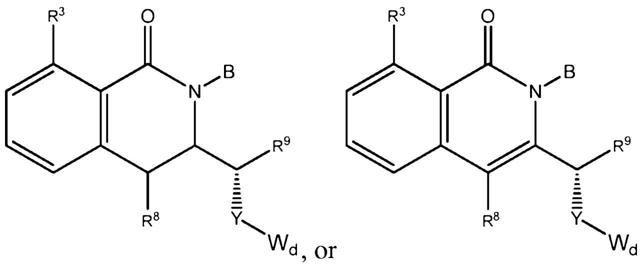
Formula (II)

[00212] For example, the compound of Formula (II) can have a structure of Formula (IIa) or (IIb):



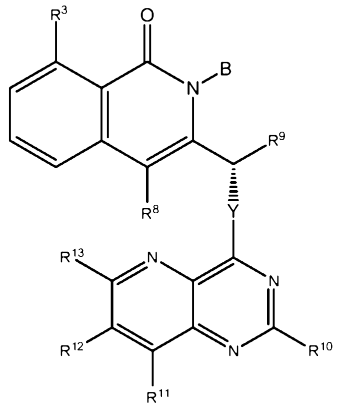
Formula (IIa) or Formula (IIb)

[00213] In other embodiments, the compound of Formula (II) has the structure of Formula (IIIa) or (IIIb):

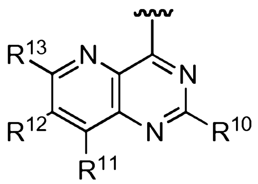
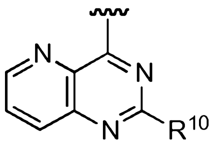
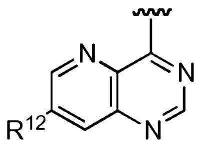
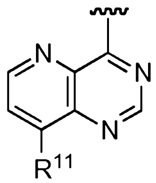
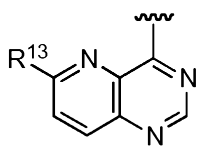
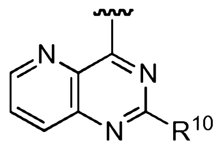
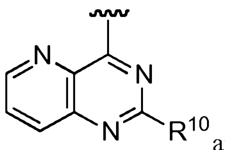
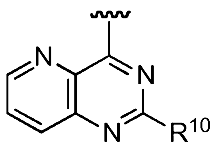


Formula (IIIa) or Formula (IIIb)

[00214] In some embodiments, the compound of Formula (II) has a structure of Formula (IIIb-1):

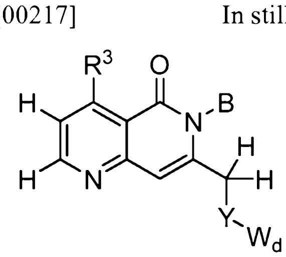
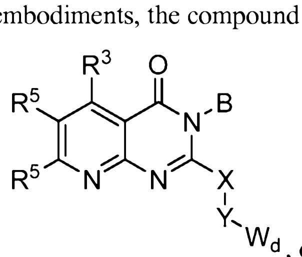
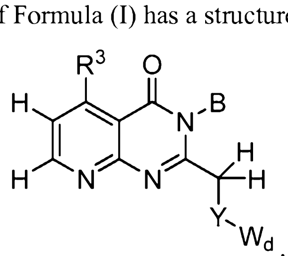


Formula (IIIb-1).

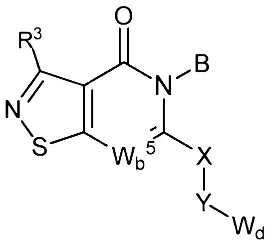
[00215] In some embodiments of compounds of Formula (IIa), (IIb), (IIIa), (IIIb), or (IIIb-1), W_d is  . In some embodiments of compounds of Formula (IIa), (IIb), (IIIa), (IIIb), or (IIIb-1), W_d is a structure selected from : , , , or . In some embodiments of compounds of Formula (IIa), (IIb), (IIIa), (IIIb), or (IIIb-1), W_d is  and R^{10} is hydrogen, amino or halo. For example, W_d is  and R^{10} is Cl-. In another instance of a compound of Formula (IIa), (IIb), (IIIa), (IIIb), or (IIIb-1), W_d is  and R^{10} is hydrogen.

[00216] In some embodiments of compounds of Formula (IIa), (IIb), (IIIa), (IIIb), or (IIIb-1), B is aryl substituted with 0-3 occurrences of R^2. For example, B is phenyl substituted with 0-3 occurrences of R^2. In some embodiments of compounds of Formula (IIa), (IIb), (IIIa), (IIIb), or (IIIb-1), B is unsubstituted phenyl. In other embodiments of compounds of Formula (IIa), (IIb), (IIIa), (IIIb), or (IIIb-1), B is phenyl substituted with 1 occurrence of R^2. R^2 is, in some instances, halo or alkyl. In other embodiments of compounds of Formula (IIa), (IIb), (IIIa), (IIIb), or (IIIb-1), B is cycloalkyl or heterocyclyl.

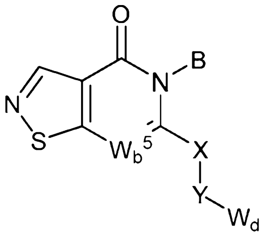
[00217] In still other embodiments, the compound of Formula (I) has a structure selected from :

, , or .

[00218] In some embodiments, the compound of Formula (I) has the structure of Formula (IVa) or Formula (IVb):

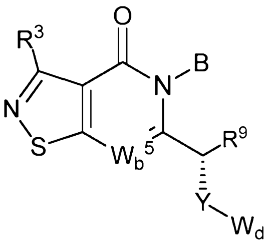


or

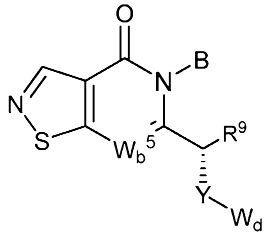


Formula (IVa) Formula (IVb).

[00219] For example, the compound of Formula (IVa) or Formula (IVb) has the structure of Formula (Va) or Formula (Vb):

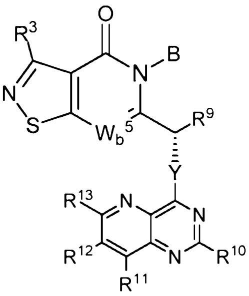


or



Formula (Va) Formula (Vb).

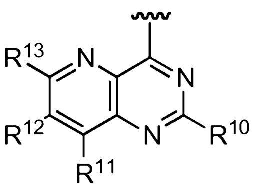
[00220] In some embodiments, the compound of Formula (I) has a structure of Formula (Va-1):



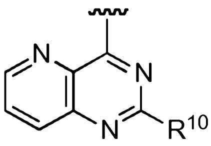
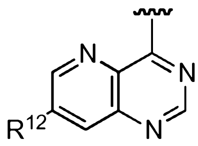
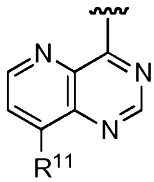
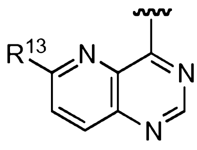
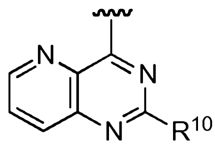
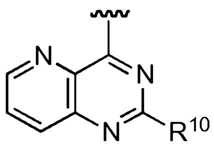
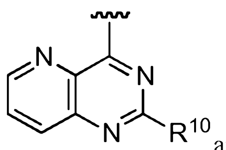
Formula (Va-1).

[00221] In some embodiments of compounds of Formula (IVa), (IVb), (Va), (Vb), or (Va-1), Wb^5 is CR^8. For example, Wb^5 is CH. In some embodiments, the compound is a compound of Formula (IVa), (IVb), (Va), (Vb), or (Va-1), where R^5 is H. In other embodiments of a compound of Formula (IVa), (IVb), (Va), (Vb), or (Va-1), R^5 is selected from hydrogen, alkyl, cycloalkyl, halo, aryl, and heteroaryl. For example, R^5 is selected from methyl, chloro or pyrazolo.

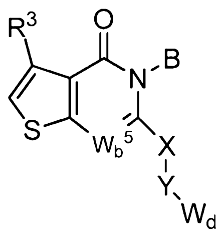
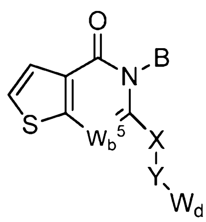
[00222] In some embodiments of compounds of Formula (IVa), (IVb), (Va), (Vb), or (Va-1), W_d is



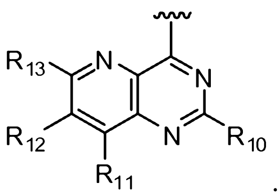
. In some embodiments of compounds of Formula (IVa), (IVb), (Va), (Vb), or (Va-1), W_d is a structure selected from :

, , , or . In some embodiments of compounds of Formula (IVa), (IVb), (Va), (Vb), or (Va-1), W_d is  and R^{10} is hydrogen, amino or halo. For example, W_d is  and R^{10} is Cl-. In another instance of a compound of Formula (IVa), (IVb), (Va), (Vb), or (Va-1), W_d is  and R^{10} is hydrogen. In some embodiments of compounds of Formula (IVa), (IVb), (Va), (Vb), or (Va-1), B is aryl substituted with 0-3 occurrences of R^2. For example, B is phenyl substituted with 0-3 occurrences of R^2. In some embodiments of compounds of Formula (IVa), (IVb), ((Va), (Vb), or (Va-1), B is unsubstituted phenyl. In other embodiments of compounds of Formula (IVa), (IVb), (Va), (Vb), or (Va-1), B is phenyl substituted with 1 occurrence of R^2. R^2 is, in some instances, halo or alkyl. In other embodiments of compounds of Formula (IVa), (IVb), (Va), (Vb), or (Va-1), B is cycloalkyl or heterocyclyl.

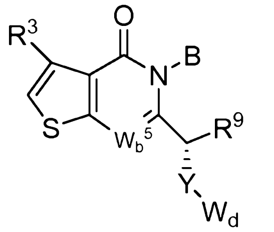
[00223] In other embodiments, the compound of Formula (I) has the structure of Formula (VIa) or Formula (VIb):

 or 

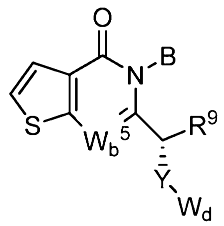
Formula (VIa) Formula (VIb).

[00224] In some embodiments of the compound of Formula (VIa) or (VIb), W_d is .

[00225] In other embodiments, the compound of Formula (VIa) or (VIb) has the structure of Formula (VIIa) or (VIIb):

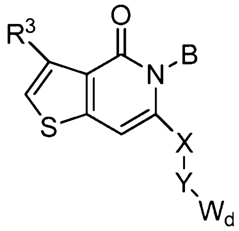


or

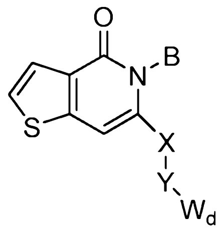


Formula (VIIa) Formula (VIIb).

[00226] In some embodiments, the compound of Formula (VIIa) or (VIIb) has the structure of Formula (VIIIa) or (VIIIb):

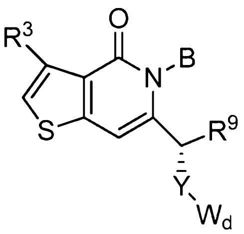


or

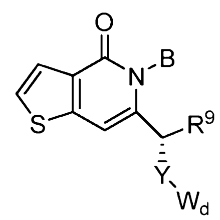


Formula (VIIIa) Formula (VIIIb).

[00227] In some embodiments, the compound of Formula (VIIa) or (VIIb) has the structure of Formula (IXa) or (IXb):

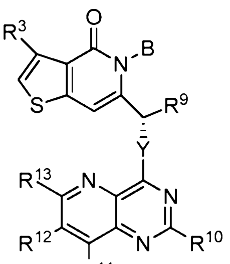


or



Formula (IXa) Formula (IXb).

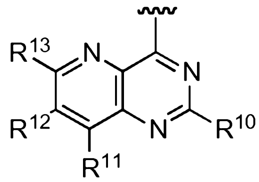
[00228] In some embodiments, the compound of Formula (I) has a structure of Formula (IXa-1):

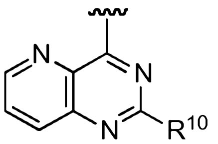
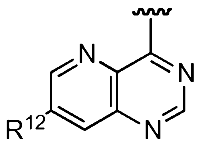
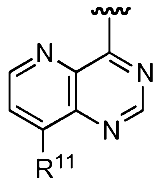
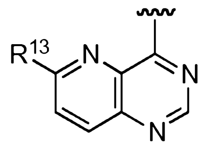
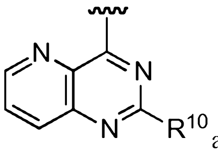
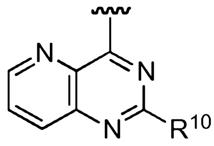
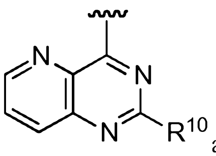


Formula (IXa-1).

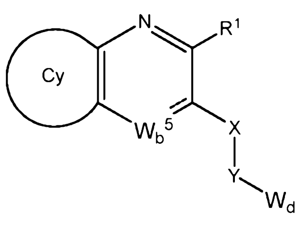
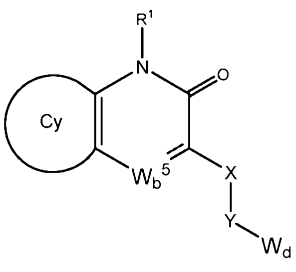
[00229] In some embodiments, R^3 is selected from alkyl, cycloalkyl, halo, aryl, and heteroaryl. For example, R^3 is selected from methyl, chloro, and pyrazolo.

[00230] In some embodiments, B is aryl substituted with 0-3 occurrences of R^2. For example, B is phenyl substituted with 0-3 occurrences of R^2. B is, *e.g.*, unsubstituted phenyl. Alternatively, B is phenyl substituted with 1 occurrence of R^2. R^2 can be, for instance, halo or alkyl. In other embodiments, B is cycloalkyl. In other embodiments, B is heterocyclyl.

[00231] For example, the compound of Formula (I) is a compound of Formula (VIa), (VIb), (VIIa), (VIIb), (VIIIa), (VIIIb), (IXa), (IXb), or (IXa-1), where R^3 is H. In other embodiments of a compound of Formula (VIa), (VIIa), (VIIIa), or (IXa), R^3 is selected from hydrogen, alkyl, cycloalkyl, halo, aryl, and heteroaryl. For example, R^3 is selected from methyl, chloro or pyrazolo. In some embodiments of compounds of Formula (VIa), (VIb), (VIIa), (VIIb), (VIIIa), (VIIIb), (IXa), (IXb), or (IXa-1), W_d is . In some embodiments of compounds of Formula (VIa), (VIb), (VIIa), (VIIb), (VIIIa), (VIIIb), (IXa), (IXb), or (IXa-1), W_d is a structure selected from :

, , , or . In some embodiments of compounds of Formula (VIa), (VIb), (VIIa), (VIIb), (VIIIa), (VIIIb), (IXa), (IXb), or (IXa-1), W_d is  and R^{10} is hydrogen, amino or halo. For example, W_d is  and R^{10} is Cl-. In another instance of a compound of Formula (VIa), (VIb), (VIIa), (VIIb), (VIIIa), (VIIIb), (IXa), (IXb), or (IXa-1), W_d is  and R^{10} is hydrogen. In some embodiments of compounds of Formula (VIa), (VIb), (VIIa), (VIIb), (VIIIa), (VIIIb), (IXa), (IXb), or (IXa-1), B is aryl substituted with 0-3 occurrences of R^2. For example, B is phenyl substituted with 0-3 occurrences of R^2. In some embodiments of compounds of Formula (VIa), (VIb), (VIIa), (VIIb), (VIIIa), (VIIIb), (IXa), (IXb), or (IXa-1), B is unsubstituted phenyl. In other embodiments of compounds of Formula (VIa), (VIb), (VIIa), (VIIb), (VIIIa), (VIIIb), (IXa), (IXb), or (IXa-1), B is phenyl substituted with 1 occurrence of R^2. R^2 is, in some instances, halo or alkyl. In other embodiments of compounds of Formula (VIa), (VIb), (VIIa), (VIIb), (VIIIa), (VIIIb), (IXa), (IXb), or (IXa-1), B is cycloalkyl or heterocyclyl.

[00232] In another aspect, provided herein are compounds of Formula (X) or (XI):

 or 

Formula (X) Formula (XI),

or an enantiomer, a mixture of enantiomers, or a mixture of two or more diastereomers thereof, or its pharmaceutically acceptable forms thereof, wherein:

W_b^5 is N, CHR^8, or CR^8;

R^8 is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heteroalkyl, alkoxy, amido, amino, acyl, acyloxy, sulfonamido, halo, cyano, hydroxyl, or nitro;

Cy is aryl or heteroaryl substituted by 0-1 occurrences of R^3 and 0-3 occurrences of R^5;

R^1 is –(L)-$R^{1'}$;

L is a bond, -S-, -N(R^{15})-, -C(R^{15})$_2$-, -C(=O)-, or –O-;

$R^{1'}$ is hydrogen, alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, alkoxy, heterocyclyloxy, amido, amino, acyl, acyloxy, alkoxycarbonyl, sulfonamido, halo, cyano, hydroxyl, nitro, phosphate, urea, carbonate, substituted nitrogen,or NR′R″ wherein R′ and R″ are taken together with nitrogen to form a cyclic moiety;

each R^{15} is independently hydrogen, alkyl, cycloalkyl, or heteroalkyl;

R^3 is alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, fluoroalkyl, heteroalkyl, alkoxy, amido, amino, acyl, acyloxy, sulfonamido, halo, cyano, heteroaryl, aryl, hydroxyl, or nitro; wherein each of the above substituents can be substituted with 0, 1, 2, or 3 R^{17};

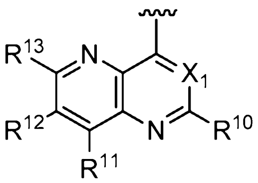
each R^5 is independently alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, alkoxy, heterocyclyloxy, amido, amino, acyl, acyloxy, alkoxycarbonyl, sulfonamido, halo, cyano, hydroxyl, nitro, phosphate, urea, carbonate, or NR′R″ wherein R′ and R″ are taken together with nitrogen to form a cyclic moiety;

X is absent or is –(CH(R^{16}))$_z$–;

Y is absent, -O-, -S-, -S(=O)-, -S(=O)$_2$-, -N(R^{16})-, -C(=O)-(CHR^{16})$_z$-, -C(=O)-, -N(R^{16})-C(=O)-, or -N(R^{16})-C(=O)NH-,-N(R^{16})C(R^{16})$_2$-, or -C(=O)-N(R^{16})-(CHR^{16})$_z$-;

each z is an integer of 1, 2, 3, or 4;

each R^{16} is independently hydrogen, alkyl, cycloalkyl, heterocyclyl, heteroalkyl, aryl, halo or heteroaryl; and

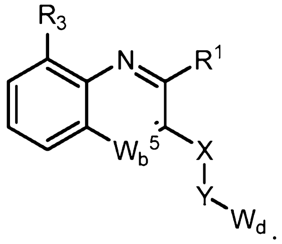
W_d is 

,

wherein X_1 is N or CR^{14};

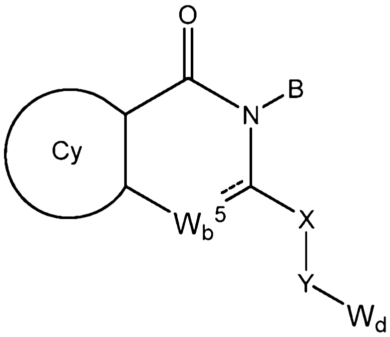
wherein R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, and R^{17} are independently hydrogen, alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, alkoxy, heterocyclyloxy, amido, amino, acyl, acyloxy, alkoxycarbonyl, sulfonamido, halo, cyano, hydroxyl, nitro, phosphate, urea, carbonate, oxo, or NR′R″ wherein R′ and R″ are taken together with nitrogen to form a cyclic moiety.

[00233] In some embodiments, the compound is a compound of Formula (X). For example, the compound has the Formula:



[00234] In some embodiments, Cy is a 5- or 6-membered ring. In some embodiments, Cy is a 6-membered ring, such as a 6-membered aryl ring. For instance, Cy is a 6-membered ring, including *e.g.* phenyl. In other embodiments, W_b^5 is CH. In yet other embodiments, R^{11} is H. In still other embodiments, R^{12} is H. In other embodiments, X-Y is $-CH_2-N(CH_3)$.

[00235] In one aspect, provided herein are compounds are provided of Formula (I):



Formula (I)

or an enantiomer, a mixture of enantiomers, or a mixture of two or more diastereomers thereof, or its pharmaceutically acceptable forms thereof, wherein

Cy is aryl or heteroaryl substituted by 0-1 occurrences of R^3 and 0-3 occurrences of R^5;

W_b^5 is CR^8, CHR^8, or N;

R^8 is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heteroalkyl, alkoxy, amido, amino, acyl, acyloxy, sulfonamido, halo, cyano, hydroxyl, or nitro;

B is hydrogen, alkyl, amino, heteroalkyl, cycloalkyl, heterocyclyl, heterocyclylalkyl, aryl or heteroaryl, each of which is substituted with 0-4 occurrences of R^2;

each R^2 is independently alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, alkoxy, amido, amino, acyl, acyloxy, alkoxycarbonyl, sulfonamido, halo, cyano, hydroxyl, nitro, phosphate, urea or carbonate;

X is absent or is $-(CH(R^9))_z-$;

Y is absent, -O-, -S-, -S(=O)-, $-S(=O)_2-$, $-N(R^9)-$, $-C(=O)-(CHR^9)_z-$, -C(=O)-, $-N(R^9)-C(=O)-$, or $-N(R^9)-C(=O)NH-$, $-N(R^9)C(R^9)_2-$, or $-C(=O)-N(R^9)-(CHR^9)_z$;

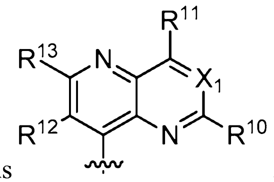
each z is independently an integer of 1, 2, 3, or 4;

wherein when W_b^5 is N, no more than one of X or Y is absent;

R^3 is alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, fluoroalkyl, heteroalkyl, alkoxy, amido, amino, acyl, acyloxy, sulfinyl, sulfonyl, sulfoxide, sulfone, sulfonamido, halo, cyano, heteroaryl, aryl, hydroxyl, or nitro; wherein each of the above substituents can be substituted with 0, 1, 2, or 3 R^{17};

each R^5 is independently alkyl, alkenyl, alkynyl, cycloalkyl, heteroalkyl, alkoxy, amido, amino, acyl, acyloxy, sulfonamido, halo, cyano, hydroxyl, or nitro;

each R^9 is independently hydrogen, alkyl, cycloalkyl, or heteroalkyl; and

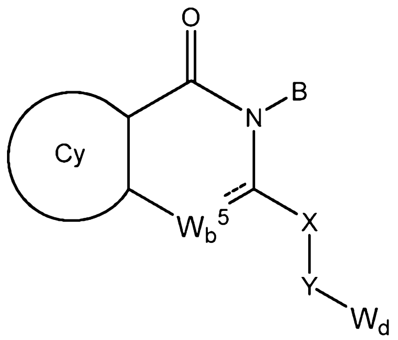
W_d is 

,

wherein X_1 is N or CR^{14};

wherein R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, and R^{17} are independently hydrogen, alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, alkoxy, heterocyclyloxy, amido, amino, acyl, acyloxy, alkoxycarbonyl, sulfonamido, halo, cyano, hydroxyl, nitro, phosphate, urea, carbonate, carboxylic acid, oxo, or NR′R″ wherein R′ and R″ are taken together with nitrogen to form a cyclic moiety.

[00236] In one aspect, provided herein are compounds of Formula (XII):



Formula (XII)

or an enantiomer, a mixture of enantiomers, or a mixture of two or more diastereomers thereof, or its pharmaceutically acceptable forms thereof, wherein

Cy is aryl or heteroaryl substituted by 0-1 occurrences of R^3 and 0-3 occurrences of R^5;

W_b^5 is CR^8, CHR^8, or N,

R^8 is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heteroalkyl, alkoxy, amido, amino, acyl, acyloxy, sulfonamido, halo, cyano, hydroxyl, or nitro;

B is hydrogen, alkyl, amino, heteroalkyl, cycloalkyl, heterocyclyl, aryl or heteroaryl, each of which is substituted with 0-4 R^2;

R^2 is alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, alkoxy, amido, amino, acyl, acyloxy, alkoxycarbonyl, sulfonamido, halo, cyano, hydroxyl, nitro, phosphate, urea or carbonate;

X is absent or is $-(CH(R^9))_z-$;

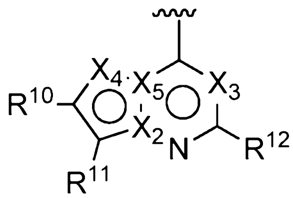
Y is absent, -O-, -S-, -S(=O)-, -S(=O)$_2$-, -N(R^9)-, -C(=O)-(CHR^9)$_z$-, -C(=O)-, -N(R^9)-C(=O)-, -N(R^9)-C(=O)NH-,-N(R^9)C(R^9)$_2$-, or -C(=O)-N(R^9)-(CHR^9)$_z$;

each z is independently an integer of 1, 2, 3, or 4;

R^3 is alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, haloalkyl, heteroalkyl, alkoxy, amido, amino, acyl, acyloxy, sulfinyl, sulfonyl, sulfoxide, sulfone, sulfonamido, halo, cyano, aryl, heteroaryl, hydroxyl, or nitro; wherein each of the above substituents can be substituted with 0, 1, 2, or 3 R^{17};

each R^5 is independently alkyl, alkenyl, alkynyl, cycloalkyl, heteroalkyl, alkoxy, amido, amino, acyl, acyloxy, sulfonamido, halo, cyano, hydroxyl, or nitro;

each R^9 is independently hydrogen, alkyl, cycloalkyl, or heteroalkyl; and

W$_d$ is 

,

wherein one of X$_5$ and X$_2$ is N and one of X$_5$ and X$_2$ is C;

X$_3$ and X$_4$ are each independently CR^{13} or N;

X$_2$ and X$_3$ are not both N; and

each R^{10}, R^{11}, R^{12}, R^{13}, and R^{17} is independently hydrogen, alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, alkoxy, heterocyclyloxy, amido, amino, acyl, acyloxy, alkoxycarbonyl, sulfonamido, halo, cyano, hydroxyl, nitro, phosphate, urea, carbonate, oxo, or NR′R″ wherein R′ and R″ are taken together with nitrogen to form a cyclic moiety.

[00237] In certain embodiments, W$_b$^{5} is CR^8. In some embodiments, R^8 is hydrogen.

[00238] In certain embodiments, X^3 is CR^{13}. In some embodiments, R^{13} is hydrogen. In some embodiments, X^3 is N.

[00239] In certain embodiments, X^4 is CR^{13}. In some embodiments, R^{13} is hydrogen. In some embodiments, X^4 is N.

[00240] In some embodiments, Cy is aryl or heteroaryl substituted with 0-1 occurrences of R^3 and 0-3 occurrences of R^5. In some embodiments, Cy is aryl or heteroaryl substituted with 0 occurrences of R^3 and 0-3 occurrences of R^5. In some embodiments, Cy is aryl (*e.g.*, phenyl) substituted with 0-1 occurrences of R^3 and 0-3 occurrences of R^5. In some embodiments, Cy is phenyl substituted with 1 occurrence of R^3 and 0 occurrences of R^5.

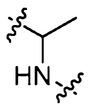
[00241] In some embodiments, Cy is heteroaryl substituted with 0-1 occurrences of R^3 and 0-3 occurrences of R^5. In some embodiments, Cy is 5-membered heteroaryl (*e.g.*, thiophenyl or isothiazolyl) substituted with 0-1 occurrences of R^3 and 0-3 occurrences of R^5. In some embodiments, Cy is thiophenyl substituted with 0 occurrences of R^3 and 1 occurrence of R^5. In some embodiments, Cy is thiophenyl substituted with 0-1 occurrence of R^3 and 0 occurrence of R^5. In some embodiments, Cy is thiophenyl substituted with 1 occurrence of R^3 and 0 occurrence of R^5. In some embodiments, Cy is isothiazolyl substituted with 0 occurrences of R^3 and 1 occurrence of R^5. In some embodiments, Cy is isothiazolyl substituted with 0-1 occurrence of R^3 and 0 occurrence of R^5. In some

embodiments, Cy is isothiazolyl substituted with 1 occurrence of R^3 and 0 occurrence of R^5. In some embodiments, Cy is 6-membered heteroaryl (*e.g.*, pyridinyl).

[00242] In certain embodiments, R^3 is halo (*e.g.*, chloro). In some embodiments, R^3 is heteroaryl (*e.g.*, 1-methyl-4-pyrazolyl).

[00243] In some embodiments, X is $-(CH(R^9))_z$-. In some embodiments, z is 1. In some embodiments, R^9 is C_{1-10} alkyl (*e.g.*, methyl).

[00244] In some embodiments, is absent, -O-, $-NH(R^9)$-, or $-S(=O)_2$-. In certain embodiments, Y is absent. In some embodiments, Y is $-N(R^9)$-. In some embodiments, R^9 is hydrogen.

[00245] In certain embodiments, X-Y is 

. In some embodiments, X-Y is $-CH_2-N(CH_3)$. In some embodiments, X-Y is (S)-$CH(CH_3)$-NH-. In some embodiments, X-Y is (R)-$CH(CH_3)$-NH-.

[00246] In certain embodiments, B is aryl or heteroaryl substituted with 0-4 occurrences of R^2. In some embodiments, B is aryl (*e.g.*, 6-membered aryl) substituted with 0-4 occurrences of R^2. In some embodiments, B is phenyl substituted with 0-4 occurrences of R^2. In some embodiments, B is phenyl substituted with 0 occurrences of R^2. In some embodiments, B is phenyl substituted with 1 occurrence of R^2. In some embodiments, R^2 is phenyl substituted at the ortho position. In some embodiments, R^2 is phenyl substituted at the meta position. In some embodiments, R^2 is phenyl substituted at the para position. In some embodiments, R^2 is halo (*e.g.*, fluoro).

[00247] In certain embodiments, B is cycloalkyl substituted with 0-4 occurrences of R^2. In some embodiments, B is cycloalkyl (*e.g.*, cyclopropyl) substituted with 0 occurrences of R^2.

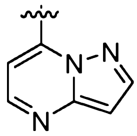
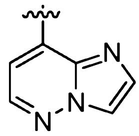
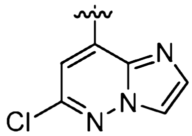
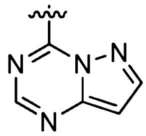
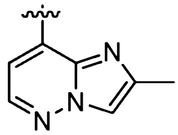
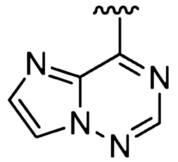
[00248] In certain embodiments, B is alkyl substituted with 0-4 occurrences of R^2. In some embodiments, B is alkyl (*e.g.*, methyl or ethyl) substituted with 0 occurrences of R^2. In some embodiments, B is alkyl (*e.g.*, methyl or ethyl) substituted with 1 occurrence of R^2. In some embodiments, R^2 is heterocyclyl (*e.g.*, pyrrolyl).

[00249] In certain embodiments, X^1 is N and X^2 is C. In some embodiments, X^1 is C and X^2 is N.

[00250] In certain embodiments, R^{10} is hydrogen. In some embodiments, R^{10} is alkyl (*e.g.*, methyl).

[00251] In certain embodiments, R^{11} is hydrogen.

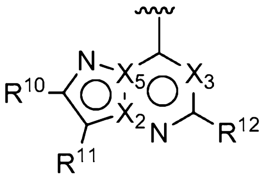
[00252] In certain embodiments, R^{12} is hydrogen. In some embodiments, R^{12} is halo (*e.g.*, chloro).

[00253] In certain embodiments, W_d is . In some embodiments, W_d is . In some embodiments, W_d is . In some embodiments, W_d is . In some embodiments, W_d is . In some embodiments, W_d is .

[00254] In some embodiments, R^3 is halo, alkyl, alkoxy, heteroaryl, or cycloalkyl. For example, R^3 is CH_3, CH_2CH_3, CF_3, Cl, or F. In other embodiments, R^3 is CH_3, CF_3, or Cl. In other embodiments, each R^3 and R^5 is independently selected from CH_3, OCH_3, CF_3, and halo. In certain embodiments, R^3 is halo (*e.g.*, chloro). In some embodiments, R^3 is heteroaryl (*e.g.*, 1-methyl-4-pyrazolyl).

[00255] In some embodiments, B is cycloalkyl, heterocyclyl, aryl, or heteroaryl, which is substituted with 0-4 occurrences of R^2, R^3 is H, halo, alkyl, alkoxy, aryl, cycloalkyl, or heteroaryl, each R^5 is H, halo, alkyl, alkoxy, aryl, cycloalkyl, or heteroaryl, and R^9 is hydrogen or alkyl.

[00256] In some embodiments, R^5 is selected from alkyl, cycloalkyl, halo, aryl, and heteroaryl. For example, R^5 is selected from methyl, chloro, and pyrazolo.

[00257] In various embodiments, W_d is .

[00258] In such embodiments, X_3 is CR^{13} or N; each R^{10}, R^{11}, R^{12} and R^{13} is independently hydrogen, alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, alkoxy, heterocyclyloxy, amido, amino, acyl, acyloxy, alkoxycarbonyl, sulfonamido, halo, cyano, hydroxyl, nitro, phosphate, urea, carbonate, or NR′R″ wherein R′ and R″ are taken together with nitrogen to form a cyclic moiety; and one of X_1 and X_2 is N and one of X_1 and X_2 is C.

[00259] For example, X_1 is N and X_2 is C. Alternatively, X_1 is C and X_2 is N. In some embodiments, X_3 is CR^{13} or N. In other embodiments, X_4 is CR^{13} or N.

[00260] In some embodiments, X_3 is CR^{13}. For example, R^{13} is H. In other embodiments, X_3 is N.

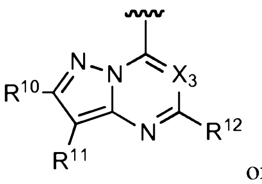
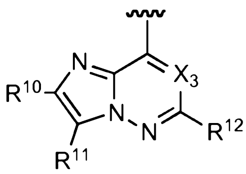
[00261] In some embodiments, X_4 is CR^{13}. For example, R^{13} is H. In other embodiments, X_4 is N.

[00262] In some embodiments of the compound of Formula (I), at least one of R^{10}, R^{11}, R^{12} and R^{13} is hydrogen, cyano, halo, unsubstituted or substituted alkyl, unsubstituted or substituted alkynyl, or unsubstituted or substituted alkenyl. In some embodiments, at least one of R^{10}, R^{11}, R^{12} and R^{13} is unsubstituted or substituted aryl. In some embodiments, at least one of R^{10}, R^{11}, R^{12} and R^{13} is unsubstituted or substituted heteroaryl, which includes,

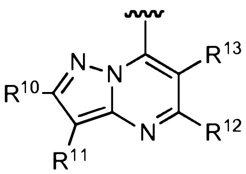
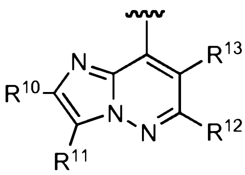
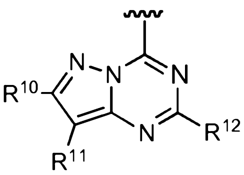
but is not limited to, heteroaryl having a five membered ring, heteroaryl having a six membered ring, heteroaryl with at least one nitrogen ring atom, heteroaryl with two nitrogen ring atoms, monocylic heteroaryl, and bicylic heteroaryl. In some embodiments, at least one of R^{10}, R^{11}, R^{12} and R^{13} is unsubstituted or substituted heterocyclyl, which includes, but is not limited to, heterocyclyl with one nitrogen ring atom, heterocyclyl with one oxygen ring atom, heterocyclyl with one sulfur ring atom, 5 membered heterocyclyl, 6 membered heterocyclyl, saturated heterocyclyl, unsaturated heterocyclyl, heterocyclyl having an unsaturated moiety connected to the heterocyclyl ring, heterocyclyl substituted by oxo, and heterocyclyl substituted by two oxo. In some embodiments, at least one of R^{10}, R^{11}, R^{12} and R^{13} is unsubstituted or substituted cycloalkyl, including, but not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloalkyl substituted by one oxo; or cycloalkyl having an unsaturated moiety connected to the cycloalkyl ring. In some embodiments, at least one of R^{10}, R^{11}, R^{12} and R^{13} is unsubstituted or substituted amido, unsubstituted or substituted acyloxy, unsubstituted or substituted alkoxycarbonyl, unsubstituted or substituted acyl, or unsubstituted or substituted sulfonamido. In some embodiments, R^{10}, R^{11}, R^{12}, and R^{13} are independently selected from hydrogen, alkyl, heteroalkyl, alkenyl, alkynyl, alkoxy, amido, amino, acyl, acyloxy, alkoxycarbonyl, sulfonamido, halo, cyano, and hydroxyl. In some embodiments, R^{10}, R^{11}, R^{12}, and R^{13} are independently selected from hydrogen, amino, and chloro. In some embodiments, R^{10} is selected from amino and chloro.

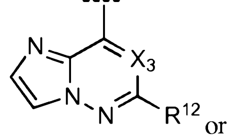
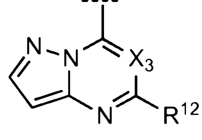
[00263] In some embodiments, when at least one of R^{10}, R^{11}, R^{12} and R^{13} is alkyl, alkynyl, alkenyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, alkoxycarbonyl, amido, acyloxy, acyl, or sulfonamido, it is substituted with one or more of alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, alkoxy, amido, amino, acyl, acyloxy, alkoxycarbonyl, sulfonamido, halo, cyano, hydroxy or nitro, each of which alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, alkoxy, amido, amino, acyl, acyloxy, alkoxycarbonyl, or sulfonamido may itself be substituted.

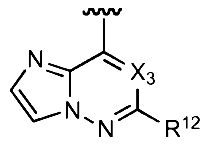
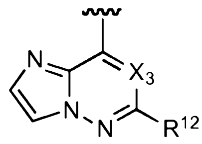
[00264] In some embodiments, W_d is:

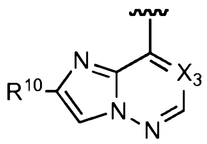
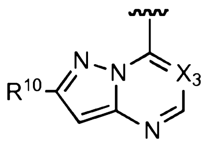

or

.

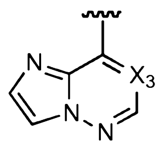
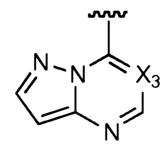
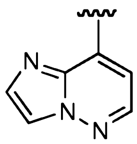
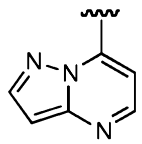
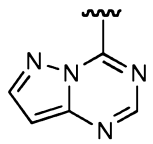
[00265] In some embodiments of compounds of Formula (I), W_d is a structure selected from:


,

, or

.

[00266] In some embodiments, W_d is  or  and R^{12} is hydrogen or halo.

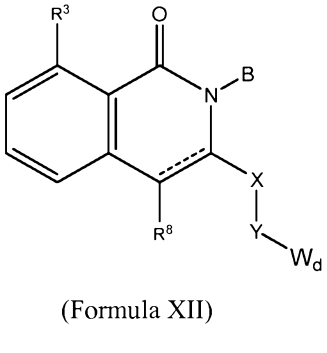
For example, W_d is  and R^{12} is Cl. In another instance, W_d is  and R^{12} is hydrogen.

[00267] In other embodiments, W_d is  or  and R^{10} is hydrogen or halo.

[00268] In still other embodiments, W_d is  or . For example, W_d is ,  or .

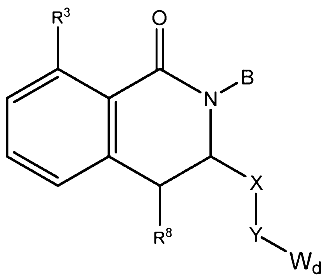
[00269] In some embodiments, Cy is aryl substituted with 0-1 occurrences of R^3 and 0-3 occurrences of R^5. For example, Cy is phenyl substituted with 1 occurrence of R^3 and 0 occurrences of R^5. In other embodiments, Cy is heteroaryl substituted with 0-1 occurrences of R^3 and 0-3 occurrences of R^5. Cy may be, for example, pyridinyl, pyridazinyl, thiophenyl, furanyl, pyrrolyl, thiazolyl, or isothiazolyl. In some embodiments, Cy is 5-membered heteroaryl substituted with 0-1 occurrences of R^3 and 0-3 occurrences of R^5. In other embodiments, Cy is 6-membered heteroaryl substituted with 0-1 occurrences of R^3 and 0-3 occurrences of R^5. In some embodiments, Cy is aryl, thiophenyl, or isothiazolyl. In some embodiments, Cy is thiophenyl substituted with 0 occurrences of R^3 and 1 occurrence of R^5. In some embodiments, Cy is thiophenyl substituted with 0-1 occurrence of R^3 and 0 occurrence of R^5. In some embodiments, Cy is thiophenyl substituted with 1 occurrence of R^3 and 0 occurrence of R^5. In some embodiments, Cy is isothiazolyl substituted with 0 occurrences of R^3 and 1 occurrence of R^5. In some embodiments, Cy is isothiazolyl substituted with 0-1 occurrence of R^3 and 0 occurrence of R^5. In some embodiments, Cy is isothiazolyl substituted with 1 occurrence of R^3 and 0 occurrence of R^5.

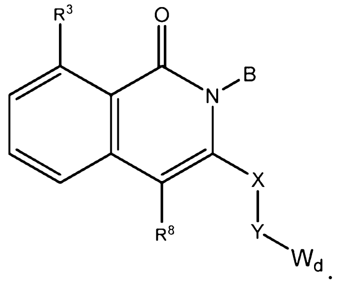
[00270] In some embodiments, the compound of Formula (XII) has the structure of Formula (XIII):



(Formula XII)

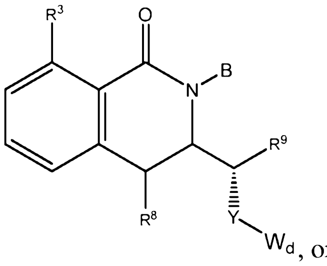
[00271] For example, the compound of Formula (I) can have a structure of Formula (XIIIa) or (XIIIb):



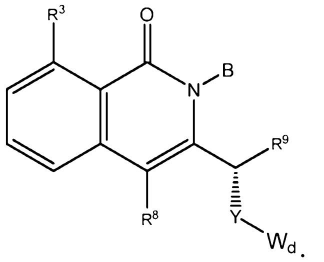


Formula (XIIIa) or Formula (XIIIb)

[00272] In other embodiments, the compound of Formula (XIIIa) or (XIIIb) has the structure of Formula (XIVa) or (XIVb):

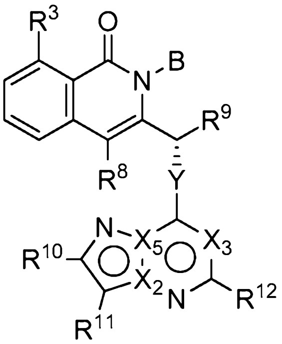


, or



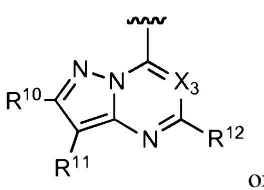
Formula (XIVa) or Formula (XIVb)

[00273] In some embodiments, the compound of Formula (XIII) has a structure of Formula (XIVb-1):

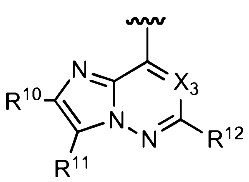


Formula (XIVb-1).

[00274] In some embodiments of compounds of Formula (XIIIa), (XIIIb), (XIVa), (XIVb), or (XIVb-1), W_d is:

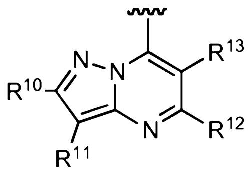
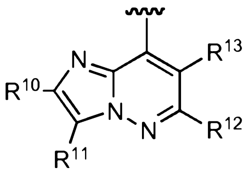
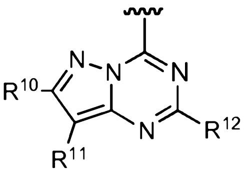


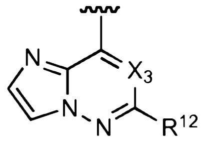
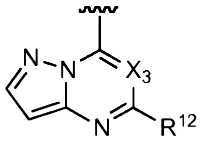
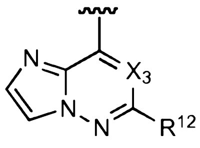
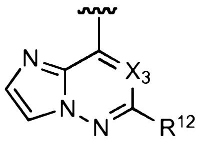
or

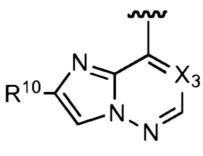
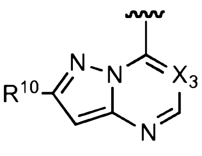


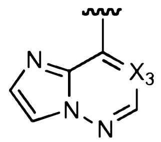
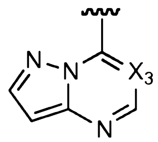
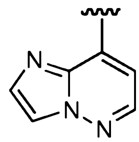
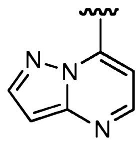
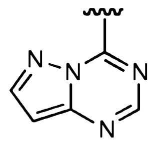
.

[00275] In some embodiments of compounds of Formula (XIIIa), (XIIIb), (XIVa), (XIVb), or (XIVb-1), W_d is:

, , or .

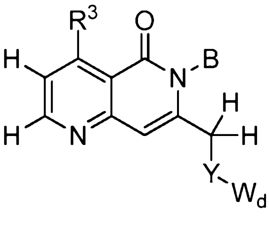
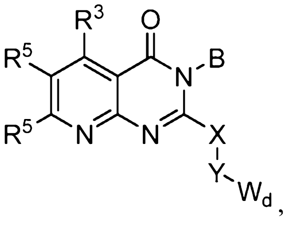
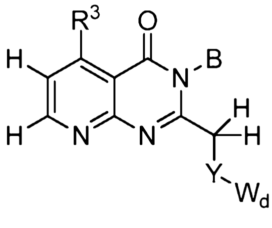
[00276] In some embodiments of compounds of Formula (XIIIa), (XIIIb), (XIVa), (XIVb), or (XIVb-1), W_d is  or  and R^{12} is hydrogen or halo. For example, W_d is  and R^{12} is Cl- In another instance, W_d is  and R^{12} is hydrogen.

[00277] In other embodiments of compounds of Formula (XIIIa), (XIIIb), (XIVa), (XIVb), or (XIVb-1), Wd is  or  and R^{10} is hydrogen or halo.

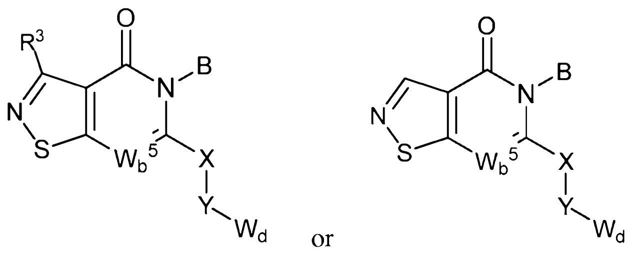
[00278] In still other embodiments of compounds of Formula (XIIIa), (XIIIb), (XIVa), (XIVb), or (XIVb-1), W_d is  or . For example, W_d is , , or .

[00279] In some embodiments of compounds of Formula (XIIIa), (XIIIb), (XIVa), (XIVb), or (XIVb-1), B is aryl substituted with 0-3 occurrences of R^2. For example, B is phenyl substituted with 0-3 occurrences of R^2. In some embodiments of compounds of Formula (XIIIa), (XIIIb), (XIVa), (XIVb), or (XIVb-1), B is unsubstituted phenyl. In other embodiments of compounds of Formula (XIIIa), (XIIIb), (XIVa), (XIVb), or (XIVb-1), B is phenyl substituted with 1 occurrence of R^2. R^2 is, in some instances, halo or alkyl. In other embodiments of compounds of Formula ((XIIIa), (XIIIb), (XIVa), (XIVb), or (XIVb-1), B is cycloalkyl or heterocyclyl.

[00280] In still other embodiments, the compound of Formula (XII) is a compound which has a structure selected from:

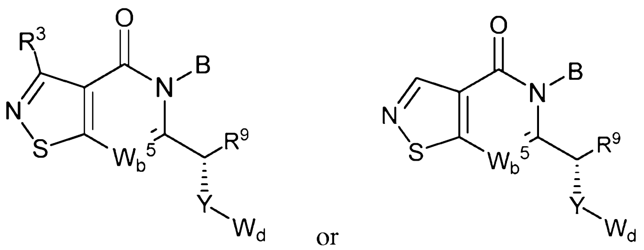
, , and .

[00281] In some embodiments, the compound of Formula (XIV) has the structure of Formula (XVa) or Formula (XVb):



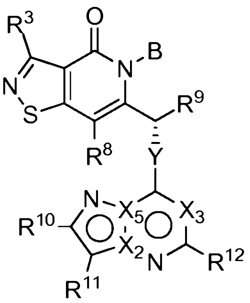
Formula (XVa) Formula (XVb).

[00282] In other embodiments, the compound of Formula (XVa) or (XVb) is a compound of Formula (XVIa) or (XVIb):



Formula (XVIa) Formula (XVIb).

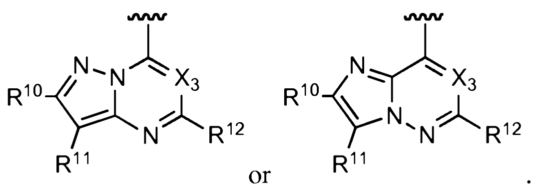
[00283] In some embodiments, the compound of Formula (XII) has a structure of Formula (XVIa-1):



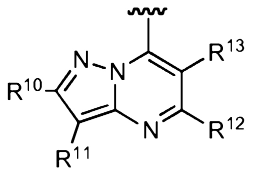
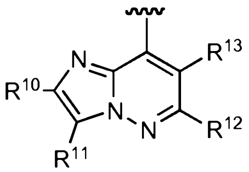
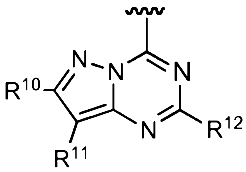
Formula (XVIa-1).

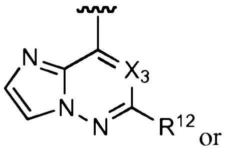
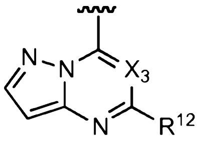
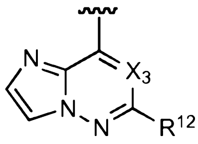
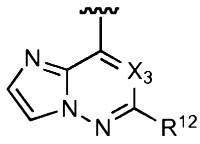
[00284] In some embodiments of compounds of Formula (XVa), (XVb), (XVIa), (XVIb), or (XVIa-1), Wb^5 is CR^8. For example, W_b^5 is CH. In other embodiments of a compound of Formula (XVa) or (XVb), R^3 is selected from alkyl, cycloalkyl, halo, aryl, and heteroaryl. For example, R^3 is selected from methyl, chloro or pyrazolo.

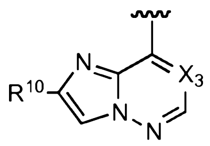
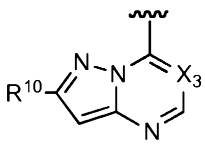
[00285] In some embodiments of compounds of Formula (XVa), (XVb), (XVIa), (XVIb), or (XVIa-1), W_d is:

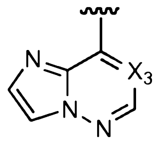
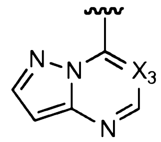
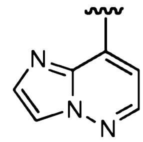
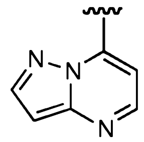
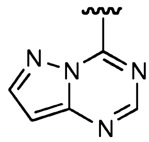


[00286] In some embodiments of of compounds of Formula (XVa), (XVb), (XVIa), (XVIb), or (XVIa-1), W_d is a structure selected from:

 ,  , and  .

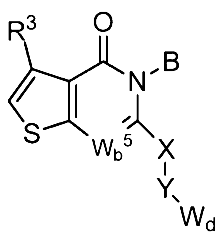
[00287] In some embodiments of compounds of Formula (XVa), (XVb), (XVIa), (XVIb), or (XVIa-1), W_d is  or  and R^{12} is hydrogen or halo. For example, W_d is  and R^{12} is Cl-. In another instance, W_d is  and R^{12} is hydrogen.

[00288] In other embodiments of compounds of Formula (XVa), (XVb), (XVIa), (XVIb), or (XVIa-1), Wd is  or  and R^{10} is hydrogen or halo.

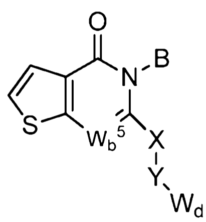
[00289] In still other embodiments of compounds of Formula (XVa), (XVb), (XVIa), (XVIb), or (XVIa-1), W_d is  or  . For example, W_d is  ,  or  .

[00290] In some embodiments of compounds of Formula (XVa), (XVb), (XVIa), (XVIb), or (XVIa-1), B is aryl substituted with 0-3 occurrences of R^2. For example, B is phenyl substituted with 0-3 occurrences of R^2. In some embodiments of compounds of Formula (XVa), (XVb), (XVIa), (XVIb), or (XVIa-1), B is unsubstituted phenyl. In other embodiments of compounds of Formula (XVa), (XVb), (XVIa), (XVIb), or (XVIa-1), B is phenyl substituted with 1 occurrence of R^2. R^2 is, in some instances, halo or alkyl. In other embodiments of compounds of Formula (XVa), (XVb), (XVIa), (XVIb), or (XVIa-1), B is cycloalkyl or heterocyclyl.

[00291] In some embodiments, the compound of Formula (I) is a compound of Formula (XVIIa) or (XVIIb):

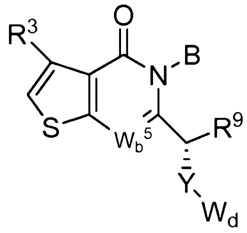


or

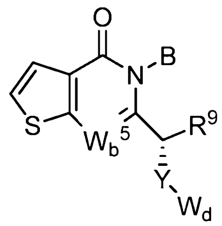


Formula (XVIIa) Formula (XVIIb).

[00292] In other embodiments, the compound of Formula (XVIIa) or (XVIIIb) has the structure of Formula (XVIIIa) or (XVIIIb):

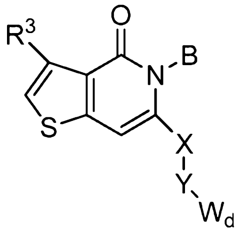


or

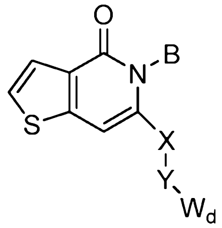


Formula (XVIIIa) Formula (XVIIIb).

[00293] In some embodiments, the compound of Formula (XVIIIa) or (XVIIIb) has the structure of Formula (XIXa) or (XIXb):

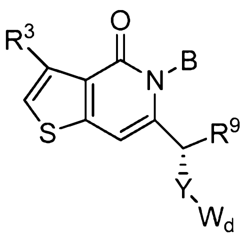


or

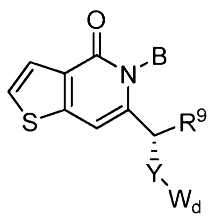


Formula (XIXa) Formula (XIXb).

[00294] In some embodiments, the compound of Formula (XVIIIa) or (XVIIIb) has the structure of Formula (XXa) or (XXb):

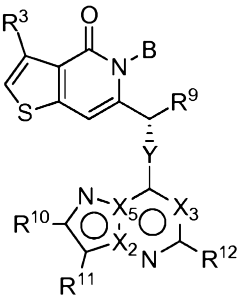


or



Formula (XXa) Formula (XXb).

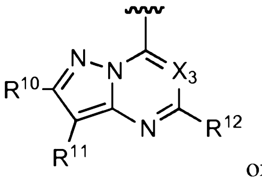
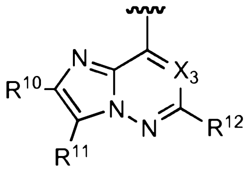
[00295] In some embodiments, the compound of Formula (XII) has a structure of Formula (XXa-1):



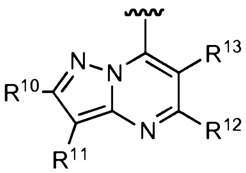
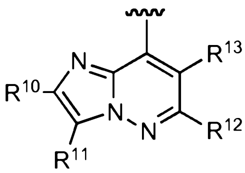
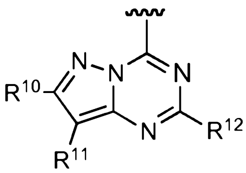
Formula (XXa-1).

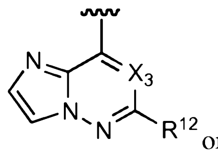
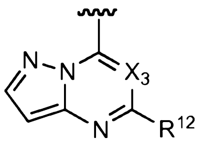
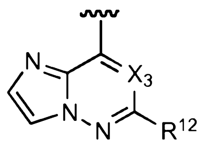
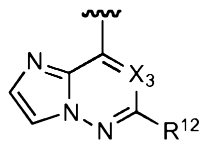
[00296] In some embodiments of a compound of Formula (XVIIa), (XVIIb), (XVIIIa), (XVIIIb), (XIXa), (XIXb), (XXa), (XXb), or (XXa-1), R^3 is selected from alkyl, cycloalkyl, halo, aryl, and heteroaryl. For

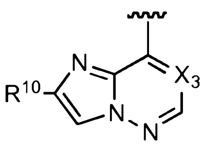
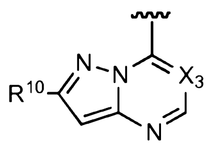
example, R^3 is selected from methyl, chloro or pyrazolo. In some embodiments of compounds of Formula (XVIIa), (XVIIb), (XVIIIa), (XVIIIb), (XIXa), (XIXb), (XXa), (XXb), or (XXa-1), W_d is:

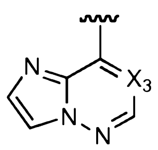
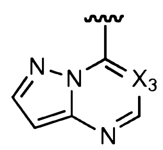
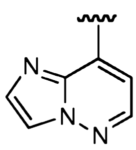
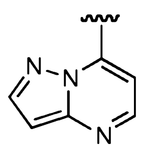
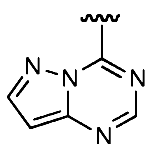
 or  .

[00297] In some embodiments of of compounds of Formula (XVIIa), (XVIIb), (XVIIIa), (XVIIIb), (XIXa), (XIXb), (XXa), (XXb), or (XXa-1), W_d is a structure selected from:

 ,  , and  .

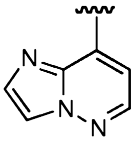
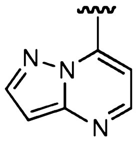
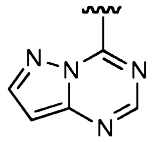
[00298] In some embodiments of compounds of Formula (XVIIa), (XVIIb), (XVIIIa), (XVIIIb), (XIXa), (XIXb), (XXa), (XXb), or (XXa-1), W_d is  or  and R^{12} is hydrogen or halo. For example, W_d is  and R^{12} is Cl-. In another instance, W_d is  and R^{12} is hydrogen.

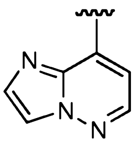
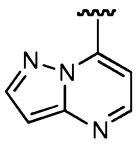
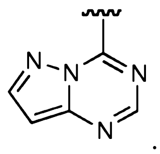
[00299] In other embodiments of compounds of Formula (XVIIa), (XVIIb), (XVIIIa), (XVIIIb), (XIXa), (XIXb), (XXa), (XXb), or (XXa-1), W_d is  or  and R^{10} is hydrogen or halo.

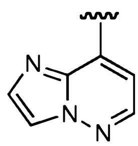
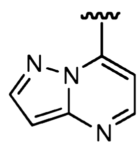
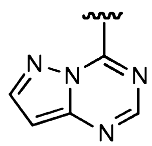
[00300] In still other embodiments of compounds of Formula (XVIIa), (XVIIb), (XVIIIa), (XVIIIb), (XIXa), (XIXb), (XXa), (XXb), or (XXa-1), W_d is  or  . For example, W_d is  ,  or  .

[00301] In some embodiments of compounds of Formula (XVIIa), (XVIIb), (XVIIIa), (XVIIIb), (XIXa), (XIXb), (XXa), (XXb), or (XXa-1), B is aryl substituted with 0-3 occurrences of R^2. For example, B is

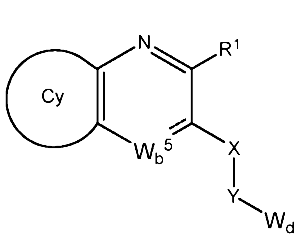
phenyl substituted with 0-3 occurrences of R^2. In some embodiments of compounds of Formula (XVIIa), (XVIIb), (XVIIIa), (XVIIIb), (XIXa), (XIXb), (XXa), (XXb), or (XXa-1), B is unsubstituted phenyl. In other embodiments of compounds of Formula (XVIIa), (XVIIb), (XVIIIa), (XVIIIb), (XIXa), (XIXb), (XXa), (XXb), or (XXa-1), B is phenyl substituted with 1 occurrence of R^2. R^2 is, in some instances, halo or alkyl. In other embodiments of compounds of Formula (XVIIa), (XVIIb), (XVIIIa), (XVIIIb), (XIXa), (XIXb), (XXa), (XXb), or (XXa-1), B is cycloalkyl or heterocyclyl.

[00302] In some embodiments of the compound of Formula (XII), B is aryl or heteroaryl substituted with 0 or 1 occurrences of R^2 and Cy is a 5- or 6-membered aryl or heteroaryl group. For example, B is aryl substituted with 0 or 1 occurrences of R^2 and Cy is a 5- or 6-membered aryl or heteroaryl group. In another example, B is aryl or heteroaryl substituted with 0 or 1 occurrence of R^2 and Cy is a 6-membered aryl group. Cy is, for instance, phenyl substituted with alkyl, fluroalkyl, aryl, heteroaryl or halo. In such embodiments, W_d can be, for example, ,  or .

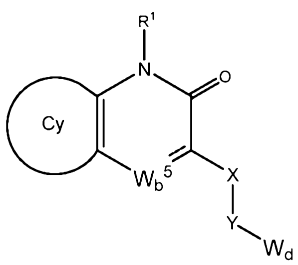
[00303] In other embodiments of the compound of Formula (XII), B is aryl or heteroaryl substituted with 0 or 1 occurrences of R^2, Cy is a 5- or 6-membered aryl or heteroaryl group, X is $-(CH(R^9))_z$- and Y is -$NH(R^9)$-, wherein each R^9 is chosen independently. For example, -X-Y- is -$CH_2(CH_3)$-NH-. In some embodiments, B is aryl substituted with 0 or 1 occurrences of R^2 and Cy is a 5- or 6-membered aryl or heteroaryl group. In another example, B is aryl or heteroaryl substituted with 0 or 1 occurrence of R^2 and Cy is a 6-membered aryl group. Cy is, for instance, phenyl substituted with alkyl, fluroalkyl, aryl, heteroaryl or halo. In such embodiments, W_d can be, for example, ,  or .

[00304] In some embodiments, the compound disclosed herein is a compound of Formula (XIIIb) where R^3 is halo, alkyl, heteroalkyl, fluoroalkyl, alkenyl, alkynyl, cycloalkyl, heteroaryl, or heterocyclyl; X is -$CH(R^9)$-, where R^9 is methyl or ethyl; R^8 is H; Y is –NH-; and W_d is ,  or .

[00305] In another aspect, provided herein is a compound of formula (XXI) or (XXII):



or



Formula (XXI) Formula (XXII),

or an enantiomer, a mixture of enantiomers, or a mixture of two or more diastereomers thereof, or its pharmaceutically acceptable forms thereof, wherein:

W_b^5 is N, CHR^8 or CR^8;

R^8 is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heteroalkyl, alkoxy, amido, amino, acyl, acyloxy, sulfonamido, halo, cyano, hydroxyl, or nitro;

Cy is aryl or heteroaryl substituted by 0-1 occurrences of R^3 and 0-3 occurrences of R^5;

R^1 is –(L)-$R^{1'}$;

L is a bond, -S-, -$N(R_{15})$-, -$C(R_{15})_2$-, -C(=O)-, or –O-;

$R^{1'}$ is hydrogen, alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, alkoxy, heterocyclyloxy, amido, amino, acyl, acyloxy, alkoxycarbonyl, sulfonamido, halo, cyano, hydroxy, nitro, phosphate, urea, carbonate, substituted nitrogen,or NR′R″ wherein R′ and R″ are taken together with nitrogen to form a cyclic moiety;

each R^{15} is independently hydrogen, alkyl, cycloalkyl, or heteroalkyl;

R^3 is alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, haloalkyl, heteroalkyl, alkoxy, amido, amino, acyl, acyloxy, sulfinyl, sulfonyl, sulfoxide, sulfone, sulfonamido, halo, cyano, heteroaryl, aryl, hydroxyl, or nitro; wherein each of the above substituents can be substituted with 0, 1, 2, or 3 R^{17};

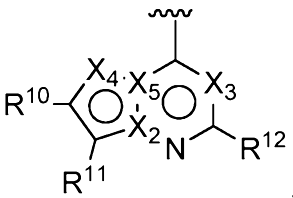
each R^5 is independently alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, alkoxy, heterocyclyloxy, amido, amino, acyl, acyloxy, alkoxycarbonyl, sulfonamido, halo, cyano, hydroxy, nitro, phosphate, urea, carbonate, or NR′R″ wherein R′ and R″ are taken together with nitrogen to form a cyclic moiety;

X is absent or is –$(CH(R^9))_z$;

Y is absent, -O-, -S-, -S(=O)-, -$S(=O)_2$-, -$N(R^9)$-, -C(=O)-$(CHR^9)_z$-, -C(=O)-, -$N(R^9)$-C(=O)-, or -$N(R^9)$-C(=O)NH-,-$N(R^9)C(R^9)_2$-, or -C(=O)-$N(R^9)$-$(CHR^9)_z$-;

each z is an integer of 1, 2, 3, or 4;

each R^9 is independently hydrogen, alkyl, cycloalkyl, heterocyclyl, heteroalkyl, aryl, halo or heteroaryl; and

W_d is 

,

wherein one of X_5 and X_2 is N and one of X_5 and X_2 is C;

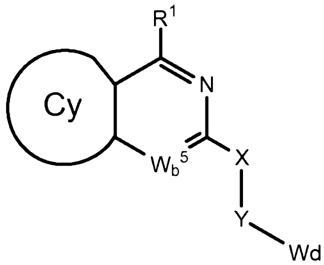
wherein X_3 and X_4 are each independently selected from CR^{13} and N; and

each R^{10}, R^{11}, R^{12}, R^{13}, and R^{17} is independently hydrogen, alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, alkoxy, heterocyclyloxy, amido, amino, acyl, acyloxy, alkoxycarbonyl, sulfonamido, halo, cyano, hydroxyl, nitro, phosphate, urea, carbonate, oxo, or NR′R″ wherein R′ and R″ are taken together with nitrogen to form a cyclic moiety.

[00306] In some embodiments, Cy is a 5- or 6-membered ring. For instance, Cy is a 6-membered ring, including *e.g.* phenyl. In other embodiments, Wb5 is CH. In yet other embodiments, R^{10}, R^{11}, R^{12}, and R^{13} are H. In some embodiments, X-Y is $-CH_2-N(CH_3)$.

[00307] In some embodiments, Cy is a 6-membered ring, such as a 6-membered aryl ring. In other embodiments, W_b^5 is CH. In still other embodiments, -X-Y- is $-CH_2-N(CH_3)$.

[00308] In another aspect, provided herein is a compound of Formula (XXIII):



Formula (XXIII)

or an enantiomer, a mixture of enantiomers, or a mixture of two or more diastereomers thereof, or its pharmaceutically acceptable forms thereof, wherein

W_b^5 is N or CR^8;

R^8 is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heteroalkyl, alkoxy, amido, amino, acyl, acyloxy, sulfonamido, halo, cyano, hydroxyl, or nitro;

Cy is aryl or heteroaryl substituted by 0-1 occurrences of R^3 and 0-3 occurrences of R^5;

R^1 is $-(L)-R^{1'}$;

L is a bond, -S-, $-N(R^{16})-$, $-C(R^{15})_2-$, -C(=O)-, or –O-;

$R^{1'}$ is hydrogen, alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, heterocyclylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, alkoxy, heterocycloalkyloxy, amido, amino, acyl, acyloxy, alkoxycarbonyl, sulfonamido, halo, cyano, hydroxy, nitro, phosphate, urea, carbonate, substituted nitrogen,or NR′R″ wherein R′ and R″ are taken together with nitrogen to form a cyclic moiety;

R^3 is alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, haloalkyl, heteroalkyl, alkoxy, amido, amino, acyl, acyloxy, sulfinyl, sulfonyl, sulfoxide, sulfone, sulfonamido, halo, cyano, heteroaryl, aryl, hydroxyl, or nitro; wherein each of the above substituents can be substituted with 0, 1, 2, or 3 R^{17};

each R^5 is independently alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, alkoxy, heterocycloalkyloxy, amido, amino, acyl, acyloxy, alkoxycarbonyl, sulfonamido, halo, cyano, hydroxy, nitro, phosphate, urea, carbonate, or NR′R″ wherein R′ and R″ are taken together with nitrogen to form a cyclic moiety;

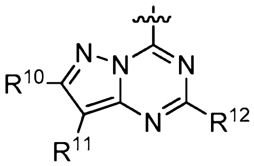
X is absent or is $-(CH(R^{14}))_z$;

Y is absent, -O-, -S-, -S(=O)-, $-S(=O)_2-$, $-N(R^9)-$, $-C(=O)-(CHR^{14})_z-$, -C(=O)-, $-N(R^9)-C(=O)-$, or $-N(R^9)-C(=O)NH-$,$-N(R^9)C(R^{14})_2-$, or $-C(=O)-(CHR^{14})_z-$;

each z is an integer of 1, 2, 3, or 4;

each R^9 and R^{16} is independently hydrogen, alkyl, cycloalkyl, heterocyclyl, heteroalkyl, aryl, or heteroaryl;

each R^{14} and R^{15} is independently hydrogen, alkyl, aryl, heteroaryl or halo; and

W_d is ,

wherein R^{10}, R^{11}, R^{12}, and R^{17} are independently hydrogen, alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, alkoxy, heterocycloalkyloxy, amido, amino, acyl, acyloxy, alkoxycarbonyl, sulfonamido, halo, cyano, hydroxy, nitro, phosphate, urea, carbonate, oxo, or NR′R″ wherein R′ and R″ are taken together with nitrogen to form a cyclic moiety.

[00309] In some embodiments, R^5 is halo, alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heteroaryl, or heterocyclyl. In some embodiments, R^5 is alkyl (*e.g.*, methyl) or halo (*e.g.*, chloro). In some embodiments, R^5 is halo (*e.g.*, chloro).

[00310] In certain embodiments, n is 1 and L is -C(=O)- or –O-. In some embodiments, L is –C(=O)-.

[00311] In certain embodiments, $R^{1'}$ is alkyl or NR′R″ wherein R′ and R″ are taken together with nitrogen to form a cyclic moiety. In some embodiments, R′ and R″ are taken together with nitrogen to form a heterocyclic moiety (*e.g.*, morpholinyl).

[00312] In certain embodiments, X is $-(CH(R^9))_z$-. In some embodiments, z is 1. In some embodiments, X is $-CH_2-$ or $-CH(CH_3)-$. In some embodiments, the carbon of the $-CH(CH_3)-$ moiety has a (S) stereochemical configuration. In some embodiments, the carbon of the $-CH(CH_3)-$ moiety has- a (R) stereochemical configuration.

[00313] In certain embodiments, Y is absent, -O-, $-NH(R^9)-$, or $-S(=O)_2-$. In some embodiments, R^9 is methyl or hydrogen.

[00314] In certain embodiments, -X-Y- is $-CH_2-N(CH_3)$. In some embodiments, X-Y is (S)-$CH(CH_3)$-NH-. In some embodiments, -X-Y- is (R)-$CH(CH_3)$-NH-.

[00315] In certain embodiments, R^{10}, R^{11} and R^{12} are independently selected from hydrogen, amino, and chloro. In some embodiments, R^{10} is amino or chloro.

[00316] In some embodiments, Cy is aryl substituted with 0-3 occurrences of R^5. For example, Cy is phenyl substituted with 1 occurrence of R^3.

[00317] In some embodiments, R^3 is halo, alkyl, heteroalkyl, fluoroalkyl, alkenyl, alkynyl, cycloalkyl, heteroaryl, or heterocyclyl. For example, R^3 is alkyl or halo.

[00318] In other embodiments, L is -(C(=O)- or –O-.

[00319] In some embodiments, $R^{1'}$ is substituted alkyl, substituted nitrogen, or NR′R″ wherein R′ and R″ are taken together with nitrogen to form a cyclic moiety. For instance, the cyclic moiety is a heterocyclic or heteroaryl group such as a morpholino group. In other instances, $R^{1'}$ is substituted alkyl, including alkyl which is substituted with a heterocyclyl group.

[00320] In some embodiments, X is absent or is $-(CH(R^9))_z$-. In some embodiments, R^9 is methyl or hydrogen. For example, z is 1. In some instances, X is $-CH_2$- or $-CH(CH_3)$-. In some embodiments, the carbon of the $-CH(CH_3)$- moiety has a (S) stereochemical configuration. Alternatively, the carbon of the $-CH(CH_3)$- moiety has a (R) stereochemical configuration. In some embodiments, Y is absent, -O-, $-NH(R^9)$-, or $-S(=O)_2$-. In some embodiments, -X-Y- is $-CH_2-N(CH_3)$. Alternatively, -X-Y- is (S)-$CH(CH_3)$-NH-or (R)-$CH(CH_3)$-NH-.

[00321] In some embodiments, R^{10}, R^{11} and R^{12} are independently selected from hydrogen, alkyl, heteroalkyl, alkenyl, alkynyl, alkoxy, amido, amino, acyl, acyloxy, alkoxycarbonyl, sulfonamido, halo, cyano, and hydroxyl. For example, R^{10}, R^{11} and R^{12} are independently selected from hydrogen, amino, and chloro. In one instance, R^{10} is amino or chloro.

[00322] In some embodiments, Cy is aryl or heteroaryl group substituted by 0-1 occurrences of R^3 and 0-3 occurrences of R^5. In some embodiments, Cy is aryl substituted with 0-1 occurrences or R^3 and 0-3 occurrences of R^5. For example, Cy is phenyl substituted with 1 occurrence of R^3 and 0 occurrences of R^5. In other embodiments, Cy is phenyl substituted with 0 occurrences of R^3 and 0 occurrences of R^5. In other embodiments, Cy is heteroaryl substituted with 0-1 occurrences of R^3 and 0-3 occurrences of R^5. Cy can be, for example, pyridinyl, pyridazinyl, thiophenyl, furanyl, pyrrolyl, thiazolyl, or isothiazolyl. In some embodiments, Cy is 5-membered heteroaryl substituted with 0-1 occurrences of R^3 and 0-3 occurrences of R^5. In other embodiments, Cy is 6-membered heteroaryl substituted with 0-1 occurrences of R^3 and 0-3 occurrences of R^5. In some embodiments, Cy is aryl, thiophenyl, or isothiazolyl. For example, Cy is thiophenyl substituted with 0 occurrences of R^3 and 1 occurrence of R5. In another example, Cy is isothiazolyl substituted with 0 occurrences of R^3 and 1 occurrence of R^5.

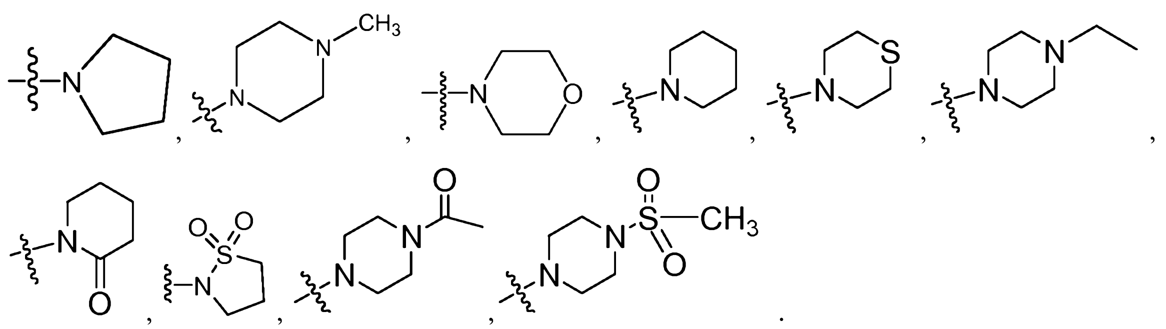
[00323] In some embodiments or compounds of Formula (XXIII), $R^{1'}$ can be hydrogen, alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, alkoxy, heterocyclyloxy, amido, amino, acyl, acyloxy, alkoxycarbonyl, sulfonamido, halo, cyano, hydroxyl, nitro, phosphate, urea, carbonate or NR′R″, wherein R′ and R″ are taken together with nitrogen to form a cyclic moiety.

[00324] In some embodiments of compounds of Formula (XXIII), $R^{1'}$ can be hydrogen, or unsubstituted or substituted alkyl (including, but not limited to, $-CH_3$, $-CH_2CH_3$, n-propyl, isopropyl, *n*- butyl, *tert*-butyl, *sec*-butyl, pentyl, hexyl, and heptyl). In other embodiments, $R^{1'}$ is unsubstituted or substituted alkenyl (including, but not limited to, unsubstituted or substituted C_2-C_5alkenyl such as, for example, vinyl, allyl, 1-methyl propen-1-yl, butenyl, or pentenyl) or unsubstituted or substituted alkynyl (including, but not limited to, unsubstituted or substituted C_2-C_5alkynyl such as acetylenyl, propargyl, butynyl, or pentynyl). Alternatively, $R^{1'}$ is unsubstituted or substituted aryl (including, but not limited to, monocyclic or bicyclic aryl) or unsubstituted or substituted arylalkyl (including, but not limited to, monocyclic or bicyclic aryl linked to alkyl wherein alkyl includes, but is not limited to, CH_3, $-CH_2CH_3$, n-propyl, isopropyl, *n*- butyl, *sec*-butyl, and pentyl). In some other embodiments, $R^{1'}$ is unsubstituted or substituted heteroaryl, including, but not limited to, monocyclic and bicyclic heteroaryl. Monocyclic heteroaryl $R^{1'}$includes, but is not limited to, pyrrolyl, thienyl, furyl, pyridinyl, pyranyl, pyrimidinyl, pyrazinyl, pyridazinyl, imidazolyl, thiazolyl, pyrazolyl, and oxazolyl. Bicyclic heteroaryl $R^{1'}$ includes, but is not limited to, benzothiophenyl, benzofuryl, indolyl, quinolinyl, isoquinolinyl, benzimidazolyl, benzoxazolyl,

benzothiazolyl, quinazolinyl, azaindolyl, pyrazolopyrimidinyl, purinyl, pyrrolo [1, 2-b]pyridazinyl, pyrrolopyrimidinyl, indazolyl, pyrazolylpyridinyl, imidazo[1, 2-a]pyridinyl, and pyrrolo[1, 2-f][1, 2, 4]triazinyl.

[00325] Also provided herein are compounds of Formula (XXIII) wherein $R^{1'}$ is unsubstituted or substituted heteroarylalkyl, including, but not limited to, monocyclic and bicyclic heteroaryl as described above, that are linked to alkyl, which in turn includes, but is not limited to, CH_3, $-CH_2CH_3$, n-propyl, isopropyl, *n*- butyl, *sec*-butyl, and pentyl. In some embodiments, $R^{1'}$ is unsubstituted or substituted cycloalkyl (including, but not limited to, cyclopropyl, cyclobutyl, and cyclopentyl) or unsubstituted or substituted heteroalkyl (non-limiting examples include ethoxymethyl, methoxymethyl, and diethylaminomethyl). In some further embodiments, $R^{1'}$ is unsubstituted or substituted heterocyclyl which includes, but is not limited to, pyrrolidinyl, tetrahydrofuranyl, piperidinyl, tetrahydropyranyl, thiazolidinyl, imidazolidinyl, morpholinyl, and piperazinyl. In yet other embodiments of the compounds of Formula (XXIII), $R^{1'}$ is unsubstituted or substituted alkoxy including, but not limited to, C_1-C_4alkoxy such as methoxy, ethoxy, propoxy or butoxy. $R^{1'}$ can also be unsubstituted or substituted heterocyclyloxy, including but not limited to, 4-NH piperidin-1-yl-oxy, 4-methyl piperidin-1-yl-oxy, 4-ethyl piperidin-1-yl-oxy, 4-isopropyl-piperidin-1-yl-oxy, and pyrrolidin-3-yl-oxy. In other embodiments, $R^{1'}$ is unsubstituted or substituted amino, wherein the substituted amino includes, but is not limited to, dimethylamino, diethylamino, di-isopropyl amino, N-methyl N-ethyl amino, and dibutylamino. In some embodiments, $R^{1'}$ is unsubstituted or substituted acyl, unsubstituted or substituted acyloxy, unsubstituted or substituted C_1-C_4acyloxy, unsubstituted or substituted alkoxycarbonyl, unsubstituted or substituted amido, or unsubstituted or substituted sulfonamido. In other embodiments, $R^{1'}$ is halo, selected from –I, -F, -Cl, and -Br. In some embodiments, $R^{1'}$ is selected from cyano, hydroxyl, nitro, phosphate, urea, or carbonate. In some embodiments, $R^{1'}$ can be $-CH_3$, $-CH_2CH_3$, n-propyl, isopropyl, *n*- butyl, *tert*- butyl, *sec*-butyl, pentyl, hexyl, heptyl, $-OCH_3$, $-OCH_2CH_3$, or $-CF_3$.

[00326] In some embodiments, $R^{1'}$ of the compounds of Formula (XXIII) can also be NR′R″ wherein R′ and R″ are taken together with the nitrogen to form a cyclic moiety having from 3 to 8 ring atoms. The cyclic moiety so formed may further include one or more heteroatoms which are selected from S, O, and N. The cyclic moiety so formed is unsubstituted or substituted, including, but not limited to, morpholinyl, azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, isothiazolidinyl 1,2, dioxide, and thiomorpholinyl. Further non-limiting exemplary cyclic moieites are the following :



[00327] Also provided herein are compounds of Formula (XXIII), wherein when $R^{1'}$ is alkyl, alkenyl, alkynyl, cycloalkyl, heteroalkyl, heterocyclyl, heterocyclyloxy, aryl, arylalkyl, heteroaryl, heteroarylalkyl, acyl, alkoxy, amido, amino, sulfonamido, acyloxy, alkoxycarbonyl, or NR′R″, (wherein R′ and R″ are taken together with

nitrogen to form a cyclic moiety), wherein $R^{1'}$ is optionally substituted with one or more of the following substituents: alkyl, alkenyl, alkynyl, cycloalkyl, heteroalkyl, heterocyclyl, heterocyclyloxy, aryl, arylalkyl, heteroaryl, heteroarylalkyl, acyl, alkoxy, amido, amino, sulfonamido, acyloxy, alkoxycarbonyl, halo, cyano, hydroxyl, nitro, phosphate, urea, carbonate, or NR′R″ wherein R′ and R″ are taken together with nitrogen to form a cyclic moiety. Each of the above substituents can be further substituted with one or more substituents chosen from alkyl, alkoxy, amido, amino, sulfonamido, acyloxy, alkoxycarbonyl, halo, cyano, hydroxyl, nitro, oxo, phosphate, urea, and carbonate.

[00328] For example, provided herein are compounds wherein when $R^{1'}$ is alkyl, the alkyl is substituted with NR′R″ wherein R′ and R″ are taken together with the nitrogen to form a cyclic moiety. The cyclic moiety so formed can be unsubstituted or substituted. Non-limiting exemplary cyclic moieties include, but are not limited to, morpholinyl, azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, and thiomorpholinyl. In other examples of the compounds of Formula (XXIII), when $R^{1'}$ is alkyl, the alkyl is substituted with heterocyclyl, which includes, but is not limited to, oxetanyl, azetidinyl, tetrahydrofuranyl, pyrrolyl, tetrahydropyranyl, piperidinyl, morpholinyl, and piperazinyl. All of the above listed heterocyclyl substituents can be unsubstituted or substituted.

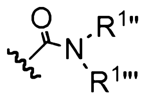
[00329] In yet other examples of the compounds of Formula (XXIII), when $R^{1'}$ is alkyl, the alkyl is substituted with a 5, 6, 7, 8, 9, or 10 membered monocyclic or bicyclic heteroaryl, which is unsubstituted or substituted. In some embodiments, the monocyclic heteroaryl includes, but is not limited to, pyrrolyl, thienyl, furyl, pyridinyl, pyranyl, pyrimidinyl, pyrazinyl, pyridazinyl, imidazolyl, thiazolyl, pyrazolyl, and oxazolyl. The bicyclic heteroaryl includes, but is not limited to, benzothiophenyl, benzofuryl, indolyl, quinolinyl, isoquinolinyl, benzimidazolyl, benzoxazolyl, benzothiazolyl, quinazolinyl, azaindolyl, pyrazolopyrimidinyl, purinyl, pyrrolo [1, 2-b]pyridazinyl, pyrrolopyrimidinyl, indazolyl, pyrazolylpyridinyl, imidazo[1, 2-a]pyridinyl, and pyrrolo[1, 2-f][1, 2, 4]triazinyl.

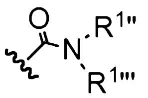
[00330] In some embodiments of the compound of Formula (XXIII), L is $-N(R^2)-$, wherein R^2 is hydrogen, unsubstituted or substituted C_1-C_{10}alkyl (which includes but is not limited to $-CH_3$, $-CH_2CH_3$, n-propyl, isopropyl, *n*- butyl, *tert*- butyl, *sec*-butyl, pentyl, hexyl, and heptyl), or unsubstituted or substituted C_3-C_7cycloalkyl (which includes but is not limited to cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl). In other embodiments of the compound of Formula (XXIII), R^2 is unsubstituted or substituted heterocyclyl (which includes but is not limited to oxetanyl, tetrahydrofuranyl, pyrrolidinyl, tetrahydropyranyl, piperidinyl, and piperazinyl), or unsubstituted or substituted C_2-C_{10}heteroalkyl (which includes but is not limited to methoxyethoxy, methoxymethyl, and diethylaminoethyl). Alternatively, R^2 is unsubstituted or substituted monocyclic heteroaryl (which includes but is not limited to pyrrolyl, thienyl, furyl, pyridinyl, pyranyl, pyrimidinyl, pyrazinyl, pyridazinyl, imidazolyl, thiazolyl, pyrazolyl, and oxazolyl) or unsubstituted or substituted monocyclic aryl.

[00331] In some embodiments of the compound of Formula (XXIII), R^1 is $-OR^{1'}$, wherein $R^{1'}$ is hydrogen or alkyl. In another example of the compound of Formula (XXIII), R^1 is –O-alkyl, where alkyl is isopropyl.

[00332] In other embodiments of the compound of Formula (XXIII), R^1 is $-NHR^{1'}$, $-N(CH_3)R^{1'}$, $-N(CH_2CH_3)R^{1'}$, $-N(CH(CH_3)_2)R^{1'}$, or $-OR^{1'}$, wherein $R^{1'}$ is unsubstituted or substituted heterocyclyl (nonlimiting

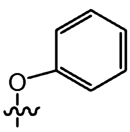
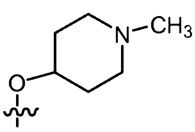
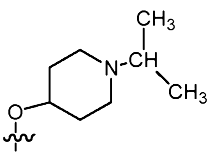
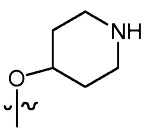
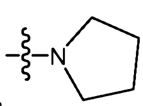
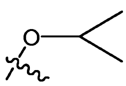
examples thereof include 4-NH piperidin-1-yl, 4-methyl piperidin-1-yl, 4-ethyl piperidin-1-yl, 4-isopropyl-piperidin-1-yl, and pyrrolidin-3-yl), unsubstituted or substituted monocyclic aryl, or unsubstituted or substituted monocyclic heteroaryl (including, but not limited to, pyrrolyl, thienyl, furyl, pyridinyl, pyranyl, pyrimidinyl, pyrazinyl, pyridazinyl, imidazolyl, thiazolyl, pyrazolyl, and oxazolyl.). In one example, R^1 is –O-aryl, *i.e.* phenoxy. In another example, R^1 is –O-(4-methyl)piperidin-1-yl or –O-(4-isopropyl)piperidin-1-yl.

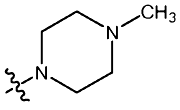
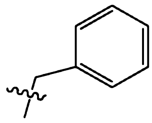
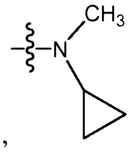
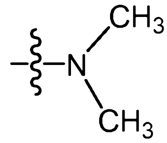
[00333] In some embodiments of compounds of Formula (XXIII), $R^{1'}$ is an amido group of the Formula , where $R^{1''}$ and $R^{1'''}$ are each independently hydrogen, alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, or $R^{1''}$ and $R^{1'''}$ are taken together with nitrogen to form a cyclic moiety.

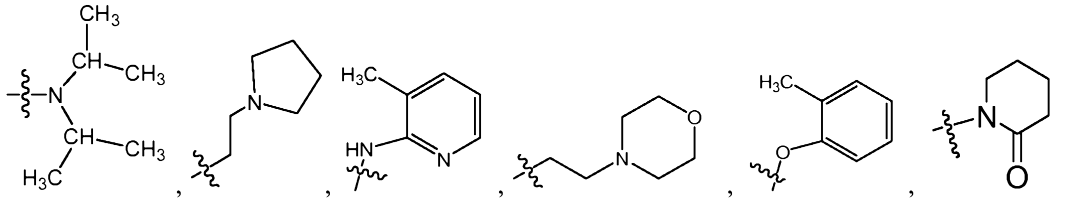
[00334] Also provided herein are compounds of Formula (XXIII), wherein when $R^{1'}$ is alkyl, alkenyl, alkynyl, cycloalkyl, heteroalkyl, heterocyclyl, heterocyclyloxy, aryl, arylalkyl, heteroaryl, heteroarylalkyl, acyl, alkoxy, amido, amino, sulfonamido, acyloxy, alkoxycarbonyl, or NR′R″ (wherein R′ and R″ are taken together with nitrogen to form a cyclic moiety), then $R^{1'}$ is optionally substituted with an amido group of the Formula: , where $R^{1''}$ and $R^{1'''}$ are each independently hydrogen, alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, or $R^{1''}$ and $R^{1'''}$ are taken together with nitrogen to form a cyclic moiety.

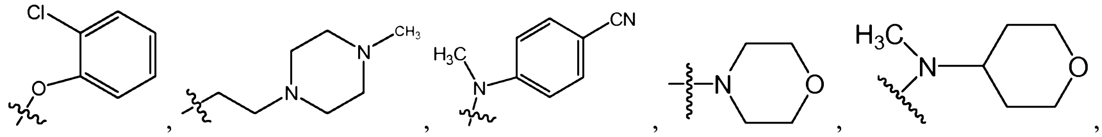
[00335] When $R^{1''}$ and $R^{1'''}$ are taken together with the nitrogen to form a cyclic moiety, the cyclic moiety can have, for example, from 3 to 8 ring atoms. The cyclic moiety so formed can further include one or more heteroatoms which are selected from S, O, and N. In some embodiments, the cyclic moiety so formed is unsubstituted or further substituted with a group which is hydrogen, alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, alkoxy, heterocyclyloxy, amido, amino, acyl, acyloxy, alkoxycarbonyl, sulfonamido, thio, sulfoxide, sulfone, halo, cyano, hydroxyl, nitro, phosphate, urea, or carbonate.

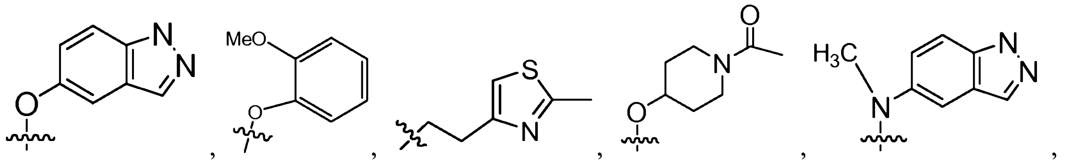
[00336] In some embodiments of the compound of Formula (XXIII), R^1 is one of the following moieties:

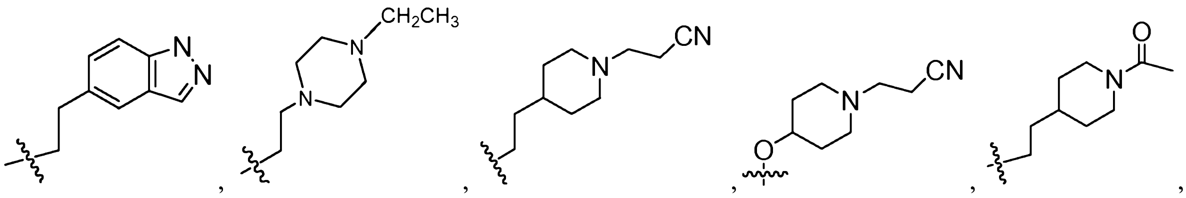
, , , , , ,

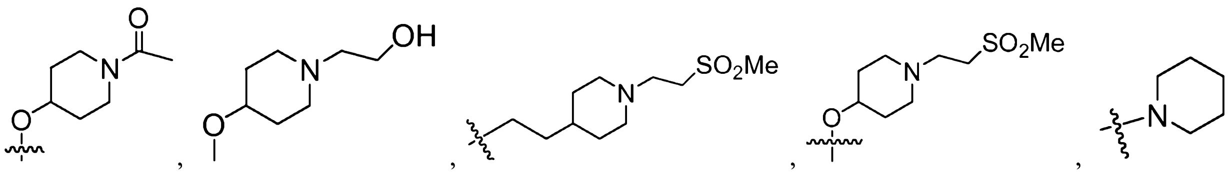
, , $-CH(CH_3)_2$, H , , ,

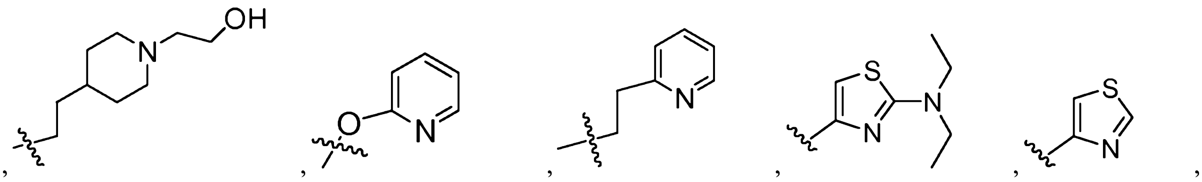












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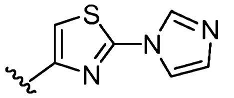

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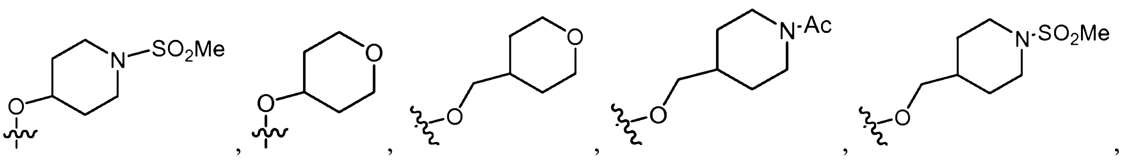
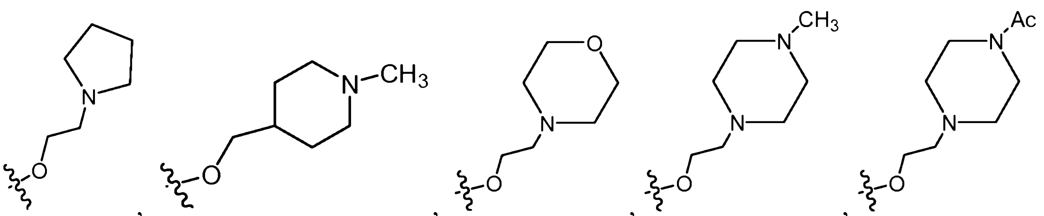
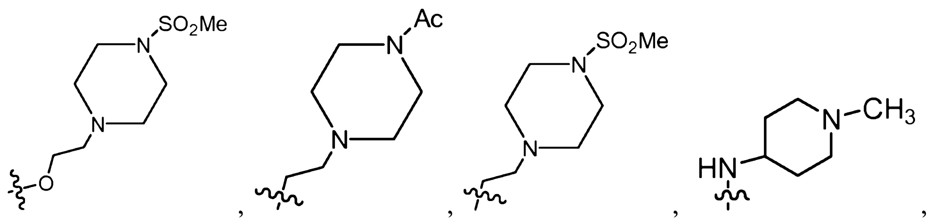
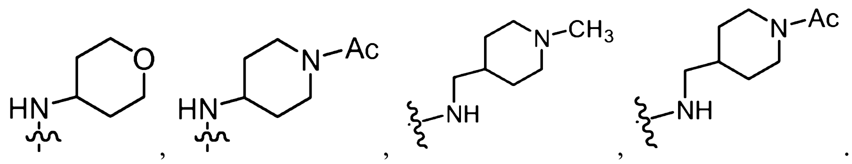
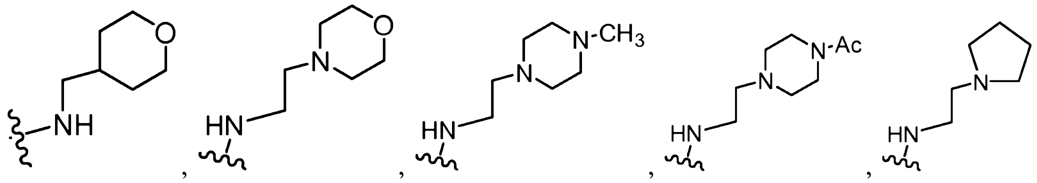
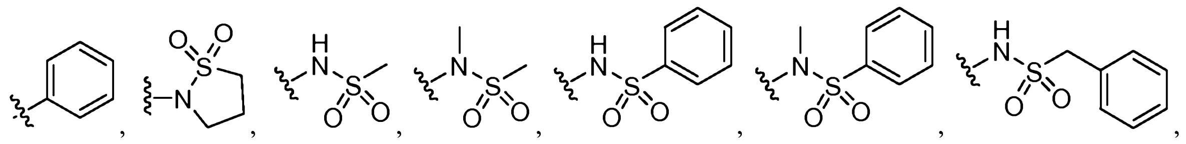


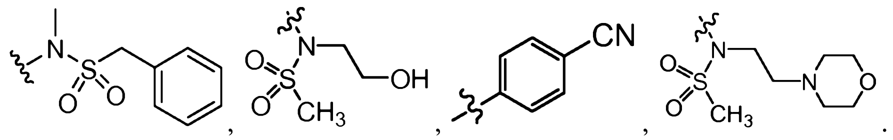




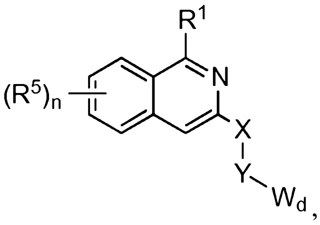


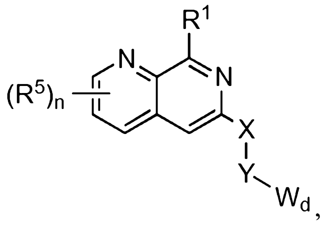


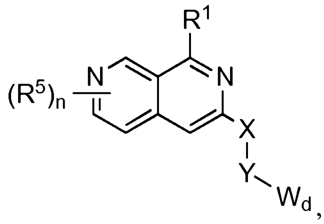


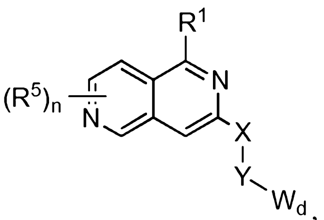


[00337] In some embodiments of compounds of Formula (XXIII), the compound is selected from:

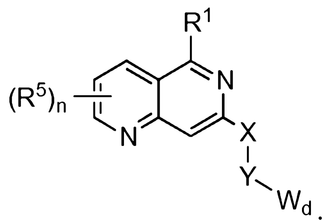






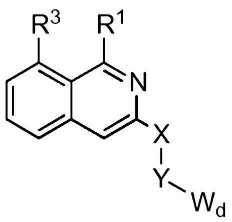


, and



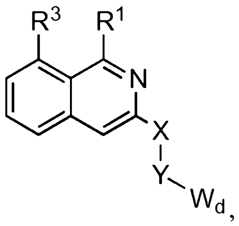
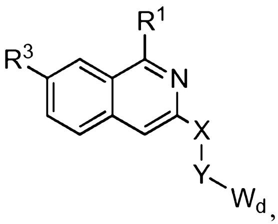
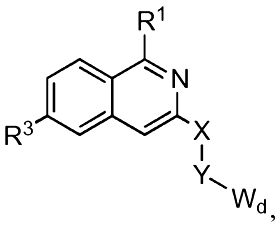
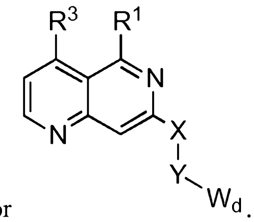
.

[00338] In some embodiments, the compound of Formula (XXIII) has the Formula (XXIV):

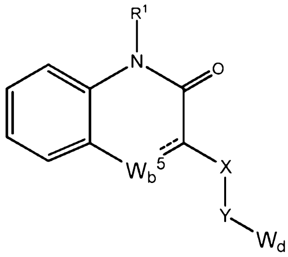


Formula (XXIV).

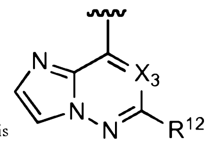
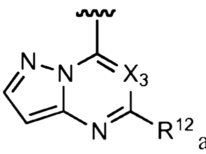
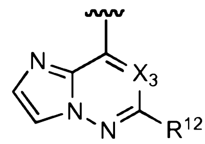
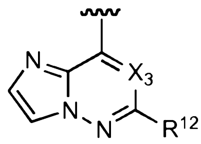
[00339] Alternatively, the compound has the Formula:

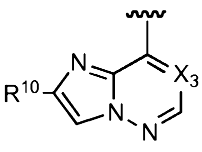
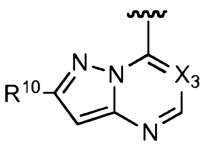
, , , or .

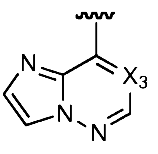
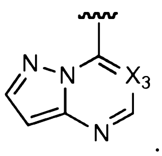
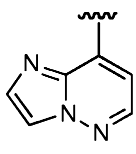
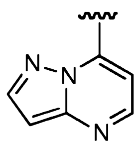
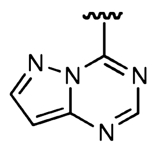
[00340] For example, the compound has the Formula (XXIIa):

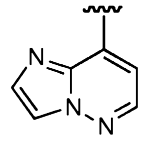
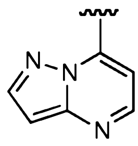
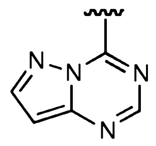


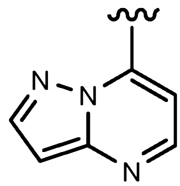
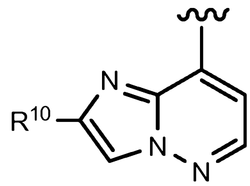
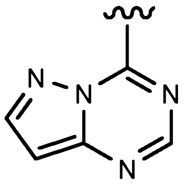
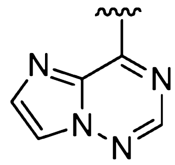
(Formula XXIIa).

[00341] In some embodiments o_f compounds of Formula (XXI), (XXII or (XXIIa), W_d is  or  an$^{d\ R12}$ is hydrogen or halo. For example, W_d is  and R^{12} is Cl-. In another instance, W_d is  and R^{12} is hydrogen.

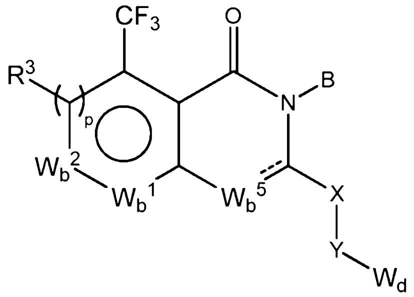
[00342] In other embodiments of compounds of Formula (XXI), (XXII or (XXIIa), W_d is  or  and R^{10} is hydrogen or halo.

[00343] In still other embodiments of compounds of Formula (XXI), (XXII or (XXIIa), W_d is  or . For example, W_d is ,  or .

[00344] In some embodiments, the compound described herein is a compound of Formula (XXI), (XXII or (XXIIa), where W_b^5 is N; X is -CH(R^9)-, where R^9 is methyl or ethyl; Y is –NH-; and W_d is ,  or .

In some embodiments, W_d is . In other embodiments, W_d is . In yet other embodiments, W_d is . In some embodiments, W_d is .

[00345] In one aspect, provided herein are compounds of Formula (XXV):



Formula (XXV)

or an enantiomer, a mixture of enantiomers, or a mixture of two or more diastereomers thereof, or its pharmaceutically acceptable forms thereof, wherein

W_b^1 and W_b^2 are each independently CR^3, S, O, N or NR^{13}, wherein at least one of W_b^1 and W_b^2 is CR^3, N or NR^{13};

p is 0, 1, 2 or 3;

W_b^5 is CR^8, CHR^8, or N;

R^8 is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heteroalkyl, alkoxy, amido, amino, acyl, acyloxy, sulfonamido, halo, cyano, hydroxyl, or nitro;

B is hydrogen, alkyl, amino, heteroalkyl, cycloalkyl, heterocyclyl, heterocyclylalkyl, aryl or heteroaryl, each of which is substituted with 0-4 occurrences of R^2;

X is absent or is –$(CH(R^9))_z$-;

Y is absent, -O-, -S-, -S(=O)-, $-S(=O)_2-$, $-N(R^9)-$, $-C(=O)-(CHR^9)_z-$, -C(=O)-, $-N(R^9)-C(=O)-$, or $-N(R^9)-C(=O)NH-$,$-N(R^9)C(R^9)_2-$, or $-C(=O)-N(R^9)-(CHR^9)_z$;

each z is independently an integer of 1, 2, 3, or 4;

wherein when W_b^5 is N, no more than one of X or Y is absent;

each R^2 is independently alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, alkoxy, amido, amino, acyl, acyloxy, alkoxycarbonyl, sulfonamido, halo, cyano, hydroxyl, nitro, phosphate, urea or carbonate;

each R^3 is independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, fluoroalkyl, heteroalkyl, alkoxy, amido, amino, acyl, acyloxy, sulfinyl, sulfonyl, sulfoxide, sulfone, sulfonamido, halo, cyano, heteroaryl, aryl, hydroxyl, or nitro;

each R^9 is independently hydrogen, alkyl, cycloalkyl, heterocyclyl or heteroalkyl;

W_d is heterocyclyl, aryl, cycloalkyl, or heteroaryl which is optionally substituted with one or more R^b, R^{11} or R^{12};

wherein each R^b is independently hydrogen, halo, phosphate, urea, carbonate, alkyl, alkenyl, alkynyl, cycloalkyl, amino, heteroalkyl, or heterocyclyl; and

each R^{11} and R^{12} is independently hydrogen, alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, alkoxy, heterocyclyloxy, amido, amino, acyl, acyloxy, alkoxycarbonyl, sulfonamido, halo, haloalkyl, cyano, hydroxyl, nitro, phosphate, urea, carboxylic acid, carbonate, or NR′R″, wherein R′ and R″ are taken together with nitrogen to form a cyclic moiety.

[00346] In certain embodiments, W_b^5 is CR^8. In some embodiments, R^8 is hydrogen.

[00347] In certain embodiments, W_b^1 is CR^3. In some embodiments, W_b^1 is N. In some embodiments, W_b^1 is S. In some embodiments, W_b^1 is O.

[00348] In certain embodiments, W_b^2 is CR^3. In some embodiments, W_b^2 is N. In some embodiments, W_b^1 is S. In some embodiments, W_b^1 is O.

[00349] In some embodiments, W_b^1 and W_b^2 are CR^3. In some embodiments, W_b^1 is S and W_b^2 is CR^3. In some embodiments, W_b^1 is S and W_b^2 is N.

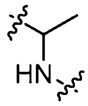
[00350] In certain embodiments, each R^3 is independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, fluoroalkyl, heteroalkyl, alkoxy, amido, amino, acyl, acyloxy, sulfinyl, sulfonyl, sulfoxide, sulfone, sulfonamido, halo, cyano, heteroaryl, aryl, hydroxyl, or nitro. In some embodiments, each R^3 is independently hydrogen, alkyl, cycloalkyl, heterocyclyl, fluoroalkyl, alkoxy, halo, cyano, heteroaryl or aryl. In some embodiments, R^3 is hydrogen, alkyl, fluoroalkyl, alkoxy or aryl. In some embodiments, each R^3 is hydrogen.

[00351] In certain embodiments, p is 0. In some embodiments, p is 1.

[00352] In certain embodiments, B is aryl (*e.g.*, 6-membered aryl) substituted with 0-4 occurrences of R^2. In some embodiments, B is phenyl substituted with 0-4 occurrences of R^2. In some embodiments, B is phenyl substituted with 0 occurrences of R^2. In some embodiments, B is phenyl substituted with 1 occurrence of R^2. In some embodiments, R^2 is halo (*e.g.*, fluoro).

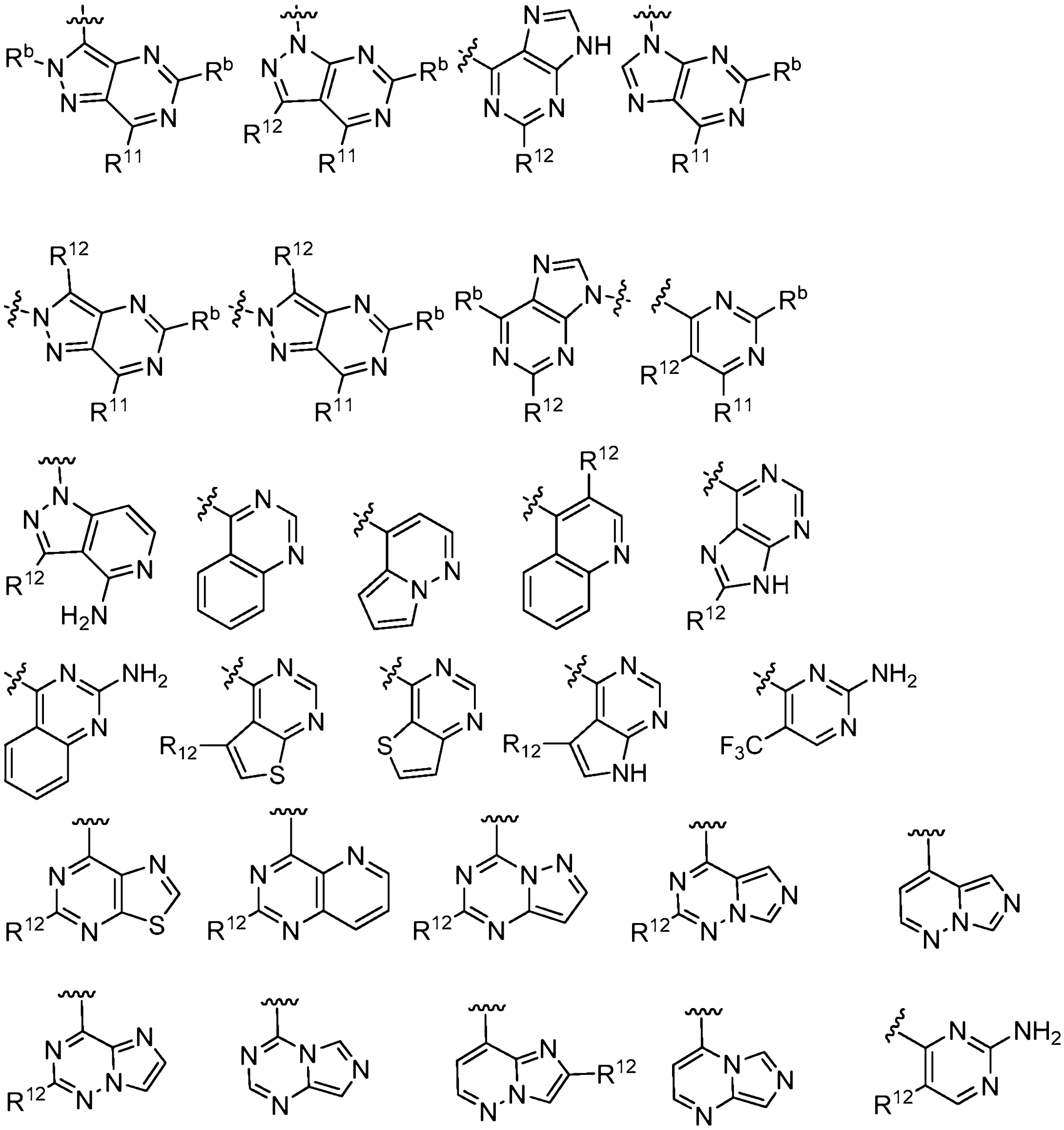
[00353] In some embodiments, X is $-(CH(R^9))_z-$. In some embodiments, z is 1. In some embodiments, R^9 is C_{1-10} alkyl (*e.g.*, methyl).

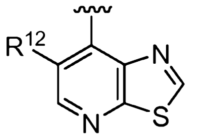
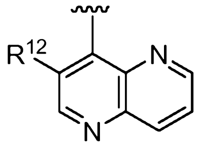
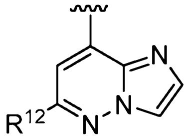
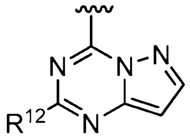
[00354] In some embodiments, is absent, -O-, $-NH(R^9)-$, or $-S(=O)_2-$. In certain embodiments, Y is absent. In some embodiments, Y is $-N(R^9)-$. In some embodiments, R^9 is hydrogen.

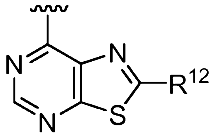
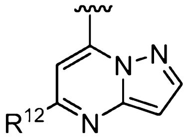
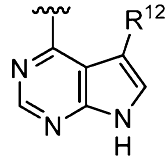
[00355] In certain embodiments, X-Y is 

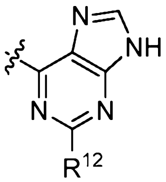
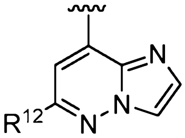
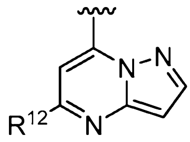
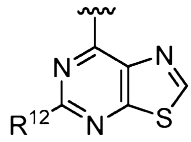
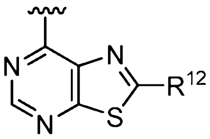
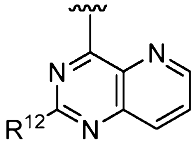
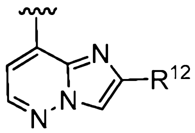
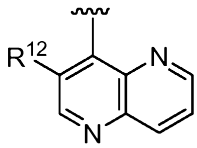
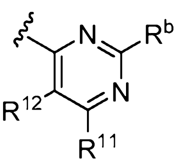
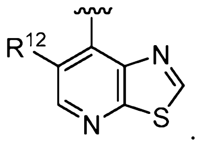
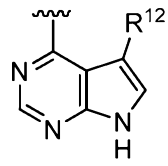
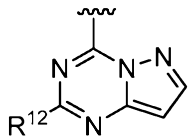
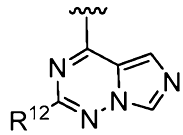
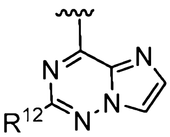
. In some embodiments, X-Y is $-CH_2-N(CH_3)$. In some embodiments, X-Y is (S)-$CH(CH_3)$-NH-. In some embodiments, X-Y is (R)-$CH(CH_3)$-NH-.

[00356] In some embodiments, W_d is aryl. In some embodiments, W_d is heteroaryl (*e.g.*, a bicyclic heteroaryl). In some embodiments, W_d is selected from:



  and  .

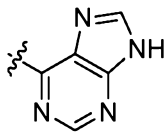
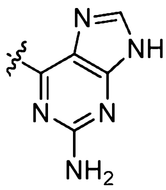
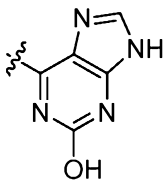
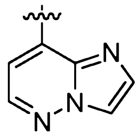
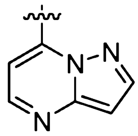
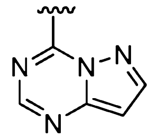
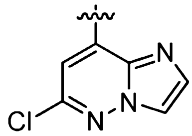
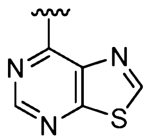
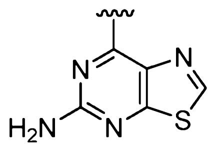
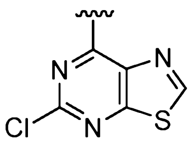
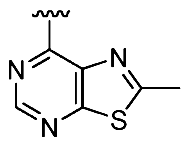
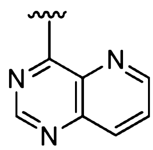
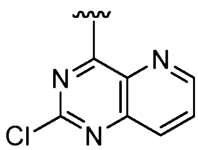
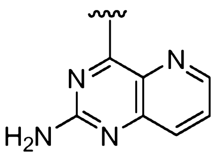
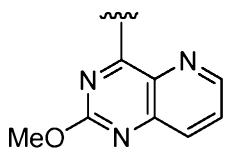
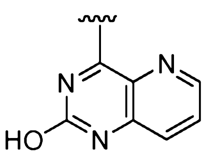
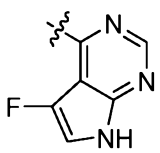
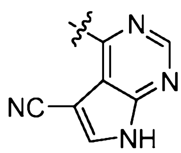
[00357] In some embodiments, W_d is  . In other embodiments, W_d is  . In some embodiments, W_d is  . In some embodiments, W_d is  . In certain embodiments, W_d is  . In some embodiments, W_d is  . In certain embodiments, W_d is  . In certain embodiments, W_d is  . In certain embodiments, W_d is  . In certain embodiments, W_d is  . In some embodiments, W_d is  . In some embodiments, W_d is  . In some embodiments, W_d is  . In some embodiments, W_d is  .

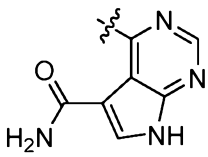
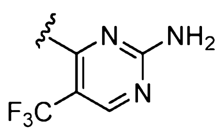
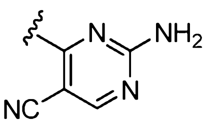
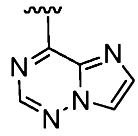
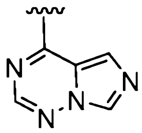
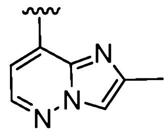
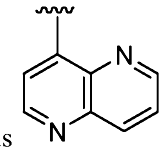
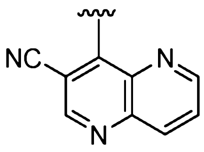
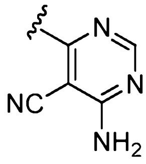
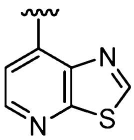
[00358] In certain embodiments, R^{12} is hydrogen, alkyl, alkoxy, hydroxyl, haloalkyl, halo, cyano, amino or amido. In some embodiments, R^{12} is hydrogen. In some embodiments, R^{12} is halo (*e.g.*, chloro or fluoro). In some embodiments, R^{12} is cyano. In some embodiments, R^{12} is amino. In some embodiments, R^{12} is amido (*i.e.*,

-C(=O)NH_2). In some embodiments, R^{12} is alkyl (*e.g.*, methyl). In some embodiments, R^{12} is haloalkyl (*e.g.*, trifluoromethyl). In some embodiments, R^{12} is alkoxy (*e.g.*, methoxy). In some embodiments, R^{12} is hydroxyl.

[00359] In certain embodiments, R^{11} is hydrogen or amino. In some embodiments, R^{11} is amino.

[00360] In certain embodiments, R^b is hydrogen or amino. In some embodiments, R^b is hydrogen. In some embodiments, R^b is amino.

[00361] In some embodiments, W_d is . In some embodiments, W_d is . In some embodiments, W_d is . In some embodiments, W_d is . In some embodiments, W_d is . In some embodiments, W_d is . In some embodiments, W_d is . In some embodiments, W_d is . In some embodiments, W_d is . In some embodiments, W_d is . In some embodiments, W_d is . In some embodiments, W_d is . In some embodiments, W_d is . In some embodiments, W_d is . In some embodiments, W_d is . In some embodiments, W_d is . In some embodiments, W_d is . In some embodiments, W_d is .

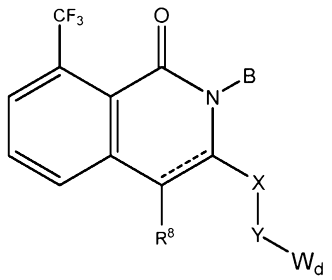
In some embodiments, W_d is . In some embodiments, W_d is . In some embodiments, W_d is . In some embodiments, W_d is . In some embodiments, W_d is . In some embodiments, W_d is . In some embodiments, W_d is . In some embodiments, W_d is . In some embodiments, W_d is . In some embodiments, W_d is .

[00362] In some embodiments of the compound of Formula (XXV), at least one of R^{11} and R^{12} is hydrogen, cyano, halo, unsubstituted or substituted alkyl, unsubstituted or substituted alkynyl, or unsubstituted or substituted alkenyl. In some embodiments, at least one of R^{11} and R^{12} is unsubstituted or substituted aryl. In some embodiments, at least one of R^{11} and R^{12} is unsubstituted or substituted heteroaryl, which includes, but is not limited to, heteroaryl having a 5 membered ring, heteroaryl having a six membered ring, heteroaryl with at least one nitrogen ring atom, heteroaryl with two nitrogen ring atoms, monocylic heteroaryl, and bicylic heteroaryl. In some embodiments, at least one of R^{11} and R^{12} is unsubstituted or substituted heterocyclyl, which includes, but is not limited to, heterocyclyl with one nitrogen ring atom, heterocyclyl with one oxygen ring atom, heterocyclyl with one sulfur ring atom, 5 membered heterocyclyl, 6 membered heterocyclyl, saturated heterocyclyl, unsaturated heterocyclyl, heterocyclyl having an unsaturated moiety connected to the heterocyclyl ring, heterocyclyl substituted by oxo, and heterocyclyl substituted by two oxo. In some embodiments, at least one of R^{11} and R^{12} is unsubstituted or substituted cycloalkyl, including, but not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloalkyl, each of which can be substituted by one oxo, and cycloalkyl having an unsaturated moiety connected to the cycloalkyl ring. In some embodiments, at least one of R^{11} and R^{12} is unsubstituted or substituted amido, unsubstituted or substituted acyloxy, unsubstituted or substituted alkoxycarbonyl, unsubstituted or substituted acyl, or unsubstituted or substituted sulfonamido.

[00363] In some embodiments, when at least one of R^{11} and R^{12} is alkyl, alkynyl, alkenyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, alkoxycarbonyl, amido, acyloxy, acyl, or sulfonamido, it is substituted with one or more of alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, alkoxy, amido, amino, acyl,

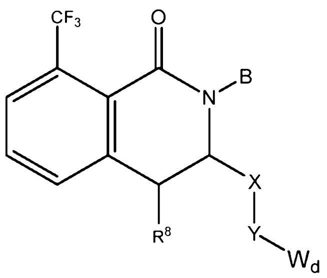
acyloxy, alkoxycarbonyl, sulfonamido, halo, cyano, hydroxyl or nitro, each of which alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, alkoxy, amido, amino, acyl, acyloxy, alkoxycarbonyl, or sulfonamido can itself be substituted.

[00364] In certain embodiments, the compound of Formula (XXV) has a structure of Formula (XXVI):

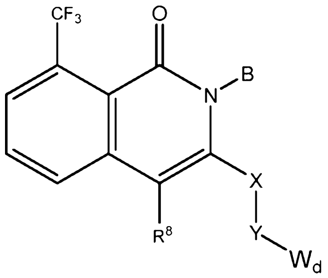


Formula (XXVI).

[00365] In some embodiments, the compound of Formula (XXVI) has a structure of Formula (XXVIa) or (XXVIb):

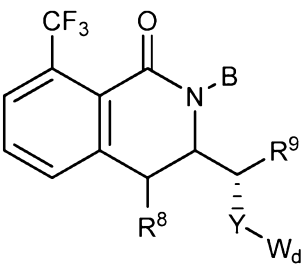


or

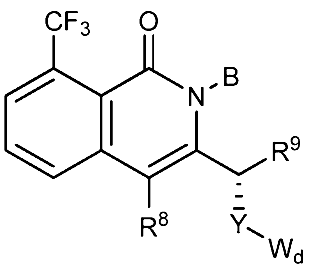


Formula (XXVIa) Formula (XXVIb).

[00366] In some embodiments, the compound of Formula (XXVI) has a structure of Formula (XXVIIa) or (XXVIIb):



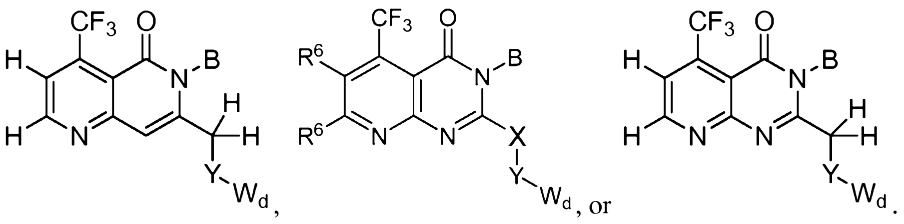
or



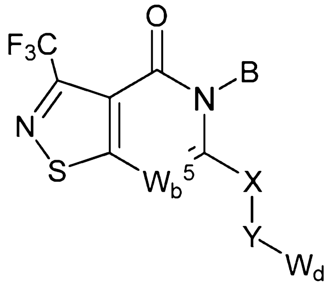
Formula (XXVIIa) Formula (XXVIIb).

[00367] In some embodiments of compounds of Formula (XXVIa), (XXVIb), (XXVIIa), or (XXVIIb), B is aryl substituted with 0-3 occurrences of R^2. For example, B is phenyl substituted with 0-3 occurrences of R^2. In some embodiments of compounds of Formula (XXVIa), (XXVIb), (XXVIIa), or (XXVIIb), B is unsubstituted phenyl. In other embodiments of compounds of Formula (XXVIa), (XXVIb), (XXVIIa), or (XXVIIb), B is phenyl substituted with 1 occurrence of R^2. R^2 is, in some instances, halo or alkyl. In other embodiments of compounds of Formula (XXVIa), (XXVIb), (XXVIIa), or (XXVIIb), B is cycloalkyl or heterocyclyl.

[00368] In still other embodiments, the compound of Formula (I) has a structure selected from:

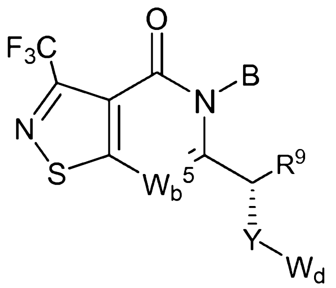


[00369] In certain embodiments, the compound of Formula (XXV) has a structure of Formula (XXVIII):



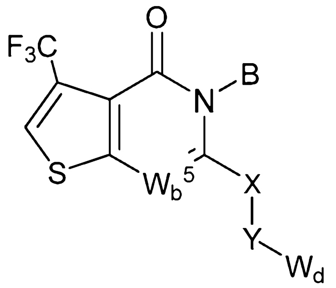
Formula (XXVIII).

[00370] In some embodiments, the compound of Formula (XXVIII) has a structure of Formula (XXIX):



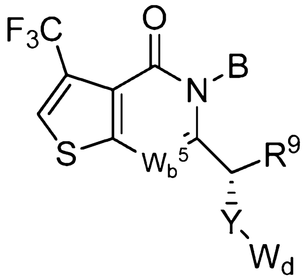
Formula (XXIX).

[00371] In certain embodiments, the compound of Formula (XXV) has a structure of Formula (XXX):



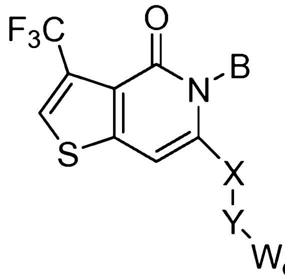
Formula (XXX).

[00372] In certain embodiments, the compound of Formula (XXX) has a structure of Formula (XXXI):



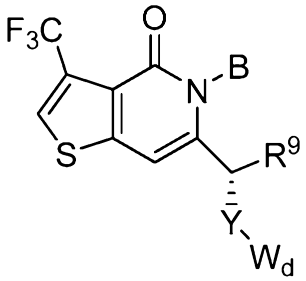
Formula (XXXI).

[00373] In certain embodiments, the compound of Formula (XXX) has a structure of Formula (XXXII):



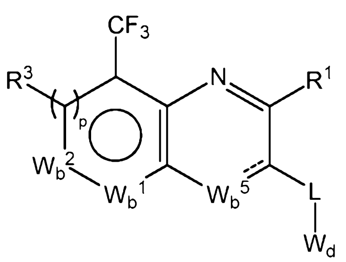
Formula (XXXII).

[00374] In some embodiments, the compound of Formula (XXXII) has a structure of Formula (XXXIII):

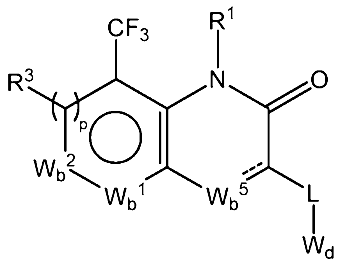


Formula (XXXIII).

[00375] In another aspect, provided herein is a compound of Formula (XXXIV) or (XXXV):



or



Formula (XXXIV) Formula (XXXV)

or an enantiomer, a mixture of enantiomers, or a mixture of two or more diastereomers thereof, or their pharmaceutically acceptable forms thereof, wherein:

W_b^1 and W_b^2 are each independently CR^3, S, O, N or NR^{13}, wherein at least one of W_b^1 and W_b^2 is CR^3, N or NR^{13};

p is 0, 1, 2 or 3;

W_b^5 is CR^8, CHR^8, or N;

R^8 is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heteroalkyl, alkoxy, amido, amino, acyl, acyloxy, sulfonamido, halo, cyano, hydroxyl, or nitro;

R^1 is –(L)-$R^{1'}$;

L is a bond, -S-, -N(R^{15})-, -C(=O)-, or –O-;

$R^{1'}$ is hydrogen, alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, alkoxy, heterocyclyloxy, amido, amino, acyl, acyloxy, alkoxycarbonyl, sulfonamido, halo, cyano, hydroxyl, nitro, phosphate, urea, carbonate, substituted nitrogen, or NR′R″ wherein R′ and R″ are taken together with nitrogen to form a cyclic moiety;

each R^{15} is independently hydrogen, alkyl, cycloalkyl, or heteroalkyl;

X is absent or is –(CH(R^{16}))$_z$;

Y is absent, -O-, -S-, -S(=O)-, -S(=O)$_2$-, -N(R^{16})-, -C(=O)-(CHR^{16})$_z$-, -C(=O)-, -N(R^{16})-C(=O)-, or -N(R^{16})-C(=O)NH-,-N(R^{16})C(R^{16})$_2$-, or -C(=O)-N(R^{16})-(CHR^{16})$_z$-;

each z is an integer of 1, 2, 3, or 4;

each R^3 is independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, fluoroalkyl, heteroalkyl, alkoxy, amido, amino, acyl, acyloxy, sulfinyl, sulfonyl, sulfoxide, sulfone, sulfonamido, halo, cyano, heteroaryl, aryl, hydroxyl, or nitro;

each R^{13} is independently hydrogen, alkyl, cycloalkyl, heterocyclyl or heteroalkyl;

each R^{16} is independently hydrogen, alkyl, cycloalkyl, heterocyclyl, heteroalkyl, aryl, halo or heteroaryl;

W_d is heterocyclyl, aryl, cycloalkyl, or heteroaryl which is optionally substituted with one or more R^b, R^{11} or R^{12};

wherein each R^b is independently hydrogen, halo, phosphate, urea, carbonate, alkyl, alkenyl, alkynyl, cycloalkyl, amino, heteroalkyl, or heterocyclyl; and

each R^{11} and R^{12} is independently hydrogen, alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, alkoxy, heterocyclyloxy, amido, amino, acyl, acyloxy, alkoxycarbonyl, sulfonamido, halo, haloalkyl, cyano, hydroxyl, nitro, phosphate, urea, carboxylic acid, carbonate, or NR′R″, wherein R′ and R″ are taken together with nitrogen to form a cyclic moiety.

[00376] In certain embodiments, W_b^1 is CR^3 and W_b^2 is CR^3.

[00377] In certain embodiments, W_b^5 is CH.

[00378] In certain embodiments, L is a bond, -N(R^{15})- or -C(=O)-.

[00379] For all structures disclosed herein, the following embodimentsapply to their corresponding variable positions.

[00380] In some embodiments of the compounds disclosed herein, B is aryl or heteroaryl substituted with 0 or 1 occurrences of R^2 and Cy is a 5- or 6-membered aryl or heteroaryl group. For example, B is aryl substituted with 0 or 1 occurrences of R^2 and Cy is a 5- or 6-membered aryl or heteroaryl group. In another example,

B is aryl or heteroaryl substituted with 0 or 1 occurrence of R^2 and Cy is a 6-membered aryl group. Cy is, for instance, phenyl substituted with alkyl, fluoroalkyl, aryl, heteroaryl or halo.

[00381] In other embodiments of the the compounds disclosed herein, B is aryl or heteroaryl substituted with 0 or 1 occurrences of R^2, Cy is a 5- or 6-membered aryl or heteroaryl group, X is $-(CH(R^9))_z$- and Y is $-NH(R^9)$-, wherein each R^9 is chosen independently from hydrogen, alkyl, cycloalkyl, and heteroalkyl. For example, X-Y is $-CH_2(CH_3)$-NH-. In some embodiments, B is aryl substituted with 0 or 1 occurrences of R^2 and Cy is a 5- or 6-membered aryl or heteroaryl group. In another example, B is aryl or heteroaryl substituted with 0 or 1 occurrence of R^2 and Cy is a 6-membered aryl group. Cy is, for instance, phenyl substituted with alkyl, fluoroalkyl, aryl, heteroaryl or halo.

[00382] In some embodiments, B is cycloalkyl, heterocyclyl, aryl, or heteroaryl, which is substituted with 0-4 occurrences of R^2, R^3 is H, halo, alkyl, alkoxy, aryl, cycloalkyl, or heteroaryl, each R^5 is H, halo, alkyl, alkoxy, aryl, cycloalkyl, or heteroaryl, and R^9 is hydrogen or alkyl.

[00383] In some embodiments, B is unsubstituted or substituted alkyl, including, but not limited to, $-(CH_2)_2-NR^aR^a$, wherein each R^a is independently hydrogen, alkyl, fluoroalkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocyclyl, heterocyclylalkyl, heteroaryl or heteroarylalkyl, or NR^aR^a are combined together to form a cyclic moiety, which includes but is not limited to piperidinyl, piperazinyl, and morpholinyl. In some embodiments, B is unsubstituted or substituted amino. In some embodiments, B is unsubstituted or substituted heteroalkyl.

[00384] In some embodiments, B is selected from unsubstituted or substituted aryl, including, but not limited to, unsubstituted or substituted phenyl; unsubstituted or substituted heteroaryl including, but not limited to, pyridin-2-yl, pyridin-3-yl, pyridin-4-yl, pyrimidin-4-yl, pyrimidin-2-yl, pyrimidin-5-yl, or pyrazin-2-yl, unsubstituted or substituted monocyclic heteroaryl, unsubstituted or substituted bicyclic heteroaryl, heteroaryl having two heteroatoms as ring atoms, unsubstituted or substituted heteroaryl comprising a nitrogen ring atom, heteroaryl comprising two nitrogen ring atoms, heteroaryl having a nitrogen and a sulfur as ring atoms, unsubstituted or substituted heterocyclyl including, but not limited to, morpholinyl, tetrahydropyranyl, piperazinyl, and piperidinyl, unsubstituted or substituted cycloalkyl including, but not limited to, cyclopentyl and cyclohexyl.

[00385] In some embodiments, B is unsubstituted or substituted with one or more R^2 substituents. In some embodiments, R^2 is alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, heteroaryl alkoxy, amido, amino, acyl, acyloxy, alkoxycarbonyl, sulfonamido, halo, cyano, hydroxyl or nitro, each of which alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, alkoxy, amido, amino, acyl, acyloxy, or sulfonamido, can itself be substituted.

[00386] In some embodiments, R^2 is unsubstituted or substituted alkyl, unsubstituted or substituted heteroalkyl, unsubstituted or substituted alkenyl, unsubstituted or substituted alkynyl, unsubstituted or substituted cycloalkyl, or unsubstituted or substituted heterocyclyl. In some embodiments, R^2 is unsubstituted or substituted aryl, unsubstituted or substituted arylalkyl, unsubstituted or substituted heteroaryl, or unsubstituted or substituted heteroarylalkyl. In some embodiments, R^2 is unsubstituted or substituted alkoxy, unsubstituted or substituted amido, unsubstituted or substituted amino. In some embodiments, R^2 is unsubstituted or substituted acyl, unsubstituted or substituted acyloxy, unsubstituted or substituted alkoxycarbonyl, or unsubstituted or substituted sulfonamido. In

some embodiments, R^2 is halo, selected from –I, -F, -Cl, or -Br. In some embodiments, R^2 is selected from cyano, hydroxyl, nitro and a carbonate. In some embodiments, R^2 is unsubstituted or substituted phosphate. In some embodiments, R^2 is unsubstituted or substituted urea. In some embodiments, when R^2 is alkyl, R^2 is methyl, ethyl, propyl, isopropyl, *n*- butyl, *tert*- butyl, *sec*-butyl, pentyl, hexyl or heptyl.

[00387] In some embodiments, when R^2 is alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, alkoxy, amido, amino, acyl, acyloxy, alkoxycarbonyl, sulfonamido, or hydroxyl, it is substituted by phosphate, substituted by urea, or substituted by carbonate.

[00388] In some embodiments, when R^2 is alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, alkoxy, amido, amino, acyl, acyloxy, alkoxycarbonyl, or sulfonamido, it is substituted by one or more of alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, alkoxy, amido, amino, acyl, acyloxy, alkoxycarbonyl, sulfonamido, halo, cyano, hydroxyl or nitro, each of which alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, alkoxy, amido, amino, acyl, acyloxy, alkoxycarbonyl, or sulfonamido can itself be substituted.

[00389] In some embodiments, there are no occurrences of R^2. In other embodiments, there is one occurrence of R^2. In still other embodiments, there are two occurrences of R^2. In yet other embodiments, there are three occurrences of R^2. In yet other embodiments, there are four occurrences of R^2. For example, in some embodiments B is aryl or heteroaryl and there there are no occurrences of R^2. In other instances, B is aryl or heteroaryl and there there is one occurrence of R^2 where R^2 is alkyl or halo.

[00390] In some embodiments, R^3 is halo, alkyl, alkoxy, heteroaryl, or cycloalkyl. For example, R^3 is H, CH_3, CH_2CH_3, CF_3, Cl, or F. In other embodiments, R^3 is CH_3, CF_3, or Cl. In other embodiments, each R^3 and R^8 is independently selected from H, CH_3, OCH_3, CF_3, and halo.

[00391] In some embodiments, R^3 is unsubstituted or substituted alkyl, unsubstituted or substituted alkenyl, or unsubstituted or substituted alkynyl. In some embodiments, R^3 is unsubstituted or substituted aryl, unsubstituted or substituted heteroaryl, unsubstituted or substituted cycloalkyl, or unsubstituted or substituted heterocyclyl. In some embodiments, R^3 is unsubstituted or substituted alkoxy, unsubstituted or substituted amido, unsubstituted or substituted amino. In some embodiments, R^3 is unsubstituted or substituted acyl, unsubstituted or substituted acyloxy, unsubstituted or substituted alkoxycarbonyl, or unsubstituted or substituted sulfonamido. In some embodiments, R^3 is halo, selected from –I, -F, -Cl, or -Br. In some embodiments, R^3 is halo, alkyl, alkoxy, heteroaryl, or cycloalkyl. For example, R^3 is CH_3, CH_2CH_3, CF_3, Cl, or F. In some instances, R^3 is CH_3, CF_3, or Cl.

[00392] In some embodiments, R^3 is selected from cyano, hydroxyl, and nitro. In some embodiments, when R^3 is alkyl, R^3 is methyl, ethyl, propyl, isopropyl, *n*- butyl, *tert*- butyl, *sec*-butyl, pentyl, hexyl or heptyl. In some embodiments, R^3 is $-CF_3$, $-CH_2F$ or $–CHF_2$.

[00393] In some embodiments, when R^3 is alkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, heterocyclyl, alkoxy, amido, amino, acyl, acyloxy, alkoxycarbonyl,or sulfonamido, it is substituted with one or more of alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, alkoxy, amido, amino, acyl, acyloxy, alkoxycarbonyl, sulfonamido, halo, cyano, hydroxyl or nitro, each of which alkyl, heteroalkyl, alkenyl,

alkynyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, alkoxy, amido, amino, acyl, acyloxy, alkoxycarbonyl, or sulfonamido can itself be substituted.

[00394] In some embodiments, R^3 is a 5-membered heteroaryl group. Such groups include, for example, pyrrole, furan, thiophene, triazole, oxazole, pyrazole, and isoxazole. In other embodiments, R^3 is a 5-membered nonaromatic heterocycle, including, but not limited to, oxazoline and oxazolidinone. In still other embodiments, R^3 is a 6-membered heteroaryl group including pyridine, pyrazine, pyrimidine and pyridazine. Alternatively, R^3 is a 6-membered nonaromatic heterocycle, including moieties such as morpholino or piperidino. In other embodiments, R^3 is a fused 5/6-bicyclic heteroaryl, for example benzothiazole, benzoxazole, benzisoxazole, indazole, benzimidazole, benzothiophene, indole, isoindole, purine, or pyrazolopyrimidine. In yet other embodiments, R^3 is a fused 5/6-bicyclic nonaromatic heterocycle.

[00395] In some embodiments, R^3 is a C_1-C_6 alkyl group substituted with a 5-membered heteroaryl, a 5-membered heterocycle, a 6-membered heteroaryl, a 6-membered nonaromatic heterocycle, a fused 5/6-bicyclic heteroaryl, or a fused 5/6-bicyclic nonaromatic heterocycle. Alternatively, R^3 is amino, sulfinyl, sulfonyl, sulfoxide, sulfone, or alkoxy wherein the N, S, and O heteroatom has a covalent bond either directly or through a C_1-C_6 alkyl group to a 5-membered heteroaryl, a 5-membered nonaromatic heterocycle, a 6-membered heteroaryl, a 6-membered heterocycle, a fused 5/6-bicyclic heteroaryl, or a fused 5/6-bicyclic heterocycle.

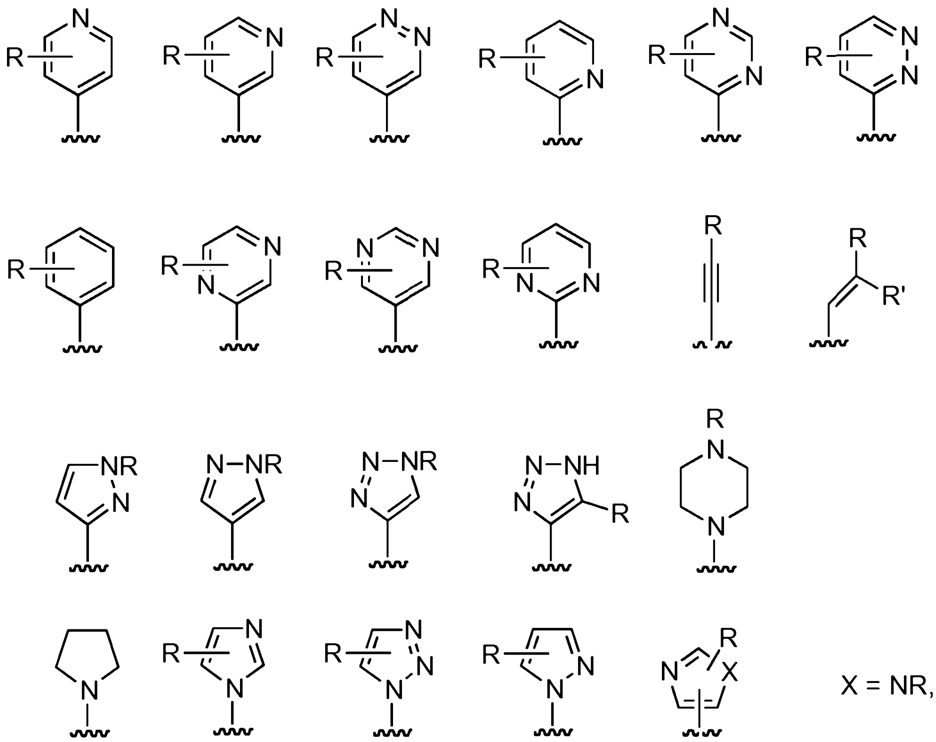
[00396] In other embodiments, R^3 is a C_1-C_6 alkyl group substituted with a fused polycyclic group, wherein the polycyclic group has greater than two rings and is carbocyclic or heterocyclic; C_1-C_6 alkyl group substituted with a bridged cycloalkyl or bridged heterocyclic group; C_1-C_6 alkyl group substituted with a spirocyclic cycloalkyl or spirocyclic heterocyclic group; or branched C_4-C_{12} alkyl group, wherein said branched alkyl group contains at least one terminal t-butyl group.

[00397] Each of the embodiments named above for R^3 is unsubstituted or optionally additionally substituted with an alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, alkoxy, amido, amino, acyl, acyloxy, alkoxycarbonyl, sulfonamido, halo, cyano, hydroxyl or nitro group.

[00398] In certain embodiments, R^3 is a substituted or unsubstituted heterocyclyl or heteroaryl group selected from pyridine, pyrazole, piperazine, and pyrrolidine, wherein the substituent can be a C_1-C_6 alkyl group or a halogen.

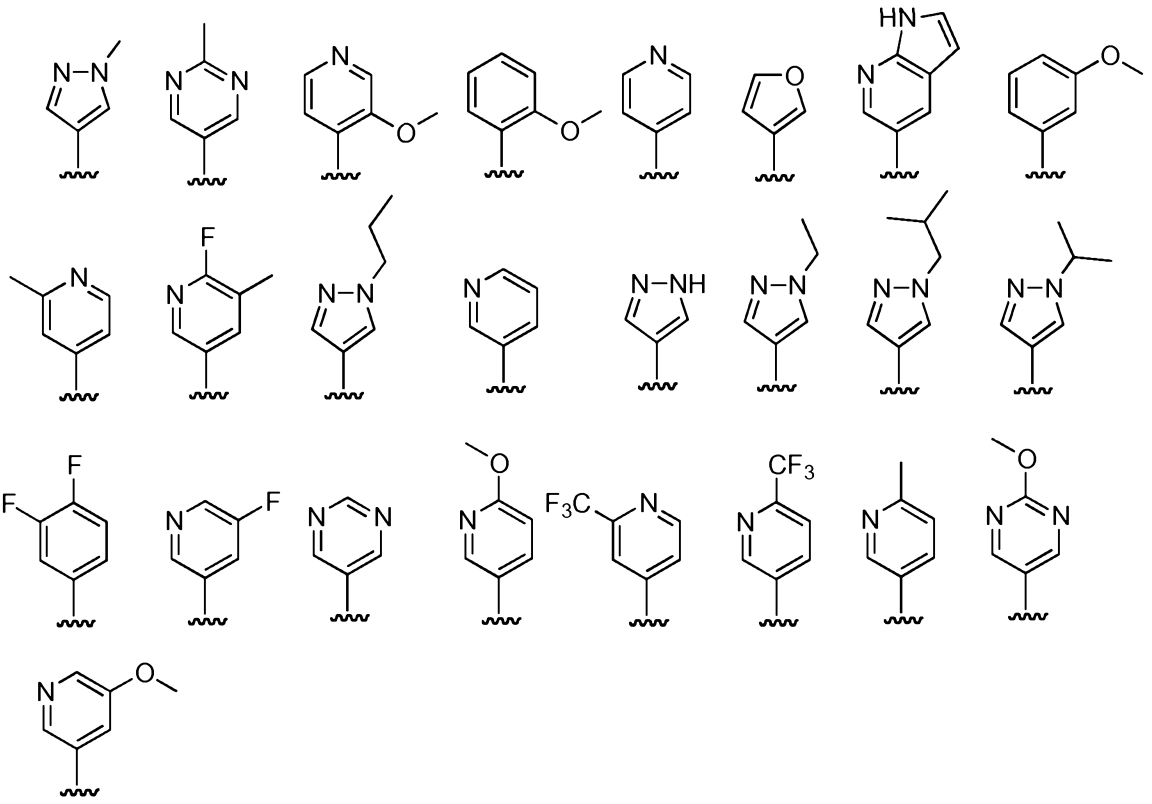
[00399] In some embodiments, a compound is provided wherein R^3 is selected from a 5-membered heteroaryl such as pyrrole, a furan, and a thiophene group; 5-membered heterocycle such as pyrrolidine, a tetrahydrofuran, or a tetrahydrothiophene group; 6-membered heteroaryl such as pyridine, pyrazine, pyrimidine, and pyridazine; 6-membered heterocycle such as piperidine, tetrahydropyran, and thiane; and fused 5/6-bicyclic heteroaryl such as indole, isoindole, benzofuran, isobenzofuran, benzothiophene, benzimidazole, indazole, benzoxazole, benzisoxazole, and purine. In certain embodiments, R^3 is a substituted or unsubstituted group selected from pyridine, pyrazole, piperazine, and pyrrolidine. By way of non-limiting example, the R^3 group can be substituted with a C_1-C_6 alkyl group or a halogen. For example, the R^3 group can be substituted with a methyl group.

[00400] In some embodiments, a compound is provided wherein R^3 is selected from



X = NR, S, O

wherein R is H, C_1-C_6 alkyl, C_1-C_6 alkoxy, halo and haloalkyl. In certain embodiments, R is methyl. In other embodiments, a compound is provided wherein R^3 is selected from:



[00401] In some embodiments, each R^5 is independently unsubstituted or substituted alkyl (including, but not limited to, unsubstituted or substituted C_1-C_4alkyl). In some embodiments, each R^5 is independently unsubstituted or substituted alkenyl including, but not limited to, unsubstituted or substituted C_2-C_5alkenyl. In some embodiments, each R^5 is independently unsubstituted or substituted alkynyl including, but not limited to, unsubstituted or substituted C_2-C_5alkynyl. In some embodiments, each R^5 is independently unsubstituted or substituted cycloalkyl including, but not limited to, unsubstituted or substituted C_3-C_5cycloalkyl. In some embodiments, each R^5 is independently unsubstituted or substituted heterocyclyl. In some embodiments, each R^5 is independently unsubstituted or substituted heteroalkyl including, but not limited to, unsubstituted or substituted C_1-C_4heteroalkyl. In some embodiments, each R^5 is independently unsubstituted or substituted alkoxy including, but not limited to, unsubstituted or substituted C_1-C_4alkoxy. In some embodiments, each R^5 is independently unsubstituted or substituted amido including, but not limited to, unsubstituted or substituted C_1-C_4amido. In some embodiments, each R^5 is independently unsubstituted or substituted amino. In some embodiments, each R^5 is independently unsubstituted or substituted acyl, unsubstituted or substituted acyloxy, unsubstituted or substituted C_1-C_4acyloxy, unsubstituted or substituted alkoxycarbonyl, unsubstituted or substituted sulfonamido, or unsubstituted or substituted C_1-C_4sulfonamido. In some embodiments, each R^5 is independently halo, selected from –I, -F, -Cl, and -Br. In some embodiments, each R^5 is independently selected from cyano, hydroxyl, and nitro. In some other embodiments, each R^5 is independently $-CH_3$, $-CH_2CH_3$, n-propyl, isopropyl, $-OCH_3$, $-OCH_2CH_3$, or $-CF_3$.

[00402] In some embodiments, when R^5 is alkyl, alkenyl, alkynyl, cycloalkyl, heteroalkyl, acyl, alkoxy, amido, amino, acyloxy, alkoxycarbonyl, or sulfonamido, R^5 is independently optionally substituted with one or more of alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, alkoxy, amido, amino, acyl, acyloxy, alkoxycarbonyl, sulfonamido, halo, cyano, hydroxyl or nitro, each of which alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, alkoxy, amido, amino, acyl, acyloxy, alkoxycarbonyl, or sulfonamido can itself be substituted.

[00403] In some embodiments, no R^5 moieties are present.

[00404] In some embodiments, X is absent. In some embodiments, X is $–(CH(R^9))_z$-, and z is an integer of 1, 2, 3 or 4.

[00405] In some embodiments, R^9 is unsubstituted or substituted alkyl including, but not limited to, unsubstituted or substituted C_1-C_{10}alkyl. In some embodiments, R^9 is unsubstituted or substituted cycloalkyl including, but not limited to, unsubstituted or substituted C_3-C_7cycloalkyl. In some embodiments, R^9 is ethyl, methyl or hydrogen. In some embodiments, R^9 is unsubstituted or substituted heterocyclyl including, but not limited to, unsubstituted or substituted C_2-C_{10}heteroalkyl. In some embodiments, R^9 is unsubstituted or substituted heteroalkyl including, but not limited to, unsubstituted or substituted C_2-C_{10}heteroalkyl.

[00406] Also provided herein are compounds wherein R^9 is hydrogen, and X is $-CH_2$-, $-CH_2CH_2$-, $-CH_2CH_2CH_2$-, $-CH(CH_3)$-, or $-CH(CH_2CH_3)$-. In other embodiments, X is $–(CH(R^9))_z$- , R^9 is not hydrogen, and z is an integer of 1. When X is-$CH(R^9)$- and R^9 is not hydrogen, then the compound can adopt either an (S)- or (R)-stereochemical configuration with respect to the CH carbon. In some embodiments, the compound is a racemic

mixture of (S)- and (R) isomers with respect to the CH carbon. In other embodiments, provided herein is a mixture of a given disclosed compound wherein individual compounds of the mixture exist predominately in an (S)- or (R)- isomeric configuration. For example, the compound mixture has an (S)-enantiomeric excess of greater than about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, about 95%, about 96%, about 97%, about 98%, about 99%, about 99.5%, or more at the X carbon. In other embodiments, the compound mixture has an (S)-enantiomeric excess of greater than about 55% to about 99.5%, greater than about about 60% to about 99.5%, greater than about 65% to about 99.5%, greater than about 70% to about 99.5%, greater than about 75% to about 99.5%, greater than about 80% to about 99.5%, greater than about 85% to about 99.5%, greater than about 90% to about 99.5%, greater than about 95% to about 99.5%, greater than about 96% to about 99.5%, greater than about 97% to about 99.5%, greater than about 98% to greater than about 99.5%, greater than about 99% to about 99.5%, or more.

[00407] In other embodiments, the compound mixture has an (R)-enantiomeric excess of greater than about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, about 95%, about 96%, about 97%, about 98%, about 99%, about 99.5%, or more at the X carbon. In some other embodiments, the compound mixture has an (R)-enantiomeric excess of greater than about 55% to about 99.5%, greater than about about 60% to about 99.5%, greater than about 65% to about 99.5%, greater than about 70% to about 99.5%, greater than about 75% to about 99.5%, greater than about 80% to about 99.5%, greater than about 85% to about 99.5%, greater than about 90% to about 99.5%, greater than about 95% to about 99.5%, greater than about 96% to about 99.5%, greater than about 97% to about 99.5%, greater than about 98% to greater than about 99.5%, greater than about 99% to about 99.5%, or more.

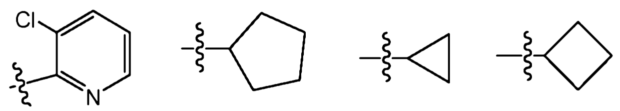
[00408] In some embodiments of the compounds disclosed herein, X is -CH(R^9)-, R^9 is methyl or ethyl, and the compound is the (S)- isomer.

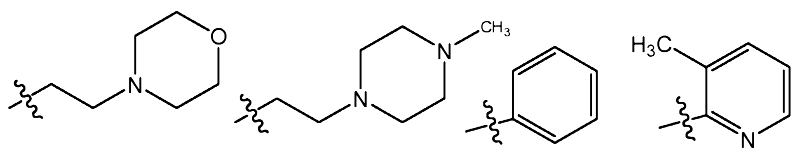
[00409] In some embodiments of the compounds disclosed herein, Y is absent.

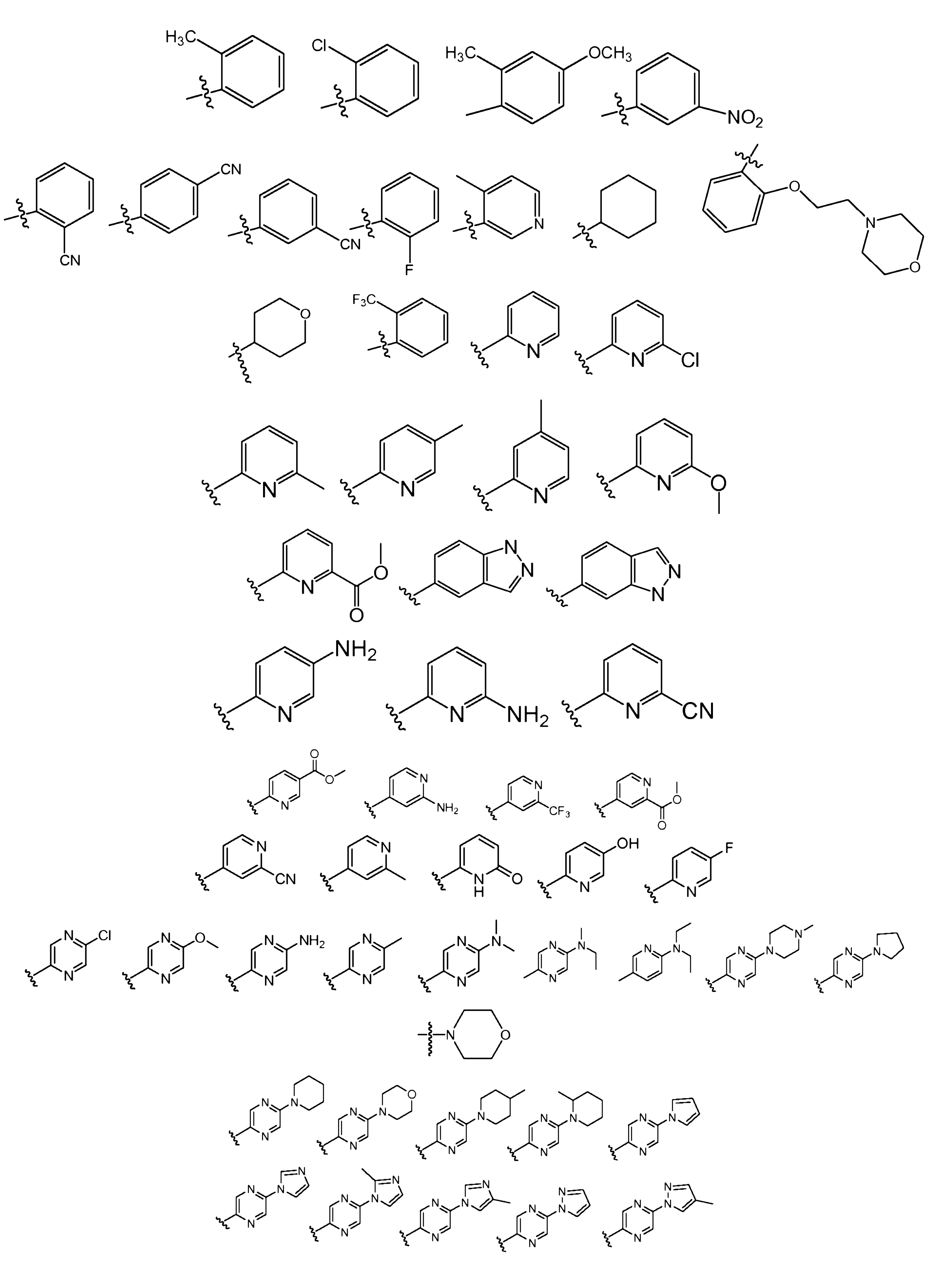
[00410] In some embodiments, Y is -O-, -S-, -S(=O)-, -S(=O)$_2$-, -C(=O)-, -N(R^9)(C=O)-, -N(R^9)(C=O)NH-, -N(R^9)C(R^9)$_2$- (such as-N(R^9)CH_2-, including, but not limited to, -N(CH_3)CH_2-, N(CH(CH_3)$_2$)CH_2 - or N(CH_2CH_3)CH_2-), -N(R^9)-, –N(CH_3)-, –N(CH_2CH_3)-, or –N(CH(CH_3)$_2$)-. In some embodiments, Y is -C(=O)-(CHR^9)$_z$- and z is an integer of 1, 2, 3, or 4.

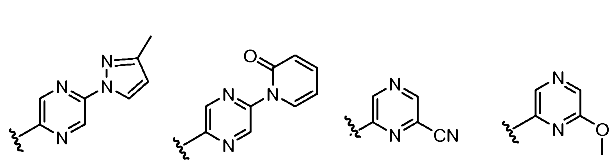
[00411] In some embodiments, at least one of X and Y is present. In some embodiments of the the compounds disclosed herein, -XY- is -CH_2-, -CH_2-N(CH_3), -CH_2-N(CH_2CH_3), -CH(CH_3)-NH-, (S) -CH(CH_3)-NH-, or (R) -CH(CH_3)-NH-. In other embodiments, X-Y is -N(CH_3).CH_2-, N(CH_2CH_3) CH_2-, -N(CH(CH_3)$_2$)CH_2-, or -NHCH_2-.

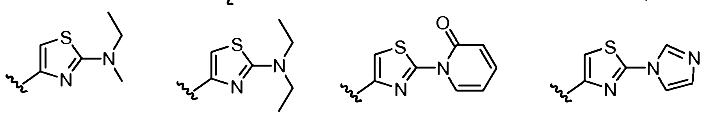
[00412] In some embodiments, B is one of the following moieties:

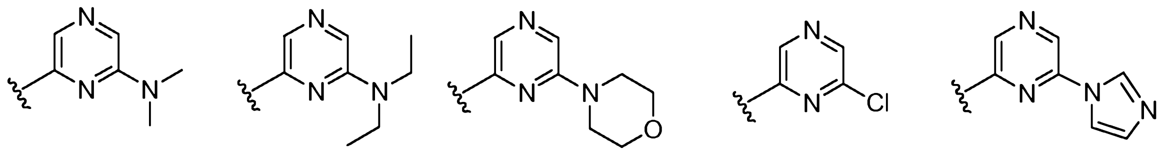
$-CH_3$ $-CH_2CH_3$ $-CH(CH_3)_2$ 

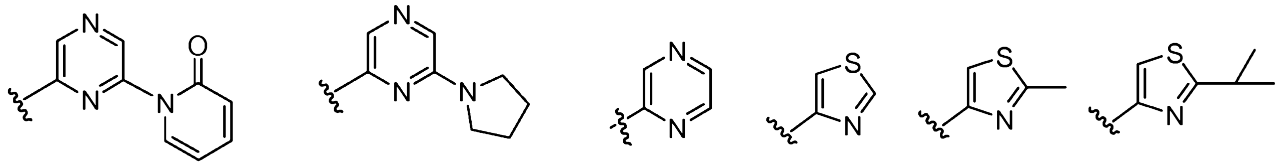












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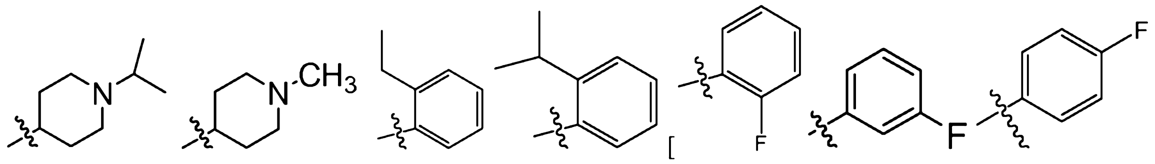

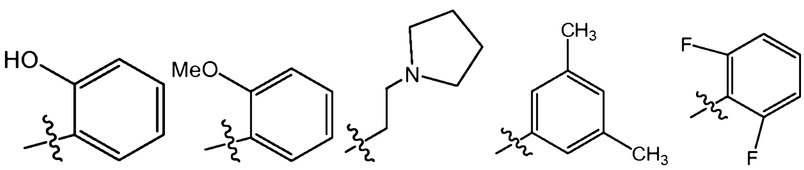

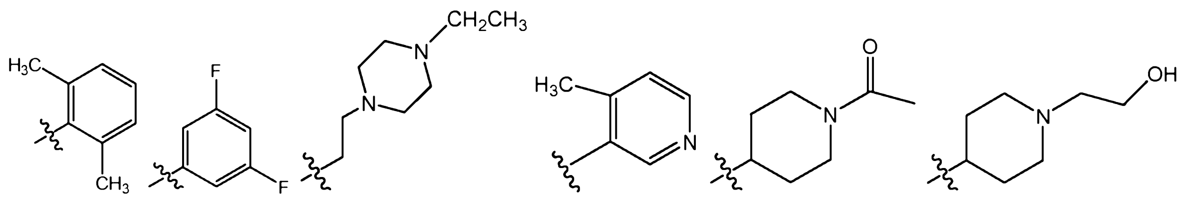

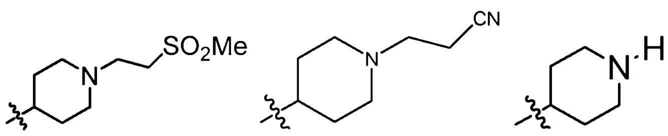

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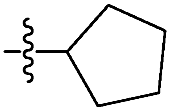
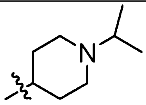
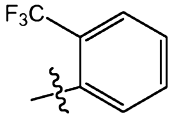
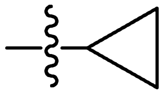
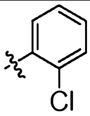
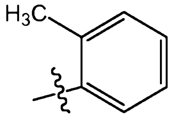
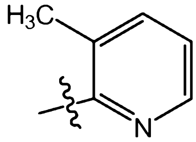
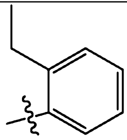
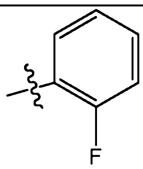
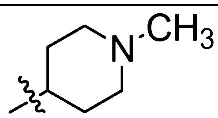
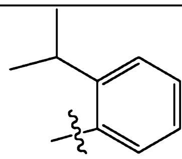
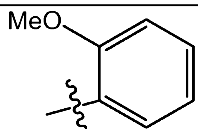
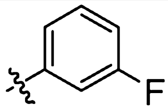
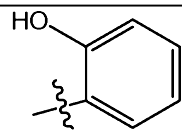
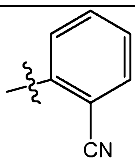
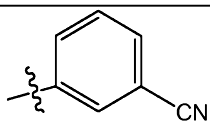
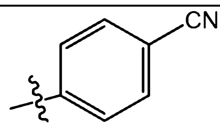
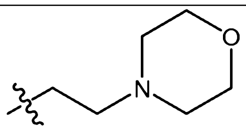
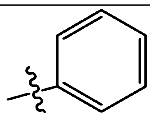
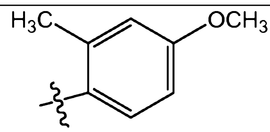
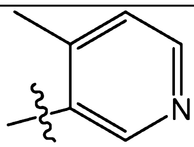
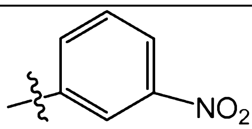
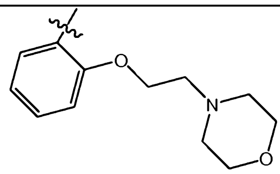
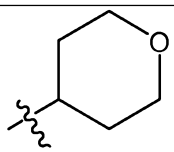
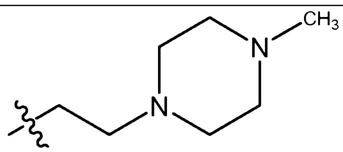
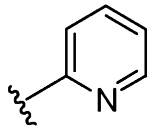
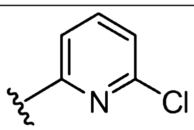
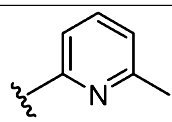
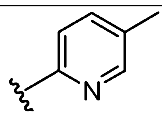
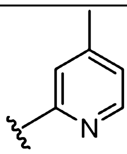
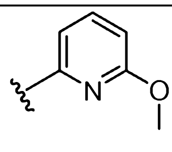
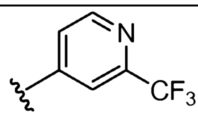
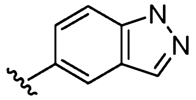
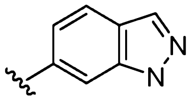
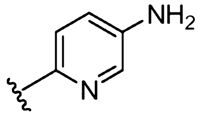
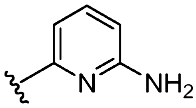
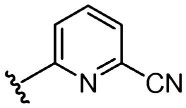
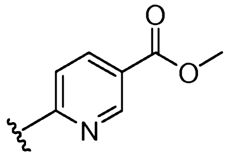
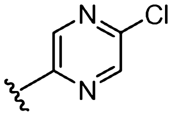
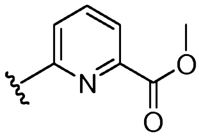
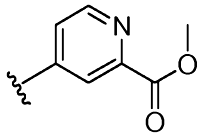
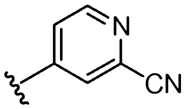
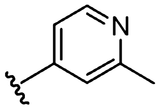
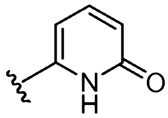
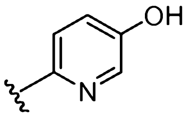
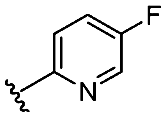
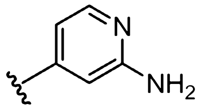
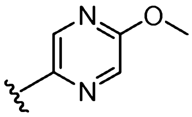
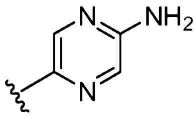
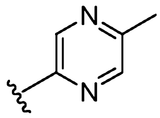
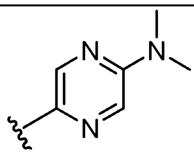
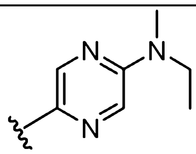
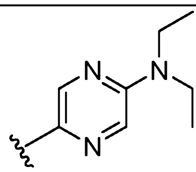
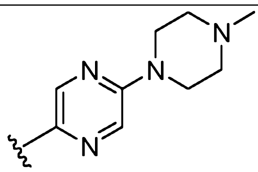
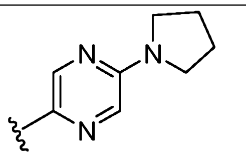
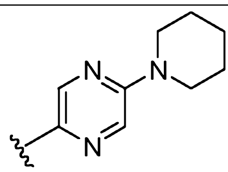
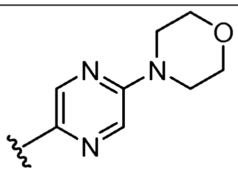
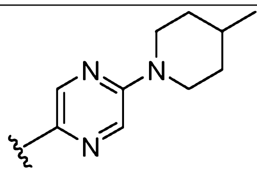
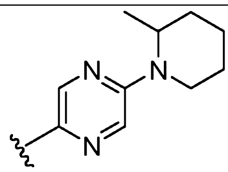
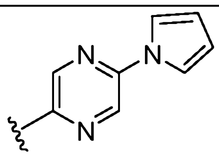
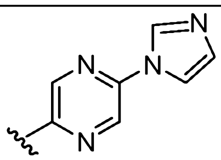
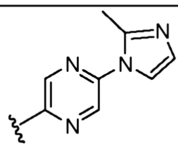
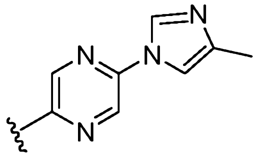
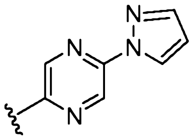
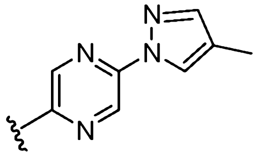
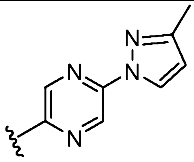
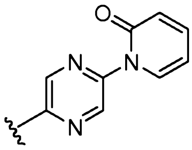
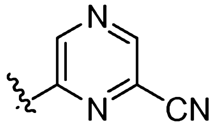
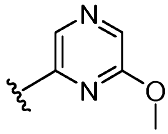
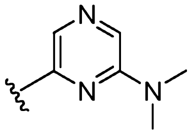
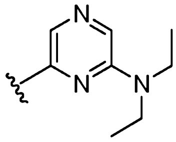
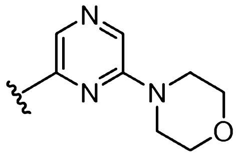
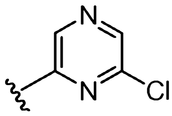
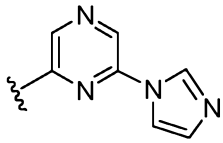
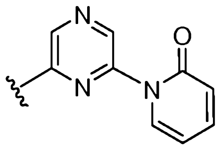
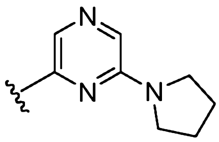
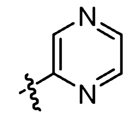
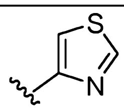
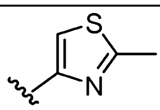
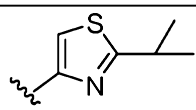
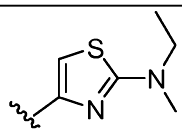
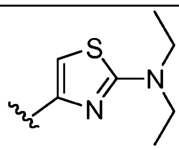
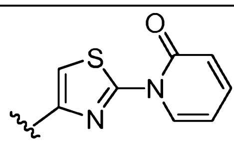
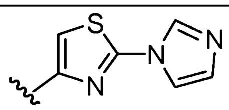
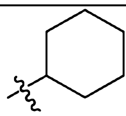
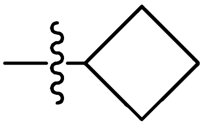
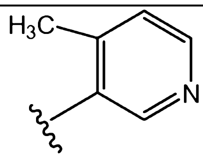
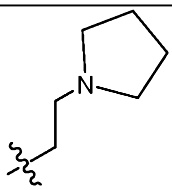
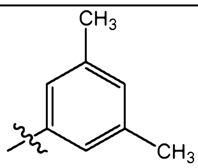
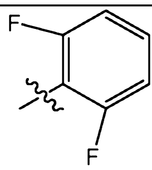
[00413] In one aspect, B is selected from the moieties presented in Table 1.

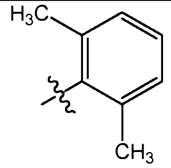
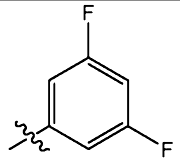
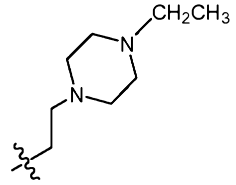
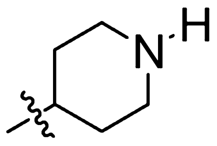
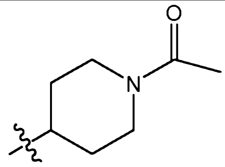
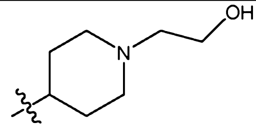
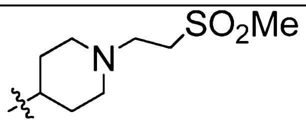
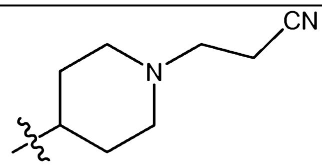
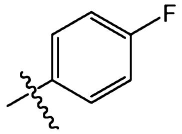
Table 1. Illustrative B moieties of the compounds described herein.

Sub-class #	B	Sub-class #	B	Sub-class #	B

B-1		B-2		B-3	-CH(CH_3)$_2$
B-4		B-5		B-6	
B-7		B-8		B-9	
B-10		B-11		B-12	
B-13		B-14		B-15	
B-16		B-17		B-18	
B-19		B-20		B-21	
B-22		B-23		B-24	
B-25		B-26		B-27	
B-28		B-29		B-30	
B-31		B-32		B-33	

B-34		B-35		B-36	
B-37		B-38		B-39	
B-40		B-41		B-42	
B-43		B-44		B-45	
B-46		B-47		B-48	
B-49		B-50		B-51	
B-52		B-53		B-54	
B-55		B-56		B-57	
B-58		B-59		B-60	
B-61		B-62		B-63	

B-64		B-65		B-66	
B-67		B-68		B-69	
B-70		B-71		B-72	
B-73		B-74		B-75	
B-76		B-77		B-78	
B-79		B-80		B-81	
B-82		B-83		B-84	
B-85		B-86		B-87	$-CH_3$
B-88	$-CH_2CH_3$	B-89		B-90	
B-91		B-92		B-93	

B-94		B-95		B-96	
B-97		B-98		B-99	
B-100		B-101		B-102	

[00414] In some embodiments, one or more compounds described herein bind to a PI3 kinase *(e.g.*, bind selectively). In some embodiments, one or more compounds described herein bind selectively to a γ or δ subtype of a PI3 kinase.

[00415] In some embodiments, the IC_{50} of a subject compound for p110α, p110β, p110γ, or p110δ is less than about 1 μM, less than about 100 nM, less than about 50 nM, less than about 10 nM, less than 1 nM or even less than about 0.5 nM. In some embodiments, the IC_{50} of a subject compound for mTor is less than about 1 μM, less than about 100 nM, less than about 50 nM, less than about 10 nM, less than 1 nM or even less than about 0.5 nM. In some other embodiments, one or more subject compounds exhibit dual binding specificity and are capable of inhibiting a PI3 kinase (*e.g.*, a class I PI3 kinase) as well as a protein kinase (*e.g.*, mTor) with an IC_{50} value less than about 1 μM, less than about 100 nM, less than about 50 nM, less than about 10 nM, less than 1 nM or even less than about 0.5 nM. One or more subject compounds are capable of inhibiting tyrosine kinases including, for example, DNA-dependent protein kinase (Pubmed protein accession number (PPAN) AAA79184), Abl tyrosine kinase (CAA52387), Bcr-Abl, hemopoietic cell kinase (PPAN CAI19695), Src (PPAN CAA24495), vascular endothelial growth factor receptor 2 (PPAN ABB82619), vascular endothelial growth factor receptor-2 (PPAN ABB82619), epidermal growth factor receptor (PPAN AG43241), EPH receptor B4 (PPAN EAL23820), stem cell factor receptor (PPAN AAF22141), Tyrosine-protein kinase receptor TIE-2 (PPAN Q02858), fms-related tyrosine kinase 3 (PPAN NP_004110), platelet-derived growth factor receptor alpha (PPAN NP_990080), RET (PPAN CAA73131), and functional mutants thereof. In some embodiments, the tyrosine kinase is Abl, Bcr-Abl, EGFR, or Flt-3, and any other kinases listed in the Tables herein.

[00416] In some embodiments, non-limiting exemplary compounds exhibit one or more functional characteristics disclosed herein. For example, one or more subject compounds bind specifically to a PI3 kinase. In some embodiments, the IC_{50} of a subject compound for p110α, p110β, p110γ, or p110δ is less than about 1 μM, less than about 100 nM, less than about 50 nM, less than about 10 nM, less than about 1 nM, less than about 0.5 nM, less than about 100 pM, or less than about 50 pM.

[00417] In some embodiments, one or more of the subject compounds can selectively inhibit one or more members of type I or class I phosphatidylinositol 3-kinases (PI3-kinase) with an IC_{50} value of about 100 nM, 50 nM, 10 nM, 5 nM, 100 pM, 10 pM or 1 pM, or less as measured in an *in vitro* kinase assay.

[00418] In some embodiments, one or more of the subject compounds can selectively inhibit one or two members of type I or class I phosphatidylinositol 3-kinases (PI3-kinase) such as PI3-kinase α, PI3-kinase β, PI3-kinase γ, and PI3-kinase δ. In some aspects, some of the subject compounds selectively inhibit PI3-kinase δ as compared to all other type I PI3-kinases. In other aspects, some of the subject compounds selectively inhibit PI3-kinase δ and PI3-kinase γ as compared to the rest of the type I PI3-kinases. In yet other aspects, some of the subject compounds selectively inhibit PI3-kinase α and PI3-kinase β as compared to the rest of the type I PI3-kinases. In still yet some other aspects, some of the subject compounds selectively inhibit PI3-kinase δ and PI3-kinase α as compared to the rest of the type I PI3-kinases. In still yet some other aspects, some of the subject compounds selectively inhibit PI3-kinase δ and PI3-kinase β as compared to the rest of the type I PI3-kinases, or selectively inhibit PI3-kinase δ and PI3-kinase α as compared to the rest of the type I PI3-kinases, or selectively inhibit PI3-kinase α and PI3-kinase γ as compared to the rest of the type I PI3-kinases, or selectively inhibit PI3-kinase γ and PI3-kinase β as compared to the rest of the type I PI3-kinases.

[00419] In yet another aspect, an inhibitor that selectively inhibits one or more members of type I PI3-kinases, or an inhibitor that selectively inhibits one or more type I PI3-kinase mediated signaling pathways, alternatively can be understood to refer to a compound that exhibits a 50% inhibitory concentration (IC_{50}) with respect to a given type I PI3-kinase, that is at least about 10-fold, at least about 20-fold, at least about 50-fold, at least about 100-fold, at least about 1000-fold, at least about 10,000-fold, or lower, than the inhibitor's IC_{50} with respect to the rest of the other type I PI3-kinases. In one embodiment, an inhibitor selectively inhibits PI3-kinase δ as compared to PI3-kinase β with at least about 10-fold lower IC_{50} for PI3-kinase δ. In certain embodiments, the IC_{50} for PI3-kinase δ is below about 100 nM, while the IC_{50} for PI3-kinase β is above about 1000 nM. In certain embodiments, the IC_{50} for PI3-kinase δ is below about 50 nM, while the IC_{50} for PI3-kinase β is above about 5000 nM. In certain embodiments, the IC_{50} for PI3-kinase δ is below about 10 nM, while the IC_{50} for PI3-kinase β is above about 1000 nM, above about 5,000 nM, or above about 10,000 nM.

Pharmaceutical Compositions

[00420] In some embodiments, provided herein are pharmaceutical compositions comprising one or more compounds as disclosed herein, or a pharmaceutically acceptable form thereof (*e.g.,* pharmaceutically acceptable salts, hydrates, solvates, isomers, prodrugs, and isotopically labeled derivatives), and one or more pharmaceutically acceptable excipients carriers, including inert solid diluents and fillers, diluents, including sterile aqueous solution and various organic solvents, permeation enhancers, solubilizers and adjuvants. In some embodiments, a pharmaceutical composition described herein includes a second active agent such as an additional therapeutic agent, (*e.g.*, a chemotherapeutic).

1. Formulations

[00421] Pharmaceutical compositions can be specially formulated for administration in solid or liquid form, including those adapted for the following: oral administration, for example, drenches (aqueous or non-aqueous solutions or suspensions), tablets (*e.g.*, those targeted for buccal, sublingual, and systemic absorption), capsules, boluses, powders, granules, pastes for application to the tongue, and intraduodenal routes; parenteral administration, including intravenous, intraarterial, subcutaneous, intramuscular, intravascular, intraperitoneal or infusion as, for example, a sterile solution or suspension, or sustained-release formulation; topical application, for example, as a cream, ointment, or a controlled-release patch or spray applied to the skin; intravaginally or intrarectally, for example, as a pessary, cream, stent or foam; sublingually; ocularly; pulmonarily; local delivery by catheter or stent; intrathecally, or nasally.

[00422] Examples of suitable aqueous and nonaqueous carriers which can be employed in pharmaceutical compositions include water, ethanol, polyols (such as glycerol, propylene glycol, polyethylene glycol, and the like), and suitable mixtures thereof, vegetable oils, such as olive oil, and injectable organic esters, such as ethyl oleate. Proper fluidity can be maintained, for example, by the use of coating materials, such as lecithin, by the maintenance of the required particle size in the case of dispersions, and by the use of surfactants.

[00423] These compositions can also contain adjuvants such as preservatives, wetting agents, emulsifying agents, dispersing agents, lubricants, and/or antioxidants. Prevention of the action of microorganisms upon the compounds described herein can be ensured by the inclusion of various antibacterial and antifungal agents, for example, paraben, chlorobutanol, phenol sorbic acid, and the like. It can also be desirable to include isotonic agents, such as sugars, sodium chloride, and the like into the compositions. In addition, prolonged absorption of the injectable pharmaceutical form can be brought about by the inclusion of agents which delay absorption such as aluminum monostearate and gelatin.

[00424] Methods of preparing these formulations or compositions include the step of bringing into association a compound described herein and/or the chemotherapeutic with the carrier and, optionally, one or more accessory ingredients. In general, the formulations are prepared by uniformly and intimately bringing into association a compound as disclosed herein with liquid carriers, or finely divided solid carriers, or both, and then, if necessary, shaping the product.

[00425] Preparations for such pharmaceutical compositions are well-known in the art. See, *e.g.*, Anderson, Philip O.; Knoben, James E.; Troutman, William G, eds., *Handbook of Clinical Drug Data*, Tenth Edition, McGraw-Hill, 2002; Pratt and Taylor, eds., *Principles of Drug Action*, Third Edition, Churchill Livingston, New York, 1990; Katzung, ed., *Basic and Clinical Pharmacology*, Ninth Edition, McGraw Hill, 20037ybg; Goodman and Gilman, eds., *The Pharmacological Basis of Therapeutics*, Tenth Edition, McGraw Hill, 2001; *Remingtons Pharmaceutical Sciences*, 20th Ed., Lippincott Williams & Wilkins., 2000; Martindale, *The Extra Pharmacopoeia*, Thirty-Second Edition (The Pharmaceutical Press, London, 1999); all of which are incorporated by reference herein in their entirety. Except insofar as any conventional excipient medium is incompatible with the compounds provided herein, such as by producing any undesirable biological effect or otherwise interacting in a deleterious manner with any other component(s) of the pharmaceutically acceptable composition, the excipient's use is contemplated to be within the scope of this disclosure.

[00426] In some embodiments, the concentration of one or more of the compounds provided in the disclosed pharmaceutical compositions is less than about 100%, about 90%, about 80%, about 70%, about 60%, about 50%, about 40%, about 30%, about 20%, about 19%, about 18%, about 17%, about 16%, about 15%, about 14%, about 13%, about 12%, about 11%, about 10%, about 9%, about 8%, about 7%, about 6%, about 5%, about 4%, about 3%, about 2%, about 1%, about 0.5%, about 0.4%, about 0.3%, about 0.2%, about 0.1%, about 0.09%, about 0.08%, about 0.07%, about 0.06%, about 0.05%, about 0.04%, about 0.03%, about 0.02%, about 0.01%, about 0.009%, about 0.008%, about 0.007%, about 0.006%, about 0.005%, about 0.004%, about 0.003%, about 0.002%, about 0.001%, about 0.0009%, about 0.0008%, about 0.0007%, about 0.0006%, about 0.0005%, about 0.0004%, about 0.0003%, about 0.0002%, or about 0.0001% w/w, w/v or v/v.

[00427] In some embodiments, the concentration of one or more of the compounds as disclosed herein is greater than about 90%, about 80%, about 70%, about 60%, about 50%, about 40%, about 30%, about 20%, about 19.75%, about 19.50%, about 19.25% about 19%, about 18.75%, about 18.50%, about 18.25%, about 18%, about 17.75%, about 17.50%, about 17.25%, about 17%, about 16.75%, about 16.50%, about 16.25%, about 16%, about 15.75%, about 15.50%, about 15.25%, about 15%, about 14.75%, about 14.50%, about 14.25%, about 14%, about 13.75%, about 13.50%, about 13.25%, about 13%, about 12.75%, about 12.50%, about 12.25%, about 12%, about 11.75%, about 11.50%, about 11.25%, about 11%, about 10.75%, about 10.50%, about 10.25%, about 10%, about 9.75%, about 9.50%, about 9.25%, about 9%, about 8.75%, about 8.50%, about 8.25%, about 8%, about 7.75%, about 7.50%, about 7.25%, about 7%, about 6.75%, about 6.50%, about 6.25%, about 6%, about 5.75%, about 5.50%, about 5.25%, about 5%, about 4.75%, about 4.50%, about 4.25%, about 4%, about 3.75%, about 3.50%, about 3.25%, about 3%, about 2.75%, about 2.50%, about 2.25%, about 2%, about 1.75%, about 1.50%, about 1.25%, about 1%, about 0.5%, about 0.4%, about 0.3%, about 0.2%, about 0.1%, about 0.09%, about 0.08%, about 0.07%, about 0.06%, about 0.05%, about 0.04%, about 0.03%, about 0.02%, about 0.01%, about 0.009%, about 0.008%, about 0.007%, about 0.006%, about 0.005%, about 0.004%, about 0.003%, about 0.002%, about 0.001%, about 0.0009%, about 0.0008%, about 0.0007%, about 0.0006%, about 0.0005%, about 0.0004%, about 0.0003%, about 0.0002%, or about 0.0001% w/w, w/v, or v/v.

[00428] In some embodiments, the concentration of one or more of the compounds as disclosed herein is in the range from approximately 0.0001% to approximately 50%, approximately 0.001% to approximately 40 %, approximately 0.01% to approximately 30%, approximately 0.02% to approximately 29%, approximately 0.03% to approximately 28%, approximately 0.04% to approximately 27%, approximately 0.05% to approximately 26%, approximately 0.06% to approximately 25%, approximately 0.07% to approximately 24%, approximately 0.08% to approximately 23%, approximately 0.09% to approximately 22%, approximately 0.1% to approximately 21%, approximately 0.2% to approximately 20%, approximately 0.3% to approximately 19%, approximately 0.4% to approximately 18%, approximately 0.5% to approximately 17%, approximately 0.6% to approximately 16%, approximately 0.7% to approximately 15%, approximately 0.8% to approximately 14%, approximately 0.9% to approximately 12%, approximately 1% to approximately 10% w/w, w/v or v/v. v/v.

[00429] In some embodiments, the concentration of one or more of the compounds as disclosed herein is in the range from approximately 0.001% to approximately 10%, approximately 0.01% to approximately 5%,

approximately 0.02% to approximately 4.5%, approximately 0.03% to approximately 4%, approximately 0.04% to approximately 3.5%, approximately 0.05% to approximately 3%, approximately 0.06% to approximately 2.5%, approximately 0.07% to approximately 2%, approximately 0.08% to approximately 1.5%, approximately 0.09% to approximately 1%, approximately 0.1% to approximately 0.9% w/w, w/v or v/v.

[00430] In some embodiments, the amount of one or more of the compounds as disclosed herein is equal to or less than about 10 g, about 9.5 g, about 9.0 g, about 8.5 g, about 8.0 g, 7.5 g, about 7.0 g, about 6.5 g, about 6.0 g, about 5.5 g, about 5.0 g, about 4.5 g, about 4.0 g, about 3.5 g, about 3.0 g, about 2.5 g, about 2.0 g, about 1.5 g, about 1.0 g, about 0.95 g, about 0.9 g, about 0.85 g, about 0.8 g, about 0.75 g, about 0.7 g, about 0.65 g, about 0.6 g, about 0.55 g, about 0.5 g, about 0.45 g, about 0.4 g, about 0.35 g, about 0.3 g, about 0.25 g, about 0.2 g, about 0.15 g, about 0.1 g, about 0.09 g, about 0.08 g, about 0.07 g, about 0.06 g, about 0.05 g, about 0.04 g, about 0.03 g, about 0.02 g, about 0.01 g, about 0.009 g, about 0.008 g, about 0.007 g, about 0.006 g, about 0.005 g, about 0.004 g, about 0.003 g, about 0.002 g, about 0.001 g, about 0.0009 g, about 0.0008 g, about 0.0007 g, about 0.0006 g, about 0.0005 g, about 0.0004 g, about 0.0003 g, about 0.0002 g, or about 0.0001 g.

[00431] In some embodiments, the amount of one or more of the compounds as disclosed herein is more than about about 0.0001 g, about 0.0002 g, about 0.0003 g, about 0.0004 g, about 0.0005 g, about 0.0006 g, about 0.0007 g, about 0.0008 g, about 0.0009 g, about 0.001 g, about 0.0015 g, about 0.002 g, about 0.0025 g, about 0.003 g, about 0.0035 g, about 0.004 g, about 0.0045 g, about 0.005 g, about 0.0055 g, about 0.006 g, about 0.0065 g, about 0.007 g, about 0.0075 g, about 0.008 g, about 0.0085 g, about 0.009 g, about 0.0095 g, about 0.01 g, about 0.015 g, about 0.02 g, about 0.025 g, about 0.03 g, about 0.035 g, about 0.04 g, about 0.045 g, about 0.05 g, about 0.055 g, about 0.06 g, about 0.065 g, about 0.07 g, about 0.075 g, about 0.08 g, about 0.085 g, about 0.09 g, about 0.095 g, about 0.1 g, about 0.15 g, about 0.2 g, about 0.25 g, about 0.3 g, about 0.35 g, about 0.4 g, about 0.45 g, about 0.5 g, about 0.55 g, about 0.6 g, about 0.65 g, about 0.7 g, about 0.75 g, about 0.8 g, about 0.85 g, about 0.9 g, about 0.95 g, about 1 g, about 1.5 g, about 2 g, about 2.5, about 3 g, about 3.5, about 4 g, about 4.5 g, about 5 g, about 5.5 g, about 6 g, about 6.5g, about 7 g, about 7.5g, about 8 g, about 8.5 g, about 9 g, about 9.5 g, or about 10 g.

[00432] In some embodiments, the amount of one or more of the compounds as disclosed herein is in the range of about 0.0001 - about 10 g, about 0.0005 – about 9 g, about 0.001 – about 8 g, about 0.005 – about 7 g, about 0.01 – about 6 g, about 0.05 – about 5 g, about 0.1 – about 4 g, about 0.5 – about 4 g, or about 1 – about 3 g.

1A. Formulations for oral administration

[00433] In some embodiments, provided herein are pharmaceutical compositions for oral administration containing a compound as disclosed herein, and a pharmaceutical excipient suitable for oral administration. In some embodiments, provided herein are pharmaceutical compositions for oral administration containing: (i) an effective amount of a disclosed compound; optionally (ii) an effective amount of one or more second agents; and (iii) one or more pharmaceutical excipients suitable for oral administration. In some embodiments, the pharmaceutical composition further contains: (iv) an effective amount of a third agent.

[00434] In some embodiments, the pharmaceutical composition can be a liquid pharmaceutical composition suitable for oral consumption. Pharmaceutical compositions suitable for oral administration can be

presented as discrete dosage forms, such as capsules, cachets, or tablets, or liquids or aerosol sprays each containing a predetermined amount of an active ingredient as a powder or in granules, a solution, or a suspension in an aqueous or non-aqueous liquid, an oil-in-water emulsion, or a water-in-oil liquid emulsion. Such dosage forms can be prepared by any of the methods of pharmacy, but all methods include the step of bringing the active ingredient into association with the carrier, which constitutes one or more ingredients. In general, the pharmaceutical compositions are prepared by uniformly and intimately admixing the active ingredient with liquid carriers or finely divided solid carriers or both, and then, if necessary, shaping the product into the desired presentation. For example, a tablet can be prepared by compression or molding, optionally with one or more accessory ingredients. Compressed tablets can be prepared by compressing in a suitable machine the active ingredient in a free-flowing form such as powder or granules, optionally mixed with an excipient such as, but not limited to, a binder, a lubricant, an inert diluent, and/or a surface active or dispersing agent. Molded tablets can be made by molding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent.

[00435] The present disclosure further encompasses anhydrous pharmaceutical compositions and dosage forms comprising an active ingredient, since water can facilitate the degradation of some compounds. For example, water can be added (*e.g.,* about 5%) in the pharmaceutical arts as a means of simulating long-term storage in order to determine characteristics such as shelf-life or the stability of formulations over time. Anhydrous pharmaceutical compositions and dosage forms can be prepared using anhydrous or low moisture containing ingredients and low moisture or low humidity conditions. For example, pharmaceutical compositions and dosage forms which contain lactose can be made anhydrous if substantial contact with moisture and/or humidity during manufacturing, packaging, and/or storage is expected. An anhydrous pharmaceutical composition can be prepared and stored such that its anhydrous nature is maintained. Accordingly, anhydrous pharmaceutical compositions can be packaged using materials known to prevent exposure to water such that they can be included in suitable formulary kits. Examples of suitable packaging include, but are not limited to, hermetically sealed foils, plastic or the like, unit dose containers, blister packs, and strip packs.

[00436] An active ingredient can be combined in an intimate admixture with a pharmaceutical carrier according to conventional pharmaceutical compounding techniques. The carrier can take a wide variety of forms depending on the form of preparation desired for administration. In preparing the pharmaceutical compositions for an oral dosage form, any of the usual pharmaceutical media can be employed as carriers, such as, for example, water, glycols, oils, alcohols, flavoring agents, preservatives, coloring agents, and the like in the case of oral liquid preparations (such as suspensions, solutions, and elixirs) or aerosols; or carriers such as starches, sugars, micro-crystalline cellulose, diluents, granulating agents, lubricants, binders, and disintegrating agents can be used in the case of oral solid preparations, in some embodiments without employing the use of lactose. For example, suitable carriers include powders, capsules, and tablets, with the solid oral preparations. In some embodiments, tablets can be coated by standard aqueous or nonaqueous techniques.

[00437] Binders suitable for use in pharmaceutical compositions and dosage forms include, but are not limited to, corn starch, potato starch, or other starches, gelatin, natural and synthetic gums such as acacia, sodium alginate, alginic acid, other alginates, powdered tragacanth, guar gum, cellulose and its derivatives (*e.g.,* ethyl

cellulose, cellulose acetate, carboxymethyl cellulose calcium, sodium carboxymethyl cellulose), polyvinyl pyrrolidone, methyl cellulose, pre-gelatinized starch, hydroxypropyl methyl cellulose, microcrystalline cellulose, and mixtures thereof.

[00438] Examples of suitable fillers for use in the pharmaceutical compositions and dosage forms disclosed herein include, but are not limited to, talc, calcium carbonate (*e.g.*, granules or powder), microcrystalline cellulose, powdered cellulose, dextrates, kaolin, mannitol, silicic acid, sorbitol, starch, pre-gelatinized starch, and mixtures thereof.

[00439] Disintegrants can be used in the pharmaceutical compositions as provided herein to provide tablets that disintegrate when exposed to an aqueous environment. Too much of a disintegrant can produce tablets which can disintegrate in the bottle. Too little can be insufficient for disintegration to occur and can thus alter the rate and extent of release of the active ingredient(s) from the dosage form. Thus, a sufficient amount of disintegrant that is neither too little nor too much to detrimentally alter the release of the active ingredient(s) can be used to form the dosage forms of the compounds disclosed herein. The amount of disintegrant used can vary based upon the type of formulation and mode of administration, and can be readily discernible to those of ordinary skill in the art. About 0.5 to about 15 weight percent of disintegrant, or about 1 to about 5 weight percent of disintegrant, can be used in the pharmaceutical composition. Disintegrants that can be used to form pharmaceutical compositions and dosage forms include, but are not limited to, agar-agar, alginic acid, calcium carbonate, microcrystalline cellulose, croscarmellose sodium, crospovidone, polacrilin potassium, sodium starch glycolate, potato or tapioca starch, other starches, pre-gelatinized starch, other starches, clays, other algins, other celluloses, gums or mixtures thereof.

[00440] Lubricants which can be used to form pharmaceutical compositions and dosage forms include, but are not limited to, calcium stearate, magnesium stearate, mineral oil, light mineral oil, glycerin, sorbitol, mannitol, polyethylene glycol, other glycols, stearic acid, sodium lauryl sulfate, talc, hydrogenated vegetable oil (*e.g.*, peanut oil, cottonseed oil, sunflower oil, sesame oil, olive oil, corn oil, and soybean oil), zinc stearate, ethyl oleate, ethylaureate, agar, or mixtures thereof. Additional lubricants include, for example, a syloid silica gel, a coagulated aerosol of synthetic silica, or mixtures thereof. A lubricant can optionally be added, in an amount of less than about 1 weight percent of the pharmaceutical composition.

[00441] When aqueous suspensions and/or elixirs are desired for oral administration, the active ingredient therein can be combined with various sweetening or flavoring agents, coloring matter or dyes and, for example, emulsifying and/or suspending agents, together with such diluents as water, ethanol, propylene glycol, glycerin and various combinations thereof.

[00442] The tablets can be uncoated or coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate can be employed. Formulations for oral use can also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, for example, peanut oil, liquid paraffin or olive oil.

[00443] Surfactant which can be used to form pharmaceutical compositions and dosage forms include, but are not limited to, hydrophilic surfactants, lipophilic surfactants, and mixtures thereof. That is, a mixture of hydrophilic surfactants can be employed, a mixture of lipophilic surfactants can be employed, or a mixture of at least one hydrophilic surfactant and at least one lipophilic surfactant can be employed.

[00444] A suitable hydrophilic surfactant can generally have an HLB value of at least about 10, while suitable lipophilic surfactants can generally have an HLB value of or less than about 10. An empirical parameter used to characterize the relative hydrophilicity and hydrophobicity of non-ionic amphiphilic compounds is the hydrophilic-lipophilic balance ("HLB" value). Surfactants with lower HLB values are more lipophilic or hydrophobic, and have greater solubility in oils, while surfactants with higher HLB values are more hydrophilic, and have greater solubility in aqueous solutions. Hydrophilic surfactants are generally considered to be those compounds having an HLB value greater than about 10, as well as anionic, cationic, or zwitterionic compounds for which the HLB scale is not generally applicable. Similarly, lipophilic (*i.e.,* hydrophobic) surfactants are compounds having an HLB value equal to or less than about 10. However, HLB value of a surfactant is merely a rough guide generally used to enable formulation of industrial, pharmaceutical and cosmetic emulsions.

[00445] Hydrophilic surfactants can be either ionic or non-ionic. Suitable ionic surfactants include, but are not limited to, alkylammonium salts; fusidic acid salts; fatty acid derivatives of amino acids, oligopeptides, and polypeptides; glyceride derivatives of amino acids, oligopeptides, and polypeptides; lecithins and hydrogenated lecithins; lysolecithins and hydrogenated lysolecithins; phospholipids and derivatives thereof; lysophospholipids and derivatives thereof; carnitine fatty acid ester salts; salts of alkylsulfates; fatty acid salts; sodium docusate; acylactylates; mono- and di-acetylated tartaric acid esters of mono- and di-glycerides; succinylated mono- and di-glycerides; citric acid esters of mono- and di-glycerides; and mixtures thereof.

[00446] Within the aforementioned group, ionic surfactants include, by way of example: lecithins, lysolecithin, phospholipids, lysophospholipids and derivatives thereof; carnitine fatty acid ester salts; salts of alkylsulfates; fatty acid salts; sodium docusate; acylactylates; mono- and di-acetylated tartaric acid esters of mono- and di-glycerides; succinylated mono- and di-glycerides; citric acid esters of mono- and di-glycerides; and mixtures thereof.

[00447] Ionic surfactants can be the ionized forms of lecithin, lysolecithin, phosphatidylcholine, phosphatidylethanolamine, phosphatidylglycerol, phosphatidic acid, phosphatidylserine, lysophosphatidylcholine, lysophosphatidylethanolamine, lysophosphatidylglycerol, lysophosphatidic acid, lysophosphatidylserine, PEG-phosphatidylethanolamine, PVP-phosphatidylethanolamine, lactylic esters of fatty acids, stearoyl-2-lactylate, stearoyl lactylate, succinylated monoglycerides, mono/diacetylated tartaric acid esters of mono/diglycerides, citric acid esters of mono/diglycerides, cholylsarcosine, caproate, caprylate, caprate, laurate, myristate, palmitate, oleate, ricinoleate, linoleate, linolenate, stearate, lauryl sulfate, teracecyl sulfate, docusate, lauroyl carnitines, palmitoyl carnitines, myristoyl carnitines, and salts and mixtures thereof.

[00448] Hydrophilic non-ionic surfactants can include, but are not limited to, alkylglucosides; alkylmaltosides; alkylthioglucosides; lauryl macrogolglycerides; polyoxyalkylene alkyl ethers such as polyethylene glycol alkyl ethers; polyoxyalkylene alkylphenols such as polyethylene glycol alkyl phenols; polyoxyalkylene alkyl

phenol fatty acid esters such as polyethylene glycol fatty acids monoesters and polyethylene glycol fatty acids diesters; polyethylene glycol glycerol fatty acid esters; polyglycerol fatty acid esters; polyoxyalkylene sorbitan fatty acid esters such as polyethylene glycol sorbitan fatty acid esters; hydrophilic transesterification products of a polyol with at least one member of glycerides, vegetable oils, hydrogenated vegetable oils, fatty acids, and sterols; polyoxyethylene sterols, derivatives, and analogues thereof; polyoxyethylated vitamins and derivatives thereof; polyoxyethylene-polyoxypropylene block copolymers; and mixtures thereof; polyethylene glycol sorbitan fatty acid esters and hydrophilic transesterification products of a polyol with at least one member of triglycerides, vegetable oils, and hydrogenated vegetable oils. The polyol can be glycerol, ethylene glycol, polyethylene glycol, sorbitol, propylene glycol, pentaerythritol, or a saccharide.

[00449] Other hydrophilic-non-ionic surfactants include, without limitation, PEG-10 laurate, PEG-12 laurate, PEG-20 laurate, PEG-32 laurate, PEG-32 dilaurate, PEG-12 oleate, PEG-15 oleate, PEG-20 oleate, PEG-20 dioleate, PEG-32 oleate, PEG-200 oleate, PEG-400 oleate, PEG-15 stearate, PEG-32 distearate, PEG-40 stearate, PEG-100 stearate, PEG-20 dilaurate, PEG-25 glyceryl trioleate, PEG-32 dioleate, PEG-20 glyceryl laurate, PEG-30 glyceryl laurate, PEG-20 glyceryl stearate, PEG-20 glyceryl oleate, PEG-30 glyceryl oleate, PEG-30 glyceryl laurate, PEG-40 glyceryl laurate, PEG-40 palm kernel oil, PEG-50 hydrogenated castor oil, PEG-40 castor oil, PEG-35 castor oil, PEG-60 castor oil, PEG-40 hydrogenated castor oil, PEG-60 hydrogenated castor oil, PEG-60 corn oil, PEG-6 caprate/caprylate glycerides, PEG-8 caprate/caprylate glycerides, polyglyceryl-10 laurate, PEG-30 cholesterol, PEG-25 phyto sterol, PEG-30 soya sterol, PEG-20 trioleate, PEG-40 sorbitan oleate, PEG-80 sorbitan laurate, polysorbate 20, polysorbate 80, POE-9 lauryl ether, POE-23 lauryl ether, POE-10 oleyl ether, POE-20 oleyl ether, POE-20 stearyl ether, tocopheryl PEG-100 succinate, PEG-24 cholesterol, polyglyceryl-10oleate, Tween 40, Tween 60, sucrose monostearate, sucrose monolaurate, sucrose monopalmitate, PEG 10-100 nonyl phenol series, PEG 15-100 octyl phenol series, and poloxamers.

[00450] Suitable lipophilic surfactants include, by way of example only: fatty alcohols; glycerol fatty acid esters; acetylated glycerol fatty acid esters; lower alcohol fatty acids esters; propylene glycol fatty acid esters; sorbitan fatty acid esters; polyethylene glycol sorbitan fatty acid esters; sterols and sterol derivatives; polyoxyethylated sterols and sterol derivatives; polyethylene glycol alkyl ethers; sugar esters; sugar ethers; lactic acid derivatives of mono- and di-glycerides; hydrophobic transesterification products of a polyol with at least one member of glycerides, vegetable oils, hydrogenated vegetable oils, fatty acids and sterols; oil-soluble vitamins/vitamin derivatives; and mixtures thereof. Within this group, non-limiting examples of lipophilic surfactants include glycerol fatty acid esters, propylene glycol fatty acid esters, and mixtures thereof, or are hydrophobic transesterification products of a polyol with at least one member of vegetable oils, hydrogenated vegetable oils, and triglycerides.

[00451] In one embodiment, the pharmaceutical composition can include a solubilizer to ensure good solubilization and/or dissolution of a compound as provided herein and to minimize precipitation of the compound. This can be especially important for pharmaceutical compositions for non-oral use, *e.g.*, pharmaceutical compositions for injection. A solubilizer can also be added to increase the solubility of the hydrophilic drug and/or

other components, such as surfactants, or to maintain the pharmaceutical composition as a stable or homogeneous solution or dispersion.

[00452] Examples of suitable solubilizers include, but are not limited to, the following: alcohols and polyols, such as ethanol, isopropanol, butanol, benzyl alcohol, ethylene glycol, propylene glycol, butanediols and isomers thereof, glycerol, pentaerythritol, sorbitol, mannitol, transcutol, dimethyl isosorbide, polyethylene glycol, polypropylene glycol, polyvinylalcohol, hydroxypropyl methylcellulose and other cellulose derivatives, cyclodextrins and cyclodextrin derivatives; ethers of polyethylene glycols having an average molecular weight of about 200 to about 6000, such as tetrahydrofurfuryl alcohol PEG ether (glycofurol) or methoxy PEG; amides and other nitrogen-containing compounds such as 2-pyrrolidone, 2-piperidone, ε-caprolactam, N-alkylpyrrolidone, N-hydroxyalkylpyrrolidone, N-alkylpiperidone, N-alkylcaprolactam, dimethylacetamide and polyvinylpyrrolidone; esters such as ethyl propionate, tributylcitrate, acetyl triethylcitrate, acetyl tributyl citrate, triethylcitrate, ethyl oleate, ethyl caprylate, ethyl butyrate, triacetin, propylene glycol monoacetate, propylene glycol diacetate, ε-caprolactone and isomers thereof, δ-valerolactone and isomers thereof, β-butyrolactone and isomers thereof; and other solubilizers known in the art, such as dimethyl acetamide, dimethyl isosorbide, N-methyl pyrrolidones, monooctanoin, diethylene glycol monoethyl ether, and water.

[00453] Mixtures of solubilizers can also be used. Examples include, but not limited to, triacetin, triethylcitrate, ethyl oleate, ethyl caprylate, dimethylacetamide, N-methylpyrrolidone, N-hydroxyethylpyrrolidone, polyvinylpyrrolidone, hydroxypropyl methylcellulose, hydroxypropyl cyclodextrins, ethanol, polyethylene glycol 200-100, glycofurol, transcutol, propylene glycol, and dimethyl isosorbide. In some embodiments, solubilizers include sorbitol, glycerol, triacetin, ethyl alcohol, PEG-400, glycofurol and propylene glycol.

[00454] The amount of solubilizer that can be included is not particularly limited. The amount of a given solubilizer can be limited to a bioacceptable amount, which can be readily determined by one of skill in the art. In some circumstances, it can be advantageous to include amounts of solubilizers far in excess of bioacceptable amounts, for example to maximize the concentration of the drug, with excess solubilizer removed prior to providing the pharmaceutical composition to a subject using conventional techniques, such as distillation or evaporation. Thus, if present, the solubilizer can be in a weight ratio of about 10%, 25%, 50%, 100%, or up to about 200% by weight, based on the combined weight of the drug, and other excipients. If desired, very small amounts of solubilizer can also be used, such as about 5%, 2%, 1% or even less. Typically, the solubilizer can be present in an amount of about 1% to about 100%, more typically about 5% to about 25% by weight.

[00455] The pharmaceutical composition can further include one or more pharmaceutically acceptable additives and excipients. Such additives and excipients include, without limitation, detackifiers, anti-foaming agents, buffering agents, polymers, antioxidants, preservatives, chelating agents, viscomodulators, tonicifiers, flavorants, colorants, oils, odorants, opacifiers, suspending agents, binders, fillers, plasticizers, lubricants, and mixtures thereof.

[00456] Exemplary preservatives can include antioxidants, chelating agents, antimicrobial preservatives, antifungal preservatives, alcohol preservatives, acidic preservatives, and other preservatives. Exemplary antioxidants include, but are not limited to, alpha tocopherol, ascorbic acid, acorbyl palmitate, butylated hydroxyanisole, butylated hydroxytoluene, monothioglycerol, potassium metabisulfite, propionic acid, propyl

gallate, sodium ascorbate, sodium bisulfite, sodium metabisulfite, and sodium sulfite. Exemplary chelating agents include ethylenediaminetetraacetic acid (EDTA), citric acid monohydrate, disodium edetate, dipotassium edetate, edetic acid, fumaric acid, malic acid, phosphoric acid, sodium edetate, tartaric acid, and trisodium edetate. Exemplary antimicrobial preservatives include, but are not limited to, benzalkonium chloride, benzethonium chloride, benzyl alcohol, bronopol, cetrimide, cetylpyridinium chloride, chlorhexidine, chlorobutanol, chlorocresol, chloroxylenol, cresol, ethyl alcohol, glycerin, hexetidine, imidurea, phenol, phenoxyethanol, phenylethyl alcohol, phenylmercuric nitrate, propylene glycol, and thimerosal. Exemplary antifungal preservatives include, but are not limited to, butyl paraben, methyl paraben, ethyl paraben, propyl paraben, benzoic acid, hydroxybenzoic acid, potassium benzoate, potassium sorbate, sodium benzoate, sodium propionate, and sorbic acid. Exemplary alcohol preservatives include, but are not limited to, ethanol, polyethylene glycol, phenol, phenolic compounds, bisphenol, chlorobutanol, hydroxybenzoate, and phenylethyl alcohol. Exemplary acidic preservatives include, but are not limited to, vitamin A, vitamin C, vitamin E, beta–carotene, citric acid, acetic acid, dehydroacetic acid, ascorbic acid, sorbic acid, and phytic acid. Other preservatives include, but are not limited to, tocopherol, tocopherol acetate, deteroxime mesylate, cetrimide, butylated hydroxyanisol (BHA), butylated hydroxytoluened (BHT), ethylenediamine, sodium lauryl sulfate (SLS), sodium lauryl ether sulfate (SLES), sodium bisulfite, sodium metabisulfite, potassium sulfite, potassium metabisulfite, Glydant Plus, Phenonip, methylparaben, Germall 115, Germaben II, Neolone, Kathon, and Euxyl. In certain embodiments, the preservative is an anti–oxidant. In other embodiments, the preservative is a chelating agent.

[00457] Exemplary oils include, but are not limited to, almond, apricot kernel, avocado, babassu, bergamot, black current seed, borage, cade, camomile, canola, caraway, carnauba, castor, cinnamon, cocoa butter, coconut, cod liver, coffee, corn, cotton seed, emu, eucalyptus, evening primrose, fish, flaxseed, geraniol, gourd, grape seed, hazel nut, hyssop, isopropyl myristate, jojoba, kukui nut, lavandin, lavender, lemon, litsea cubeba, macademia nut, mallow, mango seed, meadowfoam seed, mink, nutmeg, olive, orange, orange roughy, palm, palm kernel, peach kernel, peanut, poppy seed, pumpkin seed, rapeseed, rice bran, rosemary, safflower, sandalwood, sasquana, savoury, sea buckthorn, sesame, shea butter, silicone, soybean, sunflower, tea tree, thistle, tsubaki, vetiver, walnut, and wheat germ oils. Exemplary oils include, but are not limited to, butyl stearate, caprylic triglyceride, capric triglyceride, cyclomethicone, diethyl sebacate, dimethicone 360, isopropyl myristate, mineral oil, octyldodecanol, oleyl alcohol, silicone oil, and combinations thereof.

[00458] In addition, an acid or a base can be incorporated into the pharmaceutical composition to facilitate processing, to enhance stability, or for other reasons. Examples of pharmaceutically acceptable bases include amino acids, amino acid esters, ammonium hydroxide, potassium hydroxide, sodium hydroxide, sodium hydrogen carbonate, aluminum hydroxide, calcium carbonate, magnesium hydroxide, magnesium aluminum silicate, synthetic aluminum silicate, synthetic hydrocalcite, magnesium aluminum hydroxide, diisopropylethylamine, ethanolamine, ethylenediamine, triethanolamine, triethylamine, triisopropanolamine, trimethylamine, tris(hydroxymethyl)aminomethane (TRIS) and the like. Also suitable are bases that are salts of a pharmaceutically acceptable acid, such as acetic acid, acrylic acid, adipic acid, alginic acid, alkanesulfonic acid, amino acids, ascorbic acid, benzoic acid, boric acid, butyric acid, carbonic acid, citric acid, fatty acids, formic acid, fumaric acid, gluconic

acid, hydroquinosulfonic acid, isoascorbic acid, lactic acid, maleic acid, oxalic acid, para-bromophenylsulfonic acid, propionic acid, p-toluenesulfonic acid, salicylic acid, stearic acid, succinic acid, tannic acid, tartaric acid, thioglycolic acid, toluenesulfonic acid, uric acid, and the like. Salts of polyprotic acids, such as sodium phosphate, disodium hydrogen phosphate, and sodium dihydrogen phosphate can also be used. When the base is a salt, the cation can be any convenient and pharmaceutically acceptable cation, such as ammonium, alkali metals, alkaline earth metals, and the like. Examples can include, but not limited to, sodium, potassium, lithium, magnesium, calcium and ammonium.

[00459] Suitable acids are pharmaceutically acceptable organic or inorganic acids. Examples of suitable inorganic acids include hydrochloric acid, hydrobromic acid, hydriodic acid, sulfuric acid, nitric acid, boric acid, phosphoric acid, and the like. Examples of suitable organic acids include acetic acid, acrylic acid, adipic acid, alginic acid, alkanesulfonic acids, amino acids, ascorbic acid, benzoic acid, boric acid, butyric acid, carbonic acid, citric acid, fatty acids, formic acid, fumaric acid, gluconic acid, hydroquinosulfonic acid, isoascorbic acid, lactic acid, maleic acid, methanesulfonic acid, oxalic acid, para-bromophenylsulfonic acid, propionic acid, p-toluenesulfonic acid, salicylic acid, stearic acid, succinic acid, tannic acid, tartaric acid, thioglycolic acid, toluenesulfonic acid, uric acid and the like.

1B. Formulations for Parenteral Administration

[00460] In some embodiments, provided herein are pharmaceutical compositions for parenteral administration containing a compound as disclosed herein, and a pharmaceutical excipient suitable for parenteral administration. In some embodiments, provided herein are pharmaceutical compositions for parenteral administration containing: (i) an effective amount of a disclosed compound; optionally (ii) an effective amount of one or more second agents; and (iii) one or more pharmaceutical excipients suitable for parenteral administration. In some embodiments, the pharmaceutical composition further contains: (iv) an effective amount of a third agent.

[00461] The forms in which the disclosed pharmaceutical compositions can be incorporated for administration by injection include aqueous or oil suspensions, or emulsions, with sesame oil, corn oil, cottonseed oil, or peanut oil, as well as elixirs, mannitol, dextrose, or a sterile aqueous solution, and similar pharmaceutical vehicles.

Aqueous solutions in saline are also conventionally used for injection. Ethanol, glycerol, propylene glycol, liquid polyethylene glycol, and the like (and suitable mixtures thereof), cyclodextrin derivatives, and vegetable oils can also be employed.

[00462] Aqueous solutions in saline are also conventionally used for injection. Ethanol, glycerol, propylene glycol, liquid polyethylene glycol, and the like (and suitable mixtures thereof), cyclodextrin derivatives, and vegetable oils can also be employed. The proper fluidity can be maintained, for example, by the use of a coating, such as lecithin, for the maintenance of the required particle size in the case of dispersion and by the use of surfactants. The prevention of the action of microorganisms can be brought about by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, thimerosal, and the like.

[00463] Sterile injectable solutions are prepared by incorporating a compound as disclosed herein in the required amount in the appropriate solvent with various other ingredients as enumerated above, as appropriate, followed by filtered sterilization. Generally, dispersions are prepared by incorporating the various sterilized active ingredients into a sterile vehicle which contains the basic dispersion medium and the appropriate other ingredients from those enumerated above. In the case of sterile powders for the preparation of sterile injectable solutions, certain methods of preparation are vacuum-drying and freeze-drying techniques which yield a powder of the active ingredient plus any additional ingredient from a previously sterile-filtered solution thereof.

[00464] The injectable formulations can be sterilized, for example, by filtration through a bacterial–retaining filter, or by incorporating sterilizing agents in the form of sterile solid compositions which can be dissolved or dispersed in sterile water or other sterile injectable medium prior to use. Injectable compositions can contain from about 0.1 to about 5% w/w of a compound as disclosed herein.

1C. Formulations for Topical Administration

[00465] In some embodiments, provided herein are pharmaceutical compositions for topical (*e.g.*, transdermal) administration containing a compound as disclosed herein, and a pharmaceutical excipient suitable for topical administration. In some embodiments, provided herein are pharmaceutical compositions for topical administration containing: (i) an effective amount of a disclosed compound; optionally (ii) an effective amount of one or more second agents; and (iii) one or more pharmaceutical excipients suitable for topical administration. In some embodiments, the pharmaceutical composition further contains: (iv) an effective amount of a third agent.

[00466] Pharmaceutical compositions provided herein can be formulated into preparations in solid, semi-solid, or liquid forms suitable for local or topical administration, such as gels, water soluble jellies, creams, lotions, suspensions, foams, powders, slurries, ointments, solutions, oils, pastes, suppositories, sprays, emulsions, saline solutions, dimethylsulfoxide (DMSO)-based solutions. In general, carriers with higher densities are capable of providing an area with a prolonged exposure to the active ingredients. In contrast, a solution formulation can provide more immediate exposure of the active ingredient to the chosen area.

[00467] The pharmaceutical compositions also can comprise suitable solid or gel phase carriers or excipients, which are compounds that allow increased penetration of, or assist in the delivery of, therapeutic molecules across the stratum corneum permeability barrier of the skin. There are many of these penetration-enhancing molecules known to those trained in the art of topical formulation. Examples of such carriers and excipients include, but are not limited to, humectants (*e.g.*, urea), glycols (*e.g.*, propylene glycol), alcohols (*e.g.*, ethanol), fatty acids (*e.g.*, oleic acid), surfactants (*e.g.*, isopropyl myristate and sodium lauryl sulfate), pyrrolidones, glycerol monolaurate, sulfoxides, terpenes (*e.g.*, menthol), amines, amides, alkanes, alkanols, water, calcium carbonate, calcium phosphate, various sugars, starches, cellulose derivatives, gelatin, and polymers such as polyethylene glycols.

[00468] Another exemplary formulation for use in the disclosed methods employs transdermal delivery devices ("patches"). Such transdermal patches can be used to provide continuous or discontinuous infusion of a compound as provided herein in controlled amounts, either with or without another agent.

[00469] The construction and use of transdermal patches for the delivery of pharmaceutical agents is well known in the art. *See, e.g.,* U.S. Pat. Nos. 5,023,252, 4,992,445 and 5,001,139. Such patches can be constructed for continuous, pulsatile, or on demand delivery of pharmaceutical agents.

[00470] Suitable devices for use in delivering intradermal pharmaceutically acceptable compositions described herein include short needle devices such as those described in U.S. Patents 4,886,499; 5,190,521; 5,328,483; 5,527,288; 4,270,537; 5,015,235; 5,141,496; and 5,417,662. Intradermal compositions can be administered by devices which limit the effective penetration length of a needle into the skin, such as those described in PCT publication WO 99/34850 and functional equivalents thereof. Jet injection devices which deliver liquid vaccines to the dermis via a liquid jet injector and/or via a needle which pierces the stratum corneum and produces a jet which reaches the dermis are suitable. Jet injection devices are described, for example, in U.S. Patents 5,480,381; 5,599,302; 5,334,144; 5,993,412; 5,649,912; 5,569,189; 5,704,911; 5,383,851; 5,893,397; 5,466,220; 5,339,163; 5,312,335; 5,503,627; 5,064,413; 5,520,639; 4,596,556; 4,790,824; 4,941,880; 4,940,460; and PCT publications WO 97/37705 and WO 97/13537. Ballistic powder/particle delivery devices which use compressed gas to accelerate vaccine in powder form through the outer layers of the skin to the dermis are suitable. Alternatively or additionally, conventional syringes can be used in the classical mantoux method of intradermal administration.

[00471] Topically–administrable formulations can, for example, comprise from about 1% to about 10% (w/w) compound of formula **(I)**, although the concentration of the compound of formula **(I)** can be as high as the solubility limit of the compound of formula **(I)** in the solvent. In some embodiments, topically–administrable formulations can, for example, comprise from about 1% to about 9% (w/w) compound of formula **(I)**, such as from about 1% to about 8% (w/w), further such as from about 1% to about 7% (w/w), further such as from about 1% to about 6% (w/w), further such as from about 1% to about 5% (w/w), further such as from about 1% to about 4% (w/w), further such as from about 1% to about 3% (w/w), and further such as from about 1% to about 2% (w/w) compound of formula **(I).** Formulations for topical administration can further comprise one or more of the additional pharmaceutically acceptable excipients described herein.

1D. Formulations for Inhalation Administration

[00472] In some embodiments, provided herein are pharmaceutical compositions for inhalation administration containing a compound as disclosed herein, and a pharmaceutical excipient suitable for topical administration. In some embodiments, provided herein are pharmaceutical compositions for inhalation administration containing: (i) an effective amount of a disclosed compound; optionally (ii) an effective amount of one or more second agents; and (iii) one or more pharmaceutical excipients suitable for inhalation administration. In some embodiments, the pharmaceutical composition further contains: (iv) an effective amount of a third agent.

[00473] Pharmaceutical compositions for inhalation or insufflation include solutions and suspensions in pharmaceutically acceptable, aqueous or organic solvents, or mixtures thereof, and powders. The liquid or solid pharmaceutical compositions can contain suitable pharmaceutically acceptable excipients as described herein. In some embodiments, the pharmaceutical compositions are administered by the oral or nasal respiratory route for local

or systemic effect. Pharmaceutical compositions in pharmaceutically acceptable solvents can be nebulized by use of inert gases. Nebulized solutions can be inhaled directly from the nebulizing device or the nebulizing device can be attached to a face mask tent, or intermittent positive pressure breathing machine. Solution, suspension, or powder pharmaceutical compositions can be administered, *e.g.,* orally or nasally, from devices that deliver the formulation in an appropriate manner.

1E. Formulations for Ocular Administration

[00474] In some embodiments, the disclosure provides a pharmaceutical composition for treating ophthalmic disorders. The pharmaceutical composition can contain an effective amount of a compound as disclosed herein and a pharmaceutical excipient suitable for ocular administration. Pharmaceutical compositions suitable for ocular administration can be presented as discrete dosage forms, such as drops or sprays each containing a predetermined amount of an active ingredient a solution, or a suspension in an aqueous or non-aqueous liquid, an oil-in-water emulsion, or a water-in-oil liquid emulsion. Other administration foms include intraocular injection, intravitreal injection, topically, or through the use of a drug eluting device, microcapsule, implant, or microfluidic device. In some cases, the compounds as disclosed herein are administered with a carrier or excipient that increases the intraocular penetrance of the compound such as an oil and water emulsion with colloid particles having an oily core surrounded by an interfacial film. It is contemplated that all local routes to the eye can be used including topical, subconjunctival, periocular, retrobulbar, subtenon, intracameral, intravitreal, intraocular, subretinal, juxtascleral and suprachoroidal administration. Systemic or parenteral administration can be feasible including, but not limited to, intravenous, subcutaneous, and oral delivery. An exemplary method of administration will be intravitreal or subtenon injection of solutions or suspensions, or intravitreal or subtenon placement of bioerodible or non-bioerodible devices, or by topical ocular administration of solutions or suspensions, or posterior juxtascleral administration of a gel or cream formulation.

[00475] Eye drops can be prepared by dissolving the active ingredient in a sterile aqueous solution such as physiological saline, buffering solution, etc., or by combining powder compositions to be dissolved before use. Other vehicles can be chosen, as is known in the art, including, but not limited to: balance salt solution, saline solution, water soluble polyethers such as polyethyene glycol, polyvinyls, such as polyvinyl alcohol and povidone, cellulose derivatives such as methylcellulose and hydroxypropyl methylcellulose, petroleum derivatives such as mineral oil and white petrolatum, animal fats such as lanolin, polymers of acrylic acid such as carboxypolymethylene gel, vegetable fats such as peanut oil and polysaccharides such as dextrans, and glycosaminoglycans such as sodium hyaluronate. In some embodiments, additives ordinarily used in the eye drops can be added. Such additives include isotonizing agents (*e.g.,* sodium chloride, etc.), buffer agent (*e.g.,* boric acid, sodium monohydrogen phosphate, sodium dihydrogen phosphate, etc.), preservatives (*e.g.,* benzalkonium chloride, benzethonium chloride, chlorobutanol, etc.), thickeners (*e.g.,* saccharide such as lactose, mannitol, maltose, etc.; *e.g.,* hyaluronic acid or its salt such as sodium hyaluronate, potassium hyaluronate, etc.; *e.g.,* mucopolysaccharide such as chondroitin sulfate, etc.; *e.g.,* sodium polyacrylate, carboxyvinyl polymer, crosslinked polyacrylate, polyvinyl alcohol, polyvinyl pyrrolidone, methyl cellulose, hydroxy propyl methylcellulose, hydroxyethyl cellulose, carboxymethyl cellulose, hydroxy propyl cellulose or other agents known to those skilled in the art).

[00476] In some cases, the colloid particles include at least one cationic agent and at least one non-ionic sufactant such as a poloxamer, tyloxapol, a polysorbate, a polyoxyethylene castor oil derivative, a sorbitan ester, or a polyoxyl stearate. In some cases, the cationic agent is an alkylamine, a tertiary alkyl amine, a quarternary ammonium compound, a cationic lipid, an amino alcohol, a biguanidine salt, a cationic compound or a mixture thereof. In some cases, the cationic agent is a biguanidine salt such as chlorhexidine, polyaminopropyl biguanidine, phenformin, alkylbiguanidine, or a mixture thereof. In some cases, the quaternary ammonium compound is a benzalkonium halide, lauralkonium halide, cetrimide, hexadecyltrimethylammonium halide, tetradecyltrimethylammonium halide, dodecyltrimethylammonium halide, cetrimonium halide, benzethonium halide, behenalkonium halide, cetalkonium halide, cetethyldimonium halide, cetylpyridinium halide, benzododecinium halide, chlorallyl methenamine halide, rnyristylalkonium halide, stearalkonium halide or a mixture of two or more thereof. In some cases, cationic agent is a benzalkonium chloride, lauralkonium chloride, benzododecinium bromide, benzethenium chloride, hexadecyltrimethylammonium bromide, tetradecyltrimethylammonium bromide, dodecyltrimethylammonium bromide or a mixture of two or more thereof. In some cases, the oil phase is mineral oil and light mineral oil, medium chain triglycerides (MCT), coconut oil; hydrogenated oils comprising hydrogenated cottonseed oil, hydrogenated palm oil, hydrogenate castor oil or hydrogenated soybean oil; polyoxyethylene hydrogenated castor oil derivatives comprising poluoxyl-40 hydrogenated castor oil, polyoxyl-60 hydrogenated castor oil or polyoxyl-100 hydrogenated castor oil.

1F. Formulations for Controlled Release Administration

[00477] In some embodiments, provided herein are pharmaceutical compositions for controlled release administration containing a compound as disclosed herein, and a pharmaceutical excipient suitable for controlled release administration. In some embodiments, provided herein are pharmaceutical compositions for controlled release administration containing: (i) an effective amount of a disclosed compound; optionally (ii) an effective amount of one or more second agents; and (iii) one or more pharmaceutical excipients suitable for controlled release administration. In some embodiments, the pharmaceutical composition further contains: (iv) an effective amount of a third agent.

[00478] Active agents such as the compounds provided herein can be administered by controlled release means or by delivery devices that are well known to those of ordinary skill in the art. Examples include, but are not limited to, those described in U.S. Patent Nos.: 3,845,770; 3,916,899; 3,536,809; 3,598,123; and 4,008,719; 5,674,533; 5,059,595; 5,591,767; 5,120,548; 5,073,543; 5,639,476; 5,354,556; 5,639,480; 5,733,566; 5,739,108; 5,891,474; 5,922,356; 5,972,891; 5,980,945; 5,993,855; 6,045,830; 6,087,324; 6,113,943; 6,197,350; 6,248,363; 6,264,970; 6,267,981; 6,376,461; 6,419,961; 6,589,548; 6,613,358; 6,699,500 each of which is incorporated herein by reference. Such dosage forms can be used to provide slow or controlled release of one or more active agents using, for example, hydropropylmethyl cellulose, other polymer matrices, gels, permeable membranes, osmotic systems, multilayer coatings, microparticles, liposomes, microspheres, or a combination thereof to provide the desired release profile in varying proportions. Suitable controlled release formulations known to those of ordinary skill in the art, including those described herein, can be readily selected for use with the active agents provided

herein. Thus, the pharmaceutical compositions provided encompass single unit dosage forms suitable for oral administration such as, but not limited to, tablets, capsules, gelcaps, and caplets that are adapted for controlled release.

[00479] All controlled release pharmaceutical products have a common goal of improving drug therapy over that achieved by their non controlled counterparts. In some embodiments, the use of a controlled release preparation in medical treatment is characterized by a minimum of drug substance being employed to cure or control the disease, disorder, or condition in a minimum amount of time. Advantages of controlled release formulations include extended activity of the drug, reduced dosage frequency, and increased subject compliance. In addition, controlled release formulations can be used to affect the time of onset of action or other characteristics, such as blood levels of the drug, and can thus affect the occurrence of side (*e.g.*, adverse) effects.

[00480] In some embodiments, controlled release formulations are designed to initially release an amount of a compound as disclosed herein that promptly produces the desired therapeutic effect, and gradually and continually release other amounts of the compound to maintain this level of therapeutic or prophylactic effect over an extended period of time. In order to maintain this constant level of the compound in the body, the compound should be released from the dosage form at a rate that will replace the amount of drug being metabolized and excreted from the body. Controlled release of an active agent can be stimulated by various conditions including, but not limited to, pH, temperature, enzymes, water, or other physiological conditions or compounds.

[00481] In certain embodiments, the pharmaceutical composition can be administered using intravenous infusion, an implantable osmotic pump, a transdermal patch, liposomes, or other modes of administration. In one embodiment, a pump can be used (*see*, Sefton, *CRC Crit. Ref. Biomed. Eng.* 14:201 (1987); Buchwald *et al., Surgery* 88:507 (1980); Saudek *et al., N. Engl. J. Med.* 321:574 (1989)). In another embodiment, polymeric materials can be used. In yet another embodiment, a controlled release system can be placed in a subject at an appropriate site determined by a practitioner of skill, *i.e.*, thus requiring only a fraction of the systemic dose (*see*, *e.g.*, Goodson, *Medical Applications of Controlled Release*, 115-138 (vol. 2, 1984). Other controlled release systems are discussed in the review by Langer, *Science* 249:1527-1533 (1990). The one or more active agents can be dispersed in a solid inner matrix, *e.g.*, polymethylmethacrylate, polybutylmethacrylate, plasticized or unplasticized polyvinylchloride, plasticized nylon, plasticized polyethyleneterephthalate, natural rubber, polyisoprene, polyisobutylene, polybutadiene, polyethylene, ethylene-vinylacetate copolymers, silicone rubbers, polydimethylsiloxanes, silicone carbonate copolymers, hydrophilic polymers such as hydrogels of esters of acrylic and methacrylic acid, collagen, cross-linked polyvinylalcohol and cross-linked partially hydrolyzed polyvinyl acetate, that is surrounded by an outer polymeric membrane, *e.g.*, polyethylene, polypropylene, ethylene/propylene copolymers, ethylene/ethyl acrylate copolymers, ethylene/vinylacetate copolymers, silicone rubbers, polydimethyl siloxanes, neoprene rubber, chlorinated polyethylene, polyvinylchloride, vinylchloride copolymers with vinyl acetate, vinylidene chloride, ethylene and propylene, ionomer polyethylene terephthalate, butyl rubber epichlorohydrin rubbers, ethylene/vinyl alcohol copolymer, ethylene/vinyl acetate/vinyl alcohol terpolymer, and ethylene/vinyloxyethanol copolymer, that is insoluble in body fluids. The one or more active agents then diffuse

through the outer polymeric membrane in a release rate controlling step. The percentage of active agent in such parenteral compositions is highly dependent on the specific nature thereof, as well as the needs of the subject.

2. Dosage

[00482] A compound described herein can be delivered in the form of pharmaceutically acceptable compositions which comprise a therapeutically effective amount of one or more compounds described herein and/or one or more additional therapeutic agents such as a chemotherapeutic, formulated together with one or more pharmaceutically acceptable excipients. In some instances, the compound described herein and the additional therapeutic agent are administered in separate pharmaceutical compositions and can (*e.g.*, because of different physical and/or chemical characteristics) be administered by different routes (*e.g.*, one therapeutic is administered orally, while the other is administered intravenously). In other instances, the compound described herein and the additional therapeutic agent can be administered separately, but via the same route (*e.g.*, both orally or both intravenously). In still other instances, the compound described herein and the additional therapeutic agent can be administered in the same pharmaceutical composition.

[00483] The selected dosage level will depend upon a variety of factors including, for example, the activity of the particular compound employed, the route of administration, the time of administration, the rate of excretion or metabolism of the particular compound being employed, the rate and extent of absorption, the duration of the treatment, other drugs, compounds and/or materials used in combination with the particular compound employed, the age, sex, weight, condition, general health and prior medical history of the patient being treated, and like factors well known in the medical arts.

[00484] In general, a suitable daily dose of a compound described herein and/or a chemotherapeutic will be that amount of the compound which, in some embodiments, can be the lowest dose effective to produce a therapeutic effect. Such an effective dose will generally depend upon the factors described above. Generally, doses of the compounds described herein for a patient, when used for the indicated effects, will range from about 0.0001 mg to about 100 mg per day, or about 0.001 mg to about 100 mg per day, or about 0.01 mg to about 100 mg per day, or about 0.1 mg to about 100 mg per day, or about 0.0001 mg to about 500 mg per day, or about 0.001 mg to about 500 mg per day, or about 0.01 mg to 1000 mg, or about 0.01 mg to about 500 mg per day, or about 0.1 mg to about 500 mg per day, or about about 1 mg to 50 mg per day, or about 5 mg to 40 mg. An exemplary dosage is about 10 to 30 mg per day. In some embodiments, for a 70 kg human, a suitable dose would be about 0.05 to about 7 g/day, such as about 0.05 to about 2.5 g/day. Actual dosage levels of the active ingredients in the pharmaceutical compositions described herein can be varied so as to obtain an amount of the active ingredient which is effective to achieve the desired therapeutic response for a particular patient, composition, and mode of administration, without being toxic to the patient. In some instances, dosage levels below the lower limit of the aforesaid range can be more than adequate, while in other cases still larger doses can be employed without causing any harmful side effect, *e.g.*, by dividing such larger doses into several small doses for administration throughout the day.

[00485] In some embodiments, the compounds can be administered daily, every other day, three times a week, twice a week, weekly, or bi-weekly. The dosing schedule can include a "drug holiday," *i.e.*, the drug can be

administered for two weeks on, one week off, or three weeks on, one week off, or four weeks on, one week off, etc., or continuously, without a drug holiday. The compounds can be administered orally, intravenously, intraperitoneally, topically, transdermally, intramuscularly, subcutaneously, intranasally, sublingually, or by any other route.

[00486] In some embodiments, a compound as provided herein is administered in multiple doses. Dosing can be about once, twice, three times, four times, five times, six times, or more than six times per day. Dosing can be about once a month, about once every two weeks, about once a week, or about once every other day. In another embodiment, a compound as disclosed herein and another agent are administered together about once per day to about 6 times per day. In another embodiment, the administration of a compound as provided herein and an agent continues for less than about 7 days. In yet another embodiment, the administration continues for more than about 6, about 10, about 14, about 28 days, about two months, about six months, or about one year. In some cases, continuous dosing is achieved and maintained as long as necessary.

[00487] Administration of the pharmaceutical compositions as disclosed herein can continue as long as necessary. In some embodiments, an agent as disclosed herein is administered for more than about 1, about 2, about 3, about 4, about 5, about 6, about 7, about 14, or about 28 days. In some embodiments, an agent as disclosed herein is administered for less than about 28, about 14, about 7, about 6, about 5, about 4, about 3, about 2, or about 1 day. In some embodiments, an agent as disclosed herein is administered chronically on an ongoing basis, *e.g.,* for the treatment of chronic effects.

[00488] Since the compounds described herein can be administered in combination with other treatments (such as additional chemotherapeutics, radiation or surgery), the doses of each agent or therapy can be lower than the corresponding dose for single-agent therapy. The dose for single-agent therapy can range from, for example, about 0.0001 to about 200 mg, or about 0.001 to about 100 mg, or about 0.01 to about 100 mg, or about 0.1 to about 100 mg, or about 1 to about 50 mg per kilogram of body weight per day.

[00489] When a compound provided herein, is administered in a pharmaceutical composition that comprises one or more agents, and the agent has a shorter half-life than the compound provided herein unit dose forms of the agent and the compound provided herein can be adjusted accordingly.

<u>3. Kits</u>

[00490] In some embodiments, provided herein are kits. The kits can include a compound or pharmaceutical composition as described herein, in suitable packaging, and written material that can include instructions for use, discussion of clinical studies, listing of side effects, and the like. Such kits can also include information, such as scientific literature references, package insert materials, clinical trial results, and/or summaries of these and the like, which indicate or establish the activities and/or advantages of the pharmaceutical composition, and/or which describe dosing, administration, side effects, drug interactions, or other information useful to the health care provider. Such information can be based on the results of various studies, for example, studies using experimental animals involving *in vivo* models and studies based on human clinical trials.

[00491] In some embodiments, a memory aid is provided with the kit, *e.g.,* in the form of numbers next to the tablets or capsules whereby the numbers correspond with the days of the regimen which the tablets or capsules so specified should be ingested. Another example of such a memory aid is a calendar printed on the card, *e.g.,* as follows "First Week, Monday, Tuesday, . . . etc. . . . Second Week, Monday, Tuesday, . . . " etc. Other variations of memory aids will be readily apparent. A "daily dose" can be a single tablet or capsule or several tablets or capsules to be taken on a given day.

[00492] The kit can further contain another agent. In some embodiments, the compound as disclosed herein and the agent are provided as separate pharmaceutical compositions in separate containers within the kit. In some embodiments, the compound as disclosed herein and the agent are provided as a single pharmaceutical composition within a container in the kit. Suitable packaging and additional articles for use (*e.g.,* measuring cup for liquid preparations, foil wrapping to minimize exposure to air, and the like) are known in the art and can be included in the kit. In other embodiments, kits can further comprise devices that are used to administer the active agents. Examples of such devices include, but are not limited to, syringes, drip bags, patches, and inhalers. Kits described herein can be provided, marketed and/or promoted to health providers, including physicians, nurses, pharmacists, formulary officials, and the like. Kits can also, in some embodiments, be marketed directly to the consumer.

[00493] An example of such a kit is a so-called blister pack. Blister packs are well known in the packaging industry and are being widely used for the packaging of pharmaceutical unit dosage forms (tablets, capsules, and the like). Blister packs generally consist of a sheet of relatively stiff material covered with a foil of a preferably transparent plastic material. During the packaging process, recesses are formed in the plastic foil. The recesses have the size and shape of the tablets or capsules to be packed. Next, the tablets or capsules are placed in the recesses and the sheet of relatively stiff material is sealed against the plastic foil at the face of the foil which is opposite from the direction in which the recesses were formed. As a result, the tablets or capsules are sealed in the recesses between the plastic foil and the sheet. The strength of the sheet is such that the tablets or capsules can be removed from the blister pack by manually applying pressure on the recesses whereby an opening is formed in the sheet at the place of the recess. The tablet or capsule can then be removed via said opening.

[00494] Kits can further comprise pharmaceutically acceptable vehicles that can be used to administer one or more active agents. For example, if an active agent is provided in a solid form that must be reconstituted for parenteral administration, the kit can comprise a sealed container of a suitable vehicle in which the active agent can be dissolved to form a particulate-free sterile solution that is suitable for parenteral administration. Examples of pharmaceutically acceptable vehicles include, but are not limited to: Water for Injection USP; aqueous vehicles such as, but not limited to, Sodium Chloride Injection, Ringer's Injection, Dextrose Injection, Dextrose and Sodium Chloride Injection, and Lactated Ringer's Injection; water-miscible vehicles such as, but not limited to, ethyl alcohol, polyethylene glycol, and polypropylene glycol; and non-aqueous vehicles such as, but not limited to, corn oil, cottonseed oil, peanut oil, sesame oil, ethyl oleate, isopropyl myristate, and benzyl benzoate.

[00495] The present disclosure further encompasses anhydrous pharmaceutical compositions and dosage forms comprising an active ingredient, since water can facilitate the degradation of some compounds. For example, water can be added (*e.g.,* about 5%) in the pharmaceutical arts as a means of simulating long-term storage

in order to determine characteristics such as shelf-life or the stability of formulations over time. Anhydrous pharmaceutical compositions and dosage forms can be prepared using anhydrous or low moisture containing ingredients and low moisture or low humidity conditions. For example, pharmaceutical compositions and dosage forms which contain lactose can be made anhydrous if substantial contact with moisture and/or humidity during manufacturing, packaging, and/or storage is expected. An anhydrous pharmaceutical composition can be prepared and stored such that its anhydrous nature is maintained. Accordingly, anhydrous pharmaceutical compositions can be packaged using materials known to prevent exposure to water such that they can be included in suitable formulary kits. Examples of suitable packaging include, but are not limited to, hermetically sealed foils, plastic or the like, unit dose containers, blister packs, and strip packs.

Therapeutic Methods

[00496] Phosphoinositide 3-kinases (PI3Ks) are members of a conserved family of lipid kinases that regulate numerous cell functions, including proliferation, differentiation, cell survival and metabolism. Several classes of PI3Ks exist in mammalian cells, including Class IA subgroup (*e.g.*, PI3K-α, β, δ), which are generally activated by receptor tyrosine kinases (RTKs); Class IB (*e.g.*, PI3K-γ), which is activated by G-protein coupled receptors (GPCRs), among others. PI3Ks exert their biological activities via a "PI3K-mediated signaling pathway" that includes several components that directly and/or indirectly transduce a signal triggered by a PI3K, including the generation of second messenger phophotidylinositol, 3, 4, 5-triphosphate (PIP3) at the plasma membrane, activation of heterotrimeric G protein signaling, and generation of further second messengers such as cAMP, DAG, and IP3, all of which leads to an extensive cascade of protein kinase activation (reviewed in Vanhaesebroeck, B. *et al.* (2001) *Annu Rev Biochem.* 70:535-602). For example, PI3K-δ is activated by cellular receptors through interaction between the PI3K regulatory subunit (p85) SH2 domains, or through direct interaction with RAS. PIP3 produced by PI3K activates effector pathways downstream through interaction with plextrin homology (PH) domain containing enzymes (*e.g.*, PDK-1 and AKT [PKB]). (Fung-Leung WP. (2011) *Cell Signal.* 23(4):603-8). Unlike PI3K-δ, PI3K-γ is not associated with a regulatory subunit of the p85 family, but rather with a regulatory subunit in the p101 family. PI3K-γ is associated with GPCRs, and is responsible for the very rapid induction of PIP3. PI3K-γ can be also activated by RAS.

[00497] In some embodiments, provided herein are methods of modulating a PI3K kinase activity (*e.g.*, selectively modulating) by contacting the kinase with an effective amount of a compound, or a pharmaceutically acceptable form (*e.g.*, pharmaceutically acceptable salts, hydrates, solvates, isomers, prodrugs, and isotopically labeled derivatives) thereof, or pharmaceutical compositions as provided herein. Modulation can be inhibition (*e.g.*, reduction) or activation (*e.g.*, enhancement) of kinase activity. In some embodiments, provided herein are methods of inhibiting kinase activity by contacting the kinase with an effective amount of a compound as provided herein in solution. In some embodiments, provided herein are methods of inhibiting the kinase activity by contacting a cell, tissue, organ that express the kinase of interest with a compound provided herein. In some embodiments, provided herein are methods of inhibiting kinase activity in a subject by administering into the subject an effective amount of a compound as provided herein. In some embodiments, the kinase activity is inhibited (e.g., reduced) by more than

about 25%, 30%, 40%, 50%, 60%, 70%, 80%, or 90% when contacted with a compound provided herein as compared to the kinase activity without such contact. In some embodiments, provided herein are methods of inhibiting PI3 kinase activity in a subject (including mammals such as humans) by contacting said subject with an amount of a compound as provided herein sufficient to inhibit or reduce the activity of the PI3 kinase in said subject.

[00498] In some embodiments, the kinase is a lipid kinase or a protein kinase. In some embodiments, the kinase is selected from a PI3 kinase including different isoforms such as PI3 kinase α, PI3 kinase β, PI3 kinase γ, PI3 kinase δ; DNA-PK; mTor; Abl, VEGFR, Ephrin receptor B4 (EphB4); TEK receptor tyrosine kinase (TIE2); FMS-related tyrosine kinase 3 (FLT-3); Platelet derived growth factor receptor (PDGFR); RET; ATM; ATR; hSmg-1; Hck; Src; Epidermal growth factor receptor (EGFR); KIT; Inulsin Receptor (IR); and IGFR.

[00499] As used herein, a "PI3K-mediated disorder" refers to a disease or condition involving aberrant PI3K-mediated signaling pathway. In one embodiment, provided herein is a method of treating a PI3K mediated disorder in a subject, the method comprising administering a therapeutically effective amount of a compound or a pharmaceutical composition as provided herein. In some embodiments, provided herein is a method of treating a PI3K-δ or PI3K-γ mediated disorder in a subject, the method comprising administering a therapeutically effective amount of a compound or a pharmaceutical composition as provided herein. In some embodiments, provided herein is a method for inhibiting at least one of PI3K-δ and PI3K-γ, the method comprising contacting a cell expressing PI3K *in vitro* or *in vivo* with an effective amount of the compound or composition provided herein. PI3Ks have been associated with a wide range of conditions, including immunity, cancer and thrombosis (reviewed in Vanhaesebroeck, B. *et al.* (2010) *Current Topics in Microbiology and Immunology*, DOI 10.1007/82_2010_65). For example, Class I PI3Ks, particularly PI3K-γ and PI3K-δ isoforms, are highly expressed in leukocytes and have been associated with adaptive and innate immunity; thus, these PI3Ks are believed to be important mediators in inflammatory disorders and hematologic malignancies (reviewed in Harris, SJ et al. (2009) *Curr Opin Investig* Drugs 10(11):1151-62); Rommel C. et al. (2007) *Nat Rev Immunol* 7(3):191-201; Durand CA *et al.* (2009) *J Immunol.* 183(9):5673-84; Dil N, Marshall AJ. (2009) *Mol Immunol.* 46(10):1970-8; Al-Alwan MM *et al.* (2007) *J Immunol.* 178(4):2328-35; Zhang TT, *et al.* (2008) *J Allergy Clin Immunol.* 2008;122(4):811-819.e2; Srinivasan L, *et al.* (2009) *Cell* 139(3):573-86).

[00500] Numerous publications support roles of PI3K-δ, PI3K-γ, and PI3K-β in the differentiation, maintenance, and activation of immune and malignant cells, as described in more detail below.

[00501] The importance of PI3K-δ in the development and function of B-cells is supported from inhibitor studies and genetic models. PI3K-δ is an important mediator of B-cell receptor (BCR) signaling, and is upstream of AKT, calcium flux, PLCγ, MAP kinase, P70S6k, and FOXO3a activation. PI3K-δ is also important in IL4R, S1P, and CXCR5 signaling, and has been shown to modulate responses to toll-like receptors 4 and 9. Inhibitors of PI3K-δ have shown the importance of PI3K-δ in B-cell development (Marginal zone and B1 cells), B-cell activation, chemotaxis, migration and homing to lymphoid tissue, and in the control of immunoglobulin class switching leading to the production of IgE. Clayton E et al. (2002) *J Exp Med.* 196(6):753-63; Bilancio A, et al. (2006) *Blood* 107(2):642-50; Okkenhaug K. et al. (2002) *Science* 297(5583):1031-4; Al-Alwan MM *et al.* (2007) *J Immunol.*

178(4):2328-35; Zhang TT, *et al.* (2008) *J Allergy Clin Immunol.* 2008;122(4):811-819.e2; Srinivasan L, *et al.* (2009) *Cell* 139(3):573-86)

[00502] In T-cells, PI3K-δ has been demonstrated to have a role in T-cell receptor and cytokine signaling, and is upstream of AKT, PLCγ, and GSK3b. In PI3K-δ deletion or kinase-dead knock-in mice, or in inhibitor studies, T-cell defects including proliferation, activation, and differentiation have been observed, leading to reduced T helper cell 2 (TH2) response, memory T-cell specific defects (DTH reduction), defects in antigen dependent cellular trafficking, and defects in chemotaxis/migration to chemokines (*e.g.*, S1P, CCR7, CD62L). (Garçon F. *et al.* (2008) *Blood* 111(3):1464-71; Okkenhaug K *et al.* (2006). *J Immunol.* 177(8):5122-8; Soond DR, et al. (2010) *Blood* 115(11):2203-13; Reif K, (2004). J Immunol. 2004;173(4):2236-40; Ji H. *et al.* (2007) *Blood* 110(8):2940-7; Webb LM, et al. (2005) *J Immunol.* 175(5):2783-7; Liu D, *et al.* (2010) *J Immunol.* 184(6):3098-105; Haylock-Jacobs S, et al. (2011) *J Autoimmun.* 2011;36(3-4):278-87; Jarmin SJ, et al. (2008) *J Clin Invest.* 118(3):1154-64).

[00503] In neutrophils, PI3K-δ along with PI3K-γ, and PI3K-β, contribute to the responses to immune complexes, FCγRII signaling, including migration and neutrophil respiratory burst. Human neutrophils undergo rapid induction of PIP3 in response to formyl peptide receptor (FMLP) or complement component C5a (C5a) in a PI3K-γ dependent manner, followed by a longer PIP3 production period that is PI3K-δ dependent, and is essential for respiratory burst. The response to immune complexes is contributed by PI3K-δ, PI3K-γ, and PI3K-β, and is an important mediator of tissue damage in models of autoimmune disease (Randis TM *et al.* (2008) *Eur J Immunol.* 38(5):1215-24; Pinho V, (2007) *J Immunol.* 179(11):7891-8; Sadhu C. *et al.* (2003) *J Immunol.* 170(5):2647-54 ; Condliffe AM et al. (2005) *Blood* 106(4):1432-40). It has been reported that in certain autoimmune diseases, perfrential activation of PI3Kβ may be involved. (Kulkarni *et al*., *Immunology* (2011) 4(168) ra23: 1-11). It was also reported that PI3Kβ-deficient mice were highly protected in an FcγR-dependent model of autoantibody-induced skin blistering and partially protected in an FcγR-dependent model of inflammatory arthritis, whereas combined deficiency of PI3Kβ and PI3Kδ resulted in near complete protection in inflammatory arthritis. (*Id.*).

[00504] In macrophages collected from patients with chronic obstructive pulmonary disease (COPD), glucocorticoid responsiveness can be restored by treatment of the cells with inhibitors of PI3K-δ. Macrophages also rely on PI3K-δ and PI3K-γ for responses to immune complexes through the arthus reaction (FCgR and C5a signaling) (Randis TM, et al. (2008) *Eur J Immunol.* 38(5):1215-24 ; Marwick JA et al. (2009) *Am J Respir Crit Care Med.* 179(7):542-8; Konrad S, *et al.* (2008) *J Biol Chem.* 283(48):33296-303).

[00505] In mast cells, stem cell factor- (SCF) and IL3-dependent proliferation, differentiation and function are PI3K-δ dependent, as is chemotaxis. The allergen/IgE crosslinking of FCgR1 resulting in cytokine release and degranulation of the mast cells is severely inhibited by treatment with PI3K-δ inhibitors, suggesting a role for PI3K-δ in allergic disease (Ali K *et al.* (2004) *Nature* 431(7011):1007-11; Lee KS, *et al.* (2006) *FASEB J.* 20(3):455-65; Kim MS, *et al.* (2008) *Trends Immunol.* 29(10):493-501).

[00506] Natural killer (NK) cells are dependent on both PI3K-δ and PI3K-γ for efficient migration towards chemokines including CXCL10, CCL3, S1P and CXCL12, or in response to LPS in the peritoneum (Guo H, et al. (2008) *J Exp Med.* 205(10):2419-35; Tassi I, et al. (2007) *Immunity* 27(2):214-27; Saudemont A, (2009) *Proc Natl Acad Sci U S A.* 106(14):5795-800; Kim N, *et al.* (2007) *Blood* 110(9):3202-8).

[00507] The roles of PI3K-δ, PI3K-γ, and PI3K-β in the differentiation, maintenance, and activation of immune cells support a role for these enzymes in inflammatory disorders ranging from autoimmune diseases (*e.g.*, rheumatoid arthritis, multiple sclerosis) to allergic inflammatory disorders, such as asthma, and inflammatory respiratory disease such as COPD. Extensive evidence is available in experimental animal models, or can be evaluated using art-recognized animal models. In an embodiment, described herein is a method of treating inflammatory disorders ranging from autoimmune diseases (*e.g.*, rheumatoid arthritis, multiple sclerosis) to allergic inflammatory disorders, such as asthma and COPD using a compound described herein.

[00508] For example, inhibitors of PI3K-δ and/or -γ have been shown to have anti-inflammatory activity in several autoimmune animal models for rheumatoid arthritis (Williams, O. et al. (2010) Chem Biol, 17(2):123-34; WO 2009/088986; WO2009/088880; WO 2011/008302). PI3K-δ is expressed in the RA synovial tissue (especially in the synovial lining which contains fibroblast-like synoviocytes (FLS), and selective PI3K-δ inhibitors have been shown to be effective in inhibiting synoviocyte growth and survival (Bartok *et al.* (2010) *Arthritis Rheum* 62 Suppl 10:362). Several PI3K-δ and -γ inhibitors have been shown to ameliorate arthritic symptoms (*e.g.*, swelling of joints, reduction of serum-induced collagen levels, reduction of joint pathology and/or inflammation), in art-recognized models for RA, such as collagen-induced arthritis and adjuvant induced arthritis (WO 2009/088986; WO2009/088880; WO 2011/008302).

[00509] The role of PI3K-δ has also been shown in models of T-cell dependent response, including the DTH model. In the murine experimental autoimmune encephalomyelitis (EAE) model of multiple sclerosis, the PI3K-γ/δ- double mutant mice are resistant. PI3K-δ inhibitors have also been shown to block EAE disease induction and development of TH-17 cells both *in vitro* and *in vivo* (Haylock-Jacobs, S. *et al.* (2011) *J. Autoimmunity* 36(3-4):278-87).

[00510] Systemic lupus erythematosus (SLE) is a complex disease that at different stages requires memory T-cells, B-cell polyclonal expansion and differentiation into plasma cells, and the innate immune reasponse to endogenous damage associated molecular pattern molecules (DAMPS), and the inflammatory responses to immune complexes through the complement system as well as the F_C receptors. The role of PI3K-δ and PI3K-γ together in these pathways and cell types suggest that blockade with an inhibitor would be effective in these diseases. A role for PI3K in lupus is also predicted by two genetic models of lupus. The deletion of phosphatase and tensin homolog (PTEN) leads to a lupus-like phenotype, as does a transgenic activation of Class1A PI3Ks, which includes PI3K-δ. The deletion of PI3K-γ in the transgenically activated class 1A lupus model is protective, and treatment with a PI3K-γ selective inhibitor in the murine MLR/*lpr* model of lupus improves symptoms (Barber, DF *et al.* (2006) *J. Immunol.* 176(1): 589-93).

[00511] In allergic disease, PI3K-δ has been shown by genetic models and by inhibitor treatment to be essential for mast-cell activation in a passive cutaneous anaphalaxis assay (Ali K *et al.* (2008) *J Immunol.* 180(4):2538-44; Ali K, (2004) *Nature* 431(7011):1007-11). In a pulmonary measure of response to immune complexes (Arthus reaction) a PI3K-δ knockout is resistant, showing a defect in macrophage activation and C5a production. Knockout studies and studies with inhibitors for both PI3K-δ and PI3K-γ support a role for both of these enzymes in the ovalbumin induced allergic airway inflammation and hyper-responsiveness model (Lee KS *et*

al. (2006) *FASEB J*. 20(3):455-65). Reductions of infiltration of eosinophils, neutrophils, and lymphocytes as well as TH2 cytokines (IL4, IL5, and IL13) were seen with both PI3K-δ specific and dual PI3K-δ and PI3K-γ inhibitors in the Ova induced asthma model (Lee KS et al. (2006) *J Allergy Clin Immunol* 118(2):403-9).

[00512] PI3K-δ and PI3K-γ inhibition can be used in treating COPD. In the smoked mouse model of COPD, the PI3K-δ knockout does not develop smoke induced glucocorticoid resistance, while wild-type and PI3K-γ knockout mice do. An inhaled formulation of dual PI3K-δ and PI3K-γ inhibitor blocked inflammation in a LPS or smoke COPD models as measured by neutrophilia and glucocorticoid resistance (Doukas J, et al. (2009*) J Pharmacol Exp Ther*. 328(3):758-65).

[00513] Class I PI3Ks, particularly PI3K-δ and PI3K-γ isoforms, are also associated with cancers (reviewed, *e.g.*, in Vogt, PK et al. (2010) Curr Top Microbiol Immunol. 347:79-104; Fresno Vara, JA et al. (2004) *Cancer Treat Rev*. 30(2):193-204; Zhao, L and Vogt, PK. (2008) Oncogene 27(41):5486-96). Inhibitors of PI3K, *e.g.*, PI3K-δ and/or -γ, have been shown to have anti-cancer activity (*e.g.*, Courtney, KD et al. (2010) *J Clin Oncol*. 28(6):1075-1083); Markman, B et al. (2010) Ann Oncol. 21(4):683-91; Kong, D and Yamori, T (2009) Curr Med Chem. 16(22):2839-54; Jimeno, A et al. (2009) J Clin Oncol. 27:156s (suppl; abstr 3542); Flinn, IW et al. (2009) *J Clin Oncol*. 27:156s (suppl; abstr 3543); Shapiro, G et al. (2009) J Clin Oncol. 27:146s (suppl; abstr 3500); Wagner, AJ et al. (2009) *J Clin Oncol*. 27:146s (suppl; abstr 3501); Vogt, PK et al. (2006) Virology 344(1):131-8; Ward, S et al. (2003) *Chem Biol*. 10(3):207-13; WO 2011/041399; US 2010/0029693; US 2010/0305096; US 2010/0305084). In an embodiment, described herein is a method of treating cancer.

[00514] Types of cancer that can be treated with an inhibitor of PI3K (particularly, PI3K-δ and/or -γ) include, *e.g.*, leukemia, chronic lymphocytic leukemia, acute myeloid leukemia, chronic myeloid leukemia (*e.g.*, Salmena, L et al. (2008) *Cell* 133:403-414; Chapuis, N et al. (2010) *Clin Cancer Res*. 16(22):5424-35; Khwaja, A (2010) *Curr Top Microbiol Immunol.* 347:169-88); lymphoma, *e.g.*, non-Hodgkin's lymphoma (*e.g.,* Salmena, L et al. (2008) *Cell* 133:403-414); lung cancer, *e.g.*, non-small cell lung cancer, small cell lung cancer (*e.g.*, Herrera, VA et al. (2011) *Anticancer Res*. 31(3):849-54); melanoma (*e.g.*, Haluska, F et al. (2007) *Semin Oncol*. 34(6):546-54); prostate cancer (*e.g.*, Sarker, D et al. (2009) *Clin Cancer Res*. 15(15):4799-805); glioblastoma (*e.g.*, Chen, JS et al. (2008) Mol Cancer Ther. 7:841-850); endometrial cancer (*e.g.*, Bansal, N et al. (2009) Cancer Control. 16(1):8-13); pancreatic cancer (*e.g.*, Furukawa, T (2008) *J Gastroenterol*. 43(12):905-11); renal cell carcinoma (*e.g.*, Porta, C and Figlin, RA (2009) *J Urol*. 182(6):2569-77); colorectal cancer (*e.g.*, Saif, MW and Chu, E (2010) Cancer J. 16(3):196-201); breast cancer (*e.g.*, Torbett, NE et al. (2008) *Biochem J*. 415:97-100); thyroid cancer (*e.g.*, Brzezianska, E and Pastuszak-Lewandoska, D (2011) *Front Biosci*. 16:422-39); and ovarian cancer (*e.g.*, Mazzoletti, M and Broggini, M (2010) *Curr Med Chem.* 17(36):4433-47).

[00515] Numerous publications support a role of PI3K-δ and PI3K-γ in treating hematological cancers. PI3K-δ and PI3K-γ are highly expressed in the heme compartment, and some solid tumors, including prostate, breast and glioblastomas (Chen J.S. *et al.* (2008) *Mol Cancer Ther.* 7(4):841-50; Ikeda H. *et al.* (2010) *Blood* 116(9):1460-8).

[00516] In hematological cancers including acute myeloid leukemia (AML), multiple myeloma (MM), and chronic lymphocytic leukemia (CLL), overexpression and constitutive activation of PI3K-δ supports the model that

PI3K-δ inhibition would be therapeutic Billottet C, et al. (2006) *Oncogene* 25(50):6648-59; Billottet C, et al. (2009) *Cancer Res.* 69(3):1027-36; Meadows, SA, 52nd Annual ASH Meeting and Exposition; 2010 Dec 4-7; Orlando, FL; Ikeda H, et al. (2010) *Blood* 116(9):1460-8; Herman SE *et al.* (2010) *Blood* 116(12):2078-88; Herman SE *et al.* (2011). *Blood* 117(16):4323-7. In an embodiment, described herein is a method of treating hematological cancers including, but not limited to acute myeloid leukemia (AML), multiple myeloma (MM), and chronic lymphocytic leukemia (CLL).

[00517] A PI3K-δ inhibitor (CAL-101) has been evaluated in a phase 1 trial in patients with haematological malignancies, and showed activity in CLL in patients with poor prognostic characteristics. In CLL, inhibition of PI3K-δ not only affects tumor cells directly, but it also affects the ability of the tumor cells to interact with their microenvironment. This microenvironment includes contact with and factors from stromal cells, T-cells, nurse like cells, as well as other tumor cells. CAL-101 suppresses the expression of stromal and T-cell derived factors including CCL3, CCL4, and CXCL13, as well as the CLL tumor cells' ability to respond to these factors. CAL-101 treatment in CLL patients induces rapid lymph node reduction and redistribution of lymphocytes into the circulation, and affects tonic survival signals through the BCR, leading to reduced cell viability, and an increase in apoptosis. Single agent CAL-101 treatment was also active in mantle cell lymphoma and refractory non Hodgkin's lymphoma (Furman, RR, et al. 52nd Annual ASH Meeting and Exposition; 2010 Dec 4-7; Orlando, FL; Hoellenriegel, J, et al. 52nd Annual ASH Meeting and Exposition; 2010 Dec 4-7; Orlando, FL; Webb, HK, et al. 52nd Annual ASH Meeting and Exposition; 2010 Dec 4-7; Orlando, FL; Meadows, et al. 52nd Annual ASH Meeting and Exposition; 2010 Dec 4-7; Orlando, FL; Kahl, B, et al. 52nd Annual ASH Meeting and Exposition; 2010 Dec 4-7; Orlando, FL; Lannutti BJ, et al. (2011) *Blood* 117(2):591-4).

[00518] PI3K-δ inhibitors have shown activity against PI3K-δ positive gliomas *in vitro* (Kashishian A, *et al.* Poster presented at: The American Association of Cancer Research 102nd Annual Meeting; 2011 Apr 2-6; Orlando, FL). PI3K-δ is the PI3K isoform that is most commonly activated in tumors where the PTEN tumor suppressor is mutated (Ward S, et al. (2003) *Chem Biol.* 10(3):207-13). In this subset of tumors, treatment with the PI3K-δ inhibitor either alone or in combination with a cytotoxic agent can be effective.

[00519] Another mechanism for PI3K-δ inhibitors to have an affect in solid tumors involves the tumor cells' interaction with their micro-environment. PI3K-δ, PI3K-γ, and PI3K-β are expressed in the immune cells that infiltrate tumors, including tumor infiltrating lymphocytes, macrophages, and neutrophils. PI3K-δ inhibitors can modify the function of these tumor-associated immune cells and how they respond to signals from the stroma, the tumor, and each other, and in this way affect tumor cells and metastasis (Hoellenriegel, J, *et al.* 52nd Annual ASH Meeting and Exposition; 2010 Dec 4-7; Orlando, FL).

[00520] PI3K-δ is also expressed in endothelial cells. It has been shown that tumors in mice treated with PI3K-δ selective inhibitors are killed more readily by radiation therapy. In this same study, capillary network formation is impaired by the PI3K inhibitor, and it is postulated that this defect contributes to the greater killing with radiation. PI3K-δ inhibitors can affect the way in which tumors interact with their microenviroment, including stromal cells, immune cells, and endothelial cells and be therapeutic either on its own or in conjunction with another

therapy (Meadows, SA, *et al.* Paper presented at: 52[nd] Annual ASH Meeting and Exposition; 2010 Dec 4-7; Orlando, FL; Geng L, et al. (2004) *Cancer Res.* 64(14):4893-9).

[00521] In other embodiments, inhibition of PI3K (such as PI3K-δ and/or –γ) can be used to treat a neuropsychiatric disorder, *e.g.*, an autoimmune brain disorder. Infectious and immune factors have been implicated in the pathogenesis of several neuropsychiatric disorders, including, but not limited to, Sydenham's chorea (SC) (Garvey, M.A. *et al.* (2005) *J. Child Neurol.* 20:424-429), Tourette's syndrome (TS), obsessive compulsive disorder (OCD) (Asbahr, F.R. *et al.* (1998) *Am. J. Psychiatry* 155:1122-1124), attention deficit/hyperactivity disorder (AD/HD) (Hirschtritt, M.E. *et al.* (2008) *Child Neuropsychol.* 1:1-16; Peterson, B.S. *et al.* (2000) *Arch. Gen. Psychiatry* 57:364-372), anorexia nervosa (Sokol, M.S. (2000) *J. Child Adolesc. Psychopharmacol.* 10:133-145; Sokol, M.S. *et al.* (2002) *Am. J. Psychiatry* 159:1430-1432), depression (Leslie, D.L. *et al.* (2008) *J. Am. Acad. Child Adolesc. Psychiatry* 47:1166-1172), and autism spectrum disorders (ASD) (Hollander, E. *et al.* (1999) *Am. J. Psychiatry* 156:317-320; Margutti, P. *et al.* (2006) *Curr. Neurovasc. Res.* 3:149-157). A subset of childhood obsessive compulsive disorders and tic disorders has been grouped as Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococci (PANDAS). PANDAS disorders provide an example of disorders where the onset and exacerbation of neuropsychiatric symptoms is preceded by a streptococcal infection (Kurlan, R., Kaplan, E.L. (2004) *Pediatrics* 113:883-886; Garvey, M.A. *et al.* (1998) *J. Clin. Neurol.* 13:413-423). Many of the PANDAS disorders share a common mechanism of action resulting from antibody responses against streptococcal associated epitopes, such as GlcNAc, which produces neurological effects (Kirvan. C.A. *et al.* (2006) *J. Neuroimmunol.* 179:173-179). Autoantibodies recognizing central nervous system (CNS) epitopes are also found in sera of most PANDAS subjects (Yaddanapudi, K. *et al.* (2010) *Mol. Psychiatry* 15:712-726). Thus, several neuropsychiatric disorders have been associated with immune and autoimmune components, making them suitable for therapies that include PI3K-δ and/or –γ inhibition.

[00522] In certain embodiments, a method of treating (*e.g.*, reducing or ameliorating one or more symptoms of) a neuropsychiatric disorder, (*e.g.*, an autoimmune brain disorder), using a PI3K-δ and/or –γ inhibitor is described, alone or in combination therapy. For example, one or more PI3K-δ and/or –γ inhibitors described herein can be used alone or in combination with any suitable therapeutic agent and/or modalities, *e.g.*, dietary supplement, for treatment of neuropsychiatric disorders. Exemplary neuropsychiatric disorders that can be treated with the PI3K-δ and/or –γ inhibitors described herein include, but are not limited to, PANDAS disorders, Sydenham's chorea, Tourette's syndrome, obsessive compulsive disorder, attention deficit/hyperactivity disorder, anorexia nervosa, depression, and autism spectrum disorders. Pervasive Developmental Disorder (PDD) is an exemplary class of autism spectrum disorders that includes Autistic Disorder, Asperger's Disorder, Childhood Disintegrative Disorder (CDD), Rett's Disorder and PDD-Not Otherwise Specified (PDD-NOS). Animal models for evaluating the activity of the PI3K-δ and/or –γ inhibitor are known in the art. For example, a mouse model of PANDAS disorders is described in, *e.g.*, Yaddanapudi, K. *et al.* (2010) *supra*; and Hoffman, K.I. et al. (2004) *J. Neurosci.* 24:1780-1791.

[00523] In some embodiments, provided herein are methods of using the compounds, or a pharmaceutically acceptable form (*e.g.*, pharmaceutically acceptable salts, hydrates, solvates, isomers, prodrugs, and

isotopically labeled derivatives) thereof, or pharmaceutical compositions as provided herein to treat disease conditions, including, but not limited to, diseases associated with malfunctioning of one or more types of PI3 kinase. A detailed description of conditions and disorders mediated by p110δ kinase activity is set forth in Sadu et al., WO 01/81346, which is incorporated herein by reference in its entirety for all purposes.

[00524] In some embodiments, the disclosure relates to a method of treating a hyperproliferative disorder in a subject that comprises administering to said subject a therapeutically effective amount of a compound, or a pharmaceutically acceptable form (*e.g.,* pharmaceutically acceptable salts, hydrates, solvates, isomers, prodrugs, and isotopically labeled derivatives) thereof, or pharmaceutical compositions as provided herein. In some embodiments, said method relates to the treatment of cancer such as acute myeloid leukemia, thymus, brain, lung, squamous cell, skin, eye, retinoblastoma, intraocular melanoma, oral cavity and oropharyngeal, bladder, gastric, stomach, pancreatic, bladder, breast, cervical, head, neck, renal, kidney, liver, ovarian, prostate, colorectal, esophageal, testicular, gynecological, thyroid, CNS, PNS, AIDS-related (*e.g.,* Lymphoma and Kaposi's Sarcoma) or viral-induced cancer. In some embodiments, said method relates to the treatment of a non-cancerous hyperproli*ferat*ive disorder such as benign hyperplasia of the skin (e. g., psoriasis), restenosis, or prostate (e. g., benign prostatic hypertrophy (BPH)).

[00525] Patients that can be treated with compounds, or a pharmaceutically acceptable form (*e.g.,* pharmaceutically acceptable salts, hydrates, solvates, isomers, prodrugs, and isotopically labeled derivatives) thereof, or pharmaceutical compositions as provided herein, according to the methods as provided herein include, for example, but not limited to, patients that have been diagnosed as having psoriasis; restenosis; atherosclerosis; BPH; breast cancer such as a ductal carcinoma in duct tissue in a mammary gland, medullary carcinomas, colloid carcinomas, tubular carcinomas, and inflammatory breast cancer; ovarian cancer, including epithelial ovarian tumors such as adenocarcinoma in the ovary and an adenocarcinoma that has migrated from the ovary into the abdominal cavity; uterine cancer; cervical cancer such as adenocarcinoma in the cervix epithelial including squamous cell carcinoma and adenocarcinomas; prostate cancer, such as a prostate cancer selected from the following: an adenocarcinoma or an adenocarinoma that has migrated to the bone; pancreatic cancer such as epitheliod carcinoma in the pancreatic duct tissue and an adenocarcinoma in a pancreatic duct; bladder cancer such as a transitional cell carcinoma in urinary bladder, urothelial carcinomas (transitional cell carcinomas), tumors in the urothelial cells that line the bladder, squamous cell carcinomas, adenocarcinomas, and small cell cancers; leukemia such as acute myeloid leukemia (AML), acute lymphocytic leukemia, chronic lymphocytic leukemia, chronic myeloid leukemia, hairy cell leukemia, myelodysplasia, myeloproliferative disorders, NK cell leukemia (*e.g.*, blastic plasmacytoid dendritic cell neoplasm), acute myelogenous leukemia (AML), chronic myelogenous leukemia (CML), mastocytosis, chronic lymphocytic leukemia (CLL), multiple myeloma (MM), and myelodysplastic syndrome (MDS); bone cancer; lung cancer such as non-small cell lung cancer (NSCLC), which is divided into squamous cell carcinomas, adenocarcinomas, and large cell undifferentiated carcinomas, and small cell lung cancer; skin cancer such as basal cell carcinoma, melanoma, squamous cell carcinoma and actinic keratosis, which is a skin condition that sometimes develops into squamous cell carcinoma; eye retinoblastoma; cutaneous or intraocular (eye) melanoma; primary liver cancer (cancer that begins in the liver); kidney cancer; thyroid cancer such as papillary,

follicular, medullary and anaplastic; lymphoma such as diffuse large B-cell lymphoma, B-cell immunoblastic lymphoma, NK cell lymphoma (*e.g.*, blastic plasmacytoid dendritic cell neoplasm), and small non-cleaved cell lymphoma; Kaposi's Sarcoma; viral-induced cancers including hepatitis B virus (HBV), hepatitis C virus (HCV), and hepatocellular carcinoma; human lymphotropic virus-type 1 (HTLV-1) and adult T-cell leukemia/lymphoma; and human papilloma virus (HPV) and cervical cancer; central nervous system cancers (CNS) such as primary brain tumor, which includes gliomas (astrocytoma, anaplastic astrocytoma, or glioblastoma multiforme), Oligodendroglioma, Ependymoma, Meningioma, Lymphoma, Schwannoma, and Medulloblastoma; peripheral nervous system (PNS) cancers such as acoustic neuromas and malignant peripheral nerve sheath tumor (MPNST) including neurofibromas and schwannomas, malignant fibrous cytoma, malignant fibrous histiocytoma, malignant meningioma, malignant mesothelioma, and malignant mixed Müllerian tumor; oral cavity and oropharyngeal cancer such as, hypopharyngeal cancer, laryngeal cancer, nasopharyngeal cancer, and oropharyngeal cancer; stomach cancer such as lymphomas, gastric stromal tumors, and carcinoid tumors; testicular cancer such as germ cell tumors (GCTs), which include seminomas and nonseminomas, and gonadal stromal tumors, which include Leydig cell tumors and Sertoli cell tumors; thymus cancer such as to thymomas, thymic carcinomas, Hodgkin disease, non-Hodgkin lymphomas carcinoids or carcinoid tumors; rectal cancer; and colon cancer.

[00526] In one embodiment, provided herein is a method of treating an inflammation disorder, including autoimmune diseases in a subject. The method comprises administering to said subject a therapeutically effective amount of a compound, or a pharmaceutically acceptable form (*e.g.,* pharmaceutically acceptable salts, hydrates, solvates, isomers, prodrugs, and isotopically labeled derivatives) thereof, or pharmaceutical compositions as provided herein. Examples of autoimmune diseases includes but is not limited to acute disseminated encephalomyelitis (ADEM), Addison's disease, antiphospholipid antibody syndrome (APS), aplastic anemia, autoimmune hepatitis, autoimmune skin disease, coeliac disease, Crohn's disease, Diabetes mellitus (type 1), Goodpasture's syndrome, Graves' disease, Guillain-Barré syndrome (GBS), Hashimoto's disease, lupus erythematosus, multiple sclerosis, myasthenia gravis, opsoclonus myoclonus syndrome (OMS), optic neuritis, Ord's thyroiditis, oemphigus, polyarthritis, primary biliary cirrhosis, psoriasis, rheumatoid arthritis, Reiter's syndrome, Takayasu's arteritis, temporal arteritis (also known as "giant cell arteritis"), warm autoimmune hemolytic anemia, Wegener's granulomatosis, alopecia universalis (*e.g.*, inflammatory alopecia), Chagas disease, chronic fatigue syndrome, dysautonomia, endometriosis, hidradenitis suppurativa, interstitial cystitis, neuromyotonia, sarcoidosis, scleroderma, ulcerative colitis, vitiligo, and vulvodynia. Other disorders include bone-resorption disorders and thrombosis.

[00527] Inflammation takes on many forms and includes, but is not limited to, acute, adhesive, atrophic, catarrhal, chronic, cirrhotic, diffuse, disseminated, exudative, fibrinous, fibrosing, focal, granulomatous, hyperplastic, hypertrophic, interstitial, metastatic, necrotic, obliterative, parenchymatous, plastic, productive, proliferous, pseudomembranous, purulent, sclerosing, seroplastic, serous, simple, specific, subacute, suppurative, toxic, traumatic, and/or ulcerative inflammation.

[00528] Exemplary inflammatory conditions include, but are not limited to, inflammation associated with acne, anemia (*e.g.*, aplastic anemia, haemolytic autoimmune anaemia), asthma, arteritis (*e.g.*, polyarteritis,

temporal arteritis, periarteritis nodosa, Takayasu's arteritis), arthritis (*e.g.*, crystalline arthritis, osteoarthritis, psoriatic arthritis, gout flare, gouty arthritis, reactive arthritis, rheumatoid arthritis and Reiter's arthritis), ankylosing spondylitis, amylosis, amyotrophic lateral sclerosis, autoimmune diseases, allergies or allergic reactions, atherosclerosis, bronchitis, bursitis, chronic prostatitis, conjunctivitis, Chagas disease, chronic obstructive pulmonary disease, cermatomyositis, diverticulitis, diabetes (*e.g.*, type I diabetes mellitus, type 2 diabetes mellitus), a skin condition (*e.g.*, psoriasis, eczema, burns, dermatitis, pruritus (itch)), endometriosis, Guillain-Barre syndrome, infection, ischaemic heart disease, Kawasaki disease, glomerulonephritis, gingivitis, hypersensitivity, headaches (*e.g.*, migraine headaches, tension headaches), ileus (*e.g.*, postoperative ileus and ileus during sepsis), idiopathic thrombocytopenic purpura, interstitial cystitis (painful bladder syndrome), gastrointestinal disorder (*e.g.*, selected from peptic ulcers, regional enteritis, diverticulitis, gastrointestinal bleeding, eosinophilic gastrointestinal disorders (*e.g.*, eosinophilic esophagitis, eosinophilic gastritis, eosinophilic gastroenteritis, eosinophilic colitis), gastritis, diarrhea, gastroesophageal reflux disease (GORD, or its synonym GERD), inflammatory bowel disease (IBD) (*e.g.*, Crohn's disease, ulcerative colitis, collagenous colitis, lymphocytic colitis, ischaemic colitis, diversion colitis, Behcet's syndrome, indeterminate colitis) and inflammatory bowel syndrome (IBS)), lupus, multiple sclerosis, morphea, myeasthenia gravis, myocardial ischemia, nephrotic syndrome, pemphigus vulgaris, pernicious aneaemia, peptic ulcers, polymyositis, primary biliary cirrhosis, neuroinflammation associated with brain disorders (*e.g.*, Parkinson's disease, Huntington's disease, and Alzheimer's disease), prostatitis, chronic inflammation associated with cranial radiation injury, pelvic inflammatory disease, polymyalgia rheumatic, reperfusion injury, regional enteritis, rheumatic fever, systemic lupus erythematosus, scleroderma, scierodoma, sarcoidosis, spondyloarthopathies, Sjogren's syndrome, thyroiditis, transplantation rejection, tendonitis, trauma or injury (*e.g.*, frostbite, chemical irritants, toxins, scarring, burns, physical injury), vasculitis, vitiligo and Wegener's granulomatosis. In certain embodiments, the inflammatory disorder is selected from arthritis (*e.g.*, rheumatoid arthritis), inflammatory bowel disease, inflammatory bowel syndrome, asthma, psoriasis, endometriosis, interstitial cystitis and prostatistis. In certain embodiments, the inflammatory condition is an acute inflammatory condition (*e.g.*, for example, inflammation resulting from infection). In certain embodiments, the inflammatory condition is a chronic inflammatory condition (*e.g.*, conditions resulting from asthma, arthritis and inflammatory bowel disease). The compounds can also be useful in treating inflammation associated with trauma and non-inflammatory myalgia.

[00529] Immune disorders, such as auto-immune disorders, include, but are not limited to, arthritis (including rheumatoid arthritis, spondyloarthopathies, gouty arthritis, degenerative joint diseases such as osteoarthritis, systemic lupus erythematosus, Sjogren's syndrome, ankylosing spondylitis, undifferentiated spondylitis, Behcet's disease, haemolytic autoimmune anaemias, multiple sclerosis, amyotrophic lateral sclerosis, amylosis, acute painful shoulder, psoriatic, and juvenile arthritis), asthma, atherosclerosis, osteoporosis, bronchitis, tendonitis, bursitis, skin condition (*e.g.*, psoriasis, eczema, burns, dermatitis, pruritus (itch)), enuresis, eosinophilic disease, gastrointestinal disorder (*e.g.*, selected from peptic ulcers, regional enteritis, diverticulitis, gastrointestinal bleeding, eosinophilic gastrointestinal disorders (*e.g.*, eosinophilic esophagitis, eosinophilic gastritis, eosinophilic gastroenteritis, eosinophilic colitis), gastritis, diarrhea, gastroesophageal reflux disease (GORD, or its synonym GERD), inflammatory bowel disease (IBD) (*e.g.*, Crohn's disease, ulcerative colitis, collagenous colitis,

lymphocytic colitis, ischaemic colitis, diversion colitis, Behcet's syndrome, indeterminate colitis) and inflammatory bowel syndrome (IBS)), relapsing polychondritis (*e.g.*, atrophic polychondritis and systemic polychondromalacia), and disorders ameliorated by a gastroprokinetic agent (*e.g.*, ileus, postoperative ileus and ileus during sepsis; gastroesophageal reflux disease (GORD, or its synonym GERD); eosinophilic esophagitis, gastroparesis such as diabetic gastroparesis; food intolerances and food allergies and other functional bowel disorders, such as non-ulcerative dyspepsia (NUD) and non-cardiac chest pain (NCCP, including costo-chondritis)). In certain embodiments, a method of treating inflammatory or autoimmune diseases is provided comprising administering to a subject (*e.g., a* mammal) a therapeutically effective amount of a compound, or a pharmaceutically acceptable form (*e.g.,* pharmaceutically acceptable salts, hydrates, solvates, isomers, prodrugs, and isotopically labeled derivatives) thereof, or pharmaceutical compositions as provided herein, that selectively inhibit PI3K-δ and/or PI3K-γ as compared to all other type I PI3 kinases.

[00530] Such selective inhibition of PI3K-δ and/or PI3K-γ can be advantageous for treating any of the diseases or conditions described herein. For example, selective inhibition of PI3K-δ can inhibit inflammatory responses associated with inflammatory diseases, autoimmune disease, or diseases related to an undesirable immune response including, but not limited to asthma, emphysema, allergy, dermatitis, rheumatoid arthritis, psoriasis, lupus erythematosus, anaphylaxsis, or graft versus host disease. Selective inhibition of PI3K-δ can further provide for a reduction in the inflammatory or undesirable immune response without a concomittant reduction in the ability to reduce a bacterial, viral, and/or fungal infection. Selective inhibition of both PI3K-δ and PI3K-γ can be advantageous for inhibiting the inflammatory response in the subject to a greater degree than that would be provided for by inhibitors that selectively inhibit PI3K -δ or PI3K-γ alone. In one aspect, one or more of the subject methods are effective in reducing antigen specific antibody production *in vivo b*y about 2-fold, 3-fold, 4-fold, 5-fold, 7.5-fold, 10-fold, 25-fold, 50-fold, 100-fold, 250-fold, 500-fold, 750-fold, or about 1000-fold or more. In another aspect, one or more of the subject methods are effective in reducing antigen specific IgG3 and/or IgGM production *in vivo by* about 2-fold, 3-fold, 4-fold, 5-fold, 7.5-fold, 10-fold, 25-fold, 50-fold, 100-fold, 250-fold, 500-fold, 750-fold, or about 1000-fold or more.

[00531] In one aspect, one of more of the subject methods are effective in ameliorating symptoms associated with rheumatoid arthritis including, but not limited to a reduction in the swelling of joints, a reduction in serum anti-collagen levels, and/or a reduction in joint pathology such as bone resorption, cartilage damage, pannus, and/or inflammation. In another aspect, the subject methods are effective in reducing ankle inflammation by at least about 2%, 5%, 10%, 15%, 20%, 25%, 30%, 50%, 60%, or about 75% to 90%. In another aspect, the subject methods are effective in reducing knee inflammation by at least about 2%, 5%, 10%, 15%, 20%, 25%, 30%, 50%, 60%, or about 75% to 90% or more. In still another aspect, the subject methods are effective in reducing serum anti-type II collagen levels by at least about 10%, 12%, 15%, 20%, 24%, 25%, 30%, 35%, 50%, 60%, 75%, 80%, 86%, 87%, or about 90% or more. In another aspect, the subject methods are effective in reducing ankle histopathology scores by about 5%, 10%, 15%, 20%, 25%, 30%, 40%, 50%, 60%, 75%, 80%, 90% or more. In still another aspect, the subject methods are effective in reducing knee histopathology scores by about 5%, 10%, 15%, 20%, 25%, 30%, 40%, 50%, 60%, 75%, 80%, 90% or more.

[00532] In some embodiments, provided herein are methods for treating disorders or conditions in which the δ isoform of PI3K is implicated to a greater extent than other PI3K isoforms such as PI3K-α and/or -β. Selective inhibition of PI3K-δ and/or PI3K-γ can provide advantages over using less selective compounds which inhibit PI3K-α and/or -β, such as an improved side effects profile or lessened reduction in the ability to reduce a bacterial, viral, and/or fungal infection.

[00533] In other embodiments, provided herein are methods of using a compound, or a pharmaceutically acceptable form (*e.g.*, pharmaceutically acceptable salts, hydrates, solvates, isomers, prodrugs, and isotopically labeled derivatives) thereof, or pharmaceutical compositions as provided herein, to treat respiratory diseases including, but not limited to diseases affecting the lobes of lung, pleural cavity, bronchial tubes, trachea, upper respiratory tract, or the nerves and muscle for breathing. For example, methods are provided to treat obstructive pulmonary disease. Chronic obstructive pulmonary disease (COPD) is an umbrella term for a group of respiratory tract diseases that are characterized by airflow obstruction or limitation. Conditions included in this umbrella term include, but are not limited to: chronic bronchitis, emphysema, and bronchiectasis.

[00534] In another embodiment, the compounds, or a pharmaceutically acceptable form (*e.g.*, pharmaceutically acceptable salts, hydrates, solvates, isomers, prodrugs, and isotopically labeled derivatives) thereof, or pharmaceutical compositions as provided herein are used for the treatment of asthma. Also, the compounds or pharmaceutical compositions described herein can be used for the treatment of endotoxemia and sepsis. In one embodiment, the compounds or pharmaceutical compositions described herein are used to for the treatment of rheumatoid arthritis (RA). In yet another embodiment, the compounds or pharmaceutical compositions described herein is used for the treatment of contact or atopic dermatitis. Contact dermatitis includes irritant dermatitis, phototoxic dermatitis, allergic dermatitis, photoallergic dermatitis, contact urticaria, systemic contact-type dermatitis and the like. Irritant dermatitis can occur when too much of a substance is used on the skin of when the skin is sensitive to certain substance. Atopic dermatitis, sometimes called eczema, is a kind of dermatitis, an atopic skin disease.

[00535] In some embodiments, the disclosure provides a method of treating diseases related to vasculogenesis or angiogenesis in a subject that comprises administering to said subject a therapeutically effective amount of a compound, or a pharmaceutically acceptable form (*e.g.*, pharmaceutically acceptable salts, hydrates, solvates, isomers, prodrugs, and isotopically labeled derivatives) thereof, or pharmaceutical compositions as provided herein. In some embodiments, said method is for treating a disease selected from tumor angiogenesis, chronic inflammatory disease such as rheumatoid arthritis and chronic inflammatory demyelinating polyneuropathy, atherosclerosis, inflammatory bowel disease, skin diseases such as psoriasis, eczema, and scleroderma, diabetes, diabetic retinopathy, retinopathy of prematurity, age-related macular degeneration, hemangioma, glioma, melanoma, Kaposi's sarcoma and ovarian, breast, lung, pancreatic, prostate, colon and epidermoid cancer.

[00536] In addition, the compounds described herein can be used for the treatment of arteriosclerosis, including atherosclerosis. Arteriosclerosis is a general term describing any hardening of medium or large arteries. Atherosclerosis is a hardening of an artery specifically due to an atheromatous plaque.

[00537] In some embodiments, provided herein is a method of treating a cardiovascular disease in a subject that comprises administering to said subject a therapeutically effective amount of a compound as provided herein, or a pharmaceutically acceptable form (*e.g.,* pharmaceutically acceptable salts, hydrates, solvates, isomers, prodrugs, and isotopically labeled derivatives) thereof. Examples of cardiovascular conditions include, but are not limited to, atherosclerosis, restenosis, vascular occlusion and carotid obstructive disease.

[00538] In some embodiments, the disclosure relates to a method of treating diabetes in a subject that comprises administering to said subject a therapeutically effective amount of a compound as provided herein, or a pharmaceutically acceptable form (*e.g., p*harmaceutically acceptable salts, hydrates, solvates, isomers, prodrugs, and isotopically labeled derivatives) thereof, or pharmaceutical compositions as provided herein.

[00539] In addition, the compounds, or a pharmaceutically acceptable form (*e.g.,* pharmaceutically acceptable salts, hydrates, solvates, isomers, prodrugs, and isotopically labeled derivatives) thereof, or pharmaceutical compositions as provided herein, can be used to treat acne. In certain embodiments, the inflammatory condition and/or immune disorder is a skin condition. In some embodiments, the skin condition is pruritus (itch), psoriasis, eczema, burns or dermatitis. In certain embodiments, the skin condition is psoriasis. In certain embodiments, the skin condition is pruritis.

[00540] In certain embodiments, the inflammatory disorder and/or the immune disorder is a gastrointestinal disorder. In some embodiments, the gastrointestinal disorder is selected from gastrointestinal disorder (*e.g.*, selected from peptic ulcers, regional enteritis, diverticulitis, gastrointestinal bleeding, eosinophilic gastrointestinal disorders (*e.g.*, eosinophilic esophagitis, eosinophilic gastritis, eosinophilic gastroenteritis, eosinophilic colitis), gastritis, diarrhea, gastroesophageal reflux disease (GORD, or its synonym GERD), inflammatory bowel disease (IBD) (*e.g.*, Crohn's disease, ulcerative colitis, collagenous colitis, lymphocytic colitis, ischaemic colitis, diversion colitis, Behcet's syndrome, indeterminate colitis) and inflammatory bowel syndrome (IBS)). In certain embodiments, the gastrointestinal disorder is inflammatory bowel disease (IBD).

[00541] Further, the compounds, or a pharmaceutically acceptable form (*e.g.,* pharmaceutically acceptable salts, hydrates, solvates, isomers, prodrugs, and isotopically labeled derivatives) thereof, or pharmaceutical compositions as provided herein, can be used for the treatment of glomerulonephritis. Glomerulonephritis is a primary or secondary autoimmune renal disease characterized by inflammation of the glomeruli. It can be asymptomatic, or present with hematuria and/or proteinuria. There are many recognized types, divided in acute, subacute or chronic glomerulonephritis. Causes are infectious (bacterial, viral or parasitic pathogens), autoimmune or paraneoplastic.

[00542] In some embodiments, provided herein are compounds, or a pharmaceutically acceptable form (*e.g.,* pharmaceutically acceptable salts, hydrates, solvates, isomers, prodrugs, and isotopically labeled derivatives) thereof, or pharmaceutical compositions as provided herein, for the treatment of multiorgan failure. Also provided herein are compounds, or a pharmaceutically acceptable form (*e.g.,* pharmaceutically acceptable salts, hydrates, solvates, isomers, prodrugs, and isotopically labeled derivatives) thereof, or pharmaceutical compositions as provided herein, for the treatment of liver diseases (including diabetes), gall bladder disease (inluding gallstones),

pancreatitis or kidney disease (including proliferative glomerulonephritis and diabetes- induced renal disease) or pain in a subject.

[00543] In some embodiments, provided herein are compounds, or a pharmaceutically acceptable form (*e.g.*, pharmaceutically acceptable salts, hydrates, solvates, isomers, prodrugs, and isotopically labeled derivatives) thereof, or pharmaceutical compositions as provided herein, for the prevention of blastocyte implantation in a subject.

[00544] In some embodiments, provided herein are compounds, or a pharmaceutically acceptable form (*e.g.*, pharmaceutically acceptable salts, hydrates, solvates, isomers, prodrugs, and isotopically labeled derivatives) thereof, or pharmaceutical compositions as provided herein, for the treatment of disorders involving platelet aggregation or platelet adhesion, including, but not limited to Idiopathic thrombocytopenic purpura, Bernard-Soulier syndrome, Glanzmann's thrombasthenia, Scott's syndrome, von Willebrand disease, Hermansky-Pudlak Syndrome, and Gray platelet syndrome.

[00545] In some embodiments, compounds, or a pharmaceutically acceptable form (*e.g.*, pharmaceutically acceptable salts, hydrates, solvates, isomers, prodrugs, and isotopically labeled derivatives) thereof, or pharmaceutical compositions as provided herein, are provided for treating a disease which is skeletal muscle atrophy, skeletal or muscle hypertrophy. In some embodiments, provided herein are compounds, or a pharmaceutically acceptable form (*e.g.*, pharmaceutically acceptable salts, hydrates, solvates, isomers, prodrugs, and isotopically labeled derivatives) thereof, or pharmaceutical compositions as provided herein, for the treatment of disorders that include, but are not limited to, cancers as discussed herein, transplantation-related disorders (*e.g.*, lowering rejection rates, graft-versus-host disease, etc.), muscular sclerosis (MS), allergic disorders (*e.g.*, arthritis, allergic encephalomyelitis) and other immunosuppressive-related disorders, metabolic disorders (*e.g.*, diabetes), reducing intimal thickening following vascular injury, and misfolded protein disorders (*e.g.*, Alzheimer's Disease, Gaucher's Disease, Parkinson's Disease, Huntington's Disease, cystic fibrosis, macular degeneration, retinitis pigmentosa, and prion disorders) (as mTOR inhibition can alleviate the effects of misfolded protein aggregates). The disorders also include hamartoma syndromes, such as tuberous sclerosis and Cowden Disease (also termed Cowden syndrome and multiple hamartoma syndrome).

[00546] Additionally, the compounds, or a pharmaceutically acceptable form (*e.g.*, pharmaceutically acceptable salts, hydrates, solvates, isomers, prodrugs, and isotopically labeled derivatives) thereof, or pharmaceutical compositions as provided herein, can be used for the treatment of bursitis, lupus, acute disseminated encephalomyelitis (ADEM), Addison's disease, antiphospholipid antibody syndrome (APS), amyloidosis (including systemic and localized amyloidosis; and primary and secondary amyloidosis), aplastic anemia, autoimmune hepatitis, coeliac disease, crohn's disease, diabetes mellitus (type 1), eosinophilic gastroenterides, goodpasture's syndrome, graves' disease, guillain-barré syndrome (GBS), hashimoto's disease, inflammatory bowel disease, lupus erythematosus (including cutaneous lupus erythematosus and systemic lupus erythematosus), myasthenia gravis, opsoclonus myoclonus syndrome (OMS), optic neuritis, ord's thyroiditis,ostheoarthritis, uveoretinitis, pemphigus, polyarthritis, primary biliary cirrhosis, reiter's syndrome, takayasu's arteritis, temporal arteritis, warm autoimmune hemolytic anemia, wegener's granulomatosis, alopecia universalis, chagas' disease, chronic fatigue syndrome,

dysautonomia, endometriosis, hidradenitis suppurativa, interstitial cystitis, neuromyotonia, sarcoidosis, scleroderma, ulcerative colitis, vitiligo, vulvodynia, appendicitis, arteritis, arthritis, blepharitis, bronchiolitis, bronchitis, cervicitis, cholangitis, cholecystitis, chorioamnionitis, colitis, conjunctivitis, cystitis, dacryoadenitis, dermatomyositis, endocarditis, endometritis, enteritis, enterocolitis, epicondylitis, epididymitis, fasciitis, fibrositis, gastritis, gastroenteritis, gingivitis, hepatitis, hidradenitis, ileitis, iritis, laryngitis, mastitis, meningitis, myelitis, myocarditis, myositis, nephritis, omphalitis, oophoritis, orchitis, osteitis, otitis, pancreatitis, parotitis, pericarditis, peritonitis, pharyngitis, pleuritis, phlebitis, pneumonitis, proctitis, prostatitis, pyelonephritis, rhinitis, salpingitis, sinusitis, stomatitis, synovitis, tendonitis, tonsillitis, uveitis (*e.g.*, ocular uveitis), vaginitis, vasculitis, or vulvitis.

[00547] In another aspect, provided herein are methods of disrupting the function of a leukocyte or disrupting a function of an osteoclast. The method includes contacting the leukocyte or the osteoclast with a function disrupting amount of a compound as provided herein.

[00548] In another aspect, methods are provided for treating ophthalmic disease by administering one or more of the subject compounds or pharmaceutical compositions to the eye of a subject.

[00549] In certain embodiments, provided herein are methods of treating, preventing and/or managing a disease or a disorder using a compound, or a pharmaceutically acceptable form (*e.g.*, pharmaceutically acceptable salts, hydrates, solvates, isomers, prodrugs, and isotopically labeled derivatives) thereof, or pharmaceutical compositions as provided herein, wherein the disease or disorder is: Crohn's disease; cutaneous lupus; multiple sclerosis; rheumatoid arthritis; and systemic lupus erythematosus.

[00550] In other embodiments, provided herein are methods of treating, preventing and/or managing a disease or a disorder using a compound, or a pharmaceutically acceptable form (*e.g.*, pharmaceutically acceptable salts, hydrates, solvates, isomers, prodrugs, and isotopically labeled derivatives) thereof, or pharmaceutical compositions as provided herein, wherein the disease or disorder is: ankylosing spondylitis; chronic obstructive pulmonary disease; myasthenia gravis; ocular uveitis, psoriasis; and psoriatic arthritis.

[00551] In other embodiments, provided herein are methods of treating, preventing and/or managing a disease or a disorder using a compound, or a pharmaceutically acceptable form (*e.g.*, pharmaceutically acceptable salts, hydrates, solvates, isomers, prodrugs, and isotopically labeled derivatives) thereof, or pharmaceutical compositions as provided herein, wherein the disease or disorder is: adult-onset Still's disease; inflammatory alopecia; amyloidosis; antiphospholipid syndrome; autoimmune hepatitis; autoimmune skin disease, Behcet's disease; chronic inflammatory demyelinating polyneuropathy; eosinophilic gastroenteritis; inflammatory myopathies, pemphigus, polymyalgia rheumatica; relapsing polychondritis; Sjorgen's syndrome; temporal arthritis; ulcerative colitis; vasculis; vitiligo, and Wegner's granulomatosis.

[00552] In other embodiments, provided herein are methods of treating, preventing and/or managing a disease or a disorder using a compound, or a pharmaceutically acceptable form (*e.g.*, pharmaceutically acceptable salts, hydrates, solvates, isomers, prodrugs, and isotopically labeled derivatives) thereof, or pharmaceutical compositions as provided herein, wherein the disease or disorder is: gout flare; sacoidosis; and systemic sclerosis.

[00553] In certain embodiments, provided herein are methods of treating, preventing and/or managing a disease or a disorder using a compound, or a pharmaceutically acceptable form (*e.g.*, pharmaceutically acceptable

salts, hydrates, solvates, isomers, prodrugs, and isotopically labeled derivatives) thereof, or pharmaceutical compositions as provided herein, wherein the disease or disorder is: asthma; arthritis (e.g., rheumatoid arthritis and psoriatic arthritis); psoriasis; scleroderma; myositis (*e.g.*, dermatomyositis); lupus (*e.g.*, cutaneous lupus erythematosus ("CLE") or systemic lupus erythematosus ("SLE")); or Sjögren's syndrome.

[00554] Efficacy of a compound provided herein in treating, preventing and/or managing the disease or disorder can be tested using various animal models known in the art. For example: efficacy in treating, preventing and/or managing asthma can be assessed using ova induced asthma model described, for example, in Lee *et al.* (2006) *J Allergy Clin Immunol* 118(2):403-9; efficacy in treating, preventing and/or managing arthritis (*e.g.*, rheumatoid or psoriatic arthritis) can be assessed using autoimmune animal models described, for example, in Williams *et al.* (2010) *Chem Biol*, 17(2):123-34, WO 2009/088986, WO2009/088880, and WO 2011/008302; efficacy in treating, preventing and/or managing psoriasis can be assessed using transgenic or knockout mouse model with targeted mutations in epidermis, vasculature or immune cells, mouse model resulting from spontaneous mutations, and immunodeficient mouse model with xenotransplantation of human skin or immune cells, all of which are described, for example, in Boehncke *et al.* (2007) *Clinics in Dermatology*, 25: 596-605; efficacy in treating, preventing and/or managing fibrosis or fibrotic condition can be assessed using the unilateral ureteral obstruction model of renal fibrosis (*see* Chevalier *et al.*, *Kidney International* (2009) 75:1145-1152), the bleomycin induced model of pulmonary fibrosis (*see* Moore and Hogaboam, *Am. J. Physiol. Lung. Cell. Mol. Physiol.* (2008) 294:L152-L160), a variety of liver/biliary fibrosis models (*see* Chuang *et al.*, *Clin Liver Dis* (2008) 12:333-347 and Omenetti, A. *et al.* (2007) *Laboratory Investigation* 87:499-514 (biliary duct-ligated model)), or a number of myelofibrosis mouse models (*see* Varicchio, L. *et al.* (2009) *Expert Rev. Hematol.* 2(3):315-334); efficacy in treating, preventing and/or managing scleroderma can be assessed using mouse model induced by repeated local injections of bleomycin ("BLM") described, for example, in Yamamoto *et al.* (1999) *J Invest Dermatol* 112: 456-462; efficacy in treating, preventing and/or managing dermatomyositis can be assessed using myositis mouse model induced by immunization with rabbit myosin described, for example, in Phyanagi *et al.* (2009) *Arthritis & Rheumatism*, 60(10): 3118-3127; efficacy in treating, preventing and/or managing lupus (*e.g.*, CLE or SLE) can be assessed using various animal models described, for example, in Ghoreishi *et al.* (2009) *Lupus*, 19: 1029-1035, Ohl *et al.* (2011) *Journal of Biomedicine and Biotechnology*, Article ID 432595 (14 pages), Xia *et al.* (2011) *Rheumatology*, 50:2187-2196, Pau *et al.* (2012) *PLoS ONE*, 7(5):e36761 (15 pages), Mustafa *et al.* (2011) *Toxicology*, 290:156-168, Ichikawa *et al.* (2012) *Arthritis and Rheumatism*, 62(2): 493-503, Ouyang *et al.* (2012) *J Mol Med*, DOI 10.1007/s00109-012-0866-3 (10 pages), Rankin *et al.* (2012) *Journal of Immunology*, 188:1656-1667; and efficacy in treating, preventing and/or managing Sjögren's syndrome can be assessed using various mouse models described, for example, in Chiorini *et al.* (2009) *Journal of Autoimmunity*, 33: 190-196.

[00555] In one embodiment, provided herein is a method of treating, preventing and/or managing asthma. As used herein, "asthma" encompasses airway constriction regardless of the cause. Common triggers of asthma include, but are not limited to, exposure to an environmental stimulants (*e.g.*, allergens), cold air, warm air, perfume, moist air, exercise or exertion, and emotional stress. Also provided herein is a method of treating,

preventing and/or managing one or more symptoms associated with asthma. Examples of the symptoms include, but are not limited to, severe coughing, airway constriction and mucus production.

[00556] In one embodiment, provided herein is a method of treating, preventing and/or managing arthritis. As used herein, “arthritis” encompasses all types and manifestations of arthritis. Examples include, but are not limited to, crystalline arthritis, osteoarthritis, psoriatic arthritis, gouty arthritis, reactive arthritis, rheumatoid arthritis and Reiter's arthritis. In one embodiment, the disease or disorder is rheumatoid arthritis. In another embodiment, the disease or disorder is psoriatic arthritis. Also provided herein is a method of treating, preventing and/or managing one or more symptoms associated with arthritis. Examples of the symptoms include, but are not limited to, joint pain, which progresses into joint deformation, or damages in body organs such as in blood vessels, heart, lungs, skin, and muscles.

[00557] In one embodiment, provided herein is a method of treating, preventing and/or managing psoriasis. As used herein, “psoriasis” encompasses all types and manifestations of psoriasis. Examples include, but are not limited to, plaque psoriasis (*e.g.*, chronic plaque psoriasis, moderate plaque psoriasis and severe plaque psoriasis), guttate psoriasis, inverse psoriasis, pustular psoriasis, pemphigus vulgaris, erythrodermic psoriasis, psoriasis associated with inflammatory bowel disease (IBD), and psoriasis associated with rheumatoid arthritis (RA). Also provided herein is a method of treating, preventing and/or managing one or more symptoms associated with psoriasis. Examples of the symptoms include, but are not limited to: red patches of skin covered with silvery scales; small scaling spots; dry, cracked skin that may bleed; itching; burning; soreness; thickened, pitted or ridged nails; and swollen and stiff joints.

[00558] In one embodiment, provided herein is a method of treating, preventing and/or managing fibrosis and fibrotic condition. As used herein, “fibrosis” or “fibrotic condition encompasses all types and manifestations of fibrosis or fibrotic condition. Examples include, but are not limited to, formation or deposition of tissue fibrosis; reducing the size, cellularity (*e.g.*, fibroblast or immune cell numbers), composition; or cellular content, of a fibrotic lesion; reducing the collagen or hydroxyproline content, of a fibrotic lesion; reducing expression or activity of a fibrogenic protein; reducing fibrosis associated with an inflammatory response; decreasing weight loss associated with fibrosis; or increasing survival.

[00559] In certain embodiments, the fibrotic condition is primary fibrosis. In one embodiment, the fibrotic condition is idiopathic. In other embodiments, the fibrotic condition is associated with (*e.g.*, is secondary to) a disease (*e.g.*, an infectious disease, an inflammatory disease, an autoimmune disease, a malignant or cancerous disease, and/or a connective disease); a toxin; an insult (*e.g.*, an environmental hazard (*e.g.*, asbestos, coal dust, polycyclic aromatic hydrocarbons), cigarette smoking, a wound); a medical treatment (*e.g.*, surgical incision, chemotherapy or radiation), or a combination thereof.

[00560] In some embodiments, the fibrotic condition is associated with an autoimmune disease selected from scleroderma or lupus, *e.g.*, systemic lupus erythematosus. In some embodiments, the fibrotic condition is systemic. In some embodiments, the fibrotic condition is systemic sclerosis (*e.g.*, limited systemic sclerosis, diffuse systemic sclerosis, or systemic sclerosis sine scleroderma), nephrogenic systemic fibrosis, cystic fibrosis, chronic graft vs. host disease, or atherosclerosis.

[00561] In certain embodiments, the fibrotic condition is a fibrotic condition of the lung, a fibrotic condition of the liver, a fibrotic condition of the heart or vasculature, a fibrotic condition of the kidney, a fibrotic condition of the skin, a fibrotic condition of the gastrointestinal tract, a fibrotic condition of the bone marrow or a hematopoietic tissue, a fibrotic condition of the nervous system, a fibrotic condition of the eye, or a combination thereof.

[00562] In other embodiment, the fibrotic condition affects a tissue chosen from one or more of muscle, tendon, cartilage, skin (*e.g.*, skin epidermis or endodermis), cardiac tissue, vascular tissue (*e.g.*, artery, vein), pancreatic tissue, lung tissue, liver tissue, kidney tissue, uterine tissue, ovarian tissue, neural tissue, testicular tissue, peritoneal tissue, colon, small intestine, biliary tract, gut, bone marrow, hematopoietic tissue, or eye (*e.g.*, retinal) tissue.

[00563] In some embodiments, the fibrotic condition is a fibrotic condition of the eye. In some embodiments, the fibrotic condition is glaucoma, macular degeneration (e.g., age-related macular degeneration), macular edema (e.g., diabetic macular edema), retinopathy (e.g., diabetic retinopathy), or dry eye disease.

[00564] In certain embodiments, the fibrotic condition is a fibrotic condition of the lung. In certain embodiments, the fibrotic condition of the lung is chosen from one or more of: pulmonary fibrosis, idiopathic pulmonary fibrosis (IPF), usual interstitial pneumonitis (UIP), interstitial lung disease, cryptogenic fibrosing alveolitis (CFA), bronchiectasis, and scleroderma lung disease. In one embodiment, the fibrosis of the lung is secondary to a disease, a toxin, an insult, a medical treatment, or a combination thereof. For example, the fibrosis of the lung can be associated with (*e.g.*, secondary to) one or more of: a disease process such as asbestosis and silicosis; an occupational hazard; an environmental pollutant; cigarette smoking; an autoimmune connective tissue disorders (*e.g.*, rheumatoid arthritis, scleroderma and systemic lupus erythematosus (SLE)); a connective tissue disorder such as sarcoidosis; an infectious disease, e.g., infection, particularly chronic infection; a medical treatment, including but not limited to, radiation therapy, and drug therapy, e.g., chemotherapy (*e.g.*, treatment with as bleomycin, methotrexate, amiodarone, busulfan, and/or nitrofurantoin). In one embodiment, the fibrotic condition of the lung treated with the methods of the invention is associated with (*e.g.*, secondary to) a cancer treatment, e.g., treatment of a cancer (*e.g.*, squamous cell carcinoma, testicular cancer, Hodgkin's disease with bleomycin). In one embodiment, the fibrotic condition of the lung is associated with an autoimmune connective tissue disorder (*e.g.*, scleroderma or lupus, *e.g.*, SLE).

[00565] In certain embodiments, the fibrotic condition is a fibrotic condition of the liver. In certain embodiments, the fibrotic condition of the liver is chosen from one or more of: fatty liver disease, steatosis (*e.g.*, nonalcoholic steatohepatitis (NASH), cholestatic liver disease (e.g., primary biliary cirrhosis (PBC)), cirrhosis, alcohol induced liver fibrosis, biliary duct injury, biliary fibrosis, or cholangiopathies. In other embodiments, hepatic or liver fibrosis includes, but is not limited to, hepatic fibrosis associated with alcoholism, viral infection, e.g., hepatitis (*e.g.*, hepatitis C, B or D), autoimmune hepatitis, non-alcoholic fatty liver disease (NAFLD), progressive massive fibrosis, exposure to toxins or irritants (*e.g.*, alcohol, pharmaceutical drugs and environmental toxins).

[00566] In certain embodiments, the fibrotic condition is a fibrotic condition of the heart. In certain embodiments, the fibrotic condition of the heart is myocardial fibrosis (*e.g.*, myocardial fibrosis associated with radiation myocarditis, a surgical procedure complication (*e.g.*, myocardial post-operative fibrosis), infectious diseases (*e.g.*, Chagas disease, bacterial, trichinosis or fungal myocarditis)); granulomatous, metabolic storage disorders (*e.g.*, cardiomyopathy, hemochromatosis); developmental disorders (*e.g*, endocardial fibroelastosis); arteriosclerotic, or exposure to toxins or irritants (*e.g.*, drug induced cardiomyopathy, drug induced cardiotoxicity, alcoholic cardiomyopathy, cobalt poisoning or exposure). In certain embodiments, the myocardial fibrosis is associated with an inflammatory disorder of cardiac tissue (*e.g.*, myocardial sarcoidosis). In some embodiments, the fibrotic condition is a fibrotic condition associated with a myocardial infarction. In some embodiments, the fibrotic condition is a fibrotic condition associated with congestive heart failure.

[00567] In certain embodiments, the fibrotic condition is a fibrotic condition of the kidney. In certain embodiments, the fibrotic condition of the kidney is chosen from one or more of: renal fibrosis (*e.g.*, chronic kidney fibrosis), nephropathies associated with injury/fibrosis (e.g., chronic nephropathies associated with diabetes (e.g., diabetic nephropathy)), lupus, scleroderma of the kidney, glomerular nephritis, focal segmental glomerular sclerosis, IgA nephropathyrenal fibrosis associated with human chronic kidney disease (CKD), chronic progressive nephropathy (CPN), tubulointerstitial fibrosis, ureteral obstruction, chronic uremia, chronic interstitial nephritis, radiation nephropathy, glomerulosclerosis, progressive glomerulonephrosis (PGN), endothelial/thrombotic microangiopathy injury, HIV-associated nephropathy, or fibrosis associated with exposure to a toxin, an irritant, or a chemotherapeutic agent. In one embodiment, the fibrotic condition of the kidney is scleroderma of the kidney. In some embodiments, the fibrotic condition of the kidney is transplant nephropathy, diabetic nephropathy, lupus nephritis, or focal segmental glomerulosclerosis (FSGS).

[00568] In certain embodiments, the fibrotic condition is a fibrotic condition of the skin. In certain embodiments, the fibrotic condition of the skin is chosen from one or more of: skin fibrosis (*e.g.*, hypertrophic scarring, keloid), scleroderma, nephrogenic systemic fibrosis (*e.g.*, resulting after exposure to gadolinium (which is frequently used as a contrast substance for MRIs) in patients with severe kidney failure), and keloid.

[00569] In certain embodiments, the fibrotic condition is a fibrotic condition of the gastrointestinal tract. In certain embodiments, the fibrotic condition is chosen from one or more of: fibrosis associated with scleroderma; radiation induced gut fibrosis; fibrosis associated with a foregut inflammatory disorder such as Barrett's esophagus and chronic gastritis, and/or fibrosis associated with a hindgut inflammatory disorder, such as inflammatory bowel disease (IBD), ulcerative colitis and Crohn's disease. In some embodiments, the fibrotic condition of the gastrointestinal tract is fibrosis associated with scleroderma.

[00570] In certain embodiments, the fibrotic condition is a fibrotic condition of the bone marrow or a hematopoietic tissue. In certain embodiments, the fibrotic condition of the bone marrow is an intrinsic feature of a chronic myeloproliferative neoplasm of the bone marrow, such as primary myelofibrosis (also referred to herein as agnogenic myeloid metaplasia or chronic idiopathic myelofibrosis). In other embodiments, the bone marrow fibrosis is associated with (*e.g.*, is secondary to) a malignant condition or a condition caused by a clonal proliferative disease. In other embodiments, the bone marrow fibrosis is associated with a hematologic disorder (*e.g.*, a

hematologic disorder chosen from one or more of polycythemia vera, essential thrombocythemia, myelodysplasia, hairy cell leukemia, lymphoma (*e.g.*, Hodgkin or non-Hodgkin lymphoma), multiple myeloma or chronic myelogeneous leukemia (CML)). In yet other embodiments, the bone marrow fibrosis is associated with (*e.g.*, secondary to) a non-hematologic disorder (*e.g.*, a non-hematologic disorder chosen from solid tumor metastasis to bone marrow, an autoimmune disorder (*e.g.*, systemic lupus erythematosus, scleroderma, mixed connective tissue disorder, or polymyositis), an infection (*e.g.*, tuberculosis), or secondary hyperparathyroidism associated with vitamin D deficiency. In some embodiments, the fibrotic condition is idiopathic or drug-induced myelofibrosis. In some embodiments, the fibrotic condition of the bone marrow or hematopoietic tissue is associated with systemic lupus erythematosus or scleroderma.

[00571] In one embodiment, provided herein is a method of treating, preventing and/or managing scleroderma. Scleroderma is a group of diseases that involve hardening and tightening of the skin and/or other connective tissues. Scleroderma may be localized (*e.g.*, affecting only the skin) or systemic (*e.g.*, affecting other systems such as, *e.g.*, blood vessels and/or internal organs). Common symptoms of scleroderma include Raynaud's phenomenon, gastroesophageal reflux disease, and skin changes (*e.g.*, swollen fingers and hands, or thickened patches of skin). In some embodiments, the scleroderma is localized, *e.g.*, morphea or linear scleroderma. In some embodiments, the condition is a systemic sclerosis, *e.g.*, limited systemic sclerosis, diffuse systemic sclerosis, or systemic sclerosis sine scleroderma.

[00572] Localized scleroderma (localized cutaneous fibrosis) includes morphea and linear scleroderma. Morphea is typically characterized by oval-shaped thickened patches of skin that are white in the middle, with a purple border. Linear scleroderma is more common in children. Symptoms of linear scleroderma may appear mostly on one side of the body. In linear scleroderma, bands or streaks of hardened skin may develop on one or both arms or legs or on the forehead. En coup de sabre (frontal linear scleroderma or morphea en coup de sabre) is a type of localized scleroderma typically characterized by linear lesions of the scalp or face.

[00573] Systemic scleroderma (systemic sclerosis) includes, *e.g.*, limited systemic sclerosis (also known as limited cutaneous systemic sclerosis, or CREST syndrome), diffuse systemic sclerosis (also known as diffuse cutaneous systemic sclerosis), and systemic sclerosis sine scleroderma. CREST stands for the following complications that may accompany limited scleroderma: calcinosis (*e.g.*, of the digits), Raynaud's phenomenon, esophageal dysfunction, sclerodactyly, and telangiectasias. Typically, limited scleroderma involves cutaneous manifestations that mainly affect the hands, arms, and face. Limited and diffuse subtypes are distinguished based on the extent of skin involvement, with sparing of the proximal limbs and trunk in limited disease. See, *e.g.*, Denton, C.P. et al. (2006), *Nature Clinical Practice Rheumatology*, 2(3):134-143. The limited subtype also typically involves a long previous history of Raynaud's phenomenon, whereas in the diffuse subtype, onset of Raynaud's phenomenon can be simultaneous with other manifestations or might occur later. Both limited and diffuse subtypes may involve internal organs. Typical visceral manifestations of limited systemic sclerosis include isolated pulmonary hypertension, severe bowel involvement, and pulmonary fibrosis. Typical visceral manifestations of diffuse systemic sclerosis include renal crisis, lung fibrosis, and cardiac disease. Diffuse systemic sclerosis typically progresses rapidly and affects a large area of the skin and one or more internal organs (*e.g.*, kidneys, esophagus,

heart, or lungs). Systemic sclerosis sine scleroderma is a rare disorder in which patients develop vascular and fibrotic damage to internal organs in the absence of cutaneous sclerosis.

[00574] In one embodiment, provided herein is a method of treating, preventing and/or managing inflammatory myopathies. As used herein, "inflammatory myopathies" encompass all types and manifestations of inflammatory myopathies. Examples include, but are not limited to, muscle weakness (*e.g.*, proximal muscle weakness), skin rash, fatigue after walking or standing, tripping or falling, dysphagia, dysphonia, difficulty breathing, muscle pain, tender muscles, weight loss, low-grade fever, inflamed lungs, light sensitivity, calcium deposits (calcinosis) under the skin or in the muscle, as well as biological concomitants of inflammatory myopathies as disclosed herein or as known in the art. Biological concomitants of inflammatory myopathies (*e.g.*, dermatomyositis) include, *e.g.*, altered (*e.g.*, increased) levels of cytokines (*e.g.*, Type I interferons (*e.g.*, IFN-α and/or IFN-β), interleukins (*e.g.*, IL-6, IL-10, IL-15, IL-17 and IL-18), and TNF-α), TGF-β, B-cell activating factor (BAFF), overexpression of IFN inducible genes (*e.g.*, Type I IFN inducible genes). Other biological concomitants of inflammatory myopathies can include, *e.g.*, an increased erythrocyte sedimentation rate (ESR) and/or elevated level of creatine kinase. Further biological concomitants of inflammatory myopathies can include autoantibodies, *e.g.*, anti-synthetase autoantibodies (*e.g.*, anti-Jo1 antibodies), anti-signal recognition particle antibodies (anti-SRP), anti-Mi-2 antibodies, anti-p155 antibodies, anti-PM/Sci antibodies, and anti-RNP antibodies.

[00575] The inflammatory myopathy can be an acute inflammatory myopathy or a chronic inflammatory myopathy. In some embodiments, the inflammatory myopathy is a chronic inflammatory myopathy (*e.g.*, dermatomyositis, polymyositis, or inclusion body myositis). In some embodiments, the inflammatory myopathy is caused by an allergic reaction, another disease (*e.g.*, cancer or a connective tissue disease), exposure to a toxic substance, a medicine, or an infectious agent (*e.g.*, a virus). In some embodiments, the inflammatory myopathy is associated with lupus, rheumatoid arthritis, or systemic sclerosis. In some embodiments, the inflammatory myopathy is idiopathic. In some embodiments, the inflammatory myopathy is selected from polymyositis, dermatomyositis, inclusion body myositis, and immune-mediated necrotizing myopathy. In some embodiments, the inflammatory myopathy is dermatomyositis.

[00576] In another embodiment, provided herein is a method of treating, preventing and/or managing a skin condition (*e.g.*, a dermatitis). In some embodiments, the methods provided herein can reduce symptoms associated with a skin condition (*e.g.*, itchiness and/or inflammation). In some such embodiments, the compound provided herein is administered topically (*e.g.*, as a topical cream, eyedrop, nose drop or nasal spray). In some such embodiments, the compound is a PI3K delta inhibitor (*e.g.*, a PI3K inhibitor that demonstrates greater inhibition of PI3K delta than of other PI3K isoforms). In some embodiments, the PI3K delta inhibitor prevents mast cell degranulation.

[00577] As used herein, "skin condition" includes any inflammatory condition of the skin (*e.g.*, eczema or dermatitis, *e.g.*, contact dermatitis, atopic dermatitis, dermatitis herpetiformis, seborrheic dermatitis, nummular dermatitis, stasis dermatitis, perioral dermatitis), as well as accompanying symptoms (*e.g.*, skin rash, itchiness (pruritis), swelling (edema), hay fever, anaphalaxis). Frequently, such skin conditions are caused by an allergen. As used herein, a "skin condition" also includes, *e.g.*, skin rashes (*e.g.*, allergic rashes, *e.g.*, rashes resulting from

exposure to allergens such as poison ivy, poison oak, or poison sumac, or rashes caused by other diseases or conditions), insect bites, minor burns, sunburn, minor cuts, and scrapes. In some embodiments, the symptom associated with inflammatory myopathy, or the skin condition or symptom associated with the skin condition, is a skin rash or itchiness (pruritis) caused by a skin rash.

[00578] The skin condition (*e.g.*, the skin rash) may be spontaneous, or it may be induced, *e.g.*, by exposure to an allergen (*e.g.*, poison ivy, poison oak, or poison sumac), drugs, food, insect bite, inhalants, emotional stress, exposure to heat, exposure to cold, or exercise. In some embodiments, the skin condition is a skin rash (*e.g.*, a pruritic rash, e.g., utricaria). In some embodiments, the skin condition is an insect bite. In some embodiments, the skin condition is associated with another disease (*e.g.*, an inflammatory myopathy, *e.g.*, dermatomyositis).

[00579] In some embodiments, the subject (*e.g.*, the subject in need of treatment for an inflammatory myopathy and/or a skin condition) exhibits an elevated level or elevated activity of IFN-α, TNF-α, IL-6, IL-8, IL-1, or a combination thereof. In certain embodiments, the subject exhibits an elevated level of IFN-α. In some embodiments, treating (*e.g.*, decreasing or inhibiting) the inflammatory myopathy, or the skin condition, comprises inhibiting (*e.g.*, decreasing a level of, or decreasing a biological activity of) one or more of IFN-α, TNF-α, IL-6, IL-8, or IL-1 in the subject or in a sample derived from the subject. In some embodiments, the method decreases a level of IFN-α, TNF-α, IL-6, IL-8, or IL-1 in the subject or in a sample derived from the subject. In some embodiments, the method decreases a level of IFN-α in the subject or in a sample derived from the subject. In some embodiments, the level of IFN-α, TNF-α, IL-6, IL-8, or IL-1 is the level assessed in a sample of whole blood or PBMCs. In some embodiments, the level of IFN-α, TNF-α, IL-6, IL-8, or IL-1 is the level assessed in a sample obtained by a skin biopsy or a muscle biopsy. In some embodiments, the sample is obtained by a skin biopsy.

[00580] In one embodiment, provided herein is a method of treating, preventing and/or managing myositis. As used herein, "myositis" encompasses all types and manifestations of myositis. Examples include, but are not limited to, myositis ossificans, fibromyositis, idiopathic inflammatory myopathies, dermatomyositis, juvenile dermatomyositis, polymyositis, inclusion body myositis and pyomyositis. In one embodiment, the disease or disorder is dermatomyositis. Also provided herein is a method of treating, preventing and/or managing one or more symptoms associated with myositis. Examples of the symptoms include, but are not limited to: muscle weakness; trouble lifting arms; trouble swallowing or breathing; muscle pain; muscle tenderness; fatigue; fever; lung problems; gastrointestinal ulcers; intestinal perforations; calcinosis under the skin; soreness; arthritis; weight loss; and rashes.

[00581] In one embodiment, provided herein is a method of treating, preventing and/or managing lupus. As used herein, "lupus" refers to all types and manifestations of lupus. Examples include, but are not limited to, systemic lupus erythematosus; lupus nephritis; cutaneous manifestations (e.g., manifestations seen in cutaneous lupus erythematosus, e.g., a skin lesion or rash); CNS lupus; cardiovascular, pulmonary, hepatic, hematological, gastrointestinal and musculoskeletal manifestations; neonatal lupus erythematosus; childhood systemic lupus erythematosus; drug-induced lupus erythematosus; anti-phospholipid syndrome; and complement deficiency syndromes resulting in lupus manifestations. In one embodiment, the lupus is systemic lupus erythematosus (SLE), cutaneous lupus erythematosus (CLE), drug-induced lupus, or neonatal lupus. In another embodiment, the lupus is a CLE, *e.g.*, acute cutaneous lupus erythematosus (ACLE), subacute cutaneous lupus erythematosus (SCLE),

intermittent cutaneous lupus erythematosus (also known as lupus erythematosus tumidus (LET)), or chronic cutaneous lupus. In some embodiments, the intermittent CLE is chronic discloid lupus erythematosus (CDLE) or lupus erythematosus profundus (LEP) (also known as lupus erythematosus panniculitis). Types, symptoms, and pathogenesis of CLE are described, for example, in Wenzel *et al.* (2010), *Lupus*, 19, 1020-1028.

[00582] In one embodiment, provided herein is a method of treating, preventing and/or managing Sjögren's syndrome. As used herein, "Sjögren's syndrome" refers to all types and manifestations of Sjögren's syndrome. Examples include, but are not limited to, primary and secondary Sjögren's syndrome. Also provided herein is a method of treating, preventing and/or managing one or more symptoms associated with Sjögren's syndrome. Examples of the symptoms include, but are not limited to: dry eyes; dry mouth; joint pain; swelling; stiffness; swollen salivary glands; skin rashes; dry skin; vaginal dryness; persistent dry cough; and prolonged fatigue.

[00583] In some embodiments, a symptom associated with the disease or disorder provided herein is reduced by at least 10%, at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, or at least 95% relative to a control level. The control level includes any appropriate control as known in the art. For example, the control level can be the pre-treatment level in the sample or subject treated, or it can be the level in a control population (*e.g.*, the level in subjects who do not have the disease or disorder or the level in samples derived from subjects who do not have the disease or disorder). In some embodiments, the decrease is statistically significant, for example, as assessed using an appropriate parametric or non-parametric statistical comparison.

Combination Therapy

[00584] In some embodiments, provided herein are methods for combination therapies in which an agent known to modulate other pathways, or other components of the same pathway, or even overlapping sets of target enzymes are used in combination with a compound as provided herein, or a pharmaceutically acceptable form (*e.g.*, pharmaceutically acceptable salts, hydrates, solvates, isomers, prodrugs, and isotopically labeled derivatives) thereof. In one aspect, such therapy includes, but is not limited to, the combination of the subject compound with chemotherapeutic agents, therapeutic antibodies, and radiation treatment, to provide a synergistic or additive therapeutic effect.

[00585] In one aspect, a compound as provided herein, or a pharmaceutically acceptable form (*e.g.*, pharmaceutically acceptable salts, hydrates, solvates, isomers, prodrugs, and isotopically labeled derivatives) thereof, orpharmaceutical compositions as provided herein, can present synergistic or additive efficacy when administered in combination with agents that inhibit IgE production or activity. Such combination can reduce the undesired effect of high level of IgE associated with the use of one or more PI3K-δ inhibitors, if such effect occurs. This can be particularly useful in treatment of autoimmune and inflammatory disorders (AIID) such as rheumatoid arthritis. Additionally, the administration of PI3K-δ or PI3K-δ/γ inhibitors as provided herein in combination with inhibitors of mTOR can also exhibit synergy through enhanced inhibition of the PI3K pathway.

[00586] In a separate but related aspect, provided herein is a combination treatment of a disease associated with PI3K-δ comprising administering to a PI3K-δ inhibitor and an agent that inhibits IgE production or activity. Other exemplary PI3K-δ inhibitors are applicable for this combination and they are described, *e.g.,* US Patent No. 6,800,620. Such combination treatment is particularly useful for treating autoimmune and inflammatory diseases (AIID) including, but not limited to rheumatoid arthritis.

[00587] Agents that inhibit IgE production are known in the art and they include, but are not limited to, one or more of TEI-9874, 2-(4-(6-cyclohexyloxy-2-naphtyloxy)phenylacetamide)benzoic acid, rapamycin, rapamycin analogs (*i.e.,* rapalogs), TORC1 inhibitors, TORC2 inhibitors, and any other compounds that inhibit mTORC1 and mTORC2. Agents that inhibit IgE activity include, for example, anti-IgE antibodies such as for example Omalizumab and TNX-901.

[00588] For treatment of autoimmune diseases, a compound as provided herein, or a pharmaceutically acceptable form (*e.g.,* pharmaceutically acceptable salts, hydrates, solvates, isomers, prodrugs, and isotopically labeled derivatives) thereof, or pharmaceutical compositions as provided herein, can be used in combination with commonly prescribed drugs including, but not limited to Enbrel®, Remicade®, Humira®, Avonex®, and Rebif®. For treatment of respiratory diseaseses, the subject compounds or pharmaceutical compositions can be administered in combination with commonly prescribed drugs including, but not limited to Xolair®, Advair®, Singulair®, and Spiriva®.

[00589] The compounds as provided herein, or a pharmaceutically acceptable form (*e.g.,* pharmaceutically acceptable salts, hydrates, solvates, isomers, prodrugs, and isotopically labeled derivatives) thereof, or pharmaceutical compositions as provided herein, can be formulated or administered in conjunction with other agents that act to relieve the symptoms of inflammatory conditions such as encephalomyelitis, asthma, and the other diseases described herein. These agents include non-steroidal anti-inflammatory drugs (NSAIDs), *e.g.,* acetylsalicylic acid; ibuprofen; naproxen; indomethacin; nabumetone; tolmetin; etc. Corticosteroids are used to reduce inflammation and suppress activity of the immune system. An exemplary drug of this type is Prednisone. Chloroquine (Aralen) or hydroxychloroquine (Plaquenil) can also be used in some individuals with lupus. They can be prescribed for skin and joint symptoms of lupus. Azathioprine (Imuran) and cyclophosphamide (Cytoxan) suppress inflammation and tend to suppress the immune system. Other agents, *e.g.,* methotrexate and cyclosporin are used to control the symptoms of lupus. Anticoagulants are employed to prevent blood from clotting rapidly. They range from aspirin at very low dose which prevents platelets from sticking, to heparin/coumadin. Other compounds used in the treatment of lupus include belimumab (Benlysta®).

[00590] In another aspect, provided herein is a pharmaceutical composition for inhibiting abnormal cell growth in a subject which comprises an amount of a compound as provided herein, or a pharmaceutically acceptable form (*e.g.,* pharmaceutically acceptable salts, hydrates, solvates, isomers, prodrugs, and isotopically labeled derivatives) thereof, in combination with an amount of an anti-cancer agent (*e.g.,* a chemotherapeutic agent). Many chemotherapeutics are presently known in the art and can be used in combination with the compounds as provided herein.

[00591] In some embodiments, the chemotherapeutic is selected from mitotic inhibitors, alkylating agents, anti-metabolites, intercalating antibiotics, growth factor inhibitors, cell cycle inhibitors, enzymes, topoisomerase inhibitors, biological response modifiers, anti-hormones, angiogenesis inhibitors, and anti-androgens. Non-limiting examples are chemotherapeutic agents, cytotoxic agents, and non-peptide small molecules such as Gleevec® (Imatinib Mesylate), Velcade® (bortezomib), Casodex (bicalutamide), Iressa®, and Adriamycin as well as a host of chemotherapeutic agents. Non-limiting examples of chemotherapeutic agents include alkylating agents such as thiotepa and cyclosphosphamide (CYTOXAN™); alkyl sulfonates such as busulfan, improsulfan and piposulfan; aziridines such as benzodopa, carboquone, meturedopa, and uredopa; ethylenimines and methylamelamines including altretamine, triethylenemelamine, trietylenephosphoramide, triethylenethiophosphaoramide and trimethylolomelamine; BTK inhibitors such as ibrutinib (PCI-32765) and AVL-292; HDAC inhibitors usch as vorinostat, romidepsin, panobinostat, valproic acid, belinostat, mocetinostat, abrexinostat, entinostat, SB939, resminostat, givinostat, CUDC-101, AR-42, CHR-2845, CHR-3996, 4SC-202, CG200745, ACY-1215 and kevetrin; JAK/STAT inhibitors such as lestaurtinib, tofacitinib, ruxolitinib, pacritinib, CYT387, baricitinib, fostamatinib, GLPG0636, TG101348, INCB16562 and AZD1480; nitrogen mustards such as bedamustine, chlorambucil, chlornaphazine, cholophosphamide, estramustine, ifosfamide, mechlorethamine, mechlorethamine oxide hydrochloride, melphalan, novembichin, phenesterine, prednimustine, trofosfamide, uracil mustard; nitrosureas such as carmustine, chlorozotocin, fotemustine, lomustine, nimustine, ranimustine; antibiotics such as aclacinomysins, actinomycin, authramycin, azaserine, bleomycins, cactinomycin, calicheamicin, carabicin, carminomycin, carzinophilin, Casodex™ , chromomycins, dactinomycin, daunorubicin, detorubicin, 6-diazo-5-oxo-L-norleucine, doxorubicin, epirubicin, esorubicin, idarubicin, marcellomycin, mitomycins, mycophenolic acid, nogalamycin, olivomycins, peplomycin, potfiromycin, puromycin, quelamycin, rodorubicin, streptonigrin, streptozocin, tubercidin, ubenimex, zinostatin, zorubicin; anti-metabolites such as methotrexate and 5-fluorouracil (5-FU); folic acid analogues such as denopterin, methotrexate, pralatrexate, pteropterin, trimetrexate; purine analogs such as fludarabine, 6-mercaptopurine, thiamiprine, thioguanine; pyrimidine analogs such as ancitabine, azacitidine, 6-azauridine, carmofur, cytarabine, dideoxyuridine, doxifluridine, enocitabine, floxuridine, androgens such as calusterone, dromostanolone propionate, epitiostanol, mepitiostane, testolactone; anti-adrenals such as aminoglutethimide, mitotane, trilostane; folic acid replenisher such as frolinic acid; aceglatone; aldophosphamide glycoside; aminolevulinic acid; amsacrine; bestrabucil; bisantrene; edatraxate; defofamine; demecolcine; diaziquone; elfomithine; elliptinium acetate; etoglucid; gallium nitrate; hydroxyurea; lentinan; lonidamine; mitoguazone; mitoxantrone; mopidamol; nitracrine; pentostatin; phenamet; pirarubicin; podophyllinic acid; 2-ethylhydrazide; procarbazine; PSK.R™.; razoxane; sizofiran; spirogermanium; tenuazonic acid; triaziquone; 2,2',2''-trichlorotriethyla- mine; urethan; vindesine; dacarbazine; mannomustine; mitobronitol; mitolactol; pipobroman; gacytosine; arabinoside ("Ara-C"); cyclophosphamide; thiotepa; taxanes, *e.g.*, paclitaxel (TAXOL™, Bristol-Myers Squibb Oncology, Princeton, N.J.) and docetaxel (TAXOTERE™, Rhone-Poulenc Rorer, Antony, France) and ABRAXANE® (paclitaxel protein-bound particles); retinoic acid; esperamicins; capecitabine; and pharmaceutically acceptable forms (*e.g.*, pharmaceutically acceptable salts, hydrates, solvates, isomers, prodrugs, and isotopically labeled derivatives) of any of the above. Also included as suitable chemotherapeutic cell

conditioners are anti-hormonal agents that act to regulate or inhibit hormone action on tumors such as anti-estrogens including for example tamoxifen (Nolvadex™), raloxifene, aromatase inhibiting 4(5)-imidazoles, 4-hydroxytamoxifen, trioxifene, keoxifene, LY 117018, onapristone, and toremifene (Fareston); and anti-androgens such as flutamide, nilutamide, bicalutamide, leuprolide, and goserelin; chlorambucil; gemcitabine; 6-thioguanine; mercaptopurine; methotrexate; platinum analogs such as cisplatin and carboplatin; vinblastine; platinum; etoposide (VP-16); ifosfamide; mitomycin C; mitoxantrone; vincristine; vinorelbine; navelbine; novantrone; teniposide; daunomycin; aminopterin; xeloda; ibandronate; camptothecin-11 (CPT-11); topoisomerase inhibitor RFS 2000; difluoromethylornithine (DMFO). Where desired, the compounds or pharmaceutical composition as provided herein can be used in combination with commonly prescribed anti-cancer drugs such as Herceptin®, Avastin®, Erbitux®, Rituxan®, Taxol®, Arimidex®, Taxotere®, ABVD, AVICINE, Abagovomab, Acridine carboxamide, Adecatumumab, 17-N-Allylamino-17-demethoxygeldanamycin, Alpharadin, Alvocidib, 3-Aminopyridine-2-carboxaldehyde thiosemicarbazone, Amonafide, Anthracenedione, Anti-CD22 immunotoxins, Antineoplastic, Antitumorigenic herbs, Apaziquone, Atiprimod, Azathioprine, Belotecan, Bendamustine, BIBW 2992, Biricodar, Brostallicin, Bryostatin, Buthionine sulfoximine, CBV (chemotherapy), Calyculin, Crizotinib, cell-cycle nonspecific antineoplastic agents, Dichloroacetic acid, Discodermolide, Elsamitrucin, Enocitabine, Epothilone, Eribulin, Everolimus, Exatecan, Exisulind, Ferruginol, Forodesine, Fosfestrol, ICE chemotherapy regimen, IT-101, Imexon, Imiquimod, Indolocarbazole, Irofulven, Laniquidar, Larotaxel, Lenalidomide, Lucanthone, Lurtotecan, Mafosfamide, Mitozolomide, Nafoxidine, Nedaplatin, Olaparib, Ortataxel, PAC-1, Pawpaw, Pixantrone, Proteasome inhibitor, Rebeccamycin, Resiquimod, Rubitecan, SN-38, Salinosporamide A, Sapacitabine, Stanford V, Swainsonine, Talaporfin, Tariquidar, Tegafur-uracil, Temodar, Tesetaxel, Triplatin tetranitrate, Tris(2-chloroethyl)amine, Troxacitabine, Uramustine, Vadimezan, Vinflunine, ZD6126, and Zosuquidar.

[00592] In some embodiments, the chemotherapeutic is selected from hedgehog inhibitors including, but not limited to IPI-926 (*See* U.S. Patent 7,812,164). Other suitable hedgehog inhibitors include, for example, those described and provided in U.S. Patent 7,230,004, U.S. Patent Application Publication No. 2008/0293754, U.S. Patent Application Publication No. 2008/0287420, and U.S. Patent Application Publication No. 2008/0293755, the entire disclosures of which are incorporated by reference herein. Examples of other suitable hedgehog inhibitors include those described in U.S. Patent Application Publication Nos. US 2002/0006931, US 2007/0021493 and US 2007/0060546, and International Application Publication Nos. WO 2001/19800, WO 2001/26644, WO 2001/27135, WO 2001/49279, WO 2001/74344, WO 2003/011219, WO 2003/088970, WO 2004/020599, WO 2005/013800, WO 2005/033288, WO 2005/032343, WO 2005/042700, WO 2006/028958, WO 2006/050351, WO 2006/078283, WO 2007/054623, WO 2007/059157, WO 2007/120827, WO 2007/131201, WO 2008/070357, WO 2008/110611, WO 2008/112913, and WO 2008/131354. Additional examples of hedgehog inhibitors include, but are not limited to, GDC-0449 (also known as RG3616 or vismodegib) described in, *e.g.*, Von Hoff D. *et al.*, *N. Engl. J. Med.* 2009; 361(12):1164-72; Robarge K.D. *et al.*, *Bioorg Med Chem Lett.* 2009; 19(19):5576-81; Yauch, R. L. et al. (2009) *Science* 326: 572-574; Sciencexpress: 1-3 (10.1126/science.1179386); Rudin, C. *et al.* (2009) *New England J of Medicine* 361-366 (10.1056/nejma0902903); BMS-833923 (also known as XL139) described in, *e.g.*, in Siu L. *et al.*, *J. Clin. Oncol.* 2010; 28:15s (suppl; abstr 2501); and National Institute of Health Clinical Trial Identifier No.

NCT006701891; LDE-225 described, *e.g.*, in Pan S. *et al.*, *ACS Med. Chem. Lett.*, 2010; 1(3): 130–134; LEQ-506 described, *e.g.*, in National Institute of Health Clinical Trial Identifier No. NCT01106508; PF-04449913 described, *e.g.*, in National Institute of Health Clinical Trial Identifier No. NCT00953758; Hedgehog pathway antagonists provided in U.S. Patent Application Publication No. 2010/0286114; SMOi2-17 described, *e.g.*, U.S. Patent Application Publication No. 2010/0093625; SANT-1 and SANT-2 described, *e.g.*, in Rominger C.M. et al., *J. Pharmacol. Exp. Ther.* 2009; 329(3):995-1005; 1-piperazinyl-4-arylphthalazines or analogues thereof, described in Lucas B.S. et al., *Bioorg. Med. Chem. Lett.* 2010; 20(12):3618-22.

[00593] Other chemotherapeutic agents include, but are not limited to, anti-estrogens (*e.g.* tamoxifen, raloxifene, and megestrol), LHRH agonists (*e.g.* goscrclin and leuprolide), anti-androgens (*e.g.* flutamide and bicalutamide), photodynamic therapies (*e.g.* vertoporfin (BPD-MA), phthalocyanine, photosensitizer Pc4, and demethoxy-hypocrellin A (2BA-2-DMHA)), nitrogen mustards (*e.g.* cyclophosphamide, ifosfamide, trofosfamide, chlorambucil, estramustine, and melphalan), nitrosoureas (*e.g.* carmustine (BCNU) and lomustine (CCNU)), alkylsulphonates (*e.g.* busulfan and treosulfan), triazenes (*e.g.* dacarbazine, temozolomide), platinum containing compounds (*e.g.* cisplatin, carboplatin, oxaliplatin), vinca alkaloids (*e.g.* vincristine, vinblastine, vindesine, and vinorelbine), taxoids (*e.g.* paclitaxel or a paclitaxel equivalent such as nanoparticle albumin-bound paclitaxel (Abraxane), docosahexaenoic acid bound-paclitaxel (DHA-paclitaxel, Taxoprexin), polyglutamate bound-paclitaxel (PG-paclitaxel, paclitaxel poliglumex, CT-2103, XYOTAX), the tumor-activated prodrug (TAP) ANG1005 (Angiopep-2 bound to three molecules of paclitaxel), paclitaxel-EC-1 (paclitaxel bound to the erbB2-recognizing peptide EC-1), and glucose-conjugated paclitaxel, *e.g.*, 2'-paclitaxel methyl 2-glucopyranosyl succinate; docetaxel, taxol), epipodophyllins (*e.g.* etoposide, etoposide phosphate, teniposide, topotecan, 9-aminocamptothecin, camptoirinotecan, irinotecan, crisnatol, mytomycin C), anti-metabolites, DHFR inhibitors (*e.g.* methotrexate, dichloromethotrexate, trimetrexate, edatrexate), IMP dehydrogenase inhibitors (*e.g.* mycophenolic acid, tiazofurin, ribavirin, and EICAR), ribonuclotide reductase inhibitors (*e.g.* hydroxyurea and deferoxamine), uracil analogs (*e.g.* 5-fluorouracil (5-FU), floxuridine, doxifluridine, ratitrexed, tegafur-uracil, capecitabine), cytosine analogs (*e.g.* cytarabine (ara C), cytosine arabinoside, and fludarabine), purine analogs (*e.g.* mercaptopurine and Thioguanine), Vitamin D3 analogs (*e.g.* EB 1089, CB 1093, and KH 1060), isoprenylation inhibitors (*e.g.* lovastatin), dopaminergic neurotoxins (*e.g.* 1-methyl-4-phenylpyridinium ion), cell cycle inhibitors (*e.g.* staurosporine), actinomycin (*e.g.* actinomycin D, dactinomycin), bleomycin (*e.g.* bleomycin A2, bleomycin B2, peplomycin), anthracycline (*e.g.* daunorubicin, doxorubicin, pegylated liposomal doxorubicin, idarubicin, epirubicin, pirarubicin, zorubicin, mitoxantrone), MDR inhibitors (*e.g.* verapamil), Ca2+ ATPase inhibitors (*e.g.* thapsigargin), imatinib, thalidomide, lenalidomide, tyrosine kinase inhibitors (*e.g.*, axitinib (AG013736), bosutinib (SKI-606), cediranib (RECENTINTM, AZD2171), dasatinib (SPRYCEL®, BMS-354825), erlotinib (TARCEVA®), gefitinib (IRESSA®), imatinib (Gleevec®, CGP57148B, STI-571), lapatinib (TYKERB®, TYVERB®), lestaurtinib (CEP-701), neratinib (HKI-272), nilotinib (TASIGNA®), semaxanib (semaxinib, SU5416), sunitinib (SUTENT®, SU11248), toceranib (PALLADIA®), vandetanib (ZACTIMA®, ZD6474), vatalanib (PTK787, PTK/ZK), trastuzumab (HERCEPTIN®), bevacizumab (AVASTIN®), rituximab (RITUXAN®), cetuximab (ERBITUX®), panitumumab (VECTIBIX®), ranibizumab (Lucentis®), nilotinib (TASIGNA®), sorafenib (NEXAVAR®), everolimus (AFINITOR®), alemtuzumab

(CAMPATH®), gemtuzumab ozogamicin (MYLOTARG®), temsirolimus (TORISEL®), ENMD-2076, PCI-32765, AC220, dovitinib lactate (TKI258, CHIR-258), BIBW 2992 (TOVOKTM), SGX523, PF-04217903, PF-02341066, PF-299804, BMS-777607, ABT-869, MP470, BIBF 1120 (VARGATEF®), AP24534, JNJ-26483327, MGCD265, DCC-2036, BMS-690154, CEP-11981, tivozanib (AV-951), OSI-930, MM-121, XL-184, XL-647, and/or XL228), proteasome inhibitors (*e.g.*, bortezomib (Velcade)), mTOR inhibitors (*e.g.*, rapamycin, temsirolimus (CCI-779), everolimus (RAD-001), ridaforolimus, AP23573 (Ariad), AZD8055 (AstraZeneca), BEZ235 (Novartis), BGT226 (Norvartis), XL765 (Sanofi Aventis), PF-4691502 (Pfizer), GDC0980 (Genetech), SF1126 (Semafoe) and OSI-027 (OSI)), oblimersen, gemcitabine, carminomycin, leucovorin, pemetrexed, cyclophosphamide, dacarbazine, procarbizine, prednisolone, dexamethasone, campathecin, plicamycin, asparaginase, aminopterin, methopterin, porfiromycin, melphalan, leurosidine, leurosine, chlorambucil, trabectedin, procarbazine, discodermolide, carminomycin,, aminopterin, and hexamethyl melamine.

[00594] Exemplary biotherapeutic agents include, but are not limited to, interferons, cytokines (*e.g.*, tumor necrosis factor, interferon α, interferon γ), vaccines, hematopoietic growth factors, monoclonal serotherapy, immunostimulants and/or immunodulatory agents (*e.g.*, IL-1, 2, 4, 6, or 12), immune cell growth factors (*e.g.*, GM-CSF) and antibodies (*e.g.* Herceptin (trastuzumab), T-DM1, AVASTIN (bevacizumab), ERBITUX (cetuximab), Vectibix (panitumumab), Rituxan (rituximab), Bexxar (tositumomab)).

[00595] In some embodiments, the chemotherapeutic is selected from HSP90 inhibitors. The HSP90 inhibitor can be a geldanamycin derivative, *e.g.*, a benzoquinone or hygroquinone ansamycin HSP90 inhbitor (*e.g.*, IPI-493 and/or IPI-504). Non-limiting examples of HSP90 inhibitors include IPI-493, IPI-504, 17-AAG (also known as tanespimycin or CNF-1010), BIIB-021 (CNF-2024), BIIB-028, AUY-922 (also known as VER-49009), SNX-5422, STA-9090, AT-13387, XL-888, MPC-3100, CU-0305, 17-DMAG, CNF-1010, Macbecin (*e.g.*, Macbecin I, Macbecin II), CCT-018159, CCT-129397, PU-H71, or PF-04928473 (SNX-2112).

[00596] In some embodiments, the chemotherapeutic is selected from PI3K inhibitors (*e.g.*, including those PI3K inhibitors provided herein and those PI3K inhibitors not provided herein). In some embodiment, the PI3K inhibitor is an inhibitor of delta and gamma isoforms of PI3K. In some embodiments, the PI3K inhibitor is an inhibitor of alpha isoforms of PI3K. In other embodiments, the PI3K inhibitor is an inhibitor of one or more alpha, beta, delta and gamma isoforms of PI3K. Exemplary PI3K inhibitors that can be used in combination are described in, *e.g.*, WO 09/088990, WO 09/088086, WO 2011/008302, WO 2010/036380, WO 2010/006086, WO 09/114870, WO 05/113556; US 2009/0312310, and US 2011/0046165. Additional PI3K inhibitors that can be used in combination with the pharmaceutical compositions, include but are not limited to, AMG-319, GSK 2126458, GDC-0980, GDC-0941, Sanofi XL147, XL499, XL756, XL147, PF-46915032, BKM 120, CAL-101 (GS-1101), CAL 263, SF1126, PX-886, and a dual PI3K inhibitor (*e.g.*, Novartis BEZ235). In one embodiment, the PI3K inhibitor is an isoquinolinone.

[00597] In some embodiments, provided herein is a method for using the a compound as provided herein, or a pharmaceutically acceptable form (*e.g.,* pharmaceutically acceptable salts, hydrates, solvates, isomers, prodrugs, and isotopically labeled derivatives) thereof, or pharmaceutical compositions as provided herein, in combination with radiation therapy in inhibiting abnormal cell growth or treating the hyperproliferative disorder in

the subject. Techniques for administering radiation therapy are known in the art, and these techniques can be used in the combination therapy described herein. The administration of the compound as provided herein in this combination therapy can be determined as described herein.

[00598] Radiation therapy can be administered through one of several methods, or a combination of methods, including without limitation external-beam therapy, internal radiation therapy, implant radiation, stereotactic radiosurgery, systemic radiation therapy, radiotherapy and permanent or temporary interstitial brachytherapy. The term "brachytherapy," as used herein, refers to radiation therapy delivered by a spatially confined radioactive material inserted into the body at or near a tumor or other proliferative tissue disease site. The term is intended without limitation to include exposure to radioactive isotopes (*e.g.,* At-211, I-131, I-125, Y-90, Re-186, Re-188, Sm-153, Bi-212, P-32, and radioactive isotopes of Lu). Suitable radiation sources for use as a cell conditioner as provided herein include both solids and liquids. By way of non-limiting example, the radiation source can be a radionuclide, such as I-125, I-131, Yb-169, Ir-192 as a solid source, I-125 as a solid source, or other radionuclides that emit photons, beta particles, gamma radiation, or other therapeutic rays. The radioactive material can also be a fluid made from any solution of radionuclide(s), *e.g.,* a solution of I-125 or I-131, or a radioactive fluid can be produced using a slurry of a suitable fluid containing small particles of solid radionuclides, such as Au-198, Y-90. Moreover, the radionuclide(s) can be embodied in a gel or radioactive micro spheres.

[00599] Without being limited by any theory, the compounds as provided herein, or a pharmaceutically acceptable form (*e.g.,* pharmaceutically acceptable salts, hydrates, solvates, isomers, prodrugs, and isotopically labeled derivatives) thereof, or pharmaceutical compositions as provided herein, can render abnormal cells more sensitive to treatment with radiation for purposes of killing and/or inhibiting the growth of such cells. Accordingly, provided herein is a method for sensitizing abnormal cells in a subject to treatment with radiation which comprises administering to the subject an amount of a compound as provided herein or pharmaceutically acceptable forms (*e.g.,* pharmaceutically acceptable salts, hydrates, solvates, isomers, prodrugs, and isotopically labeled derivatives) thereof, which amount is effective is sensitizing abnormal cells to treatment with radiation. The amount of the compound used in this method can be determined according to the means for ascertaining effective amounts of such compounds described herein.

[00600] The compounds as provided herein, or a pharmaceutically acceptable form (*e.g.,* pharmaceutically acceptable salts, hydrates, solvates, isomers, prodrugs, and isotopically labeled derivatives) thereof, or pharmaceutical compositions as provided herein, can be used in combination with an amount of one or more substances selected from anti-angiogenesis agents, signal transduction inhibitors, and antiproliferative agents, glycolysis inhibitors, or autophagy inhibitors.

[00601] Anti-angiogenesis agents, such as MMP-2 (matrix-metalloproteinase 2) inhibitors, MMP-9 (matrix-metalloprotienase 9) inhibitors, and COX-11 (cyclooxygenase 11) inhibitors, can be used in conjunction with a compound as provided herein and pharmaceutical compositions described herein. Anti-angiogenesis agents include, for example, rapamycin, temsirolimus (CCI-779), everolimus (RAD001), sorafenib, sunitinib, and bevacizumab. Examples of useful COX-II inhibitors include CELEBREX^{TM} (alecoxib), valdecoxib, and rofecoxib. Examples of useful matrix metalloproteinase inhibitors are described in WO 96/33172 (published October 24,

1996), WO 96/27583 (published March 7, 1996), European Patent Application No. 97304971.1 (filed July 8, 1997), European Patent Application No. 99308617.2 (filed October 29, 1999), WO 98/07697 (published February 26, 1998), WO 98/03516 (published January 29, 1998), WO 98/34918 (published August 13, 1998), WO 98/34915 (published August 13, 1998), WO 98/33768 (published August 6, 1998), WO 98/30566 (published July 16, 1998), European Patent Publication 606,046 (published July 13, 1994), European Patent Publication 931, 788 (published July 28, 1999), WO 90/05719 (published May 31, 1990), WO 99/52910 (published October 21, 1999), WO 99/52889 (published October 21, 1999), WO 99/29667 (published June 17, 1999), PCT International Application No. PCT/IB98/01113 (filed July 21, 1998), European Patent Application No. 99302232.1 (filed March 25, 1999), Great Britain Patent Application No. 9912961.1 (filed June 3, 1999), United States Provisional Application No. 60/148,464 (filed August 12, 1999), United States Patent 5,863,949 (issued January 26, 1999), United States Patent 5,861,510 (issued January 19, 1999), and European Patent Publication 780,386 (published June 25, 1997), all of which are incorporated herein in their entireties by reference. In some embodiments, MMP-2 and MMP-9 inhibitors are those that have little or no activity inhibiting MMP-1. Other embodiments include those that selectively inhibit MMP-2 and/or AMP-9 relative to the other matrix-metalloproteinases (*i.e.,* MAP-1, MMP-3, MMP-4, MMP-5, MMP-6, MMP- 7, MMP-8, MMP-10, MMP-ll, MMP-12, andMMP-13). Some non-limiting examples of MMP inhibitors are AG-3340, RO 32-3555, and RS 13-0830.

[00602] Autophagy inhibitors include, but are not limited to, chloroquine, 3-methyladenine, hydroxychloroquine (Plaquenil™), bafilomycin A1, 5-amino-4-imidazole carboxamide riboside (AICAR), okadaic acid, autophagy-suppressive algal toxins which inhibit protein phosphatases of type 2A or type 1, analogues of cAMP, and drugs which elevate cAMP levels such as adenosine, LY204002, N6-mercaptopurine riboside, and vinblastine. In addition, antisense or siRNA that inhibits expression of proteins including, but not limited to ATG5 (which are implicated in autophagy), can also be used.

[00603] In some embodiments, provided herein is a method of and/or a pharmaceutical composition for treating a cardiovascular disease in a subject which comprises an amount of a compound as provided herein, or a pharmaceutically acceptable form (*e.g.,* pharmaceutically acceptable salts, hydrates, solvates, isomers, prodrugs, and isotopically labeled derivatives) thereof, and an amount of one or more therapeutic agents use for the treatment of cardiovascular diseases.

[00604] Exemplary agents for use in cardiovascular disease applications are anti-thrombotic agents, *e.g.,* prostacyclin and salicylates, thrombolytic agents, *e.g.,* streptokinase, urokinase, tissue plasminogen activator (TPA) and anisoylated plasminogen-streptokinase activator complex (APSAC), anti-platelets agents, *e.g.,* acetyl-salicylic acid (ASA) and clopidrogel, vasodilating agents, *e.g.,* nitrates, calcium channel blocking drugs, anti-proliferative agents, *e.g.,* colchicine and alkylating agents, intercalating agents, growth modulating factors such as interleukins, transformation growth factor-beta and congeners of platelet derived growth factor, monoclonal antibodies directed against growth factors, anti-inflammatory agents, both steroidal and non-steroidal, and other agents that can modulate vessel tone, function, arteriosclerosis, and the healing response to vessel or organ injury post intervention. Antibiotics can also be included in combinations or coatings. Moreover, a coating can be used to

effect therapeutic delivery focally within the vessel wall. By incorporation of the active agent in a swellable polymer, the active agent will be released upon swelling of the polymer.

[00605] The compounds as provided herein, or a pharmaceutically acceptable form (*e.g.*, pharmaceutically acceptable salts, hydrates, solvates, isomers, prodrugs, and isotopically labeled derivatives) thereof, or pharmaceutical compositions as provided herein, can be formulated or administered in conjunction with liquid or solid tissue barriers also known as lubricants. Examples of tissue barriers include, but are not limited to, polysaccharides, polyglycans, seprafilm, interceed and hyaluronic acid.

[00606] Medicaments which can be administered in conjunction with the compounds as provided herein, or a pharmaceutically acceptable form (*e.g.*, pharmaceutically acceptable salts, hydrates, solvates, isomers, prodrugs, and isotopically labeled derivatives) thereof, include any suitable drugs usefully delivered by inhalation for example, analgesics, *e.g.*, codeine, dihydromorphine, ergotamine, fentanyl or morphine; anginal preparations, *e.g.*, diltiazem; antiallergics, *e.g.* cromoglycate, ketotifen or nedocromil; anti-infectives, *e.g.*, cephalosporins, penicillins, streptomycin, sulphonamides, tetracyclines or pentamidine; antihistamines, *e.g.*, methapyrilene; anti-inflammatories, *e.g.*, beclomethasone, flunisolide, budesonide, tipredane, triamcinolone acetonide or fluticasone; antitussives, *e.g.*, noscapine; bronchodilators, *e.g.*, ephedrine, adrenaline, fenoterol, formoterol, isoprenaline, metaproterenol, phenylephrine, phenylpropanolamine, pirbuterol, reproterol, rimiterol, salbutamol, salmeterol, terbutalin, isoetharine, tulobuterol, orciprenaline or (-)-4-amino-3,5-dichloro-α-[[[6-[2-(2-pyridinyl)ethoxy]hexyl]-amino]methyl]benzenemethanol; diuretics, *e.g.*, amiloride; anticholinergics *e.g.*, ipratropium, atropine or oxitropium; hormones, *e.g.*, cortisone, hydrocortisone or prednisolone; xanthines *e.g.*, aminophylline, choline theophyllinate, lysine theophyllinate or theophylline; and therapeutic proteins and peptides, *e.g.*, insulin or glucagon. It will be clear to a person skilled in the art that, where appropriate, the medicaments can be used in the form of salts (*e.g.*, as alkali metal or amine salts or as acid addition salts) or as esters (*e.g.*, lower alkyl esters) to optimize the activity and/or stability of the medicament.

[00607] Other exemplary therapeutic agents useful for a combination therapy include, but are not limited to, agents as described above, radiation therapy, hormone antagonists, hormones and their releasing factors, thyroid and antithyroid drugs, estrogens and progestins, androgens, adrenocorticotropic hormone; adrenocortical steroids and their synthetic analogs; inhibitors of the synthesis and actions of adrenocortical hormones, insulin, oral hypoglycemic agents, and the pharmacology of the endocrine pancreas, agents affecting calcification and bone turnover: calcium, phosphate, parathyroid hormone, vitamin D, calcitonin, vitamins such as water-soluble vitamins, vitamin B complex, ascorbic acid, fat-soluble vitamins, vitamins A, K, and E, growth factors, cytokines, chemokines, muscarinic receptor agonists and antagonists; anticholinesterase agents; agents acting at the neuromuscular junction and/or autonomic ganglia; catecholamines, sympathomimetic drugs, and adrenergic receptor agonists or antagonists; and 5-hydroxytryptamine (5-HT, serotonin) receptor agonists and antagonists.

[00608] Therapeutic agents can also include agents for pain and inflammation such as histamine and histamine antagonists, bradykinin and bradykinin antagonists, 5-hydroxytryptamine (serotonin), lipid substances that are generated by biotransformation of the products of the selective hydrolysis of membrane phospholipids, eicosanoids, prostaglandins, thromboxanes, leukotrienes, aspirin, nonsteroidal anti-inflammatory agents, analgesic-

antipyretic agents, agents that inhibit the synthesis of prostaglandins and thromboxanes, selective inhibitors of the inducible cyclooxygenase, selective inhibitors of the inducible cyclooxygenase-2, autacoids, paracrine hormones, somatostatin, gastrin, cytokines that mediate interactions involved in humoral and cellular immune responses, lipid-derived autacoids, eicosanoids, β-adrenergic agonists, ipratropium, glucocorticoids, methylxanthines, sodium channel blockers, opioid receptor agonists, calcium channel blockers, membrane stabilizers and leukotriene inhibitors.

[00609] Additional therapeutic agents contemplated herein include diuretics, vasopressin, agents affecting the renal conservation of water, rennin, angiotensin, agents useful in the treatment of myocardial ischemia, anti-hypertensive agents, angiotensin converting enzyme inhibitors, β-adrenergic receptor antagonists, agents for the treatment of hypercholesterolemia, and agents for the treatment of dyslipidemia.

[00610] Other therapeutic agents contemplated herein include drugs used for control of gastric acidity, agents for the treatment of peptic ulcers, agents for the treatment of gastroesophageal reflux disease, prokinetic agents, antiemetics, agents used in irritable bowel syndrome, agents used for diarrhea, agents used for constipation, agents used for inflammatory bowel disease, agents used for biliary disease, agents used for pancreatic disease. Therapeutic agents include, but are not limited to, those used to treat protozoan infections, drugs used to treat Malaria, Amebiasis, Giardiasis, Trichomoniasis, Trypanosomiasis, and/or Leishmaniasis, and/or drugs used in the chemotherapy of helminthiasis. Other therapeutic agents include, but are not limited to, antimicrobial agents, sulfonamides, trimethoprim-sulfamethoxazole quinolones, and agents for urinary tract infections, penicillins, cephalosporins, and other, β-Lactam antibiotics, an agent containing an aminoglycoside, protein synthesis inhibitors, drugs used in the chemotherapy of tuberculosis, mycobacterium avium complex disease, and leprosy, antifungal agents, antiviral agents including nonretroviral agents and antiretroviral agents.

[00611] Examples of therapeutic antibodies that can be combined with a subject compound include but are not limited to anti-receptor tyrosine kinase antibodies (cetuximab, panitumumab, trastuzumab), anti CD20 antibodies (rituximab, tositumomab), and other antibodies such as alemtuzumab, bevacizumab, and gemtuzumab.

[00612] Moreover, therapeutic agents used for immunomodulation, such as immunomodulators, immunosuppressive agents, tolerogens, and immunostimulants are contemplated by the methods herein. In addition, therapeutic agents acting on the blood and the blood-forming organs, hematopoietic agents, growth factors, minerals, and vitamins, anticoagulant, thrombolytic, and antiplatelet drugs.

[00613] For treating renal carcinoma, one can combine a a compound as provided herein, or a pharmaceutically acceptable form (*e.g.,* pharmaceutically acceptable salts, hydrates, solvates, isomers, prodrugs, and isotopically labeled derivatives) thereof, or pharmaceutical compositions as provided herein, with sorafenib and/or avastin. For treating an endometrial disorder, one can combine a compound as provided herein with doxorubincin, taxotere (taxol), and/or cisplatin (carboplatin). For treating ovarian cancer, one can combine a compound as provided herein with cisplatin (carboplatin), taxotere, doxorubincin, topotecan, and/or tamoxifen. For treating breast cancer, one can combine a compound as provided herein with taxotere (taxol), gemcitabine (capecitabine), tamoxifen, letrozole, tarceva, lapatinib, PD0325901, avastin, herceptin, OSI-906, and/or OSI-930. For treating lung

cancer, one can combine a compound as provided herein with taxotere (taxol), gemcitabine, cisplatin, pemetrexed, Tarceva, PD0325901, and/or avastin.

[00614] In some embodiments, the disorder to be treated, prevented and/or managed is hematological cancer, *e.g.*, lymphoma (*e.g.*, T-cell lymphoma; NHL), myeloma (*e.g.*, multiple myeloma), and leukemia (*e.g.*, CLL), and a compound provided herein is used in combination with: HDAC inhibitors such as vorinostat and romidepsin; mTOR inhibitors such as everolmus; anti-folates such as pralatrexate; nitrogen mustard such as bendamustine; gemcitabine, optionally in further combination with oxaliplatin; rituximab.cyclophosphamide combination; PI3K inhibitors such as GS-1101, XL 499, GDC-0941, and AMG-319; or BTK inhibitors such as ibrutinib and AVL-292.

[00615] In certain embodiments, wherein inflammation (*e.g.*, arthritis, asthma) is treated, prevented and/or managed, a compound provided herein can be combined with, for example: PI3K inhibitors such as GS-1101, XL 499, GDC-0941, and AMG-319; BTK inhibitors such as ibrutinib and AVL-292; JAK inhibitors such as tofacitinib, fostamatinib, and GLPG0636.

[00616] In certain embodiments wherein asthma is treated, prevented and/or managed, a compound provided herein can be combined with, for example: beta 2-agonists such as, but not limited to, albuterol (Proventil®, or Ventolin®), salmeterol (Serevent®), formoterol (Foradil®), metaproterenol (Alupent®), pirbuterol (MaxAir®), and terbutaline sulfate; corticosteroids such as, but not limited to, budesonide (*e.g.*, Pulmicort®), flunisolide (*e.g.*, AeroBid Oral Aerosol Inhaler® or Nasalide Nasal Aerosol®), fluticasone (*e.g.*, Flonase® or Flovent®) and triamcinolone (*e.g.*, Azmacort®); mast cell stabilizers such as cromolyn sodium (*e.g.*, Intal® or Nasalcrom®) and nedocromil (*e.g.*, Tilade®); xanthine derivatives such as, but not limited to, theophylline (*e.g.*, Aminophyllin®, Theo-24® or Theolair®); leukotriene receptor antagonists such as, but are not limited to, zafirlukast (Accolate®), montelukast (Singulair®), and zileuton (Zyflo®); and adrenergic agonists such as, but are not limited to, epinephrine (Adrenalin®, Bronitin®, EpiPen® or Primatene Mist®).

[00617] In certain embodiments wherein arthritis is treated, prevented and/or managed, a compound provided herein can be combined with, for example: TNF antagonist (*e.g.*, a TNF antibody or fragment, a soluble TNF receptor or fragment, fusion proteins thereof, or a small molecule TNF antagonist); an antirheumatic (*e.g.*, methotrexate, auranofin, aurothioglucose, azathioprine, etanercept, gold sodium thiomalate, hydroxychloroquine sulfate, leflunomide, sulfasalzine); a muscle relaxant; a narcotic; a non-steroid anti-inflammatory drug (NSAID); an analgesic; an anesthetic; a sedative; a local anesthetic; a neuromuscular blocker; an antimicrobial (*e.g.*, an aminoglycoside, an antifungal, an antiparasitic, an antiviral, a carbapenem, cephalosporin, a fluoroquinolone, a macrolide, a penicillin, a sulfonamide, a tetracycline, another antimicrobial); an antipsoriatic; a corticosteroid; an anabolic steroid; a cytokine or a cytokine antagonist.

[00618] In certain embodiments wherein psoriasis is treated, prevented and/or managed, a compound provided herein can be combined with, for example: budesonide, epidermal growth factor, corticosteroids, cyclosporine, sulfasalazine, aminosalicylates, 6-mercaptopurine, azathioprine, metronidazole, lipoxygenase inhibitors, mesalamine, olsalazine, balsalazide, antioxidants, thromboxane inhibitors, IL-1 receptor antagonists, anti-IL-1β monoclonal antibodies, anti-IL-6 monoclonal antibodies, growth factors, elastase inhibitors, pyridinyl-

imidazole compounds, antibodies or agonists of TNF, LT, IL-1, IL-2, IL-6, IL-7, IL-8, IL-15, IL-16, IL-18, EMAP-II, GM-CSF, FGF, and PDGF, antibodies of CD2, CD3, CD4, CD8, CD25, CD28, CD30, CD40, CD45, CD69, CD90 or their ligands, methotrexate, cyclosporine, FK506, rapamycin, mycophenolate mofetil, leflunomide, NSAIDs, ibuprofen, corticosteroids, prednisolone, phosphodiesterase inhibitors, adenosine agonists, antithrombotic agents, complement inhibitors, adrenergic agents, IRAK, NIK, IKK, p38, MAP kinase inhibitors, IL-1β converting enzyme inhibitors, TNFα converting enzyme inhibitors, T-cell signaling inhibitors, metalloproteinase inhibitors, sulfasalazine, azathioprine, 6-mercaptopurines, angiotensin converting enzyme inhibitors, soluble cytokine receptors, soluble p55 TNF receptor, soluble p75 TNF receptor, sIL-1RI, sIL-1RII, sIL-6R, anti-inflammatory cytokines, IL-4, IL-10, IL-11, IL-13 and TGFβ.

[00619] In certain embodiments wherein fibrosis or fibrotic condition of the bone marrow is treated, prevented and/or managed, a compound provided herein can be combined with, for example, a Jak2 inhibitor (including, but not limited to, INCB018424, XL019, TG101348, or TG101209), an immunomodulator, *e.g.*, an IMID® (including, but not limited to thalidomide, lenalidomide, or panolinomide), hydroxyurea, an androgen, erythropoietic stimulating agents, prednisone, danazol, HDAC inhibitors, or other agents or therapeutic modalities (*e.g.*, stem cell transplants, or radiation).

[00620] In certain embodiments wherein fibrosis or fibrotic condition of the heart is treated, prevented and/or managed, a compound provided herein can be combined with, for example, eplerenone, furosemide, pycnogenol, spironolactone, TcNC100692, torasemide (*e.g.*, prolonged release form of torasemide), or combinations thereof.

[00621] In certain embodiments wherein fibrosis or fibrotic condition of the kidney is treated, prevented and/or managed, a compound provided herein can be combined with, for example, cyclosporine, cyclosporine A, daclizumab, everolimus, gadofoveset trisodium (ABLAVAR®), imatinib mesylate (GLEEVEC®), matinib mesylate, methotrexate, mycophenolate mofetil, prednisone, sirolimus, spironolactone, STX-100, tamoxifen, TheraCLEC™, or combinations thereof.

[00622] In certain embodiments wherein fibrosis or fibrotic condition of the skin is treated, prevented and/or managed, a compound provided herein can be combined with, for example, Bosentan (Tracleer), p144, pentoxifylline; pirfenidone; pravastatin, STI571, Vitamin E, or combinations thereof.

[00623] In certain embodiments wherein fibrosis or fibrotic condition of the gastrointestinal system is treated, prevented and/or managed, a compound provided herein can be combined with, for example, ALTU-135, bucelipase alfa (INN), DCI1020, EUR-1008 (ZENPEP™), ibuprofen, Lym-X-Sorb powder, pancrease MT, pancrelipase (*e.g.*, pancrelipase delayed release), pentade canoic acid (PA), repaglinide, TheraCLEC™, triheptadecanoin (THA), ULTRASE MT20, ursodiol, or combinations thereof.

[00624] In certain embodiments wherein fibrosis or fibrotic condition of the lung is treated, prevented and/or managed, a compound provided herein can be combined with, for example, 18-FDG, AB0024, ACT-064992 (macitentan), aerosol interferon-gamma, aerosolized human plasma-derived alpha-1 antitrypsin, alpha1-proteinase inhibitor, ambrisentan, amikacin, amiloride, amitriptyline, anti-pseudomonas IgY gargle, ARIKACE™, AUREXIS® (tefibazumab), AZAPRED, azathioprine, azithromycin, azithromycin, AZLI, aztreonam lysine,

BIBF1120, Bio-25 probiotic, bosentan, Bramitob® , calfactant aerosol, captopril, CC-930, ceftazidime, ceftazidime, cholecalciferol (Vitamin D3), ciprofloxacin (CIPRO®, BAYQ3939), CNTO 888, colistin CF, combined Plasma Exchange (PEX), rituximab, and corticosteroids, cyclophosphamide, dapsone, dasatinib, denufosol tetrasodium (INS37217), dornase alfa (PULMOZYME®), EPI-hNE4, erythromycin, etanercept, FG-3019, fluticasone, FTI, GC1008, GS-9411, hypertonic saline, ibuprofen, iloprost inhalation, imatinib mesylate (GLEEVEC®), inhaled sodium bicarbonate, inhaled sodium pyruvate, interferon gamma-1b, interferon-alpha lozenges, isotonic saline, IW001, KB001, losartan, lucinactant, mannitol, meropenem, meropenem infusion, miglustat, minocycline, Moli1901, MP-376 (levofloxacin solution for inhalation), mucoid exopolysaccharide P. aeruginosa immune globulin IV, mycophenolate mofetil, n-acetylcysteine, N-acetylcysteine (NAC), NaCl 6%, nitric oxide for inhalation, obramycin, octreotide, oligoG CF-5/20, Omalizumab, pioglitazone, piperacillin-tazobactam, pirfenidone, pomalidomide (CC-4047), prednisone, prevastatin, PRM-151, QAX576, rhDNAse, SB656933, SB-656933-AAA, sildenafil, tamoxifen, technetium [Tc-99m] sulfur colloid and Indium [In-111] DTPA, tetrathiomolybdate, thalidomide, ticarcillin-clavulanate, tiotropium bromide, tiotropium RESPIMAT® inhaler, tobramycin (GERNEBCIN®), treprostinil, uridine, valganciclovir (VALCYTE®), vardenafil, vitamin D3, xylitol, zileuton, or combinations thereof.

[00625] In certain embodiments wherein fibrosis or fibrotic condition of the liver is treated, prevented and/or managed, a compound provided herein can be combined with, for example, adefovir dipivoxil, candesartan, colchicine, combined ATG, mycophenolate mofetil, and tacrolimus, combined cyclosporine microemulsion and tacrolimus, elastometry, everolimus, FG-3019, Fuzheng Huayu, GI262570, glycyrrhizin (monoammonium glycyrrhizinate, glycine, L-cysteine monohydrochloride), interferon gamma-1b, irbesartan, losartan, oltipraz, ORAL IMPACT®, peginterferon alfa-2a, combined peginterferon alfa-2a and ribavirin, peginterferon alfa-2b (SCH 54031), combined peginterferon alpha-2b and ribavirin, praziquantel, prazosin, raltegravir, ribavirin (REBETOL®, SCH 18908), ritonavir-boosted protease inhibitor, pentoxyphilline, tacrolimus, tauroursodeoxycholic acid, tocopherol, ursodiol, warfarin, or combinations thereof.

[00626] In certain embodiments wherein cystic fibrosis is treated, prevented and/or managed, a compound provided herein can be combined with, for example, 552-02, 5-methyltetrahydrofolate and vitamin B12, Ad5-CB-CFTR, Adeno-associated virus-CFTR vector, albuterol, alendronate, alpha tocopherol plus ascorbic acid, amiloride HCl, aquADEKTM, ataluren (PTC124), AZD1236, AZD9668, azithromycin, bevacizumab, biaxin (clarithromycin), BIIL 283 BS (amelubent), buprofen, calcium carbonate, ceftazidime, cholecalciferol, choline supplementation, CPX, cystic fibrosis transmembrane conductance regulator, DHA-rich supplement, digitoxin, cocosahexaenoic acid (DHA), doxycycline, ECGC, ecombinant human IGF-1, educed glutathione sodium salt, ergocalciferol (vitamin D2), fluorometholone, gadobutrol (GADOVIST®, BAY86-4875), gentamicin, ghrelin, glargine, glutamine, growth hormone, GS-9411, H5.001CBCFTR, human recombinant growth hormone, hydroxychloroquine, hyperbaric oxygen, hypertonic saline, IH636 grape seed proanthocyanidin extract, insulin, interferon gamma-1b, IoGen (molecular iodine), iosartan potassium, isotonic saline, itraconazole, IV gallium nitrate (GANITE®) infusion, ketorolac acetate, lansoprazole, L-arginine, linezolid, lubiprostone, meropenem, miglustat, MP-376 (levofloxacin solution for inhalation), normal saline IV, Nutropin AQ, omega-3 triglycerides,

pGM169/GL67A, pGT-1 gene lipid complex, pioglitazone, PTC124, QAU145, salmeterol, SB656933, SB656933, simvastatin, sitagliptin, sodium 4-phenylbutyrate, standardized turmeric root extract, tgAAVCF, TNF blocker, TOBI, tobramycin, tocotrienol, unconjugated Isoflavones 100, vitamin: choline bitartrate (2-hydroxyethyl) trimethylammonium salt 1:1, VX-770, VX-809, Zinc acetate, or combinations thereof.

[00627] In some embodiments, a compound provided herein is administered in combination with an agent that inhibits IgE production or activity. In some embodiments, the PI3K inhibitor (*e.g.*, PI3Kδ inhibitor) is administered in combination with an inhibitor of mTOR. Agents that inhibit IgE production are known in the art and they include but are not limited to one or more of TEI-9874, 2-(4-(6-cyclohexyloxy-2-naphtyloxy)phenylacetamide)benzoic acid, rapamycin, rapamycin analogs (*i.e.* rapalogs), TORC1 inhibitors, TORC2 inhibitors, and any other compounds that inhibit mTORC1 and mTORC2. Agents that inhibit IgE activity include, for example, anti-IgE antibodies such as for example Omalizumab and TNX-901.

[00628] In certain embodiments wherein scleroderma is treated, prevented and/or managed, a compound provided herein can be combined with, for example: an immunosuppressant (*e.g.*, methotrexate, azathioprine (Imuran®), cyclosporine, mycophenolate mofetil (Cellcept®), and cyclophosphamide (Cytoxan®)); T-cell-directed therapy (*e.g.*, halofuginone, basiliximab, alemtuzumab, abatacept, rapamycin); B-cell directed therapy (*e.g.*, rituximab); autologous hematopoietic stem cell transplantation; a chemokine ligand receptor antagonist (*e.g.*, an agent that targets the CXCL12/CSCR4 axis (e.g., AMD3100)); a DNA methylation inhibitor (*e.g.*, 5-azacytidine); a histone dactylase inhibitor (*e.g.*, trichostatin A); a statin (*e.g.*, atorvastatin, simvastatin, pravastatin); an endothelin receptor antagonist (*e.g.*, Bosentan®); a phosphodiesterase type V inhibitor (e.g., Sildenafil®); a prostacyclin analog (*e.g.*, trepostinil); an inhibitor of cytokine synthesis and/or signaling (*e.g.*, Imatinib mesylate, Rosiglitazone, rapamycin, antitransforming growth factor β1 (anti-TGFβ1) antibody, mycophenolate mofetil, an anti-IL-6 antibody (*e.g.*, tocilizumab)); corticosteroids; nonsteroidal anti-inflammatory drugs; light therapy; and blood pressure medications (*e.g.*, ACE inhibitors).

[00629] In certain embodiments wherein inflammatory myopathies are treated, prevented and/or managed, a compound provided herein can be combined with, for example: topical creams or ointments (*e.g.*, topical corticosteroids, tacrolimus, pimecrolimus); cyclosporine (*e.g.*, topical cyclosporine); an anti-interferon therapy, *e.g.*, AGS-009, Rontalizumab (rhuMAb IFNalpha), Vitamin D3, Sifalimumab (MEDI-545), AMG 811, IFNα Kinoid, or CEP33457. In some embodiments, the other therapy is an IFN-α therapy, *e.g.*, AGS-009, Rontalizumab, Vitamin D3, Sifalimumab (MEDI-545) or IFNα Kinoid; corticosteroids such as prednisone (*e.g.*, oral prednisone); immunosuppressive therapies such as methotrexate (Trexall®, Methotrexate®, Rheumatrex®), azathioprine (Azasan®, Imuran®), intravenous immunoglobulin, tacrolimus (Prograf®), pimecrolimus, cyclophosphamide (Cytoxan®), and cyclosporine (Gengraf®, Neoral®, Sandimmune®); anti-malarial agents such as hydroxychloroquine (Plaquenil®) and chloroquine (Aralen®); total body irradiation; rituximab (Rituxan®); TNF inhibitors (e.g., etanercept (Enbrel®), infliximab (Remicade®)); AGS-009; Rontalizumab (rhuMAb IFNalpha); Vitamin D3; Sifalimumab (MEDI-545); AMG 811; IFNα Kinoid,; CEP33457; agents that inhibit IgE production such as TEI-9874, 2-(4-(6-cyclohexyloxy-2-naphtyloxy)phenylacetamide)benzoic acid, rapamycin, rapamycin analogs (*i.e.* rapalogs), TORC1 inhibitors, TORC2 inhibitors, and any other compounds that inhibit mTORC1 and

mTORC2; agents that inhibit IgE activity such as anti-IgE antibodies (*e.g.*, Omalizumab and TNX-90); and additional therapies such as physical therapy, exercise, rest, speech therapy, sun avoidance, heat therapy, and surgery.

[00630] In certain embodiments wherein myositis (*e.g.*, dermatomysitis) is treated, prevented and/or managed, a compound provided herein can be combined with, for example: corticosteroids; corticosteroid sparing agents such as, but not limited to, azathioprine and methotrexate; intravenous immunoglobulin; immunosuppressive agents such as, but not limited to, tacrolimus, cyclophosphamide and cyclosporine; rituximab; TNFα inhibitors such as, but not limited to, etanercept and infliximab; growth hormone; growth hormone secretagogues such as, but not limited to, MK-0677, L-162752, L-163022, NN703 ipamorelin, hexarelin, GPA-748 (KP102, GHRP-2), and LY444711 (Eli Lilly); other growth hormone release stimulators such as, but not limited to, Geref, GHRH (1-44), Somatorelin (GRF 1-44), ThGRF genotropin, L-DOPA, glucagon, and vasopressin; and insulin-like growth factor.

[00631] In certain embodiments wherein Sjögren's syndrome is treated, prevented and/or managed, a compound provided herein can be combined with, for example: pilocarpine; cevimeline; nonsteroidal anti-inflammatory drugs; arthritis medications; antifungal agents; cyclosporine; hydroxychloroquine; prednisone; azathioprine; and cyclophamide.

[00632] Further therapeutic agents that can be combined with a subject compound can be found in Goodman and Gilman's "*The Pharmacological Basis of Therapeutics*" Tenth Edition edited by Hardman, Limbird and Gilman or the Physician's Desk Reference, both of which are incorporated herein by reference in their entirety.

[00633] The compounds described herein can be used in combination with the agents provided herein or other suitable agents, depending on the condition being treated. Hence, in some embodiments, the compounds as provided herein will be co-administered with other agents as described above. When used in combination therapy, the compounds described herein can be administered with the second agent simultaneously or separately. This administration in combination can include simultaneous administration of the two agents in the same dosage form, simultaneous administration in separate dosage forms, and separate administration. That is, a compound described herein and any of the agents described above can be formulated together in the same dosage form and administered simultaneously. Alternatively, a compound as provided herein and any of the agents described above can be simultaneously administered, wherein both the agents are present in separate formulations. In another alternative, a compound as provided herein can be administered just followed by and any of the agents described above, or vice versa. In the separate administration protocol, a compound as provided herein and any of the agents described above can be administered a few minutes apart, or a few hours apart, or a few days apart.

[00634] Administration of the compounds as provided herein can be effected by any method that enables delivery of the compounds to the site of action. An effective amount of a compound as provided herein can be administered in either single or multiple doses by any of the accepted modes of administration of agents having similar utilities, including rectal, buccal, intranasal and transdermal routes, by intra-arterial injection, intravenously, intraperitoneally, parenterally, intramuscularly, subcutaneously, orally, topically, as an inhalant, or via an impregnated or coated device such as a stent, for example, or an artery-inserted cylindrical polymer.

[00635] When a compound as provided herein is administered in a pharmaceutical composition that comprises one or more agents, and the agent has a shorter half-life than the compound as provided herein, unit dose forms of the agent and the compound as provided herein can be adjusted accordingly.

[00636] The examples and preparations provided below further illustrate and exemplify the compounds as disclosed herein and methods of preparing such compounds. It is to be understood that the scope of the present disclosure is not limited in any way by the scope of the following examples and preparations. In the following examples molecules with a single chiral center, unless otherwise noted, exist as a racemic mixture. Those molecules with two or more chiral centers, unless otherwise noted, exist as a racemic mixture of diastereomers. Single enantiomers/diastereomers can be obtained by methods known to those skilled in the art.

EXAMPLES

Chemical Examples

[00637] The chemical entities described herein can be synthesized according to one or more illustrative schemes herein and/or techniques well known in the art.

[00638] Unless specified to the contrary, the reactions described herein take place at atmospheric pressure, generally within a temperature range from -10 °C to 200 °C. Further, except as otherwise specified, reaction times and conditions are intended to be approximate, *e.g.,* taking place at about atmospheric pressure within a temperature range of about -10 °C to about 110 °C over a period that is, for example, about 1 to about 24 hours; reactions left to run overnight in some embodiments can average a period of about 16 hours.

[00639] The terms "solvent," "organic solvent," or "inert solvent" each mean a solvent inert under the conditions of the reaction being described in conjunction therewith including, for example, benzene, toluene, acetonitrile, tetrahydrofuran ("THF"), dimethylformamide ("DMF"), chloroform, methylene chloride (or dichloromethane), diethyl ether, methanol, N-methylpyrrolidone ("NMP"), pyridine and the like. Unless specified to the contrary, the solvents used in the reactions described herein are inert organic solvents. Unless specified to the contrary, for each gram of the limiting reagent, one cc (or mL) of solvent constitutes a volume equivalent.

[00640] Isolation and purification of the chemical entities and intermediates described herein can be effected, if desired, by any suitable separation or purification procedure such as, for example, filtration, extraction, crystallization, column chromatography, thin-layer chromatography or thick-layer chromatography, or a combination of these procedures. Specific illustrations of suitable separation and isolation procedures are given by reference to the examples hereinbelow. However, other equivalent separation or isolation procedures can also be used.

[00641] When desired, the (R)- and (S)-isomers of the non-limiting exemplary compounds, if present, can be resolved by methods known to those skilled in the art, for example by formation of diastereoisomeric salts or complexes which can be separated, for example, by crystallization; via formation of diastereoisomeric derivatives which can be separated, for example, by crystallization, gas-liquid or liquid chromatography; selective reaction of

one enantiomer with an enantiomer-specific reagent, for example enzymatic oxidation or reduction, followed by separation of the modified and unmodified enantiomers; or gas-liquid or liquid chromatography in a chiral environment, for example on a chiral support, such as silica with a bound chiral ligand or in the presence of a chiral solvent. Alternatively, a specific enantiomer can be synthesized by asymmetric synthesis using optically active reagents, substrates, catalysts or solvents, or by converting one enantiomer to the other by asymmetric transformation.

[00642] The compounds described herein can be optionally contacted with a pharmaceutically acceptable acid to form the corresponding acid addition salts. Also, the compounds described herein can be optionally contacted with a pharmaceutically acceptable base to form the corresponding basic addition salts.

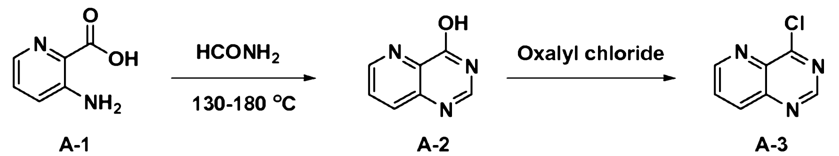
[00643] In some embodiments, disclosed compounds can generally be synthesized by an appropriate combination of generally well known synthetic methods. Techniques useful in synthesizing these chemical entities are both readily apparent and accessible to those of skill in the relevant art, based on the instant disclosure. Many of the optionally substituted starting compounds and other reactants are commercially available, *e.g.,* from Aldrich Chemical Company (Milwaukee, WI) or can be readily prepared by those skilled in the art using commonly employed synthetic methodology.

[00644] The discussion below is offered to illustrate certain of the diverse methods available for use in making the disclosed compounds and is not intended to limit the scope of reactions or reaction sequences that can be used in preparing the compounds provided herein.

<u>General Synthetic Methods</u>

[00645] The compounds herein being generally described, it will be more readily understood by reference to the following examples, which are included merely for purposes of illustration of certain aspects and embodiments, and are not intended.

(i) ***General methods for the synthesis of Cl-W_d and TsO-W_d heterocycles:***



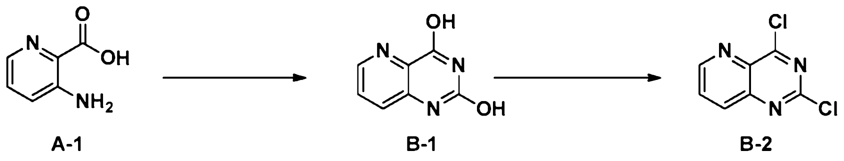
Method A:

[00646] General conditions for the preparation of 4-chloropyrido[3,2-d]pyrimidine:

[00647] 3-Aminopicolinic acid (**A-1**) (30 g, 217 mmol, 1.0 eq) is suspended in formamide (75 mL, 1.88 mol, 8.66 eq). The resulting mixture is stirred at 140 °C for 1 h and at 170 °C for 1 h and then at 180 °C for an additional 1 h. The mixture is cooled to RT and filtered. The filter cake is washed with water, and dried *in vacuo* to afford the product, pyrido[3,2-d]pyrimidin-4-ol (**A-2**).

[00648] To a stirred solution of pyrido[3,2-d]pyrimidin-4-ol (**A-2**) (16 g, 109 mmol, 1.0 eq) and DMF (0.4 mL) in DCM (200 mL) at RT, oxalyl chloride (23.2 mL, 272 mmol, 2.5 eq) is added dropwise (over 5 min) and the

resulting mixture is stirred at reflux overnight. The mixture is allowed to cool to RT and concentrated *in vacuo*. The residue is diluted with water (200 mL), neutralized with saturated aqueous $NaHCO_3$ solution below 10 °C to adjust the pH to 8-9 and then extracted with ethyl acetate (4 x 100 mL). The combined organic layers are washed with brine, dried over Na_2SO_4 and filtered. The filtrate is concentrated *in vacuo*. The residue is purified by flash column chromatography on silica gel (16-50 % ethyl acetate-petro ether) to afford the product, 4-chloropyrido[3,2-d]pyrimidine (**A-3**).

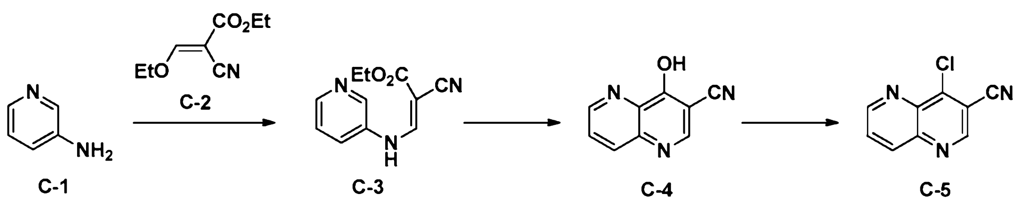


Method B:

[00649] General method for synthesis of 2,4-dichloropyrido[3,2-d]pyrimidines:

[00650] 3-Aminopicolinic acid (**A-1**) (1.0 g, 7.24 mmol, 1.0 eq), potassium cyanate (2.94 g, 36.2 mmol, 5.0 eq) and ammonium chloride (3.87 g, 72.4 mmol, 10.0 eq) are suspended in water (40 mL). The slurry is heated to 160 °C and mixed manually for 2 h as water vapour is expelled from the reaction vessel. The reaction temperature is then increased to 200 °C and stirred for 40 min. After cooling to 90 °C, hot water is added and then the mixture is allowed to cool to RT. The mixture is acidified with concentrated HCl to adjust pH to 3-4. The precipitate is collected by filtration, rinsed with water (2 x 10 mL) and dried *in vacuo* to afford the product, pyrido[3,2-d]pyrimidine-2,4-diol (**B-1**).

[00651] A mixture of pyrido[3,2-d]pyrimidine-2,4-diol (**B-1**) (360 mg, 2.21 mmol, 1.0 eq) and PCl_5 (1.84 g, 8.83 mmol, 8.0 eq) in $POCl_3$ (20 mL) is stirred at reflux for 8 h. An additional amount of PCl_5 (1.84 g, 8.83 mmol, 8.0 eq) and $POCl_3$ (20 mL) are added, and the resulting mixture is stirred at reflux for 16 h. After cooling to RT, the mixture is concentrated *in vacuo* and the residue is poured into ice-water. The mixture is neutralized with saturated Na_2CO_3 to adjust the pH to 8-9, and then extracted with DCM (3 x 20 mL). The combined organic layers are washed with brine, dried over Na_2SO_4 and filtered. The filtrate is concentrated *in vacuo* and the residue is purified by column chromatography on silica gel (10-12% ethyl acetate/petro ether) to afford the product, 2,4-dichloropyrido[3,2-d]pyrimidine (**B-2**).



Method C:

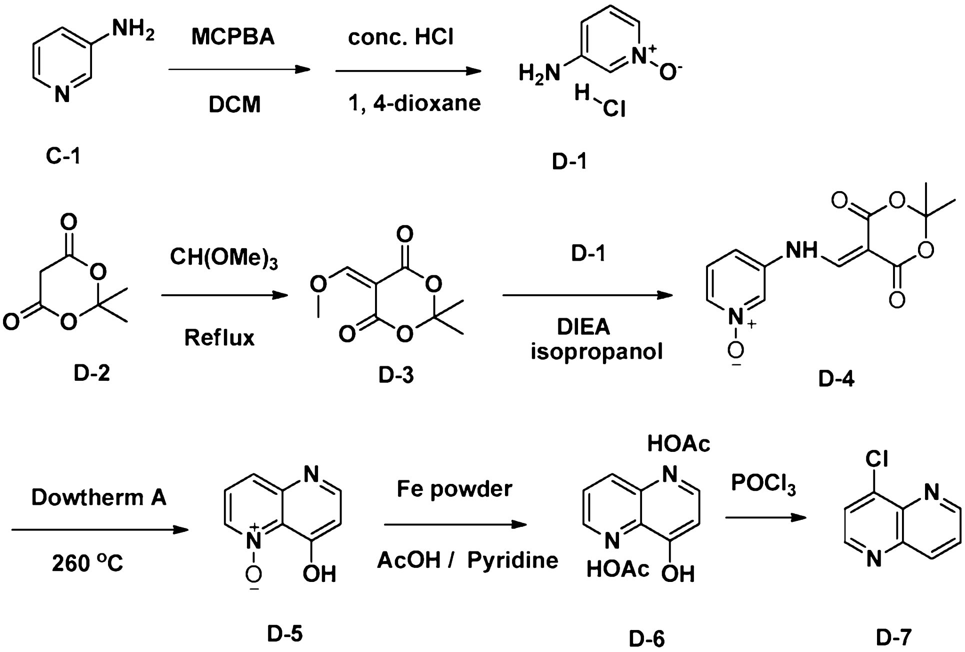
[00652] General method for synthesis of 4-chloro-1,5-naphthyridine-3-carbonitriles:

[00653] A mixture of pyridin-3-amine (**C-1**) (10.0 g, 106.3 mmol, 1.0 eq) and (E)-ethyl 2-cyano-3-ethoxyacrylate (**C-2**) (21.5 g, 127 mmol, 1.2 eq) in toluene (40 mL) is stirred at reflux under argon for 5 h and then

allowed to cool to RT. The precipitate is collected by filtration, rinsed with a mixture of petroether and ethyl acetate (v/v = 2:1, 3 x 10 mL), and then dried *in vacuo* to afford the product, ethyl 2-cyano-3-(pyridin-3-ylamino)acrylate (**C-3**).

[00654] The mixture of ethyl 2-cyano-3-(pyridin-3-ylamino)acrylate (**C-3**) (2.0 g, 9.26 mmol, 1.0 eq) in Dowtherm A (48 mL) is stirred at 260 °C for 5 h. The mixture is cooled to RT and poured into a mixture of MeOH and DCM (v/v = 1:2, 20 mL). The precipitate is filtered, rinsed with DCM, and dried *in vacuo* to afford the product, 4-hydroxy-1,5-naphthyridine-3-carbonitrile (**C-4**).

[00655] A mixture of 4-hydroxy-1,5-naphthyridine-3-carbonitrile (**C-4**) (2.0 g, 11.7 mmol, 1.0 eq) in phosphoroxychloride (40 mL, 424 mol, 36.2 eq) is stirred at reflux for 3 h. The mixture is cooled to RT and concentrated *in vacuo*. The residue is poured into ice-water (50 mL) and neutralized with saturated aqueous $NaHCO_3$ solution to adjust the pH to 8 while keeping the temperature below 5 °C. The mixture is extracted with DCM (3 x 50 mL). The combined organic layer is washed with brine, dried over Na_2SO_4 and filtered. The filtrate is concentrated *in vacuo* and the residue is purified by flash column chromatography on silica gel (1.25% MeOH-DCM) to afford the product, 4-chloro-1,5-naphthyridine-3-carbonitrile (**C-5**).



Method D

[00656] General method for synthesis of 4-chloro-1,5-naphthyridines:

[00657] To a mixture of pyridin-3-amine (**C-1**) (10.0 g, 106.3 mmol, 1.0 eq) in DCM (100 mL) at 0 °C, m-chloroperoxybenzoic acid (22.0 g, 128 mmol, 1.2 eq) is added in portions (over 15 min). The resulting mixture is allowed to warm to RT and then stirred at RT for 2 h. The reaction is quenched with water (100 mL). The organic phase is separated and the aqueous layer is extracted with DCM (2 x 100 mL). The resulting aqueous phase is neutralized with concentrated HCl to adjust the pH to 2-3. To this mixture, 1,4-dioxane (100 mL) is added and the resulting mixture is concentrated *in vacuo* to afford the product, 3-aminopyridine -1-oxide hydrochloride (**D-1**).

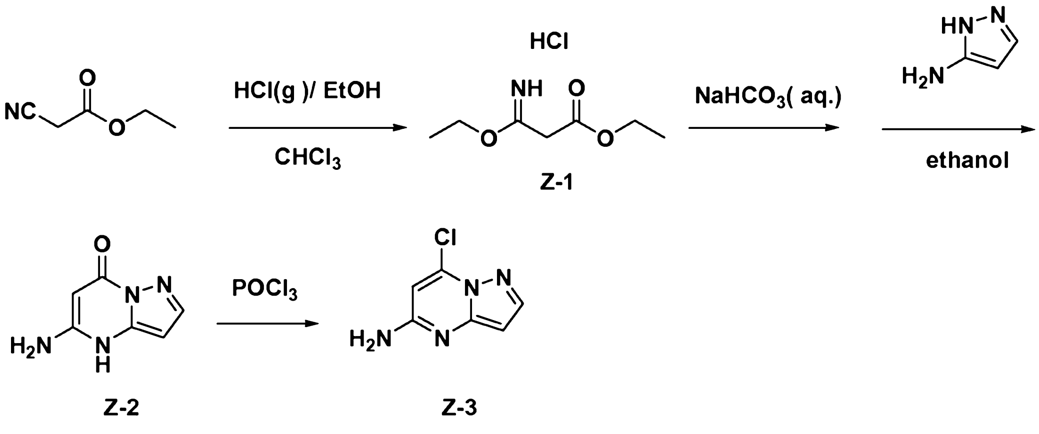
[00658] A mixture of 2,2-dimethyl-1,3-dioxane-4,6-dione (**D-2**) (10.0 g, 70 mmol, 1.0 eq) in trimethyl orthoformate (100 mL, 365 mmol, 5.0 eq) is stirred at reflux for 3 h. The resulting mixture is cooled to RT and concentrated *in vacuo*. The residue is triturated with diethyl ether and then filtered. The filter cake is washed with cooled diethyl ether and dried *in vacuo* to afford the product, 5-(methoxymethylene)-2,2-dimethyl-1,3-dioxane-4,6-dione (**D-3**).

[00659] To a mixture of 5-(methoxymethylene)-2,2-dimethyl-1,3-dioxane-4,6-dione (**D-3**) (7.6 g, 41.0 mmol, 1.0 eq) and 3-aminopyridine -1-oxide hydrochloride (**D-1**) (6.0 g, 41.0 mmol, 1.0 eq) in isopropanol (20 mL), N,N-diisopropylethylamine (7.2 mL, 53 mmol, 1.3 eq) is added and the resulting mixture is stirred at 90 °C for 20 min. The mixture is allowed to cool to RT and then poured into ice-water (50 mL). The precipitate is collected by filtration, rinsed with isopropanol (2 x 10 mL) and diethyl ether (2 x 10 mL), and then dried *in vacuo* to afford the product, 2,2-dimethyl-5-((pyridin-1-oxide 3-ylamino)methylene)-1,3-dioxane-4,6-dione (**D-4**).

[00660] The mixture of 2,2-dimethyl-5-((pyridin-1-oxide 3-ylamino)methylene)-1,3-dioxane-4,6-dione (**D-4**) (5.1 g, 19.3 mmol, 1.0 eq) in Dowtherm A (48 mL) is stirred at 260 °C for 5 - 10 min. The mixture is allowed to cool to RT and then diluted with petroleum ether. The precipitate is filtered, rinsed with petroleum ether, and dried *in vacuo* to afford the product, 1,5-naphthyridin-5-oxide 4-ol (**D-5**).

[00661] To a solution of 1,5-naphthyridin-5-oxide 4-ol (**D-5**) (330 mg, 2.0 mmol, 1.0 eq) in acetic acid (12 mL) and pyridine (2.5 mL) at RT, iron powder (456 mg, 8.15 mmol, 4.0 eq) is added in portions (over 10 min) and the resulting mixture is stirred for 2 h. The mixture is filtered and the solid is rinsed with acetic acid. The filtrate is concentrated *in vacuo*. The residue is triturated with acetone and then filtered. The filter cake is rinsed with acetone and dried *in vacuo* to afford the product, 1,5-naphthyridin-4-ol acetic acid salt (**D-6**).

[00662] A mixture of 1,5-naphthyridin- 4-ol acetic acid salt (**D-6**) (800 mg, 3.0 mmol, 1.0 eq) in phosphoroxychloride (5 mL, 53 mol, 17.6 eq) is stirred at 110 °C for 30 min, cooled to RT and then concentrated *in vacuo*. The residue is poured into ice-water (50 mL) and neutralized with saturated aqueous $NaHCO_3$ solution to adjust the pH to 8-9 while keeping the temperature below 5 °C. The mixture is stirred at RT for 30 min and then extracted with DCM (3 x 40 mL). The combined organic layers are washed with brine, dried over Na_2SO_4 and filtered. The filtrate is concentrated *in vacuo* and the residue is purified by flash column chromatography on silica gel (1-2% MeOH-DCM) to afford the product, 4-chloro-1,5-naphthyridine (**D-7**).



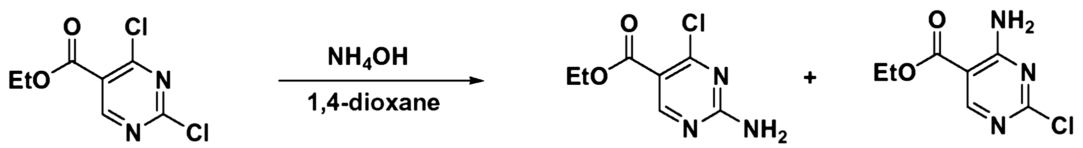
Method Z

[00663] General method for synthesis of 7-chloropyrazolo[1,5-a]pyrimidin-5-amine:

[00664] A solution of ethyl 2-cyanoacetate (100 mL, 94 mmol) in chloroform (100 mL) and ethanol (6.5 mL) is bubbled with HCl at -10° for 4 h. The reaction mixture is allowed to warm to RT slowly and then stirred at RT overnight. The mixture is concentrated *in vacuo* to remove the solvent. The residue is suspended in diethyl ether (100 mL) and stirred for 30 min. The resulting solid is collected by filtration and riseded with diethyl ether to afford ethyl 3-ethoxy-3-iminopropanoate hydrochloride (**Z-1**) as a white solid.

[00665] Sodium bicarbonate (3.9 g, 46.2 mmol) is added in small portions to a mixture of ethyl 3-ethoxy-3-iminopropanoate hydrochloride (**Z-1**) (8.6 g, 44.0 mmol) in crushed ice (100 g) and ethyl acetate (50 mL) until the pH value reaches 8-9. The organic layer is separated and the aqueous layer was extracted with ethyl acetate (2 x 50 mL). The combined organic layers are dried over anhydrous $MgSO_4$ and filtered. The filtrate is concentrated *in vacuo* to afford a colourless oil which is added to a solution of 1H-pyrazol-5-amine (3.65 g, 44.0 mmol) in ethanol (100 mL). The resulting mixture is then degassed and backfilled with argon (three cycles) and stirred at reflux overnight. The mixture is then filtered while it was still warm. The solid is rinsed with cold ethanol (25 mL) and ether (2 x 25 mL), and then dried *in vacuo* to afford 5-aminopyrazolo[1,5-a]pyrimidin-7(4H)-one (**Z-2**).

[00666] A solution of 5-aminopyrazolo[1,5-a]pyrimidin-7(4H)-one (**Z-2**) (1.5 g, 10 mmol) in phosphoryl chloride (45 mL) is stirred at reflux overnight. The reaction mixture is allowed to cool to RT and concentrated *in vacuo*. The residue is then dissolved in ice-water (25 mL) and the resulting mixture is neutralized with aqueous NaOH solution (20%) to adjust the pH to 9 – 10. The mixture is extracted with ethyl acetate (3 x 50 mL) after which the combined organic layers are washed with brine (500 mL), dried over anhydrous Na_2SO_4 and filtered. The filtrate is concentrated *in vacuo* to afford the crude product which is slurried in a mixture of DCM/MTBE (3 mL/15 mL). The resulting solid is then collected by filtration to afford 7-chloropyrazolo[1,5-a]pyrimidin-5-amine (**Z-3**).



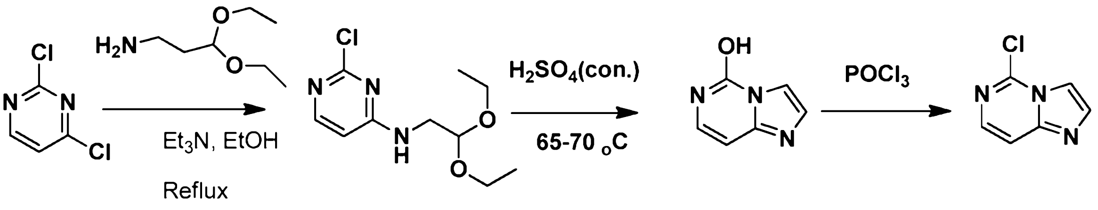
Hinge-1

Method N

[00667] General method for synthesis of 2-amino-4-chloropyrimidine-5-carboxylate:

[00668] To a stirred solution of ethyl 2,4-dichloropyrimidine-5-carboxylate (1.6 g, 7.24 mmol) in 1,4-dioxane (15 mL) at 0-5 °C under argon, ammonium hydroxide (28-30%, 2.56 mL, 21.72 mmol) is added slowly and the resulting mixture is stirred from 0 °C to RT for 2 h. The reaction is complete based on TLC (30% EA/Hex, Rf = 0.3 for ethyl 2-amino-4-chloropyrimidine-5-carboxylate (**Hinge-1**); Rf = 0.5 for ethyl 4-amino-2-chloropyrimidine-5-carboxylate) and LC-MS analysis. The mixture is partitioned between ethyl acetate and water. The organic layer is washed with brine, dried over Na_2SO_4 and filtered. The filtrate is mixed with silica gel and then concentrated *in vacuo*. The residue is loaded to the top of silica gel packed in a glass column and eluted with 0-100% ethyl acetate/hexanes to afford ethyl 2-amino-4-chloropyrimidine-5-carboxylate (**Hinge-1**).

[00669] The other regio isomer, ethyl 4-amino-2-chloropyrimidine-5-carboxylate, is also isolated.



A-1 A-2 A-3 A-4

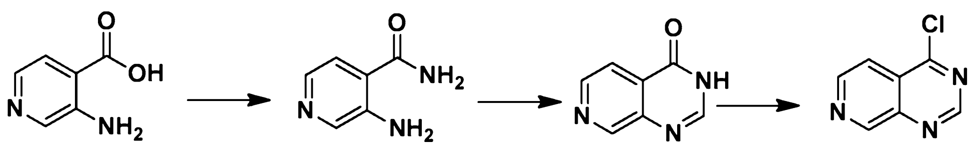
Method O

[00670] General method for synthesis of 5-chloroimidazo[1,2-c]pyrimidine:

[00671] The mixture of 2,4-dichloropyrimidine (**A-1**) (20 g, 134 mmol), 3,3-diethoxypropan-1-amine (19.6 g, 147 mmol) and Et_3N (20.5 mL, 147 mmol) in ethanol (250 mL) is stirred at RT for 24 h. The mixture is concentrated in vacuo and the residue is purified by flash column chromatography to afford the 2-chloro-N-(2,2-diethoxyethyl)pyrimidin-4-amine (**A-2**).

[00672] A mixture of 2-chloro-N-(2,2-diethoxyethyl)pyrimidin-4-amine (**A-2**) (20 g, 81.3 mmol) and H_2SO_4 (conc, 12 mL, 220 mmol) is stirred at 65-70 °C for 2 h. The reaction mixture is allowed to cool to RT, poured into ice-water (50 mL) and then basified with cold aqueous NaOH solution (10%) to adjust the pH to 1-3 while keeping inner temperature between 0-20 °C. The precipitate is collected by filtration and dried in vacuo to afford imidazo[1,2-f]pyrimidin-5-ol (**A-3**).

[00673] A mixture of imidazo[1,2-f]pyrimidin-5-ol (**A-3**) (4 g , 29.6 mmol) in phosphoroxychloride (50 mL, 530 mmol) is stirred at reflux overnight. The mixture is allowed to cool to RT and concentrated *in vacuo* to remove the phosphoroxychloride. The residue is poured into ice water (30 mL), and then neutralized with saturated aqueous $NaHCO_3$ solution to adjust the pH to 6 while keeping the temperature below 5 °C. The mixture is stirred at RT for 30 min and then extracted with ethyl acetate (20 mL × 3). The combined organic layer is washed with brine, dried over Na_2SO_4 and filtered. The filtrate was concentrated *in vacuo* and the residue was purified by flash column chromatography on silica gel (1-5 % ethyl acetate-petroleum ether) to afford 5-chloroimidazo[1,2-f]pyrimidine (**A-4**).



B-1 B-2 B-3 B-4

Method P

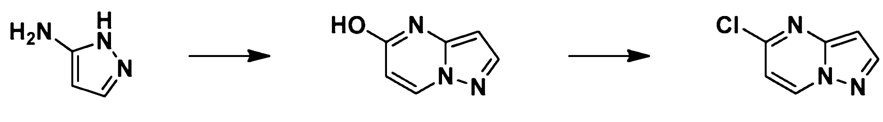
[00674] General method for synthesis of 4-chloropyrido[3,4-d]pyrimidine:

[00675] The mixture of 3-aminoisonicotinic acid (**B-1**) (7 g, 50 mmol) and DMF (0.2 mL) in thionyl chloride (100 mL) is stirred at reflux for 2 h. The mixture is then concentrated *in vacuo*. The residue is dissolved in THF (30 mL) and the resulting solution (solution A) is used directly in the next step.

[00676] To a stirred mixture of ammonium hydroxide (100 mL), the above solution A (30 mL) is added dropwise while the reaction temperature is maintained between 25 °C to 30 °C using an ice-water bath. The resulting mixture is stirred at RT for 2 h and then water (100 mL) is added. The organic layer is separated, washed with water (100 mL x 2), dried over Na_2SO_4 and filtered. The filtrate is concentrated *in vacuo* to afford the amide (**B-2**).

[00677] The mixture of compound **B-2** (2 g, 14 mmol) in triethoxy methane (50 mL) is stirred at reflux overnight. The mixture is allowed to cool to RT and filtered. The filter cake is washed with water, and dried *in vacuo* to afford compound (**B-3**).

[00678] To a stirred solution (**B-3**) (1 g, 6.7 mmol) and DMF (0.1 mL) in CH_3CN (20 mL) at RT, $POCl_3$ (10 mL) is added and the resulting mixture is stirred at reflux overnight. The mixture is allowed to cool to RT and concentrated *in vacuo*. The residue is diluted with water (30 mL), neutralized with saturated aqueous $NaHCO_3$ solution below 10 °C to adjust the PH to 8-9 and then extracted with ethyl acetate (100 mL x 4). The combined organic layer is washed with brine, dried over Na_2SO_4 and filtered. The filtrate is concentrated *in vacuo*. The residue is purified by flash column chromatography on silica gel (16-50 % ethyl acetate-petro ether) to afford compound (**B-4**).



C-1 C-2 C-3

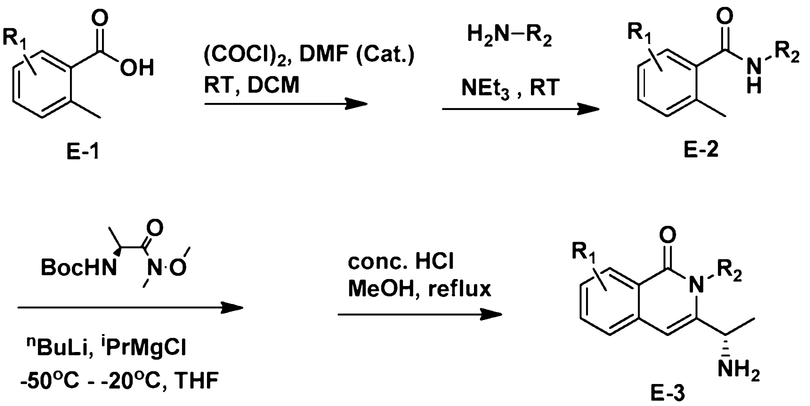
Method Q

[00679] General method for synthesis of 5-chloropyrazolo[1,5-a]pyrimidine:

[00680] To a stirred mixture of 1H-pyrazol-5-amine (4 g, 48 mmol, 1 eq) in 1,4-dioxane (20 mL), ethyl propiolate (5.08 g. 52 mmol, 1.06 eq) is added dropwise and the resulting mixture is stirred at reflux for 4 h. The mixture is cooled to RT and filtered. The filter cake is washed with water, and dried *in vacuo* to afford compound (**C-2**).

[00681] The solution of (**C-2**) (1.35 g, 10 mmol) and DMF (0.1 mL) in $POCl_3$ (10 mL) is stirred at reflux overnight. The mixture is allowed to cool to RT and concentrated *in vacuo*. The residue is diluted with water (30 mL), neutralized with saturated aqueous $NaHCO_3$ solution below 10 °C to adjust the PH to 8-9 and then extracted with ethyl acetate (30 mL x 2). The combined organic layer is washed with brine, dried over Na_2SO_4 and filtered. The filtrate is concentrated *in vacuo*. The residue is purified by flash column chromatography on silica gel (16-50 % ethyl acetate-petro ether) to afford compound (**C-3**).

(ii) General method for the synthesis of amine cores:



Method E:

[00682] General conditions for the preparation of (S)-3-(1-aminoethyl)-isoquinolin-1(2H)-ones:

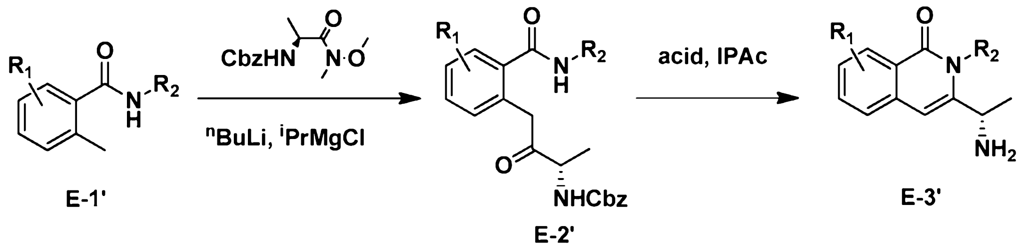
[00683] To a stirred mixture of a given o-methylbenzoic acid (**E-1**) (1.5 mol, 1 eq) and DMF (2 mL) in DCM (1275 mL) at RT, oxalyl chloride (1.65 mol, 1.1 eq) is added over 5 min and the resulting mixture is stirred at RT for 2 h. The mixture is then concentrated *in vacuo*. The residue is dissolved in DCM (150 mL) and the resulting solution (solution A) is used directly in the next step.

[00684] To a stirred mixture of aniline (1.58 mol, 1.05 eq) and triethylamine (3.15 mol, 2.1 eq) in DCM (1350 mL), the above solution A (150 mL) is added dropwise while the reaction temperature is maintained between 25 °C to 40 °C by an ice-water bath. The resulting mixture is stirred at RT for 2 h and then water (1000 mL) is added. The organic layer is separated, washed with water (2 x 1000 mL), dried over Na_2SO_4 and filtered. The filtrate is concentrated *in vacuo*. The product is suspended in n-heptane (1000 mL) and stirred at RT for 30 min. The precipitate is collected by filtration, rinsed with heptanes (500 mL) and further dried *in vacuo* to afford the amide (**E-2**).

[00685] To a stirred mixture of amide (**E-2**) (173 mmol, 1 eq) in anhydrous THF (250 mL) at -30 °C under an argon atmosphere, a solution of n-butyllithium in hexanes (432 mol, 2.5 eq) is added dropwise over 30 min while keeping inner temperature between -30 °C and -10 °C. The resulting mixture is then stirred at -30 °C for 30 min.

[00686] To a stirred mixture of (S)-tert-butyl 1-(methoxy(methyl)amino)-1-oxopropan-2- ylcarbamate (260 mmol, 1.5 eq) in anhydrous THF (250 mL) at -30 °C under an argon atmosphere, a solution of isopropylmagnesium chloride in THF (286 mmol, 1.65 eq) is added dropwise over 30 min while keeping inner temperature between -30 °C and -10 °C. The resulting mixture is stirred at -30 °C for 30 min. This solution is then slowly added to above reaction mixture while keeping the inner temperature between -30 °C and -10 °C. The resulting mixture is stirred at -15 °C for 1 h. The reaction mixture is quenched with water (50 mL) and then acidified with conc. HCl at -10 °C - 0 °C to adjust the pH to 1-3. The mixture is allowed to warm to RT and concentrated *in vacuo*. The residue is dissolved in MeOH (480 mL), and then conc. HCl (240 mL) is added quickly at RT. The resulting mixture is stirred at reflux for 1 h. The reaction mixture is concentrated *in vacuo* to reduce the volume to about 450 mL. The residue is extracted with a 2:1 mixture of heptane and ethyl acetate (2 x 500 mL). The aqueous layer is basified with concentrated ammonium hydroxide to adjust the pH to 9-10 while keeping the inner temperature between -10 °C and 0 °C. The mixture is then extracted with DCM (3 x 300 mL), washed with brine, dried over $MgSO_4$ and filtered. The

filtrate is concentrated *in vacuo* and the residue is dissolved in MeOH (1200 mL) at RT. To this solution, D- (-) -tartaric acid (21g, 140 mmol, 0.8 eq) is added in one portion at RT. After stirring at RT for 30 min, white solid precipitates out and the mixture is slurried at RT for 10 h. The solid is collected by filtration and rinsed with MeOH (3 x 50 mL). The collected solid is suspended in water (500 mL) and then neutralized with concentrated ammonium hydroxide solution at RT to adjust the pH to 9-10. The mixture is extracted with DCM (3 x 200 mL). The combined organic layers are washed with brine, dried over $MgSO_4$ and filtered. The filtrate is concentrated *in vacuo* to afford (S)-3-(1-aminoethyl)-isoquinolin-1(2H)-ones (**E-3**).

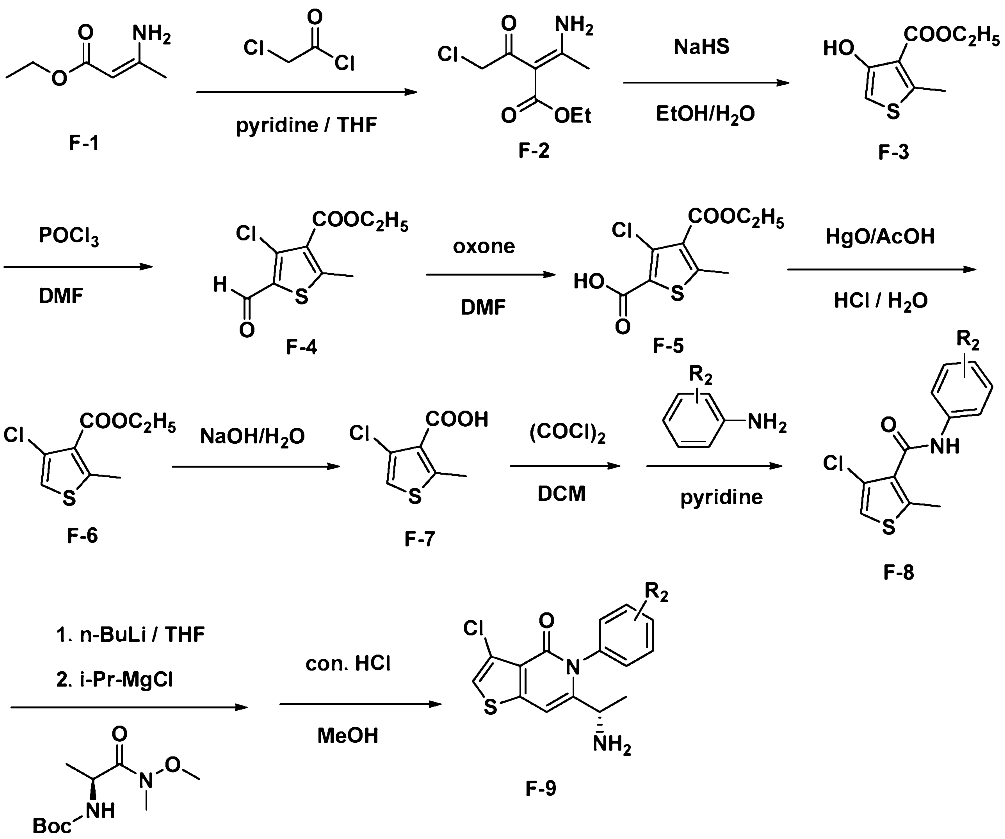


Method E':

[00687] General conditions for the preparation of (S)-3-(1-aminoethyl)-isoquinolin-1(2H)-ones:

[00688] In one embodiment, an amino compound (**E-3'**) may be prepared following Method E', wherein the intermediate (**E-1'**) may be prepared following procedures known in the art or the procedure as described in Method E. In one embodiment, intermediate (**E-2'**) may be prepared from intermediate (**E-1'**) by contacting intermediate (**E-1'**) with a base (*e.g.*, ^{n}BuLi) followed by (S)-benzyl (1-(methoxy(methyl)amino)-1-oxopropan-2-yl)carbamate. In one embodiment, the amino compound (**E-3'**) may be prepared from intermediate (**E-2'**) by cyclizing intermediate (**E-2'**) in the presence of an acid. In one embodiment, the acid is H_2SO_4. In another embodiment, the acid is HCl. In one embodiment, the amount of the acid is about 1 to 20 equivalents relative to the amount of the intermediate (**E-2'**). In one embodiment, the acid is about 5 equivalents of H_2SO_4. In one embodiment, the cyclization occurs at about room temperature to 65 °C.

[00689] In one embodiment, the cyclization provides the amino compound (**E-3'**) with a ratio of (S)-enantiomer to (R)-enantiomer of about 1:1 to 20:1. In one embodiment, the cyclization provides the amino compound (**E-3'**) with a ratio of (S)-enantiomer to (R)-enantiomer of about 1:1 to 10:1. In one embodiment, the cyclization provides the amino compound (**E-3'**) with a ratio of (S)-enantiomer to (R)-enantiomer of about 1:1 to 4:1. It is to be understood that the methods provided herein are also suitable for the preparation of (R)-enantiomer of the amino compound (**E-3'**) when (R)-benzyl (1-(methoxy(methyl)amino)-1-oxopropan-2-yl)carbamate is used in place of (S)-benzyl (1-(methoxy(methyl)amino)-1-oxopropan-2-yl)carbamate.



Method F:

[00690] General conditions for the preparation of (S)-6-(1-aminoethyl)-3-chloro-5-phenylthieno[3,2-c]pyridin-4(5H)-ones:

[00691] To a solution of ethyl-3-aminocrotonate (**F-1**) (64.6 g, 0.5 mol, 1.0 eq) and pyridine (44.5 mL, 0.55 mol, 1.1 eq) in THF (600 mL) at -20 °C, 2-chloroacetyl chloride (59.3 g, 0.53 mol, 1.05 eq) is added dropwise within 1 h. The resulting mixture is stirred from -20 °C to RT for an additional 2 h and then it is poured into H_2O (1200 mL). The mixture is extracted with ethyl acetate (3 x 1200 mL). The combined organic layer is washed with H_2O (2 x 500 mL) and brine (500 mL), dried over anhydrous Na_2SO_4 and filtered. The filtrate is concentrated *in vacuo* to reduce the volume to about 200 mL. The residue is slurried in petroether (400 mL) at RT for 30 min. The solid is collected by filtration, rinsed with petroether (200 mL), and dried *in vacuo* to afford the product, (E)-ethyl 3-amino-2-(2-chloroacetyl) but-2-enoate (**F-2**).

[00692] To a suspension of (E)-ethyl 3-amino-2-(2-chloroacetyl) but-2-enoate (**F-2**) (58.6 g, 0.29 mol, 1.0 eq) in EtOH (500 mL) at RT, 30% NaSH solution (190 g, 1.018 mol, 3.6 eq) is added dropwise over 30 min and the resulting mixture is stirred at RT for 3 h. The mixture is poured into H_2O (1.5 L) and stirred for 30 min. The precipitate is collected by filtration and rinsed with H_2O (3 x 100 mL). The collected solid is re-dissolved in ethyl acetate (500 mL), dried over anhydrous Na_2SO_4 and filtered. The filtrate is concentrated *in vacuo* to afford the product, ethyl 4-hydroxy-2-methylthiophene-3-carboxylate (**F-3**).

[00693] To a stirred solution of ethyl 4-hydroxy-2-methylthiophene-3-carboxylate (**F-3**) (20.0 g, 0.11 mol, 1.0 eq) in DMF (150 mL) at -20 °C under argon, phosphoryl chloride (49.4 g, 0.32 mol, 3.0 eq) is added dropwise

while keeping the reaction temperature below 10 °C. The resulting mixture is stirred at RT for 30 min and then at 80 °C for 1 h. The reaction mixture is cooled to RT and poured into ice-water (800 mL). The resulting mixture is neutralized with NaOAc to adjust the pH to 7 - 8. The precipitate is collected by filtration, rinsed with H_2O (150 mL), and dried *in vacuo*. The product is purified by flash column chromatography on silica gel (5% ethyl acetate-petroether) to afford the product, ethyl 4-chloro-5-formyl-2-methylthiophene-3-carboxylate (**F-4**).

[00694] To a mixture of ethyl 4-chloro-5-formyl-2-methylthiophene-3-carboxylate (**F-4**) (9.72 g, 41.77 mmol, 1.0 eq) in DMF (150 mL), Oxone (77.1 g, 125.3 mmol, 3.0 eq) is added in portions and the resulting mixture is stirred at RT overnight. The mixture is poured into H_2O (800 mL) and stirred for 30 min. The precipitate is collected by filtration, rinsed with H_2O (100 mL) and then slurried in H_2O (80 mL) for 30 min. The solid is collected by filtration, rinsed with H_2O (3 x 60 mL) and petroether (3 x 60 mL), and dried *in vacuo* to afford the product, 3-chloro-4-(ethoxycarbonyl)-5-methylthiophene-2-carboxylic acid (**F-5**).

[00695] To a stirred solution of 3-chloro-4-(ethoxycarbonyl)-5-methylthiophene-2-carboxylic acid (**F-5**) (7.79 g, 31.3 mmol, 1.0 eq) in AcOH (150 mL) at RT, HgO (7.46 g, 34.4 mmol, 1.1 eq) is added and the resulting mixture is stirred at reflux for 1 h. The reaction mixture is cooled to 50 °C – 60 °C and then aqueous HCl (750 mL, 2.4 M, 1.8 mol) is added. The resulting mixture is stirred at reflux for an additional 1 h. The mixture is allowed to cool to RT and extracted with methyl *tert*-butyl ether (3 x 200 mL). The combined organic layers are washed with sat. $NaHCO_3$ solution (3 x 200 mL), H_2O (200 mL) and brine H_2O (200 mL) sequentially. The organic layer is dried over anhydrous Na_2SO_4 and filtered. The filtrate is concentrated *in vacuo* and the residue is purified by flash column chromatography on silica gel (2% ethyl acetate-petroether) to afford the product, ethyl 4-chloro-2-methylthiophene-3-carboxylate (**F-6**).

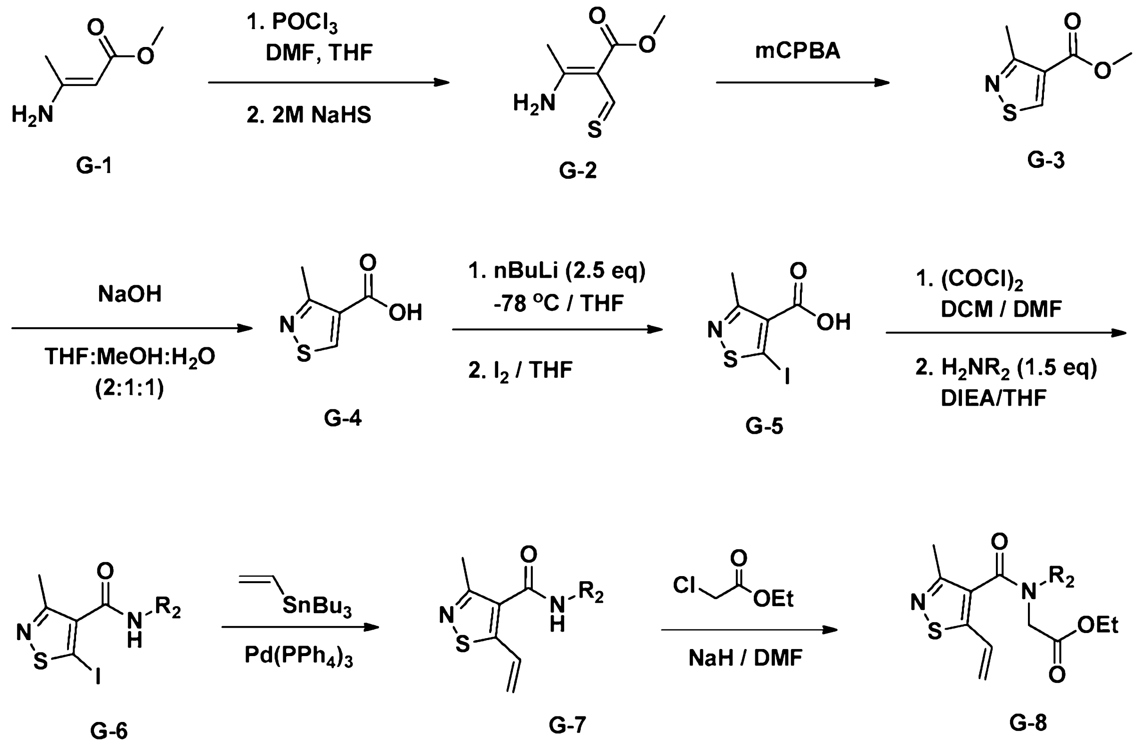
[00696] To a mixture of ethyl 4-chloro-2-methylthiophene-3-carboxylate (**F-6**) (4.98 g, 24.3 mmol, 1.0 eq) in EtOH (50 mL) ar RT, aqueous NaOH solution (20 %, 14.6 g, 73.0 mmol, 3.0 eq) is added and the resulting mixture is stirred at reflux for 1 h. The mixture is allowed to cool to RT and concentrated *in vacuo*. The residue is poured into ice water (30 mL) and neutralized with concentrated HCl to adjust the pH to 1-2 while keeping the temperature below 5 °C. The precipitate is collected by filtration, rinsed with H_2O (80 mL) and dried *in vacuo* to afford the product, 4-chloro-2-methylthiophene-3-carboxylic acid (**F-7**).

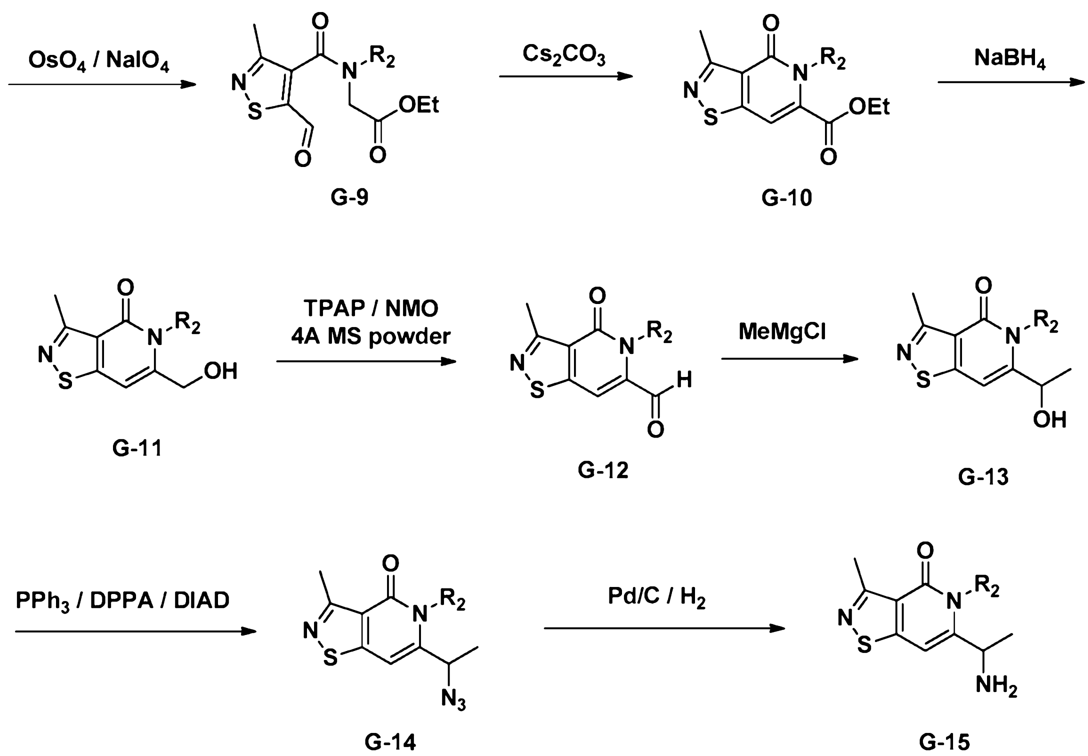
[00697] To a stirred mixture of 4-chloro-2-methylthiophene-3-carboxylic acid (**F-7**) (6.8 mmol, 1.0 eq) and DMF (three drops) in DCM (25 mL), oxalyl chloride (20.4 mmol, 3.0 eq) is added at 0-5 °C over 5 min. The resulting mixture is stirred from 0 °C to RT overnight. The mixture is concentrated *in vacuo*. The residue is dissolved in DCM (20 mL) and the resulting solution (solution C) is used directly in the next step.

[00698] To a stirred mixture of a given (R_3-substituted)phenylamine (7.47 mmol, 1.1 eq.) and pyridine (20.4 mmol, 3.0 eq.) in DCM (10 mL) at 0-5 °C, solution C is added and the resulting mixture is stirred at RT for 2 h. The mixture is diluted with DCM (150 mL), washed with aqueous HCl (1 M, 3 x 50 mL), H_2O (2 x 50 mL) and brine (2 x 50 mL) sequentially. The organic layer is dried over anhydrous Na_2SO_4 and filtered. The filtrate is concentrated *in vacuo* to afford the amide (**F-8**).

[00699] To a mixture of amide (**F-8**) (2.0 mmol, 1.0 eq.) in THF (3.5mL) at -60 °C under argon, n-butyllithium solution (2.5 M in hexanes, 2.8 mL, 7.0 mmol, 3.5 eq.) is added slowly while keeping the temperature below -50 °C. The resulting mixture is stirred below -50 °C for 30 min to form solution D.

[00700] To a stirred mixture of (S)-tert-butyl 1-(methoxy(methyl)amino)-1-oxopropan-2-ylcarbamate (2.6 mmol, 1.3 eq) in anhydrous THF (3.0 mL) at -60 °C under argon, a solution of isopropylmagnesium chloride in THF (2.0 M, 1.33 mL, 2.66 mmol, 1.33 eq.) is added dropwise over 30 min while keeping inner temperature below -50 °C. The resulting mixture is stirred below -50°C for an additional 30 min and then it is added slowly to solution D while keeping inner temperature at -50 °C. The resulting mixture is stirred between -50 °C and -40°C for 1 h and then at RT for an additional 1 h. The reaction mixture is quenched with water (5.0 mL) and acidified with aqueous HCl (5 N) at 0 °C to adjust the pH to 5-6. The mixture is concentrated *in vacuo*. The residue is dissolved in MeOH (3.0 mL) and concentrated HCl (1.5 mL) is added. The resulting mixture is stirred at reflux for 1 h and then concentrated *in vacuo* to remove MeOH. The residue is suspended in H_2O (5.0 mL) and extracted with a 1:1 mixture of heptane and ethyl acetate (3 x 20 mL). The aqueous layer is basified with saturated aqueous NH_4OH to adjust the pH to 8 – 9 and extracted with DCM (3 x 20 mL). The combined organic layers are washed with brine, dried over anhydrous Na_2SO_4 and filtered. The filtrate is concentrated *in vacuo* and the residue is purified by flash column chromatography on silica gel (10% MeOH-DCM) to afford the product (**F-9**).





Method G:

[00701] General conditions for the preparation of 6-(1-aminoethyl)-3-methyl-isothiazolo[4,5-c]pyridin-4(5H)-ones:

[00702] To a solution of methyl 3-aminocrotonate (**G-1**) (10.0 g. 86.9 mmol) in anhydrous THF (200 mL) at 0 °C, a solution of phosphoryl chloride (12.0 mL. 95.6 mmol) in anhydrous DMF (28 mL) is added dropwise (over 10 min). The resulting mixture is stirred at 0 °C for 1 h and then stirred at 30 °C for 4 h. The mixture is allowed to stand overnight in a refrigerator. Chilled ether (800 mL) is then added to the reaction mixture until a semiclear/oil residue is formed. The yellow ether layer is decanted. The oil residue is then dissolved in DCM (500 mL) and washed with NaHS aqueous solution (2.0 M). The organic layer is washed with H_2O (4 x 500 mL), dried over Na_2SO_4 and filtered. The filtrate is concentrated *in vacuo* to afford the product, methyl 3-amino-2-thioformylbut-2-enoate (**G-2**).

[00703] To a solution of methyl 3-amino-2-thioformylbut-2-enoate (**G-2**) (5.34 g, 33.5 mmol) in EtOH (250 mL), a solution of meta-chloroperoxybenzoic acid (70-75%, 12.4 g, 50.3 mmol) in EtOH (150 mL) is added and the resulting mixture is stirred at reflux for 3 h. The mixture is allowed to cool to RT, quenched with saturated aqueous NaOH solution and then extracted with ethyl acetate (2 x 200 mL). The combined organic layers are washed with brine, dried over Na_2SO_4 and filtered. The filtrate is concentrated *in vacuo* to afford the product, 3-methylisothiazole-4-carboxylate (**G-3**).

[00704] To a solution of 3-methylisothiazole-4-carboxylate (**G-3**) (4.73 g, 30.1 mmol) in THF-MeOH-H_2O (2:1:1, 50 mL), NaOH (3.61 g, 90.3 mmol) is added and the resulting mixture is stirred at 40 °C for 16 h. The mixture is allowed to cool to RT and then acidified with concentrated HCl to adjust the pH to 2-3. The precipitate is

collected by filtration, rinsed with water and dried *in vacuo* to afford the product, 3-methylisothiazole-4-carboxylic acid (**G-4**).

[00705] To a solution of 3-methylisothiazole-4-carboxylic acid (**G-4**) (3.9 g, 27.3 mmol) in anhydrous THF (150 mL) at -78 ^{o}C under argon, n-butyl lithium solution (27.3 mL, 68.3 mmol) is added dropwise and the resulting mixture is stirred at -78 ^{o}C for 1 h. To this mixture, a solution of iodide (13.9 g, 54.6 mmol) in THF (50 mL) is added slowly and the resulting mixture is stirred at RT for 1 h. The mixture is acidified with concentrated HCl to adjust the pH to 3-4, and then extracted with ethyl acetate. The organic layer is washed with aqueous Na_2SO_3 solution. The aqueous layer is extracted with ethyl acetate. The combined organic layers are washed with brine, dried over Na_2SO_4 and filtered. The filtrate is concentrated *in vacuo* to afford the product, 5-iodo-3-methylisothiazole-4-carboxylic acid (**G-5**).

[00706] To a solution of 5-iodo-3-methylisothiazole-4-carboxylic acid (**G-5**) (4.45 g, 16.5 mmol) and DMF (3 drops) in anhydrous DCM (60 mL), oxalyl chloride solution (2.0 M in DCM, 16.5 mL, 33.1 mmol) is added dropwise and the resulting mixture is stirred at RT for 2 h. The reaction mixture is concentrated *in vacuo* to afford the acyl chloride intermediate as an oil. The intermediate is dissolved in anhydrous THF (100 mL). To this mixture, a given amine R_2NH_2 (24.8 mmol) and *N,N*-diisopropylethylamine (4.09 mL, 24.8 mmol) are added dropwise. The resulting mixture is stirred at RT for 1 h. The reaction mixture is quenched with water and extracted with ethyl acetate. The combined organic layers are washed with brine, dried over Na_2SO_4 and filtered. The filtrate is concentrated *in vacuo* to afford the amide (**G-6**).

[00707] To a solution of amide (**G-6**) (18.6 mmol) and tributyl(vinyl)tin (8,19 mL, 27.9 mmol) in DMF (30 mL) under argon, $Pd(PPh_3)_4$ (1.07 g, 0.93 mmol) is added. The resulting mixture is stirred at 90 ^{o}C for 2 h. The mixture is allowed to cool to RT, quenched with water and extracted with ethyl acetate (2 x 300 mL). The combined organic layers are washed with brine, dried over Na_2SO_4 and filtered. The filtrate is concentrated *in vacuo* and the residue is purified by flash column chromatography on silica gel (0-25% ethyl acetate-hexanes) to afford the product (**G-7**).

[00708] To a solution of (**G-7**)in anhydrous DMF (70 mL) at RT, sodium hydride (60% in mineral oil, 1.52 g, 37.9 mmol) is added in portions and the resulting mixture is stirred at RT for 45 min. To this mixture, ethyl chloroacetate (4.73 mL, 44.2 mmol) is added dropwise and the resulting mixture is stirred for 2 h. The reaction mixture is quenched with water and extracted with ethyl acetate. The combined organic layers are washed with brine, dried over Na_2SO_4 and filtered. The filtrate is concentrated *in vacuo* to afford the product (**G-8**). The product obtained is used in the next step without purification.

[00709] To a solution of (**G-8**) (12.62 mmol) in 1,4-dioxane-H_2O (3:1, 100 mL) at RT, osmium tetraoxide (4% wt in H_2O, 1.0 mL, 0.13 mmol) is added and the resulting mixture is stirred for 30 min. To this mixture, sodium periodate (5.40 g, 25.24 mmol) is added and the resulting mixture is stirred at RT for 3 h. The mixture is filtered through celite and the filtrate is extracted with ethyl acetate (2 x 100 mL). The combined organic layers are washed with brine, dried over Na_2SO_4 and filtered. The filtrate is concentrated *in vacuo* to afford the product aldehyde (**G-9**). The product obtained is used in the next step without purification.

[00710] To a solution of (**G-9**) (12.68 mmol) in a mixture of EtOH and ethyl acetate (3:1, 200 mL), cesium carbonate (4.55 g, 13.95 mmol) is added and the resulting mixture is stirred at 50 °C for 2 h. The mixture is allowed to cool to RT and concentrated *in vacuo*. The residue is partitioned between water and ethyl acetate. The organic layer is washed with brine, dried over Na_2SO_4 and filtered. The filtrate is concentrated *in vacuo* and the residue is purified by flash column chromatography on silica gel (0-40% ethyl acetate-hexanes) to afford the product (**G-10**).

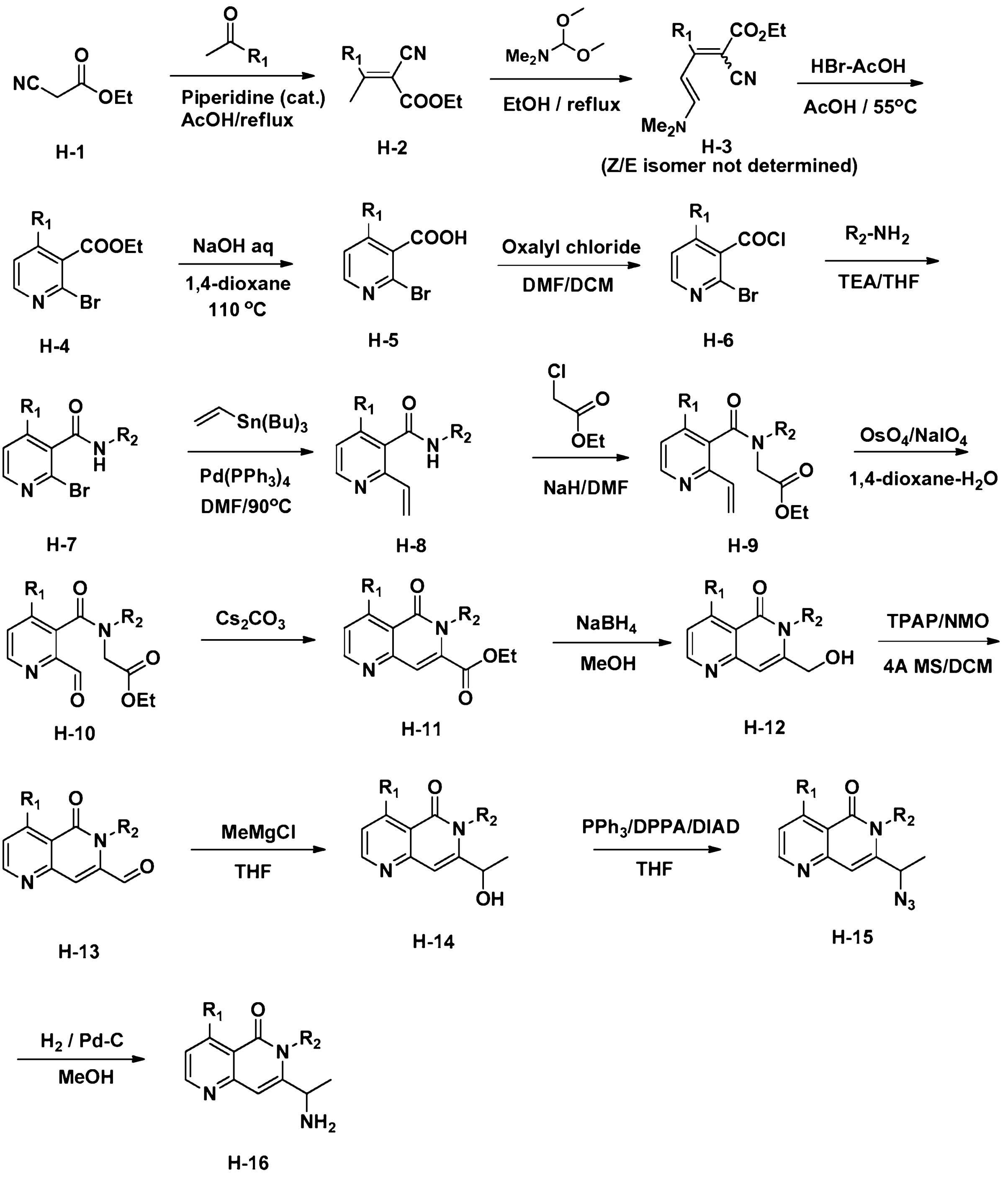
[00711] To a solution of (**G-10**) (2.48 mmol) in anhydrous MeOH (15 mL), $NaBH_4$ (936 mg, 24.75 mmol) is added in portions and the resulting mixture is stirred at RT for 16 h. The mixture is partitioned between water and ethyl acetate. The organic layer is washed with brine, dried over Na_2SO_4 and filtered. The filtrate is concentrated *in vacuo* to afford product alcohol (**G-11**).

[00712] To a solution of (**G-11**) (5.21 mmol) in anhydrous DCM (100 mL), 4Å molecular sieves (powder, 2.84 G), NMO (*N*-methylmorpholine-*N*-oxide) (1.22 g, 10.43 mmol) and TPAP (tetrapropylammonium perruthenate) (92 mg, 0.26 mmol) are added sequentially. The resulting mixture is stirred at RT for 1 h and then filtered through a celite/silica gel pad. The filtrate is concentrated *in vacuo* to afford aldehyde (**G-12**).

[00713] To a solution of (**G-12**) (1.05 g, 3.90 mmol) in anhydrous THF (100 mL) at -78 °C under argon, methylmagnesium chloride solution (3.0M in THF, 3.25 mL, 9.75 mmol) is added dropwise and the resulting mixture is stirred from -78 °C to RT for 2 h. The mixture is quenched with water (50 mL) and extracted with ethyl acetate (2 x 100 mL). The combined organic layers are washed with brine, dried over Na_2SO_4 and filtered. The filtrate is concentrated *in vacuo* to afford product (**G-13**).

[00714] To a solution of (**G-13**) (0.48 mmol) in anhydrous THF (8 mL) at 0 °C under argon, triphenyl phosphine (230 mg, 0.88 mmol) is added and the resulting mixture is stirred for 5 min. To this mixture, diphenyl phosphoryl azide (0.24 mL, 1.12 mmol) is added followed by slow addition of diisopropyl azodicarboxylate (0.17 mL, 0.88 mmol) over a 20 min period of time. The resulting mixture is stirred from 0 °C to RT for 2 h. The mixture is then partitioned between ethyl acetate and water. The organic layer is washed with brine, dried over Na_2SO_4 and filtered. The filtrate is concentrated *in vacuo* and the residue is purified by ISCO (silica gel cartridge, 0-50% ethyl acetate-hexanes) to afford the product azide (**G-14**).

[00715] A mixture of azide (**G-14**) (0.2489 mmol) and palladium (10% weight on carbon, 23 mg, 20% of starting material by weight) in anhydrous MeOH (5 mL) is degassed and flushed with hydrogen (three cycles). The reaction mixture is stirred under a hydrogen atmosphere at RT for 1 h. The mixture is filtered through celite and rinsed with ethyl acetate. The filtrate is then concentrated *in vacuo* to afford the amine (**G-15**).



Method H

[00716] General conditions for the preparation of 7-(1-aminoethyl-6-phenyl-1,6-naphthyridin-5(6H)-ones:

[00717] To a mixture of ethyl 2-cyanoacetate (**H-1**) (45.2 g, 400 mmol) and a given ketone $R_1C(O)Me$ (800 mmol) in glacial acetic acid (50 mL), piperidine (2 mL, 20 mmol) is added and the resulting mixture stirred at reflux for 24 h. The reaction mixture is allowed to cool to RT, and then concentrated *in vacuo*. The residue is diluted with water (200 mL) and extracted with ethyl acetate (3 x 200 mL). The combined organic layers are washed with

brine (50 mL), dried over Na_2SO_4 and filtered. The filtrate is concentrated *in vacuo* and the residue is purified by flash column chromatography on silica gel (0-2% ethyl acetate-petroether) to afford the product (**H-2**).

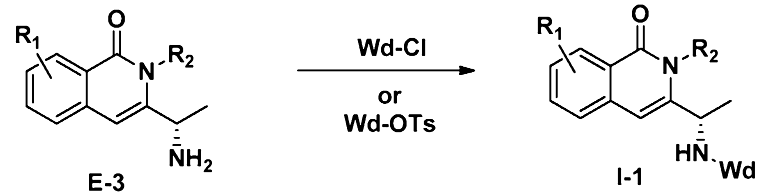
[00718] To a solution of (**H-2**) (285 mol) in absolute EtOH (300 mL), N,N-dimethylformamide dimethyl acetal (37.3 g, 313 mmol) is added dropwise and the resulting mixture is stirred at reflux for 6 h. The mixture is allowed to cool to RT, and concentrated *in vacuo* to afford the product (**H-3**). This material is used in the next step without further purification.

[00719] Dienoate (**H-3**) (148 mmol) is dissolved in AcOH (120 mL) and the mixture is stirred at 40 °C. A solution of 45% HBr-AcOH (120 mL) is added dropwise, and then the mixture is stirred at 55 °C for 2 h. The mixture is allowed to cool to RT, poured into ice-water, neutralized with solid Na_2CO_3, and then extracted with ethyl acetate (3 x 150 mL). The combined organic layer is washed with brine (50 mL), dried over Na_2SO_4 and filtered. The filtrate is concentrated *in vacuo* and the residue is purified by flash column chromatography on silica gel (5-20% ethyl acetate-petroether) to afford the product (**H-4**).

[00720] To a solution of 4-substituted ethyl 2-bromolnicotinate (**H-4**) (52 mmol) in 1,4-dioxane (15 mL), a solution of NaOH (8.0 g, 200 mmol) in H_2O (15 mL) is added and the resulting mixture is stirred at reflux for 12 h. The mixture is allowed to cool to RT, diluted with H_2O, and washed with ethyl acetate (3 x 30 mL). The aqueous layer is acidified with concentrated hydrochloric acid to adjust the pH to 1, and then extracted with ethyl acetate (3 x 50 mL). The combined organic layers are washed with brine (25 mL), dried over Na_2SO_4 and filtered. The filtrate is concentrated *in vacuo* to afford the product nicotinic acid (**H-5**).

[00721] Compound (**H-5**) is then converted to (**H-16**) in analogous fashion to (**G-15**) in Method G.

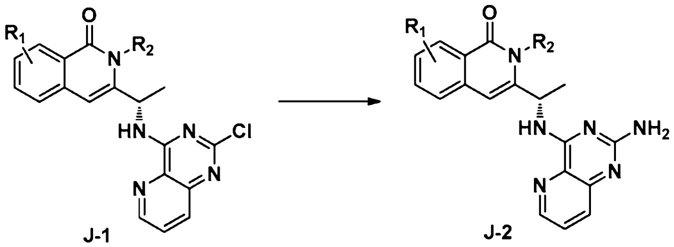
(iii) ***General conditions for attachment of W_d substituents:***



Method I

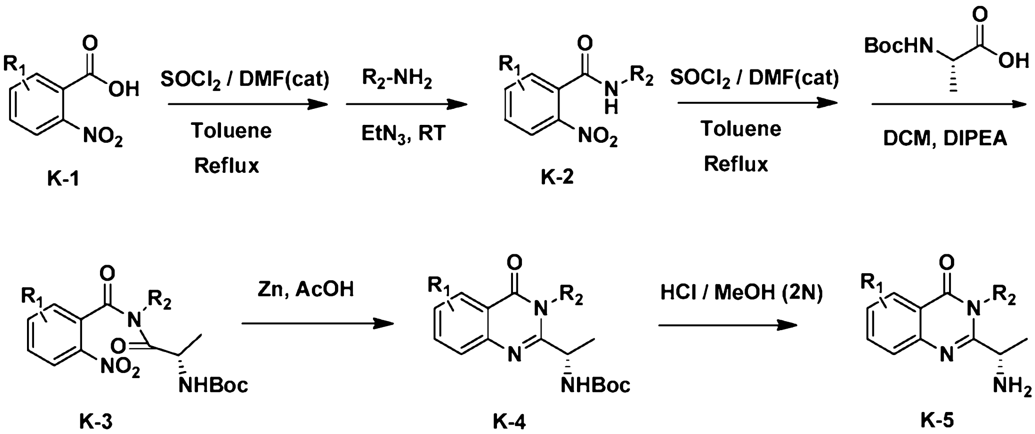
[00722] A mixture of compound (**E-3**) (1.0 mmol, 1.0 eq), Wd-Cl or Wd-OTs (1.50 mmol, 1.5 eq) and triethylamine (3.0 mmol, 3.0 eq) in n-BuOH (5 mL) is stirred at reflux for 1-5 h. The reaction mixture is allowed to cool to RT and then concentrated in *vacuo*. The residue is purified by flash column chromatography on silica gel (eluting with a mixture solvent of MeOH and DCM) to afford the product (**I-1**). The reaction can occur under other conditions known in the art that are suitable for S_NAr displacement reaction. In one embodiment, the reaction solvent is NMP.

(iv) ***General conditions for substitution of W_d:***



Method J

[00723] Quinolinone (**J-1**) (0.11 mmol, 1.0 eq) is suspended in ammonium hydroxide (10-35% solution, 20 mL) in a sealed tube and the resulting mixture is stirred at 140 °C overnight. The mixture is allowed to cool to RT and then extracted with DCM (3 x 15 mL). The combined organic layers are washed with brine, dried over Na_2SO_4 and filtered. The filtrate is concentrated *in vacuo* and the residue is purified by column chromatography on silica gel (1-2% MeOH/DCM) to afford compound (**J-2**) as the product.



Method K:

[00724] To a stirred mixture of nitrobenzoic acid (**K-1**) (1.0 mol, 1.0 eq) and DMF (2.0 mL) in toluene (800 mL), thionyl chloride (292 mL, 1.0 mol, 4.0 eq) is added dropwise (over 15 min) and the resulting mixture is stirred at reflux for 1.5 h. The mixture is allowed to cool to RT and then concentrated *in vacuo*. The residue is dissolved in DCM (100 mL) to form solution A, which is used directly in the next step.

[00725] To a stirred mixture of a given amine R_2-NH_2 (102.4 g, 1.1 mol, 1.1 eq) and triethylamine (280 mL, 2.0 mol, 2.0 eq) in DCM (700 mL), solution A is added dropwise while keeping the reaction temperature below 10 °C. The resulting mixture is allowed to warm to RT and then stirred at RT overnight. The reaction mixture is diluted with ice-water (1.0 L) and stirred for 15 min. The precipitate is collected by filtration, rinsed with isopropyl ether (3 x 100 mL) and petroleum ether (3 x 100 mL), and then dried *in vacuo* to afford product amide (**K-2**).

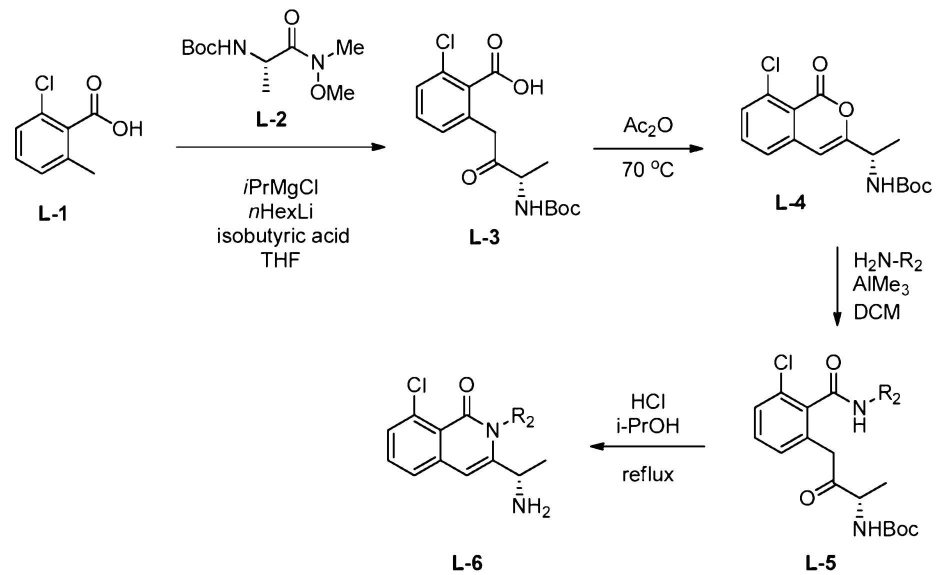
[00726] A mixture of nitro- benzamide (**K-2**) (20.0 mmol, 1.0 eq) and DMF (cat.) in toluene (60 mL) at RT, thionyl chloride (12 mL , 164 mmol, 8.2 eq) is added dropwise (over 5 min) and the resulting mixture is stirred at reflux for 2 h. The mixture is allowed to cool to RT and then concentrated *in vacuo*. The residue is dissolved in DCM (10 mL) to form solution B, which is used directly in the next step.

[00727] To a stirred mixture of N-(tert-butoxycarbonyl)-L-alanine (16.0 mmol, 0.8 eq) and N,N-diisopropylethylamine (4.0 g, 31.0 mol, 1.5 eq) in DCM (20 mL), solution B is added dropwise while keeping the reaction temperature between 0-10 °C. The resulting mixture is stirred at this temperature for 1 h and then stirred at RT overnight. The reaction mixture is quenched with ice-water (100 mL). The organic layer is separated and the aqueous layer is extracted with DCM (2 x 80 mL). The combined organic layers are washed with brine, dried over Na_2SO_4 and filtered. The filtrate is concentrated *in vacuo* and the residue is slurried in isopropyl ether (100 mL) for 15 min. The solid is collected by filtration and dried *in vacuo* to afford product (**K-3**).

[00728] To a suspension of zinc dust (7.2 g, 110 mmol, 10.0 eq) in glacial acetic acid (40 mL) at 15 ° C, a solution of (**K-3**) (11.0 mmmol, 1.0 eq) in glacial acetic acid (40 mL) is added and the resulting mixture is stirred at RT for 4 h. The mixture is poured into ice-water (200 mL) and neutralized with saturated aqueous $NaHCO_3$ solution to adjust the pH to 8. The resulting mixture is extracted with DCM (3 x 150 mL). The combined organic layers are washed with brine, dried over Na_2SO_4 and filtered. The filtrate is concentrated *in vacuo* and the residue is purified by flash chromatography on silica gel (7% ethyl acetate-petroleum ether) to afford product (**K-4**).

[00729] Compound (**K-4**) (0.5 mmol, 1.0 eq) is dissolved in hydrochloric methanol solution (2N, 20 mL) and the resulting mixture is stirred at RT for 2 h. The mixture is concentrated *in vacuo*. The residue is diluted with water (30 mL) and then neutralized with saturated aqueous $NaHCO_3$ to adjust the pH to 8 while keeping the temperature below 5 °C. The resulting mixture is extracted with DCM (3 × 30 mL). The combined organic layers are washed with brine, dried over Na_2SO_4 and filtered. The filtrate is concentrated *in vacuo* and the residue is slurried in petroleum ether (10 mL). The solid is collected by filtration and dried *in vacuo* to afford product (**K-5**).

[00730] The quinazolinone (**K-5**) can be used to synthesize compounds described herein using, for example, Method I to couple the amine to W_d groups.



Method L:

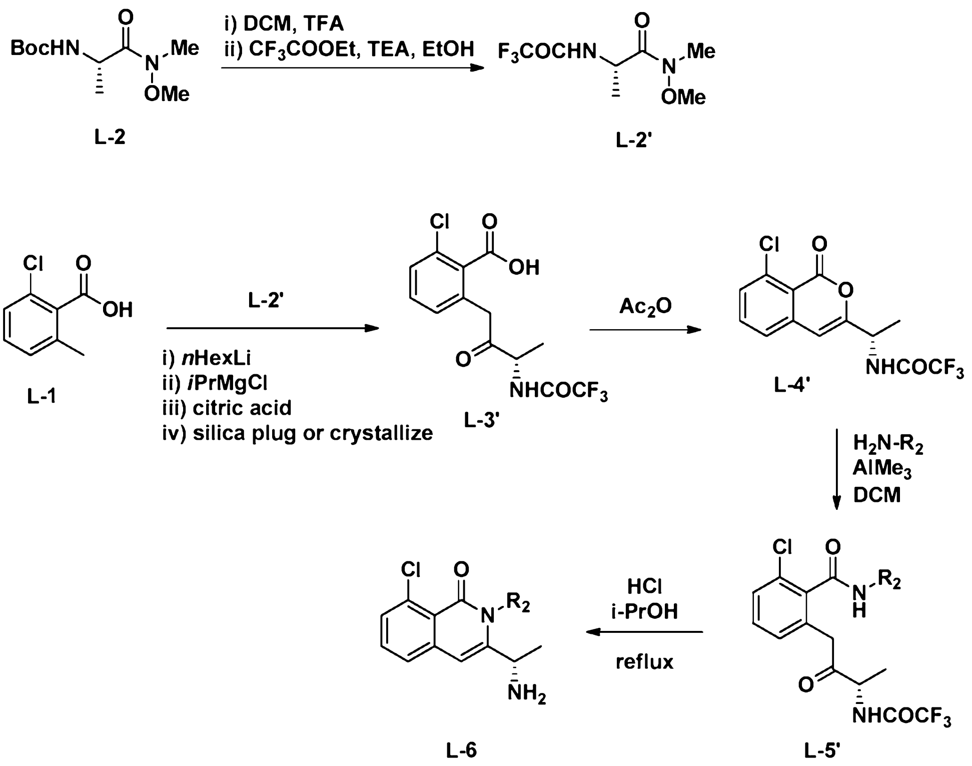
[00731] To 2-chloro-6-methylbenzoic acid (**L-1**) (8.00 g, 46.9 mmol) in a dry round bottom flask under N_2 is added 50 mL of dry THF. The resulting mixture is cooled to -25 °C. Then, n-hexyllithium (88 mL, 202 mmol) (2.3 M in hexanes) is added, and the reaction is stirred at -20 °C for about 20 min.

[00732] To compound (**L-2**) (14.16 g, 61.0 mmol) in a second dry round bottom flask under N_2 is added 70 mL of dry THF. The mixture is cooled to about -10 °C. To the cold mixture is slowly added isopropyl magnesium chloride (63.3 ml, 2 M, 127 mmol). The resulting mixture is then stirred at -10 °C for about 20 min. Then, this mixture is slowly cannulated drop wise into the flask containing the (**L-1**) reaction while maintaining the temperature at -20°C. After addition is complete, the reaction is slowly warmed to RT and stirred at RT for about 1.6 hours. The reaction mixture is then cooled to -10 °C and quickly cannulated to another flask containing 15 mL of ethyl acetate and 10 mL of isobutyric acid at -10°C under N_2. After stirring for about 5 minutes, 10 mL of water is rapidly added. The cooling bath is removed, and the reaction mixture is stirred for 10 minutes at RT. The mixture is transferred to a separation funnel, and water (200 mL) is added. The water layer is extracted with EtOAc (3 X 400 mL). The aqueous layer is then acidified with HCl (2M) to pH 3, and is extracted with EtOAc (3 X 500 mL), dried over sodium sulfate and concentrated *in vacuo*. The resulting material is purified by silica gel column chromatography using 0 – 10% MeOH in DCM to afford benzoic acid (**L-3**).

[00733] A mixture of benzoic acid (**L-3**) (5.00 g, 14.63 mmol) in acetic anhydride (10 mL) is stirred in a round bottom flask at 70 °C for about 2.5 hours. Then, the remaining acetic anhydride is removed *in vacuo*. The residue is purified using silica gel column chromatography using EtOAc/hexanes to afford lactone (**L-4**).

[00734] To a mixture of R_2-NH_2 (197 mg, 1.54 mmol) in 2 mL of DCM is added $AlMe_3$ (0.772 ml, 1.54 mmol). The mixture is stirred for about 15 min. Then, a solution of lactone (**L-4**) (100 mg, 0.309 mmol) in 2 mL of DCM is added, and the reaction is stirred at RT for about 3 hours. The reaction mixture is then quenched with addition of 10 mL of Rochelle's salt and stirring for about 2 hours. The mixture is diluted with DCM, washed with brine, dried with Na_2SO_4 and concentrated *in vacuo* to afford the amide (**L-5**) which is carried directly to the next reaction.

[00735] To the amide (**L-5**) in 5 mL of isopropanol is added 3 mL of concentrated HCl. The reaction is heated at 65 ^{O}C for about 3 hours. After cooling to RT, the mixture is concentrated *in vacuo*. The solid is suspended in 15 mL of DCM, followed by the addition of 10 mL of sat. $NaHCO_3$. This mixture is then stirred at RT for about 30 min, then 50 mL of DCM is added. The layers are separated and the organic layer is dried with Na_2SO_4 and concentrated *in vacuo* to afford isoquinolinone (**L-6**).



Method L':

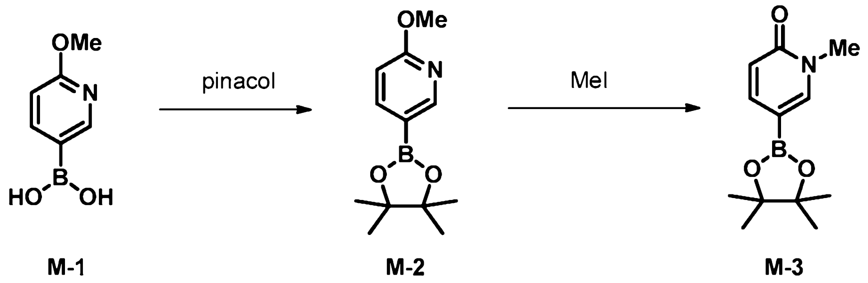
[00736] General conditions for the preparation of (S)-3-(1-aminoethyl)-isoquinolin-1(2H)-ones:

[00737] In some embodiments, isoquinolinone (**L-6**) may be prepared by following the procedures exemplified in Method L'. In one embodiment, intermediate (**L-2'**) is prepared by contacting intermediate (**L-2**) with TFA followed by CF_3COOEt. In one embodiment, benzoic acid (**L-3'**) is prepared by contacting o-methyl-benzoic acid (**L-1**) with a base (*e.g.*, nHexLi), followed by intermediate (**L-2'**), and followed by purification by silica plug or crystallization. In one embodiment, lactone (**L-4'**) is prepared by contacting benzoic acid (**L-3'**) with Ac_2O under conditions suitable for cyclization. In one embodiment, amide (**L-5'**) is prepared by contacting lactone (**L-4'**) with corresponding amine or aniline in the presence of $AlMe_3$. In one embodiment, isoquinolinone (**L-6**) is prepared by contacting amide (**L-5'**) with an acid under conditions suitable for cyclization and deprotection. In one embodiment, the acid is HCl.

[00738] In one embodiment, the cyclization provides the amino compound (**L-6**) with a ratio of (S)-enantiomer to (R)-enantiomer of about 1:1 to 20:1. In one embodiment, the cyclization provides the amino compound (**L-6**) with a ratio of (S)-enantiomer to (R)-enantiomer of about 1:1 to 10:1. In one embodiment, the cyclization provides the amino compound (**L-6**) with a ratio of (S)-enantiomer to (R)-enantiomer of about 1:1 to 4:1. It is to be understood that the methods provided herein are also suitable for the preparation of (R)-enantiomer of the amino compound (**L-6**) when (R)-enantiomer of intermediate (**L-2**) is used in place of (S)-enantiomer of (**L-2**).

[00739] A compound provided herein may contain one or more chiral center. Conventional techniques for the preparation/isolation of individual enantiomers include synthesis from a suitable optically pure precursor, asymmetric synthesis from achiral starting materials, or resolution of an enantiomeric mixture, for example, by chiral chromatography, recrystallization, resolution, diastereomeric salt formation, or derivatization into

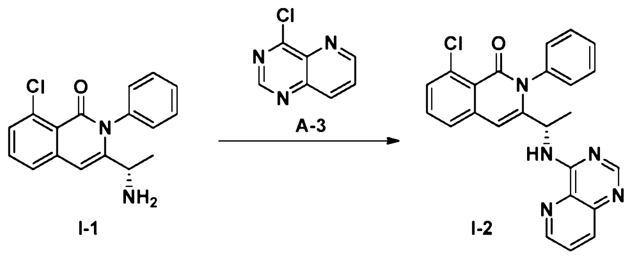
diastereomeric adducts followed by separation. In one embodiment, the enantiopurity of a compound provided herein may be improved by contacting the compound provided herein with a suitable solvent or mixture thereof, followed by filtration. In one embodiment, the solvent is a mixture of water and dichloromethane. In another embodiment, the solvent is a mixture of dichloromethane and methanol.



Method M:

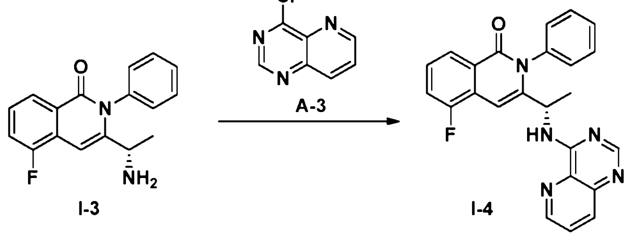
[00740] In one embodiment, the N-methyl pyridinone boronic ester (**M-3**) may be prepared following procedures exemplified in Method M. In one embodiment, pyridyl boronic ester (**M-2**) may be prepared by contacting pyridyl boronic acid (**M-1**) with pinacol under conditions suitable for the formation of boronic esters. In one embodiment, the N-methyl pyridinone boronic ester (**M-3**) may be prepared by contacting pyridyl boronic ester (**M-2**) with MeI under conditions suitable for O-methyl-to-N-methyl shifting.

Example 1



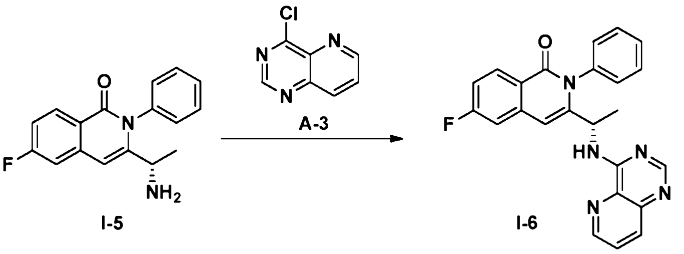
[00741] Amine I-1 was prepared according to Method E and then coupled to (**A-3**) using Method I to provide compound **I-2**. ESI-MS *m/z*: 428.0 $[M+H]^+$.

Example 2



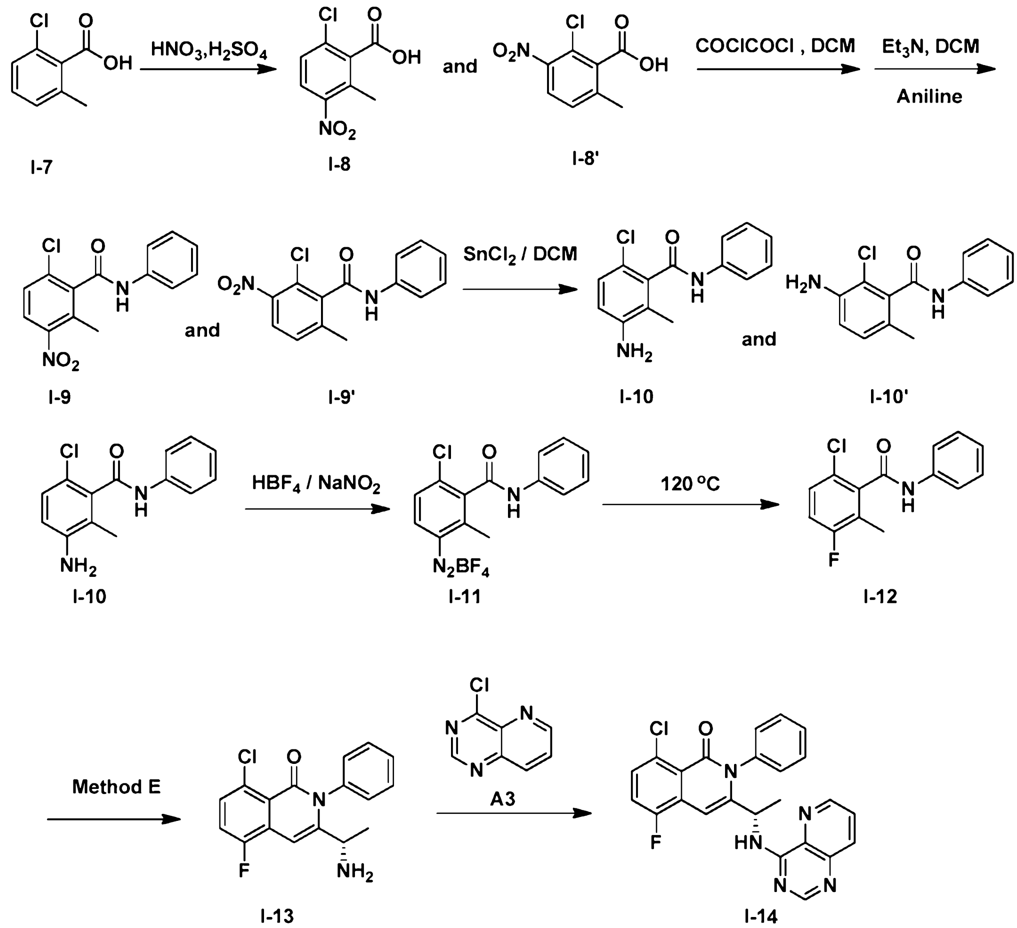
[00742] Amine **I-3** was prepared according to Method E and then coupled to (**A-3**) using Method I to provide compound **I-4**. ESI-MS *m/z*: 412.2 $[M+H]^+$.

Example 3



[00743] Amine **I-5** was prepared according to Method E and then coupled to (**A-3**) using Method I to provide compound **I-6**. ESI-MS *m/z*: 412.0 [M+H]$^+$.

Example 4



[00744] Intermediate amide **I-12** was prepared from 2-chloro-6-methylbenzoic acid **I-7** according to the following procedures:

[00745] To a solution of 2-chloro-6-methylbenzoic acid **I-7** (50 g, 294 mmol, 1.0 eq) in conc. H_2SO_4 (500 mL) at 0 °C, fuming HNO_3 (20.4 g, 324 mmol, 1.1 eq) was added slowly. The resulting mixture was stirred at 0 °C for 5 min and then stirred at RT for 2 h. The reaction mixture was poured into ice-water (800 mL) and extracted with ethyl acetate (3 x 500 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and filtered.

The filtrate was concentrated *in vacuo* to afford the product as a mixture of two regio-isomers, 6-chloro-2-methyl-3-nitrobenzoic acid **I-8** and 6-chloro-2-methyl-5-nitrobenzoic acid **I-8'**. The mixture was used directly in the next step.

[00746] To a stirred solution of above obtained regio-isomer mixture of 6-chloro-2-methyl-3-nitrobenzoic acid 8 and 6-chloro-2-methyl-5-nitrobenzoic acid **I-8'** (61.8 g, 287 mmol, 1.0 eq) and DMF (catalytic amount) in DCM (500 mL) at RT, oxalyl chloride (49 mL, 574 mmol, 2.0 eq) was added slowly (over 5 min). The resulting mixture was stirred at RT for 2 h and then concentrated *in vacuo*. The residue was dissolved in DCM (150 mL) to form solution A.

[00747] To a mixture of aniline (32 g, 344 mmol, 1.2 eq) and triethylamine (87.5 g, 861 mmol, 3.0 eq) in DCM (400 mL) at RT, solution A was added dropwise. The resulting mixture was stirred for 15 min and then quenched with water (500 mL). The organic layer was separated and the aqueous layer was extracted with DCM (3 x 500 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and filtered. The filtrate was concentrated *in vacuo* to afford the product as a mixture of two regio-isomers, 6-chloro-2-methyl-3-nitro-N-phenylbenzamide **I-9** and 2-chloro-6-methyl-3-nitro-N-phenylbenzamide **I-9'**. The mixture was used directly in the next step.

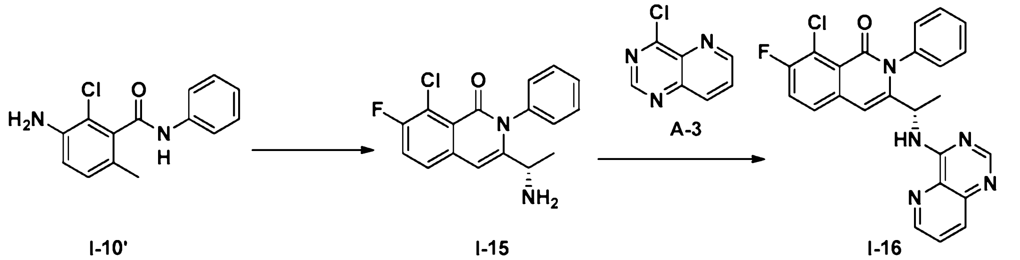
[00748] To a stirred mixture of 6-chloro-2-methyl-3-nitro-N-phenylbenzamide 9 and 2-chloro-6-methyl-3-nitro-N-phenylbenzamide **I-9'** (33.6.8 g, 116 mmol, 1.0 eq) in EtOH (400 mL), $SnCl_2 \cdot 2H_2O$ (105 g, 464 mmol, 4.0 eq) was added and the resulting mixture was stirred at reflux for 3 h. The reaction mixture was allowed to cool and concentrated *in vacuo.* The residue was poured into water (500 mL) and the mixture was extracted with ethyl acetate (5 x 500 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and filtered. The filtrate was concentrated *in vacuo* . The residue was purified by flash column chromatography on silica gel (2-20% ethyl acetate-petroleum ether) to afford the regio-isomer, 3-amino-6-chloro-2-methyl-N-phenylbenzamide **I-10**. The remaining mixture of 3-amino-6-chloro-2-methyl-N-phenylbenzamide **I-10** and 5-amino-6-chloro-2-methyl-N-phenylbenzamide **I-10'** was collected separately. Compound **I-10'** was obtained by further column chromatography purification.

[00749] To a stirred mixture of 3-amino-6-chloro-2-methyl-N-phenylbenzamide **I-10** (10.3 g, 39.6 mmol, 1.0 eq) in fluoroboric acid (42%, 72 mL) at 0 °C, a solution of sodium nitrate (5.5 g, 79.2 mmol, 2.0 eq) in H_2O (10 mL) was added dropwise over 30 min while keeping the reaction temperature between 0 °C and 5 °C. The resulting mixture was stirred at RT for 16 h. The precipitate was collected by filtration, rinsed with cold water (2 x 5 mL), and dried *in vacuo* to afford the product **I-11**. The product was used directly in the next step.

[00750] The intermediate **I-11** (12.8 g, 35.7 mmol) was heated to 120 °C and the temperature was maintained between 120 °C and 130 °C for 1 h. The mixture was cooled to 50 °C and poured into ice-water (50 mL). The resulting mixture was extracted with ethyl acetate (3 x 50 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and filtered. The filtrate was concentrated *in vacuo* and the residue was purified by flash column chromatography on silica gel (2-20% ethyl acetate-hexanes) to afford the product, 6-chloro-3-fluoro-2-methyl-N-phenylbenzamide **I-12**.

[00751] Amine **I-13** was prepared from amide **I-12** according to Method E and was then coupled to **A-3** using Method I to provide compound **I-14**. ESI-MS *m/z*: 446.0 $[M+H]^+$.

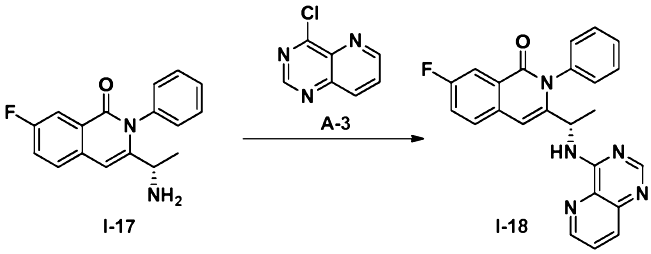
Example 5



I-10' I-15 I-16

[00752] Amine **I-15** was prepared from amide **I-10'** in analogous fashion to compound **I-13** in Example 4. Amine **I-15** was then coupled to (**A-3**) using Method I to provide compound **I-16**. ESI-MS *m/z*: 446.0 [M+H]$^+$.

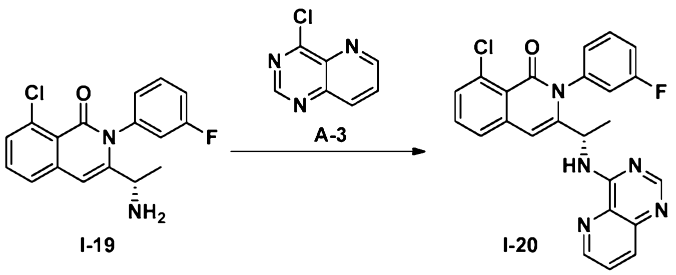
Example 6



I-17 I-18

[00753] Amine **I-17** was prepared according to Method E and was then coupled to (**A-3**) using Method I to provide compound **I-18**. ESI-MS *m/z*: 412.2 [M+H]$^+$.

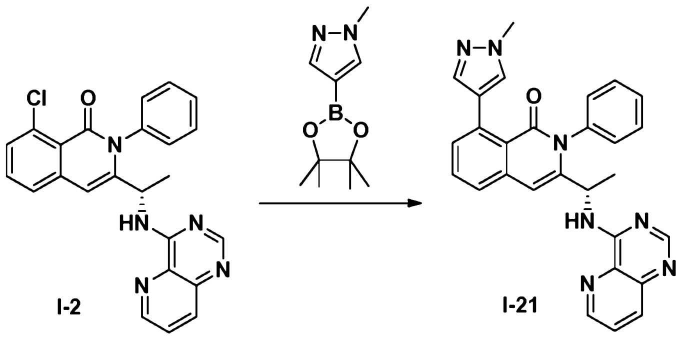
Example 7



I-19 I-20

[00754] Amine **I-19** was prepared according to Method E and was then coupled to (**A-3**) using Method I to provide compound **I-20**. ESI-MS *m/z*: 446.0 [M+H]$^+$.

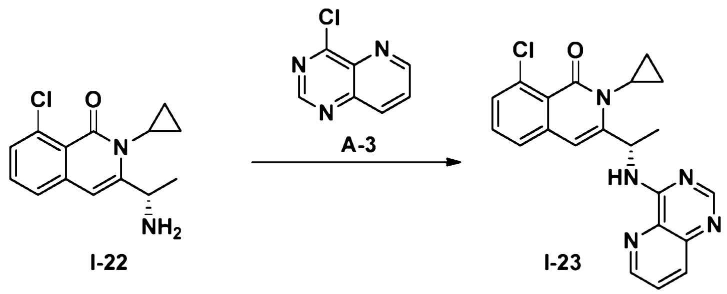
Example 8



[00755] Compound **I-2** was converted to compound **I-21** according to the following general procedure:

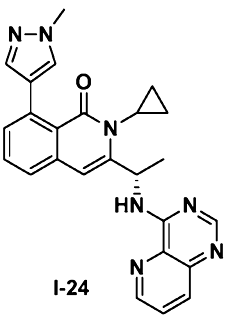
[00756] Compound **I-2** (0.2 mmol, 1.0 eq), boronic acid (0.41 mmol, 2.0 eq), $Pd(OAc)_2$ (0.04 mmol, 0.2 eq), 2-(dicyclohexylphosphino)-2',4',6'-triisopropylbiphenyl (0.12 mmol, 0.6 eq) and Na_2CO_3 (0.6 mmol, 3.0 eq) were dissolved in 1-methyl-2-pyrrolidinone (10 mL). The resulting mixture was degassed and back-filled with argon three times, and then stirred at 160 °C under an argon atmosphere for 1.5 h. The mixture was concentrated *in vacuo* and the residue was purified by flash column chromatography on silica gel (1:30, MeOH-DCM) to afford the product **I-21** as a solid; ESI-MS *m/z*: 474.2 $[M+H]^+$.

Example 9



[00757] Amine **I-22** was prepared according to Method E and was then coupled to (**A-3**) using Method I to provide compound **I-23**. ESI-MS *m/z*: 392.2 $[M+H]^+$.

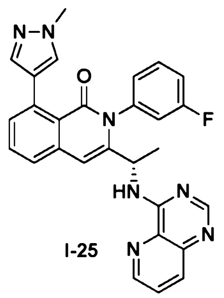
Example 10



I-24

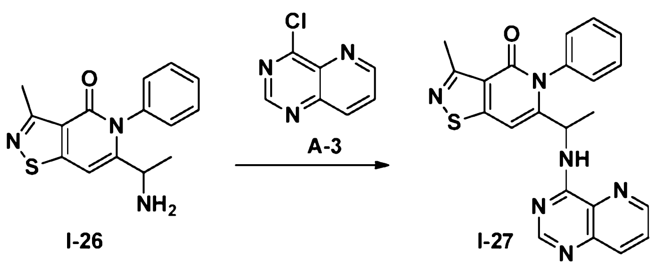
[00758] Compound **I-24** was prepared from compound **I-23** using the analogous coupling procedures for the synthesis of compound **I-21** in Example 8. ESI-MS *m/z*: 438.2 $[M+H]^+$.

Example 11



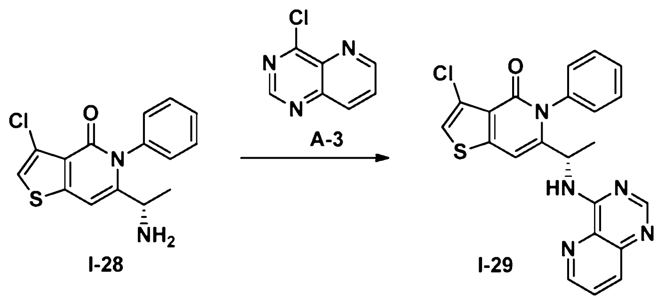
[00759] Compound **I-25** was prepared from compound **I-20** using the analogous coupling procedures for the synthesis of compound **I-21** in Example 8. ESI-MS *m/z*: 492.2 [M+H] $^+$.

Example 12



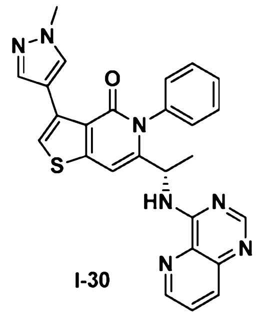
[00760] Amine **I-26** was prepared according to Method G and was then coupled to (**A-3**) using Method I to provide compound **I-27**. ESI-MS *m/z*: 415.2 [M+H]$^+$.

Example 13



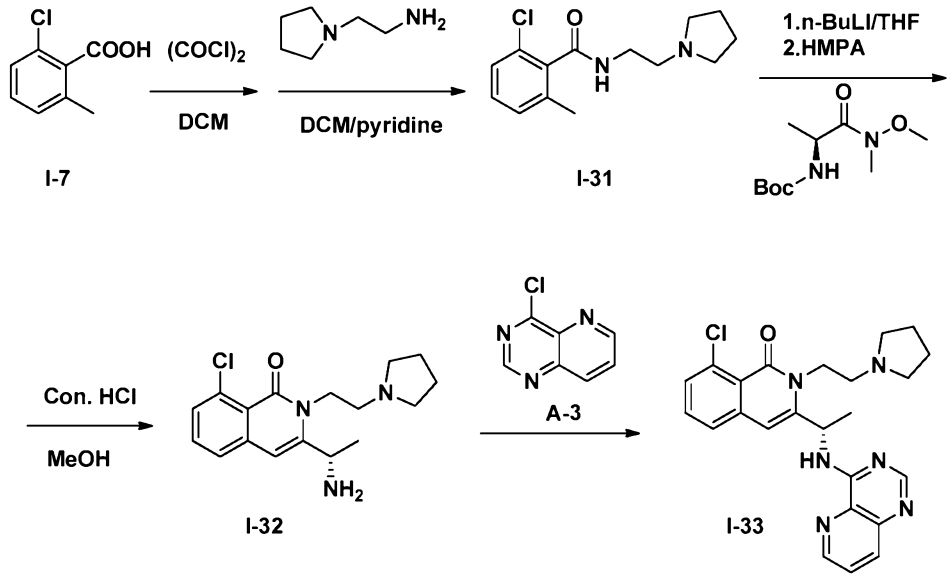
[00761] Amine **I-28** was prepared according to Method F and was then coupled to (**A-3**) using Method I to provide compound **I-29**. ESI-MS *m/z*: 434.0 [M+H]$^+$.

Example 14



[00762] Compound **I-30** was prepared from compound **I-29** using the analogous coupling procedures for the synthesis of compound **I-21** in Example 8. ESI-MS *m/z*: 480.2 [M+H]$^+$.

Example 15



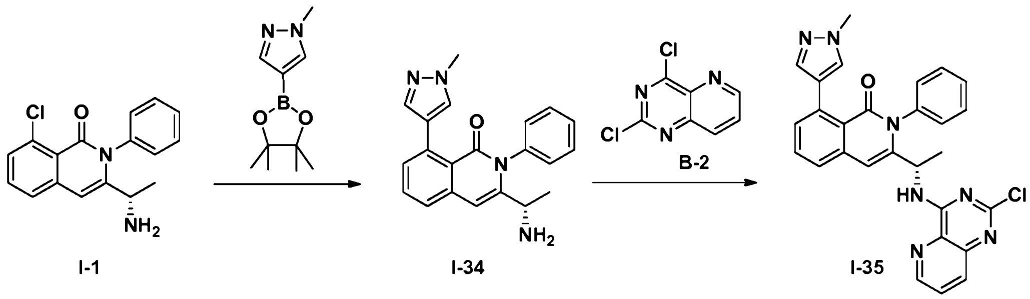
[00763] Compound **I-31** was prepared from **I-7** in analogous fashion to **E-2** in Method E and was then converted to **I-32** according to the following procedure:

[00764] To a mixture of 2-chloro-6-methyl-N-(2-(pyrrolidin-1-yl)ethyl)benzamide **I-31** (1.33 g, 5.0 mmol, 1.0 eq) and HMPA (0.87 mL, 5.0 mmol, 1.0 eq) in THF (12.5 mL) at -60 °C under argon, n-butyllithium solution (2.5 M in hexanes, 5.0 mL, 12.5 mmol, 2.5 eq) was added dropwise while keeping the temperature below -60 °C. The resulting mixture was stirred between -70 °C and -60 °C for 30 min. To this mixture, (S)-tert-butyl 1-(methoxy(methyl)amino)-1-oxopropan-2-ylcarbamate (1.39 g, 6.0 mmol, 1.2 eq) was added quickly. The resulting mixture was allowed to slowly warm to RT (over 1 h) and then stirred at RT for an additional 2 h. The reaction mixture was cooled to 0 °C, quenched with water (5.0 mL), and then acidified with aqueous HCl (5 M) to adjust the pH to 5-6. The mixture was concentrated *in vacuo*. The residue was suspended in a mixture of MeOH (20 mL) and H_2O (5.0 mL), concentrated HCl (10.0 mL) was added and the resulting mixture was stirred at reflux for 2 h. The mixture was cooled to -5 °C and basified with saturated aqueous NH_4OH to adjust the pH to 8-9. The precipitate was

filtered off and the filtrate was extracted with DCM (3 x 20 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and filtered. The filtrate was concentrated *in vacuo* and the residue was purified by flash column chromatography on silica gel (1-10% MeOH-DCM) to afford the product (S)-3-(1-aminoethyl)-8-chloro-2-(2-(pyrrolidin-1-yl)ethyl)isoquinolin-1(2H)-one **I-32**.

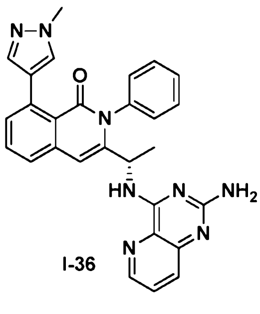
[00765] Compound **I-32** was coupled to (**A-3**) using Method I to provide compound **I-33.** ESI-MS *m/z*: 449.2 $[M+H]^+$.

Example 16



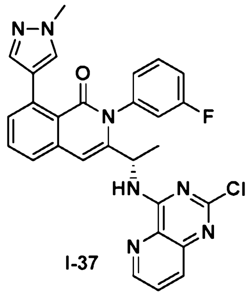
[00766] Compound **I-35** was prepared in two steps from compound **I-1**. Compound **I-1** was coupled to 1-methyl-1H-pyrazol-4-ylboronic acid pinacol ester using the procedure described in Example 8 to provide compound **I-34**. Compound **I-34** was then coupled to (**B-2**) using Method I to provide compound **I-35**. ESI-MS *m/z*: 508.2 $[M+H]^+$.

Example 17



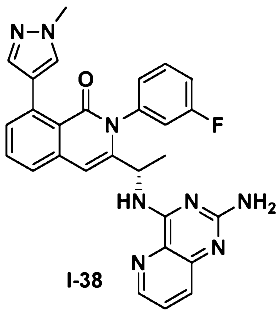
[00767] Compound **I-36** was prepared from compound **I-35** using Method J. ESI-MS *m/z*: 489.2 $[M+H]^+$.

Example 18



[00768] Compound **I-37** was prepared in analogous fashion to compound **I-35** in Example 16 except that amine **I-19** was used in place of amine **I-1**. ESI-MS *m/z*: 526.0 $[M+H]^+$.

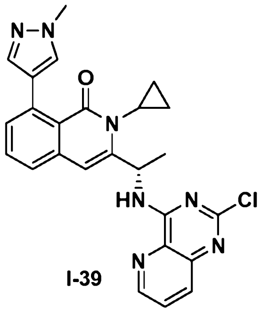
Example 19



I-38

[00769] Compound **I-38** was prepared from compound **I-37** using Method J. ESI-MS *m/z*: 507.2 $[M+H]^+$.

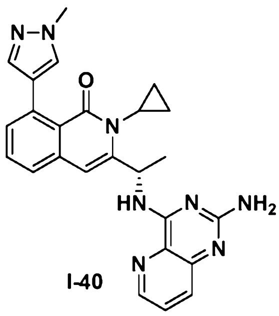
Example 20



I-39

[00770] Compound **I-39** was prepared in analogous fashion to compound **I-35** in Example 16 except that amine **I-22** was used in place of amine **I-1**. ESI-MS *m/z*: 472.2 $[M+H]^+$.

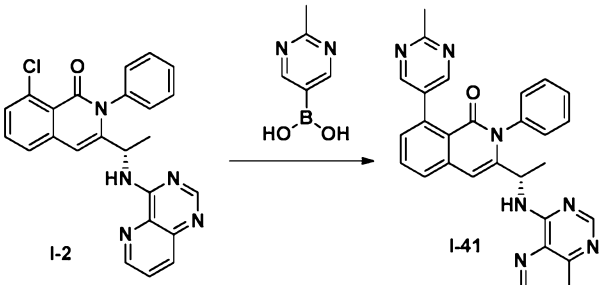
Example 21



I-40

[00771] Compound **I-40** was prepared from compound **I-39** using Method J. ESI-MS *m/z*: 453.2 $[M+H]^+$.

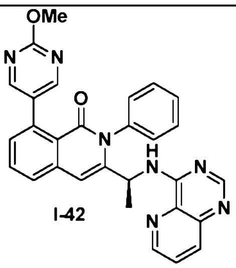
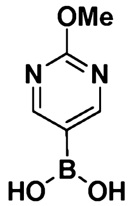
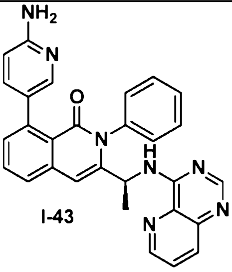
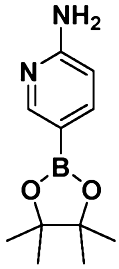
Example 22

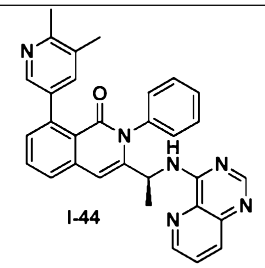
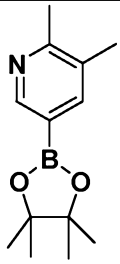
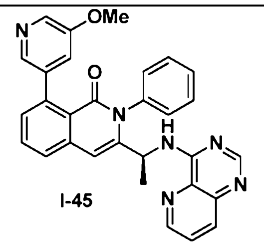
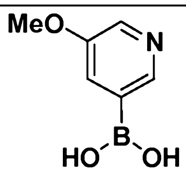
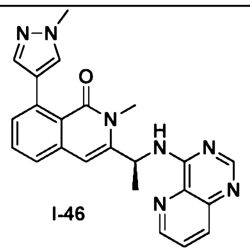
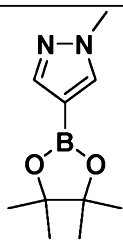
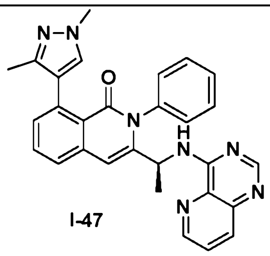
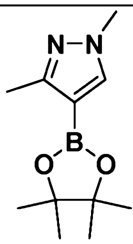
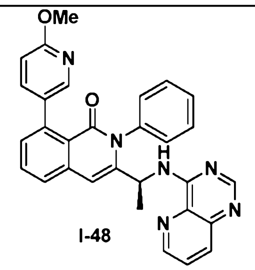
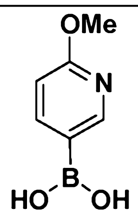


[00772] Compound **I-41** was prepared from compound **I-2** according to the following coupling procedures:

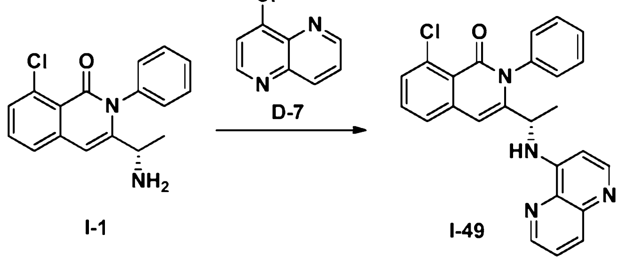
[00773] Compound **I-2** (230 umol), boronic acid (690 umol, 3 eq.), sodium carbonate (1.15 mmol, 5 eq.), RuPhos (70 μmol, 0.30 eq.), and palladium diacetate (35 umol, 0.15 eq.) were combined in a 2 mL microwave-reaction tube with a stir bar which was sealed with a septum. The atmosphere was purged three times with vacuum, backfilling with dry argon, then 1,4-dioxane (1.6 mL) and water (0.4 mL) were added. The reaction was subjected to microwave heating at 125 °C for 3h. The reaction mixture was diluted with DCM (ca. 30 mL), treated with silica gel (ca. 1 g) and concentrated; flash chromatography of this residue (on 15 g silica gel, eluting with a MeOH/DCM or EtOAc/hexanes gradient as required, approx. 750 mL total eluent) gave the product **I-41** as a light-yellow to off-white powder. ESI-MS *m/z*: 485.8 $[M+H]^+$.

[00774] The following compounds were also prepared from compound **I-2** using the analogous coupling conditions of Example 22:

Example	Compound	Boronic Acid	ESI-MS *m/z*
23	 I-42		502.4
24	 I-43		486.2

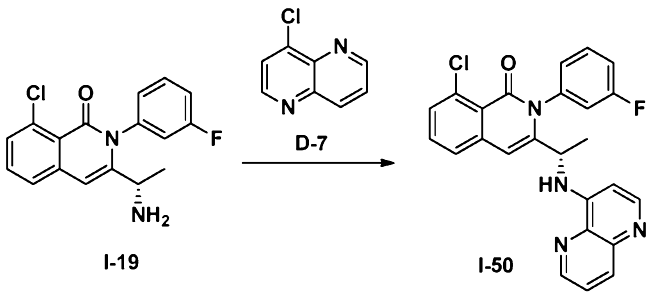
25	 I-44		499.2
26	 I-45		501.1
27	 I-46		411.4
28	 I-47		487.2
29	 I-48		501.24

Example 30



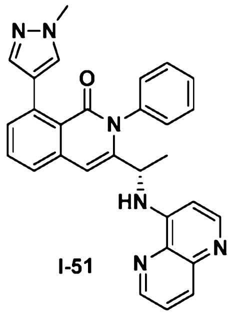
[00775] Compound **I-1** was coupled to (**D-7**) according to Method I to provide compound **I-49**. ESI-MS *m/z*: 427.2 $[M+H]^+$.

Example 31



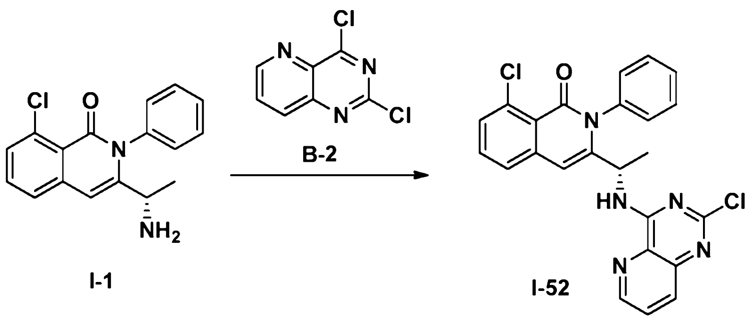
[00776] Compound **I-19** was coupled to (**D-7**) using Method I to provide compound **I-50**. ESI-MS *m/z*: 445.2 $[M+H]^+$.

Example 32



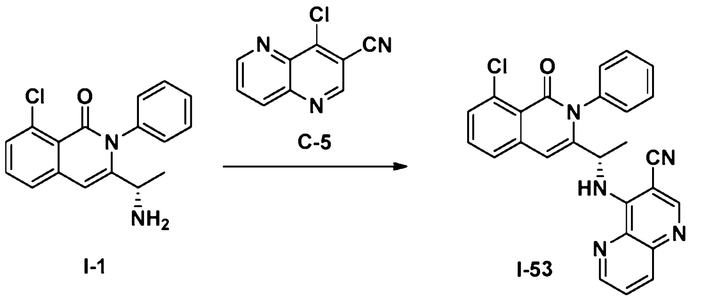
[00777] Compound **I-51** was prepared from compound **I-49** using the analogous coupling procedures for the synthesis of compound **I-21** in Example 8. ESI-MS *m/z*: 473.2 $[M+H]^+$.

Example 33



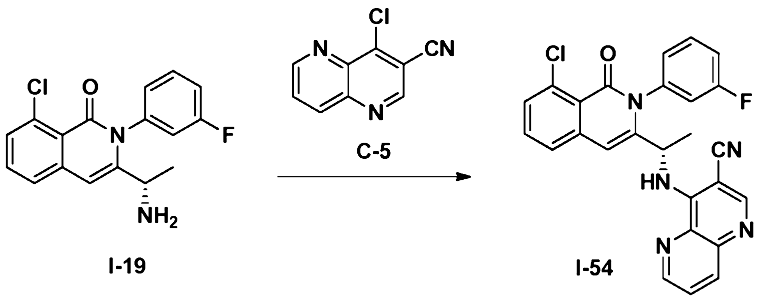
[00778] Compound **1** was coupled to (**B-2**) using Method I to provide compound **52**. ESI-MS *m/z*: 462.07 $[M+H]^+$.

Example 34



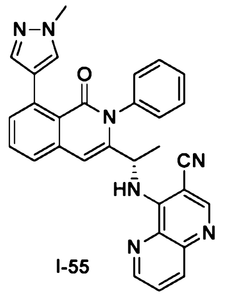
[00779] Compound **I-1** was coupled to (**C-5**) using Method I to provide compound **I-53**. ESI-MS *m/z*: 452.0 $[M+H]^+$.

Example 35



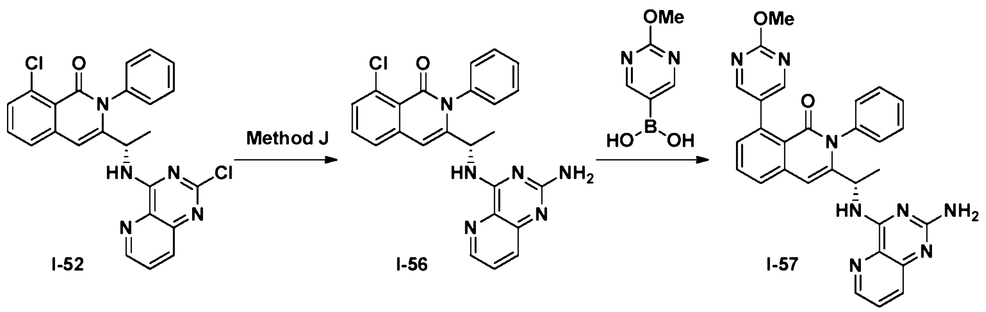
[00780] Compound **I-19** was coupled to (**C-5**) using Method I to provide compound **I-54**. ESI-MS *m/z*: 470.0 $[M+H]^+$.

Example 36



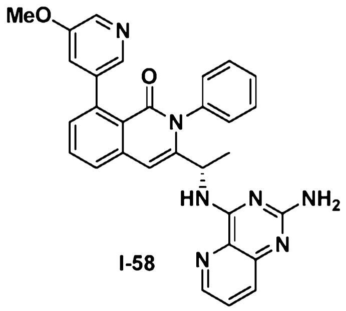
[00781] Compound **I-55** was prepared from compound **I-53** using the analogous coupling procedures for the synthesis of compound **I-21** in Example 8. ESI-MS *m/z*: 498.2 $[M+H]^+$.

Example 37



[00782] Compound **I-52** was converted to compound **I-56** using Method J. Compound **I-57** was then coupled to 2-methoxypyrimidin-5-ylboronic acid using the analogous procedure in Example 22 to provide compound **I-57**. ESI-MS *m/z*: 517.25 $[M+H]^+$.

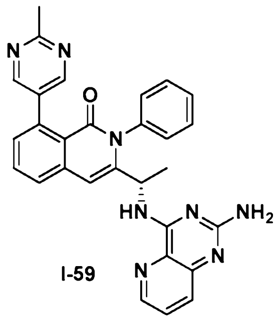
Example 38



I-58

[00783] Compound **I-58** was prepared in analogous fashion as compound **I-57** in Example 37 except that 5-methoxypyridin-3-ylboronic acid was used in place of 2-methoxypyrimidin-5-ylboronic acid. ESI-MS *m/z*: 516.25 $[M+H]^+$.

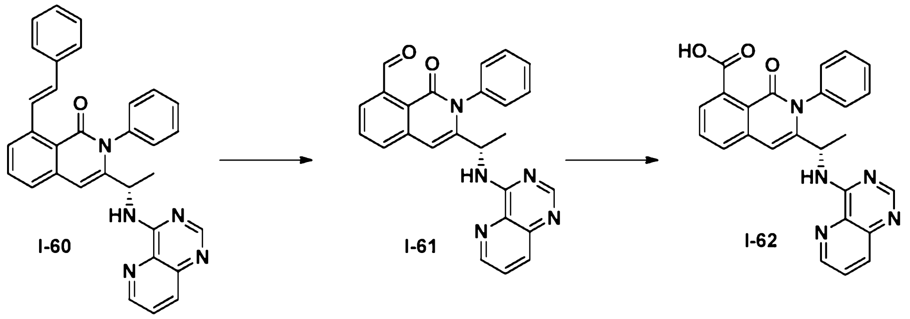
Example 39



I-59

[00784] Compound **I-59** was prepared in analogous fashion as compound **I-57** in Example 37 except that 5-methylpyrimidin-5-ylboronic acid was used in place of 2-methoxypyrimidin-5-ylboronic acid. ESI-MS *m/z*: 501.24 $[M+H]^+$.

Example 40



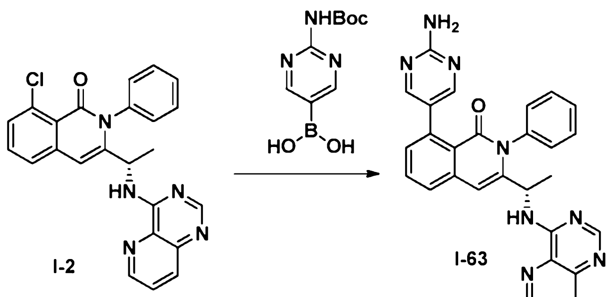
[00785] Compound **I-62** was prepared in 2 steps from compound **I-60**. Styrene **I-60** was prepared using the analogous coupling conditions in Example 22 except that styrylboronic acid was used in place of 2-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrimidine.

[00786] Compound **I-60** (0.98 mmol, 1 eq) was dissolved in THF (10 mL), tert-butanol (5 mL), and water (1.5 mL), and treated with N-methyl-morpholine N-oxide (700 mg, 6 eq) and a 4% aqueous solution of osmium tetroxide (125 μL, 0.02 eq). The reaction was stirred at ambient temperature overnight. The solvent was removed *in vacuo* and the residue was taken up in water (50 mL), excess oxidant quenched with saturated sodium sulfite solution (20 mL), and the product extracted three times with 40 mL of DCM. The combined organic phases were washed with brine and concentrated to a yellow solid.

[00787] This yellow solid was dissolved in THF (25 mL) and water (5 mL), then treated with sodium periodate (1 g, 4.7 eq) and allowed to stir at ambient temperature for 1 day. The reaction mixture was diluted with DCM, treated with silica gel (2 g) and concentrated *in vacuo*. Purification of the product by flash chromatography on silica gel, eluting with 40% to 80% EtOAc in hexanes, afforded the aldehyde **I-61**.

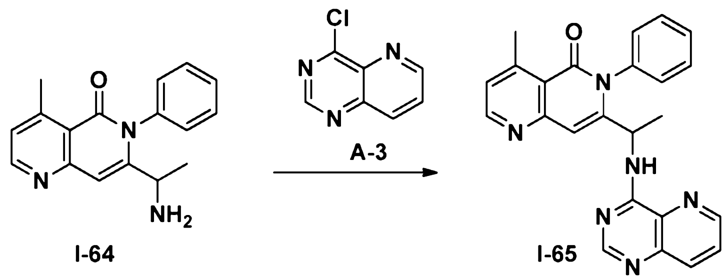
[00788] Aldehyde **I-61** (0.96 mmol, 1 eq) in THF (13 mL) and tert-butanol (3 mL) was treated with isoprene (2 mL, 20 eq.), a 2.7M aqueous solution of monobasic sodium phosphate (2 mL, 5 eq), and a 1M aqueous solution of sodium chlorite (3 mL, 3 eq). The reaction was stirred at ambient temperature during 2 days, then treated with additional 1M chlorite solution (3 mL, 3 eq), and allowed to react overnight. The reaction mixture was added to water (90 mL) and DCM (60 mL) and acidified to pH 3 by slow addition of 6M HCl (ca. 30 drops). The layers were separated and the aqueous phase extracted twice with 40 mL DCM. The combined organic phases were washed with brine, dried on sodium sulfate, and concentrated. Purification of the product by flash chromatography on silica gel, eluting with 1-5% MeOH in DCM containing 1% acetic acid, afforded the acid **I-62** as an off white solid. ESI-MS *m/z*: 436.17 $[M+H]^+$.

Example 41



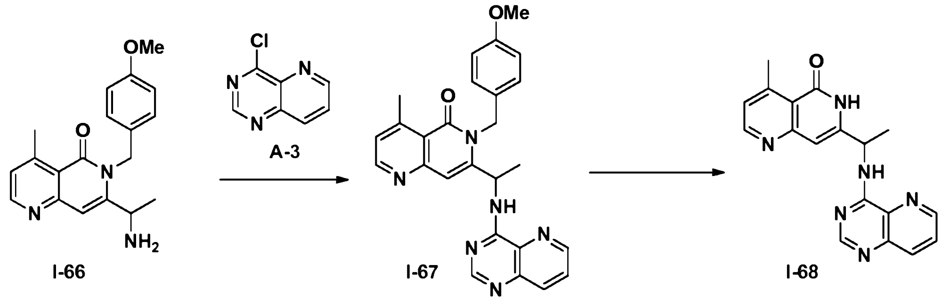
[00789] Compound **I-63** was prepared from compound **I-2** using the analogous coupling procedures in Example 22 except that 2-(tert-butoxycarbonylamino)pyrimidin-5-ylboronic acid was used in place of 2-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrimidine. ESI-MS *m/z*: 487.23 $[M+H]^+$.

Example 42



[00790] Amine **I-64** was prepared according to Method H and was then coupled to (**A-3**) using Method I to provide compound **I-65**. ESI-MS *m/z*: 409.2 [M+H]$^+$.

Example 43



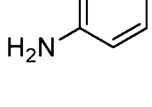
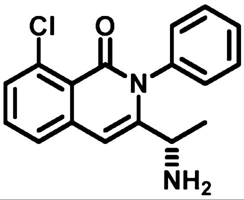
[00791] Amine **I-66** was prepared from (**H-1**) in analogous fashion to (**H-16**) in Method H except that (4-methoxyphenyl)methanamine was used in place of aniline in step 6 (amide formation). Amine **I-66** was then coupled to (**A-3**) according to Method I to provide compound **I-67**. Compound **I-67** was converted to **I-68** according to the following procedure:

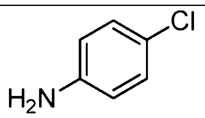
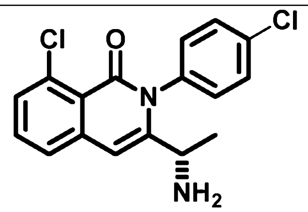
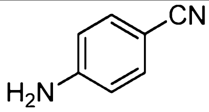
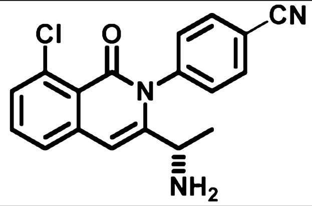
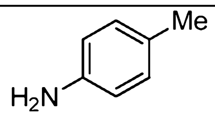
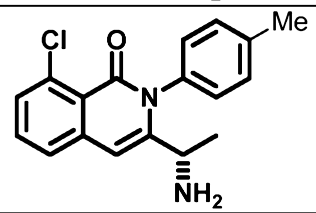
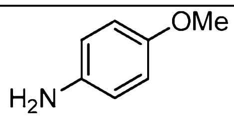
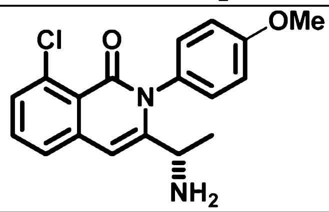
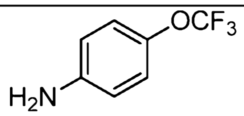
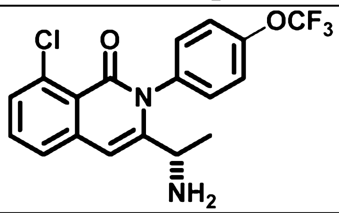
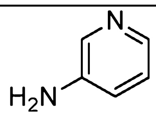
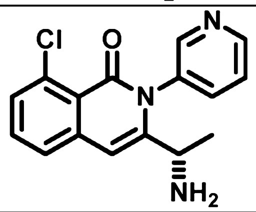
[00792] 6-(4-Methoxybenzyl)-4-methyl-7-(1-(pyrido[3,2-d]pyrimidin-4-ylamino)ethyl)-1,6-naphthyridin-5(6H)-one **I-67** (60 mg, 0.13 mmol) was dissolved in trifluoroacetic acid (4 mL) in a sealed tube and the resulting mixture was stirred at 140 °C for 48 h. The mixture was allowed to cool to RT, quenched with water and then neutralized with saturated $NaHCO_3$ aqueous solution. The mixture was extracted with ethyl acetate, washed with brine, dried with Na_2SO_4 and filtered. The filtrate was concentrated *in vacuo* to afford the product, 4-methyl-7-(1-(pyrido[3,2-d]pyrimidin-4-ylamino)ethyl)-1,6-naphthyridin-5(6H)-one **I-68**. ESI-MS *m/z*: 333.2 [M+H]$^+$.

Example 44

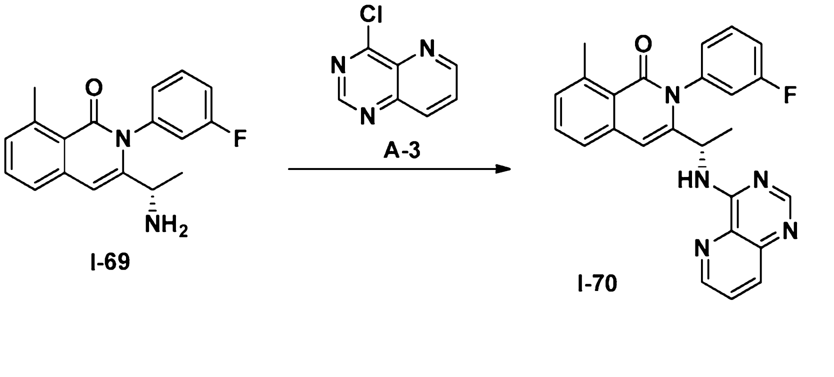
[00793] The following isoquinolinone compounds (**L-6**) were made in analogous fashion to Method L using the following R_2-NH_2 reagents.

Table 2. Compounds (**L-6**)

R_2-NH_2	Compound (L-6)	ESI-MS *m/z*: [M+H]$^+$
		299.10

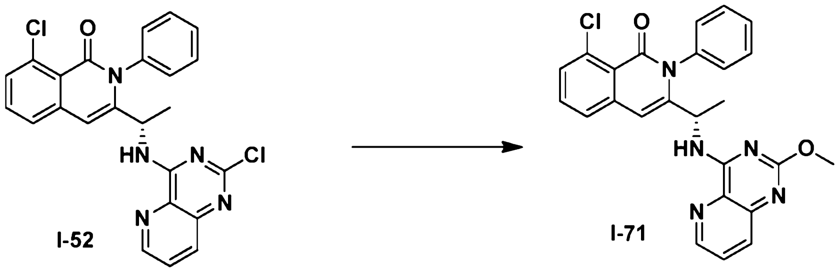
		335
		324.12
		313.10
		329.09
		383.13
		300.09

Example 45



[00794] Amine **I-69** was prepared according to Method E. It was then coupled to (**A-3**) using Method I to provide compound **I-70**. ESI-MS m/z: 426.2 [M+H]$^+$.

Example 46

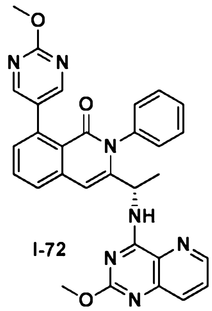


I-52

I-71

[00795] To a stirred solution of compound **I-52** (0.1 mmol, 1.0 eq) in THF (10 mL) at RT, sodium methoxide (0.2 mmol, 2 eq) was added and the resulting mixture was stirred at reflux for 1-2 h. The mixture was allowed to cool to RT and then extracted with DCM (15 mL x 3). The combined organic layers were washed with brine, dried over Na_2SO_4 and filtered. The filtrate was concentrated *in vacuo* and the residue was purified by column chromatography on silica gel (1-2% MeOH/DCM) to afford compound **I-71**. ESI-MS *m/z*: 458.1 [M+H]$^+$.

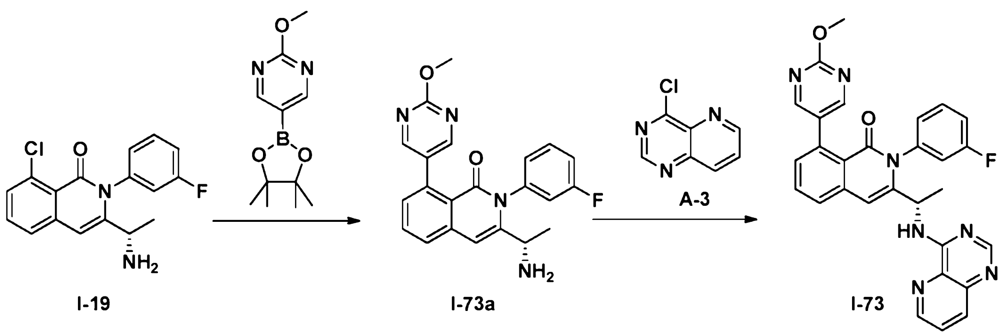
Example 47



I-72

[00796] Compound **I-72** was prepared from compound **I-71** in analogous fashion to compound **I-21** in Example 8. ESI-MS *m/z*: 532.2 [M+H]$^+$.

Example 48



I-19

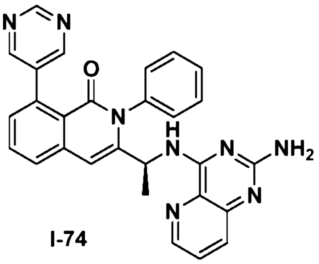
I-73a

I-73

[00797] Compound **I-73** was prepared in two steps from compound **I-19**. Compound **I-19** was coupled to 2-methoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrimidine using the procedure described in Example 8

to provide compound **I-73a**. Compound **I-73a** was then coupled to (**A-3**) using Method I to provide compound **I-73**. ESI-MS *m/z*: 520.1 $[M+H]^+$.

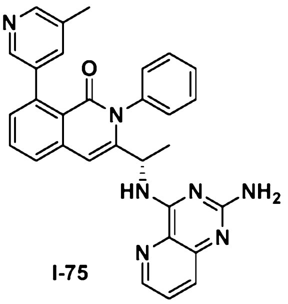
Example 49



I-74

[00798] Compound **I-74** was prepared from compound **I-56** using pyrimidin-5-ylboronic acid in the Suzuki reaction performed in analogous fashion to compound **I-21** in Example 8. ESI-MS *m/z*: 487.2 $[M+H]^+$.

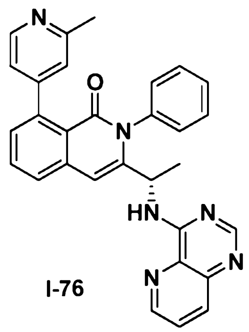
Example 50



I-75

[00799] Compound **I-75** was prepared from compound **I-56** using (5-methylpyridin-3-yl)boronic acid in the Suzuki reaction performed in analogous fashion to compound **I-21** in Example 8. ESI-MS *m/z*: 500.3 $[M+H]^+$.

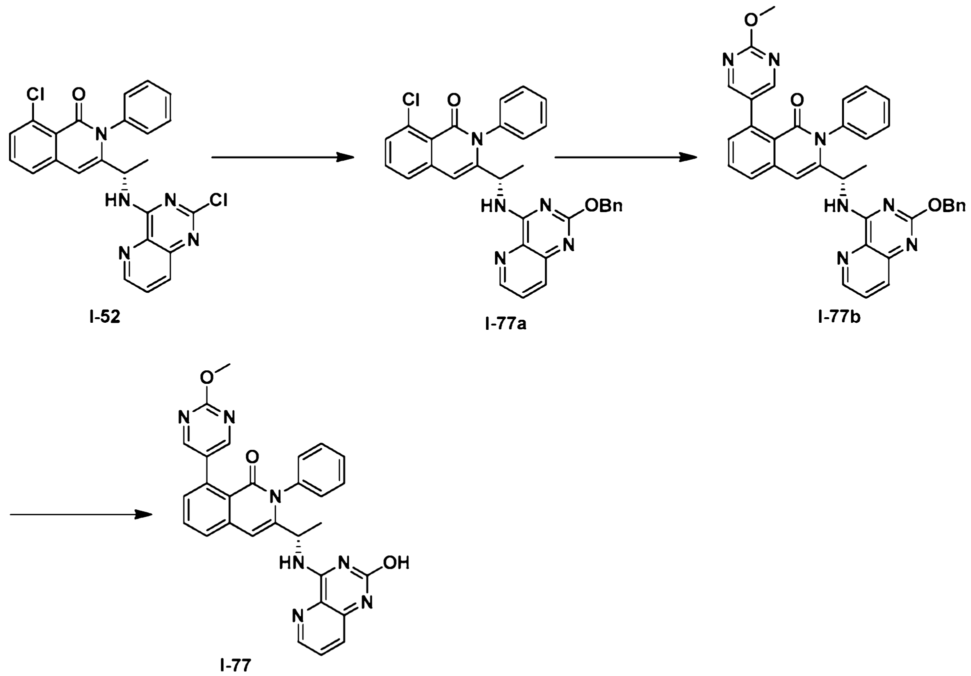
Example 51



I-76

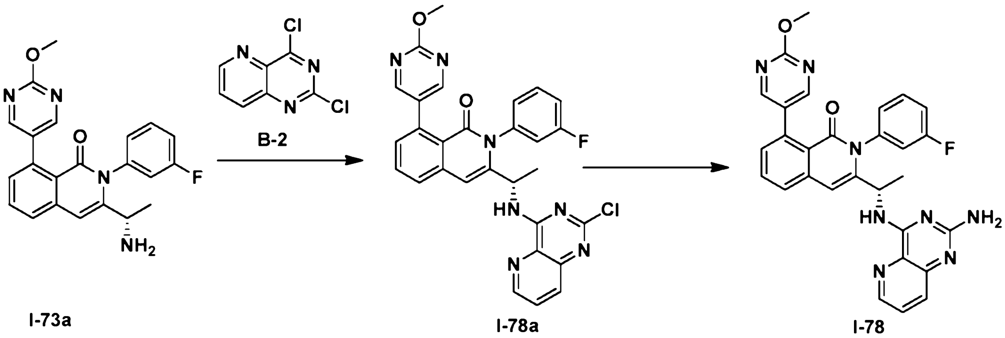
[00800] Compound **I-76** was prepared from compound **I-2** using 2-methylpyridin-4-ylboronic acid in the Suzuki reaction performed in analogous fashion to compound **I-21** in Example 8. ESI-MS *m/z*: 485.1 $[M+H]^+$.

Example 52



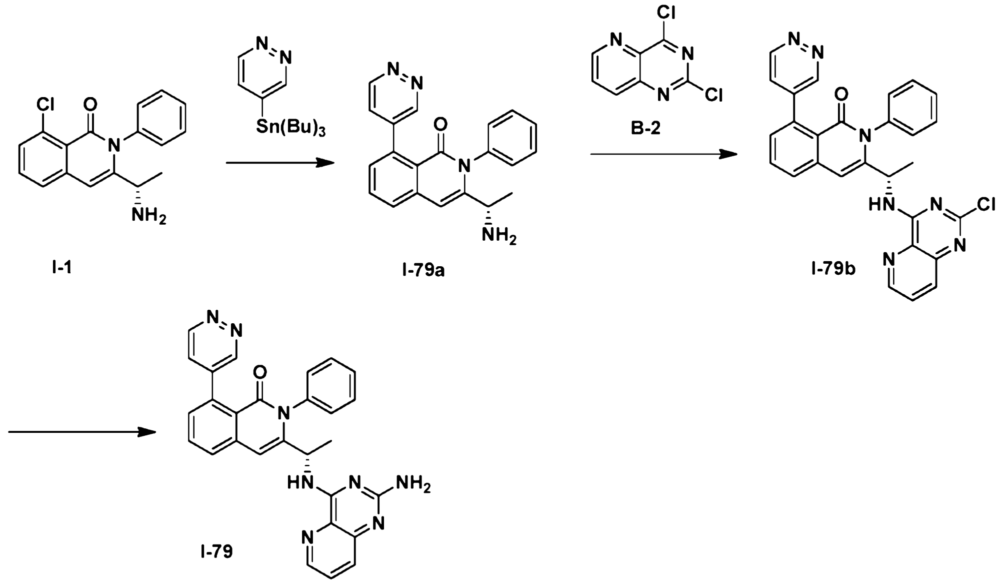
[00801] To a stirred solution of compound **I-52** (0.1 mmol, 1.0 eq) in THF (10 mL) at RT, sodium benzyloxide (0.2 mmol, 2 eq) was added and the resulting mixture was stirred at reflux for 1-2 h. The mixture was allowed to cool to RT and then extracted with DCM (15 mL x 3). The combined organic layers were washed with brine, dried over Na_2SO_4 and filtered. The filtrate was concentrated *in vacuo* and the residue was purified by column chromatography on silica gel (1-2% MeOH/DCM) to afford compound **I-77a**. ESI-MS *m/z*: 518.2 $[M+H]^+$.

Example 53



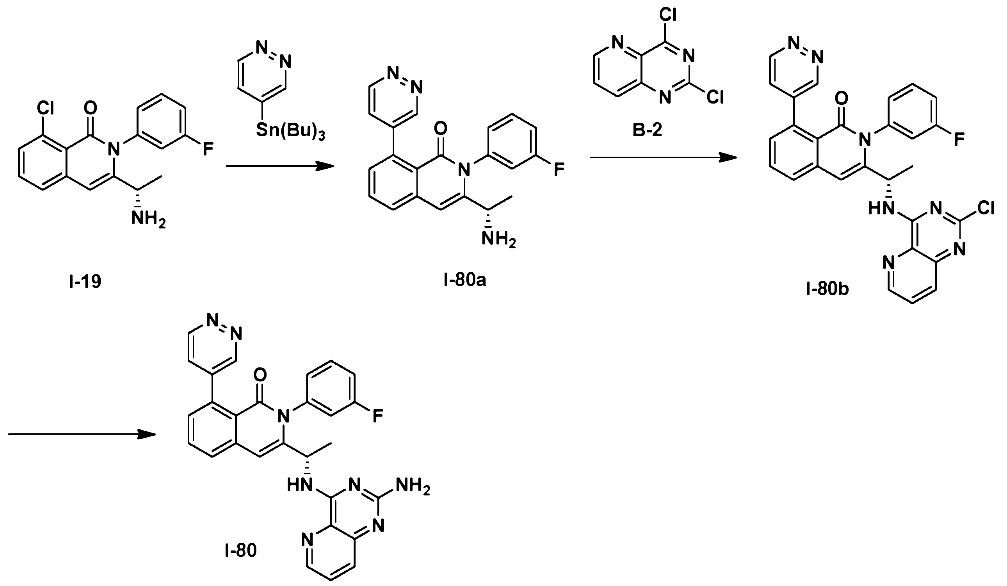
[00802] Compound **I-78** was prepared in two steps from compound **I-73a**. Compound **I-73a** was coupled to (**B-2**) using Method I to provide compound **I-78a**. Compound **I-78** was prepared from compound **I-78a** using Method J. ESI-MS *m/z*: 535.2 $[M+H]^+$.

Example 54



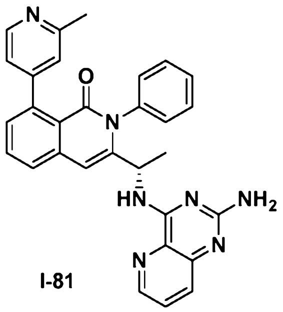
[00803] Compound **I-79** was prepared from compound **I-1** in three steps. Compound **I-1** was coupled with 4-(tributylstannyl)pyridazine using the procedure described in Example 8 to provide compound **I-79a**. Compound **I-79a** was then coupled to (**B-2**) using Method I to provide compound **I-79b**. Compound **I-79b** was converted to compound **I-79** using Method J. ESI-MS *m/z*: 487.2 $[M+H]^+$.

Example 55



[00804] Compound **I-80** was prepared in three steps from compound **I-19** in analogous fashion to **I-79** in Example 54. ESI-MS *m/z*: 505.2 $[M+H]^+$.

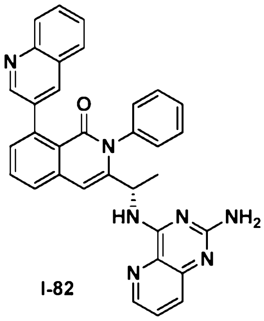
Example 56



I-81

[00805] Compound **I-81** was prepared from compound **I-56** using 2-methylpyridin-4-ylboronic acid in the Suzuki reaction performed in analogous fashion to compound **I-21** in Example 8. ESI-MS *m/z*: 500.3 $[M+H]^+$.

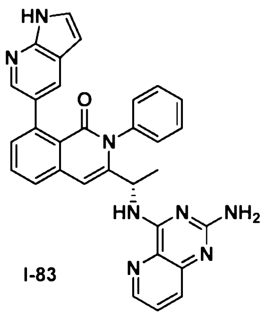
Example 57



I-82

[00806] Compound **I-82** was prepared from compound **I-56** using quinolin-3-ylboronic acid in the Suzuki reaction performed in analogous fashion to compound **I-21** in Example 8. ESI-MS *m/z*: 536.3 $[M+H]^+$.

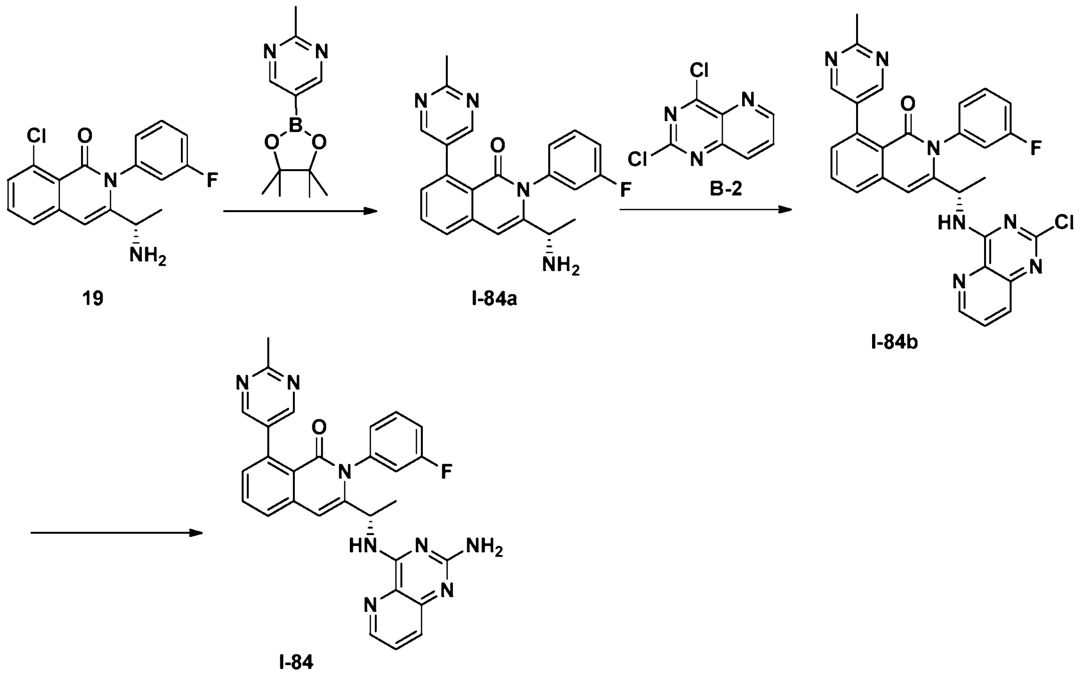
Example 58



I-83

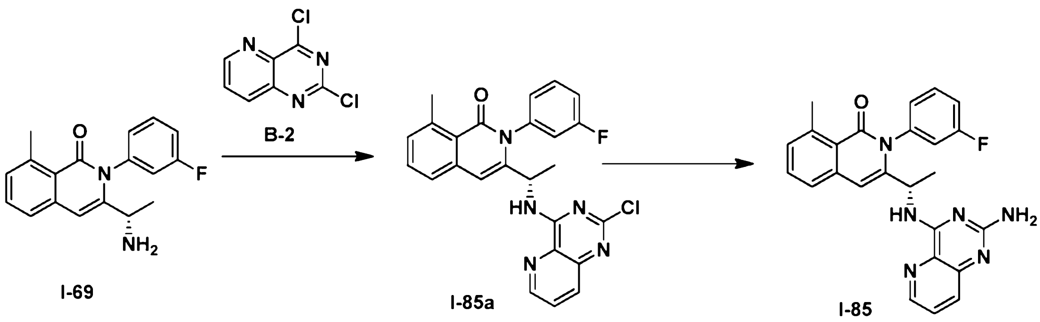
[00807] Compound **I-83** was prepared from compound **I-56** using 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrrolo[2,3-b]pyridine in the Suzuki reaction performed in analogous fashion to compound **I-21** in Example 8. ESI-MS *m/z*: 525.3 $[M+H]^+$.

Example 59



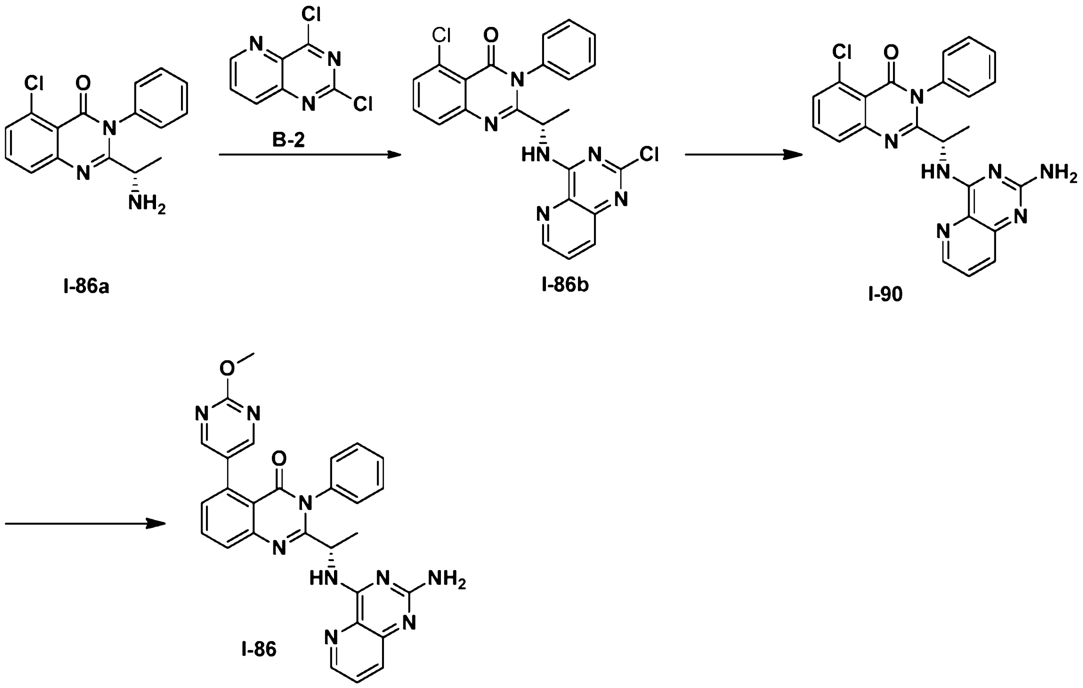
[00808] Compound **I-84** was prepared in two steps from compound **I-19** in analogous fashion to compound **I-73a** in Example 48. Compound **I-84a** was converted to compound **I-84b** in analogous fashion to compound **I-78** in Example 53. ESI-MS *m/z*: 519.2 [M+H]$^+$.

Example 60



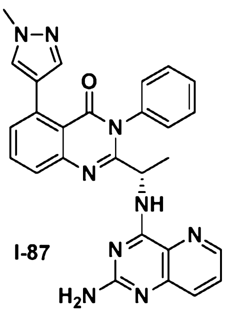
[00809] Compound **I-85** was prepared in two steps from compound **I-69**. Compound **I-69** was coupled to (**B-2**) using Method I to provide compound **I-85a**. Compound **I-85** was prepared from compound **I-85a** using Method J. ESI-MS *m/z*: 441.2 [M+H]$^+$.

Example 61



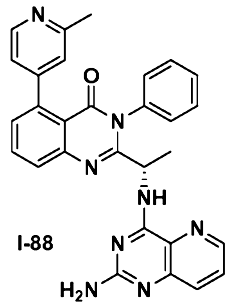
[00810] Compound **I-86a** was prepared from 2-chloro-6-nitrobenzoic acid according to MethodK. Compound **I-86a** was then coupled to (**B-2**) using Method I to provide compound **I-86b**. Compound **I-86b** was converted to compound **I-90** using Method J. Compound **I-90** was coupled to 2-methoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrimidine using the procedure described in Example 8 to provide compound **I-86**. ESI-MS *m/z*: 518.2 [M+H]$^+$.

Example 62



[00811] Compound **I-87** was prepared from **I-90** by Suzuki coupling with 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole in analogous fashion to compound **I-86**. ESI-MS *m/z*: 490.2 [M+H]$^+$.

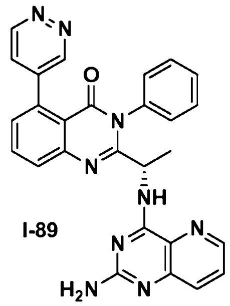
Example 63



I-88

[00812] Compound **I-88** was prepared from **I-90** by Suzuki coupling with 2-methylpyridin-4-ylboronic acid in analogous fashion to compound **I-86**. ESI-MS *m/z*: 501.2 $[M+H]^+$.

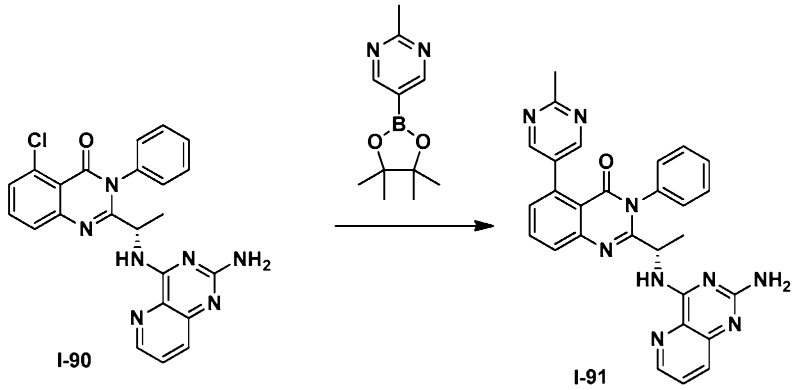
Example 64



I-89

[00813] Compound **I-90** was coupled to 4-(tributylstannyl)pyridazine using the procedure described in Example 8 to provide compound **I-89**. ESI-MS *m/z*: 488.2 $[M+H]^+$.

Example 65

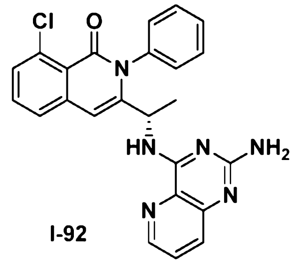


I-90 I-91

[00814] To a solution of (S)-2-(1-((2-aminopyrido[3,2-d]pyrimidin-4-yl)amino)ethyl)-5-chloro-3-phenylquinazolin-4(3H)-one (30 mg, 0.067 mmol) and 2-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrimidine (22 mg, 0.1 mmol) in 1,4-dioxane-H_2O (4:1, 2 mL) in a sealed tube, 2-dicyclohexylphosphino-2′,6′-diisopropoxybiphenyl (15.6 mg, 0.034 mmol), palladium(II) acetate (3.8 mg, 0.017 mmol), and Na_2CO_3 (21 mg, 0.20 mmol) were added sequentially. The mixture was degassed and backfilled with argon (three cycles), and then stirred at 120 °C for 1 h. The mixture was allowed to cool to RT, and then partitioned between ethyl acetate and

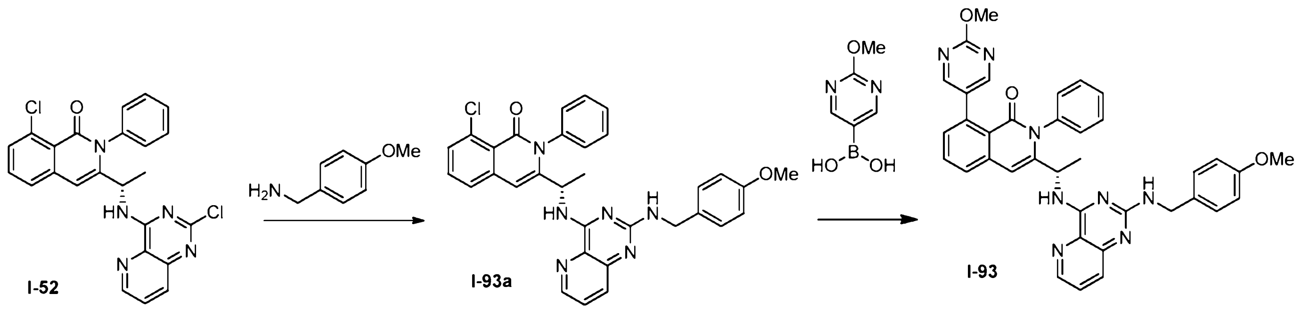
water. The organic layer was washed with brine, dried over Na_2SO_4 and filtered. The filtrate was concentrated *in vacuo* and the residue was purified by ISCO column chromatography (silica gel cartridge, 0-10% MeOH/DCM) to afford compound **I-91**, (S)-2-(1-((2-aminopyrido[3,2-d]pyrimidin-4-yl)amino)ethyl)-5-(2-methylpyrimidin-5-yl)-3-phenylquinazolin-4(3H)-one (17 mg, 50% yield). ESI-MS *m/z*: 502.2 $[M+H]^+$.

Example 66



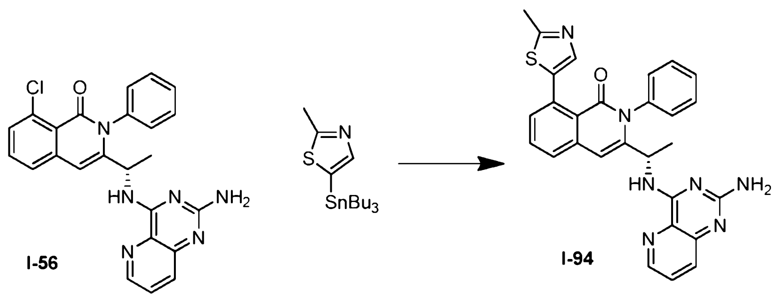
[00815] Compound **I-92** was prepared from compound **I-52** using Method J. ESI-MS *m/z*: 443.1 $[M+H]^+$.

Example 67



[00816] Compound **I-93** was prepared in two steps from compound **I-52**. Compound **I-52** was converted to compound **I-93a** using 4-methoxybenzylamine in Method J. Compound **I-93a** was coupled with 2-methoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrimidine using the procedure described in Example 8 to provide compound **I-93**. ESI-MS *m/z*: 637.4 $[M+H]^+$.

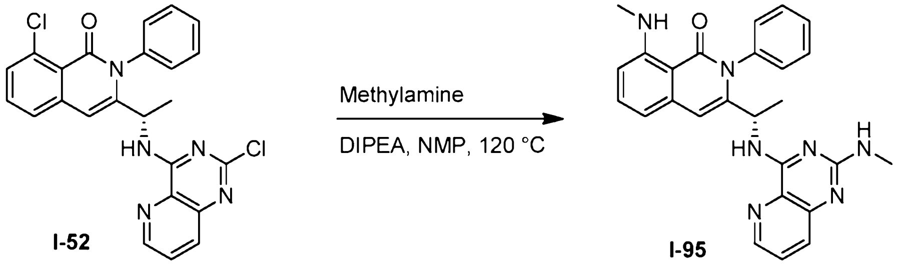
Example 68



[00817] Compound **I-56** (151 mg, 0.342 mmol), 2-Methyl-5-(tributylstannyl)thiazole (159 mg, 0.410 mmol), $PdCl_2(amphos)_2$ (24.19 mg, 0.034 mmol), $PdCl_2(amphos)_2$ (24.19 mg, 0.034 mmol) were charged in a dry

vial. The vial was evacuated and filled with Ar. Then degassed DMF (1 ml) was added and the mixture was stirred at 100 °C overnight. The reaction was cooled and the material was extracted with EtOAc and wash with water then brine. The organic layer was dried, filtered and concentrated to dryness. Purification on silica gel (12g) column and eluting with DCM/methanol (0 to 5% of methanol) provided compound **I-94**. ESI-MS *m/z*: 506.2 $[M+H]^+$.

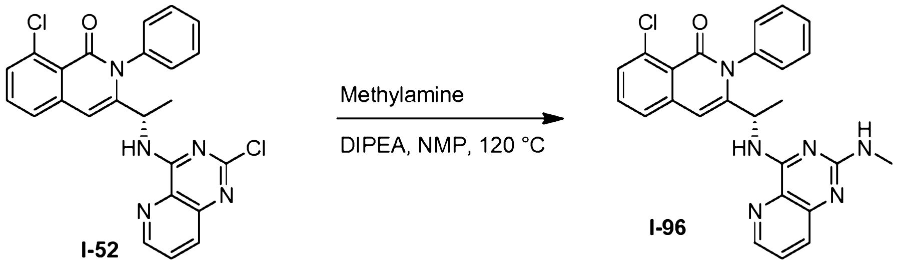
Example 69



I-52 I-95

[00818] A mixture of compound **I-52** (500 mg, 1.09 mmol, 1 equiv.), N,N-Diisopropylethylamine (0.56 mL, 3.28 mmol, 3 equiv.), 1.5 mL methylamine (40% in water, 17.2 mmols, 15.8 equiv.) in 5 mL NMP was heated in a sealed tube at 120 °C for 45 h. 1.5 mL methylamine (40% in water, 17.2 mmols, 15.8 equiv.) and 1 mL NMP were added and heated in a sealed tube at 120 °C for another 18 h. The mixture was cooled, diluted with 10 mL 1:1 mixture of saturated brine and 2.5 M sodium carbonate and 25 mL DCM. The aqueous layer was extracted with DCM (3x5 mL), the combined organic layers were washed with water (10 mL), dried over sodium sulfate and the solvents were evaporated *in vacuo.* The residue was chromatographed on silica gel (4 g, ISCO) using acetone-DCM as eluent. The product fractions were concentrated and the impurities were crystallized off and the filtrates were concentrated under reduced pressure to provide 106 mg of compound **I-95** as a light yellow solid. ESI-MS *m/z*: 452.2 $[M+H]^+$.

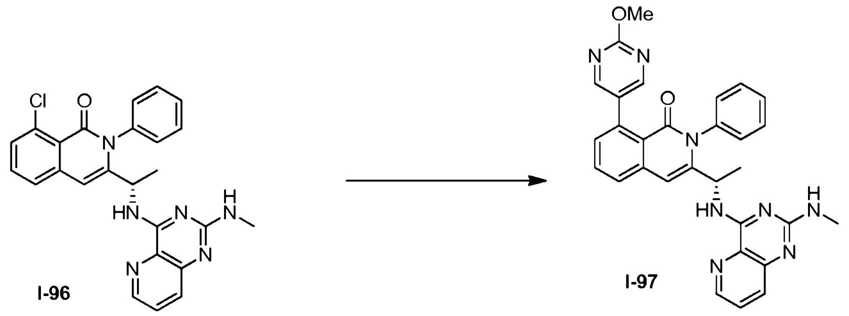
Example 70



I-52 I-96

[00819] A mixture of compound **I-52** (522 mg, 1.13 mmol, 1 equiv.), N,N-Diisopropylethylamine (0.58 mL, 3.39 mmol, 3 equiv.), 0.985 mL methylamine (40% in water, 11.2 mmols, 10 equiv.) in 5 mL NMP was heated in a sealed tube at 100 °C for 0.5 h. The clear solution was mixture was cooled to room temp, diluted with 10 mL water, added to crushed ice, the precipitated white solids were filtered under suction, washed with water (3x10 mL) and dried under high vacuum to give 516 mg compound **I-96** as a white solid. ESI-MS *m/z*: 457.2 $[M+H]^+$.

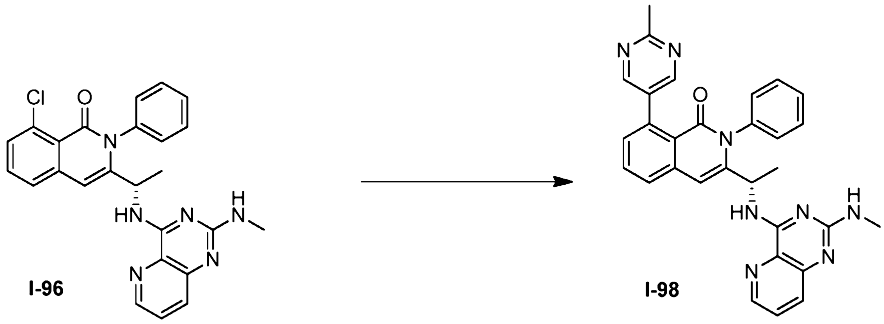
Example 71



I-96 I-97

[00820] A mixture of compound **I-96** (100 mg, 0.219 mmol, 1 equiv.), 2-Methoxypyrimidine-5-boronic acid (67.4 mg, 0.438 mmol, 2 equiv.), sodium carbonate (116 mg, 1.094 mmol, 5 equiv.), and Pd-AMPHOS catalyst (31.0 mg, 0.044 mmol, 0.2 equiv.) in 2.9 mL degassed 4:1 dioxane-water was sparged with argon for 2 min. The mixture was sealed and heated at 100 °C for 1h, cooled, diluted with 10 mL each of DCM and water. The organic layer was collected, the aqueous layer was extracted with DCM (3x10 mL), the combined DCM layers were washed with water (10 mL), brine (10 mL), dried over sodium sulfate and the solvents were removed *in vacuo*. The residue was purified on silica gel (12 g, ISCO) using 0-10% methanol in 1:1 DCM-EtOAc as eluent to provide 97 mg of compound **I-97** as a light yellow solid. ESI-MS *m/z*: 531.3 $[M+H]^+$.

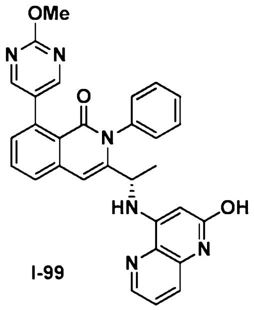
Example 72



I-96 I-98

[00821] A mixture of compound **I-96** (100 mg, 0.219 mmol, 1 equiv.), 2-Methylpyrimidine-5-pinacol boronate (96mg, 0.438 mmol, 2 equiv.), sodium carbonate (116 mg, 1.094 mmol, 5 equiv.), and Pd-AMPHOS catalyst (31.0 mg, 0.044 mmol, 0.2 equiv.) in 2.9 mL degassed 4:1 dioxane-water was sparged with argon for 2 min. The mixture was sealed and heated at 100 °C for 1h, cooled, diluted with 10 mL each of DCM and water. The organic layer was collected, the aqueous layer was extracted with DCM (3x10 mL), the combined DCM layers were washed with water (10 mL), brine (10 mL), dried over sodium sulfate and the solvents were removed *in vacuo*. The residue was purified on silica gel (12 g, ISCO) using 0-10% methanol in 1:1 DCM-EtOAc to provide 110 mg of compound **I-98** as a light yellow solid. ESI-MS *m/z*: 515.3 $[M+H]^+$.

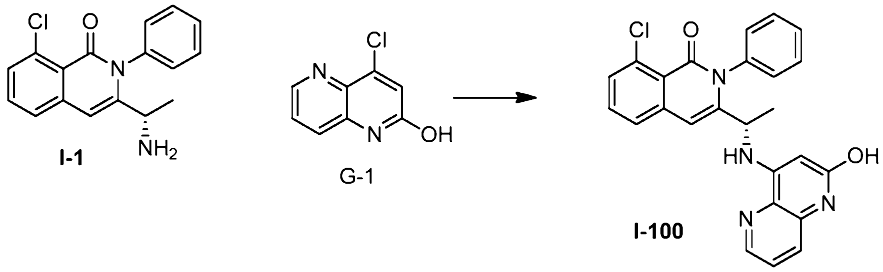
Example 73



I-99

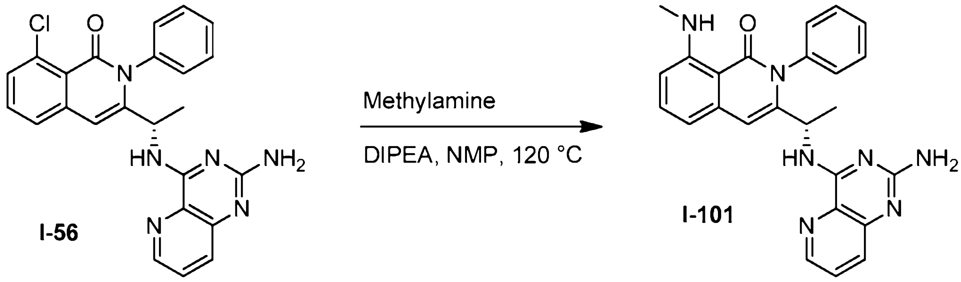
[00822] Compound **I-99** was synthesized by coupling compound **I-100** and 2-methoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrimidine using the procedure described in Example 8. ESI-MS *m/z*: 517.3 $[M+H]^+$.

Example 74



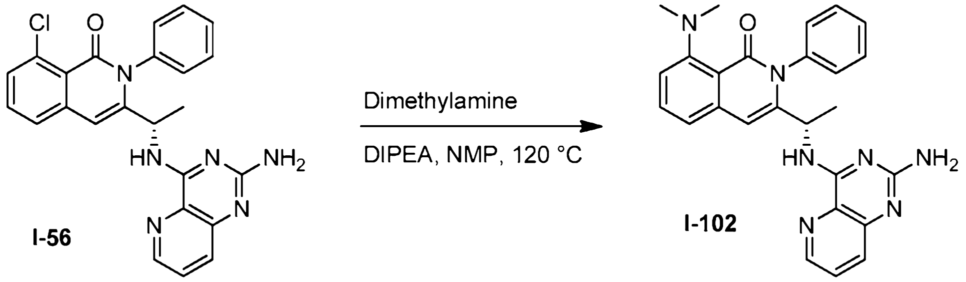
[00823] Compound **I-100** was prepared from compound **I-1** coupled to (**G-1**) (*see* Barlin, Gordon B.; Tan, Weng Lai, *Australian Journal of Chemistry* (1984), 37(12), 2469-77) using Method I. ESI-MS *m/z*: 443.2 $[M+H]^+$.

Example 75



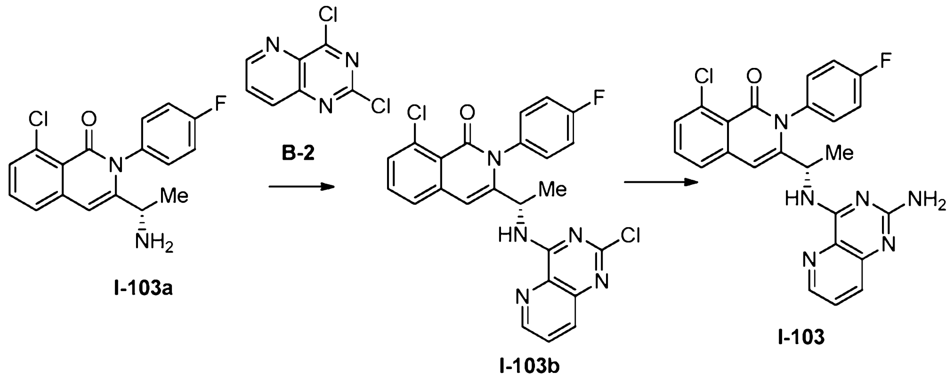
[00824] A mixture of compound **I-56** (100 mg, 0.226 mmol, 1 equiv.), N,N-Diisopropylethylamine (0.16 mL, 0.9 mmol, 4 equiv.), 1.5 mL methylamine (40% in water, excess) in 1 mL NMP was heated in a sealed tube at 120 °C for 18 h. Another 1.5 mL methylamine in water and 1 mL NMP were added, the tube was sealed and the mixture was heated at 120 °C for 52h. The contents were cooled, added to 15 mL water, the precipitate were filtered under suction, washed with water (3x10 mL) and dried under high vacuum to provide 71 mg of compound **I-101** as a white solid. ESI-MS *m/z*: 438.3 $[M+H]^+$.

Example 76



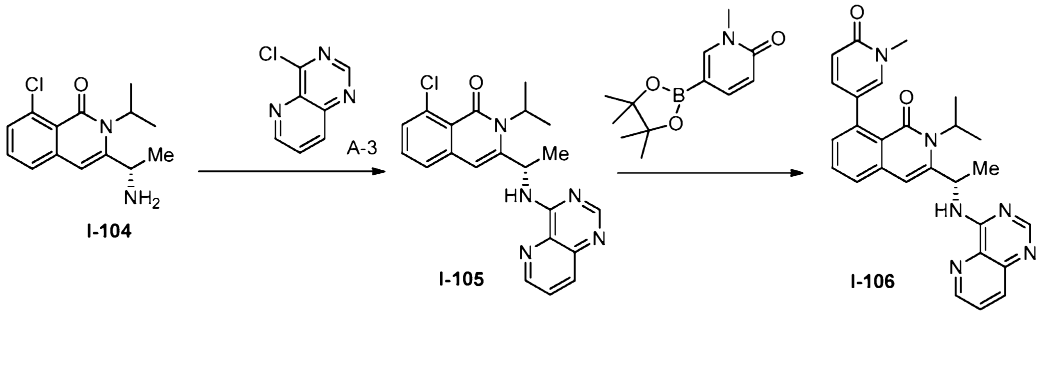
[00825] A mixture of compound **I-56** (100 mg, 0.226 mmol, 1 equiv.), N,N-Diisopropylethylamine (0.16 mL, 0.9 mmol, 4.0 equiv.), 1.13 mL dimethylamine (2.0 M in THF, 10 equiv.) in 1 mL NMP was heated in a sealed tube at 120 °C for 18 h. Another 2 mL dimethylamine in THF and 2 mL NMP were added, the tube was sealed and the mixture was heated at 120 °C for 52h. The contents were cooled, diluted with EtOAc (20 mL), added to 30 mL water, the organic layer was collected, the aqueous layer was extracted with EtOAc (3x10 mL), the combined organic layers were washed with water (20 mL), brine (10 mL), dried over sod. sulfate and the solvents were evaporated *in vacuo.* The residue was chromatographed on silica gel (4 g, ISCO) using DCM-Acetone to provide 38.8 mg of compound **I-102** as a white solid. ESI-MS *m/z*: 452.3 $[M+H]^+$.

Example 77



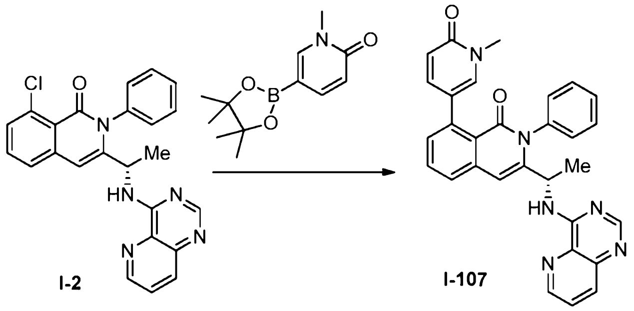
[00826] Amine **I-103a** (made by general method E) was coupled to (**B-2**) using Method I to provide compound **I-103a**. Compound **I-103** was prepared from compound **I-103a** using Method J. ESI-MS *m/z*: 461.2 $[M+H]^+$.

Example 78



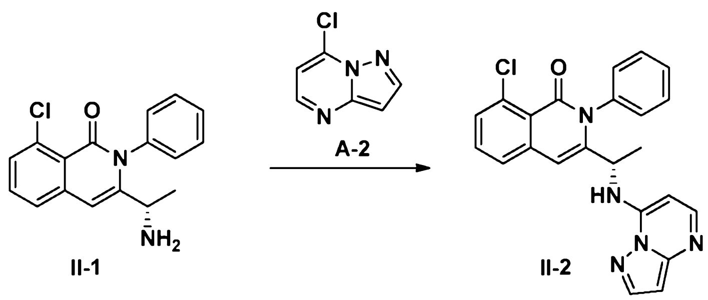
[00827] Amine **I-104** (prepared according to method L) was coupled to (**A-3**) using Method I to provide compound **I-105**. Compound **I-105** was coupled to 1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2(1H)-one in the Suzuki reaction performed in analogous fashion to compound **I-21** in Example 8 to provide compound **I-106**. ESI-MS *m/z*: 467.2 $[M+H]^+$.

Example 79



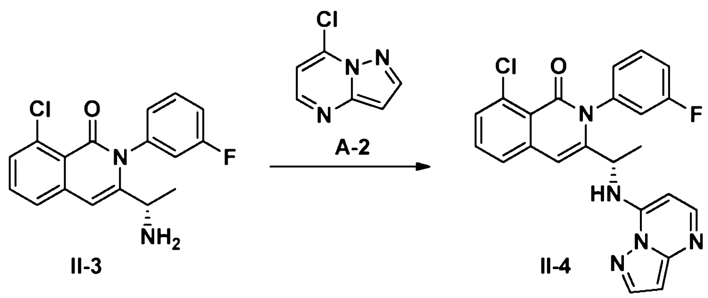
[00828] Compound **I-2** was coupled to 1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2(1H)-one in the Suzuki reaction performed in analogous fashion to compound **I-21** in Example 8 to provide compound **I-107**. ESI-MS *m/z*: 501.2 $[M+H]^+$.

Example 80



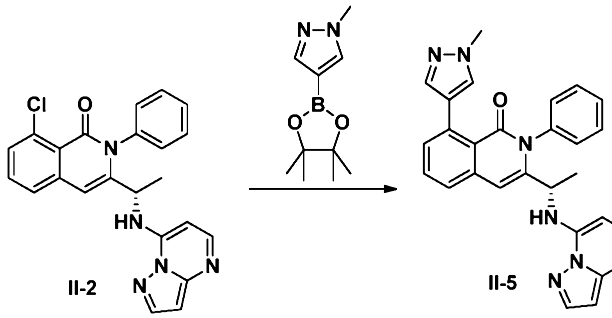
[00829] Amine **II-1** was prepared using Method E and then coupled with (**A-2**) using Method G to provide compound **II-2**. ESI-MS *m/z*: 416.0 $[M+H]^+$.

Example 81



[00830] Amine **II-3** was prepared using Method E and was then coupled with (**A-2**) using Method G to provide compound **II-4**. ESI-MS *m/z*: 434.0 $[M+H]^+$.

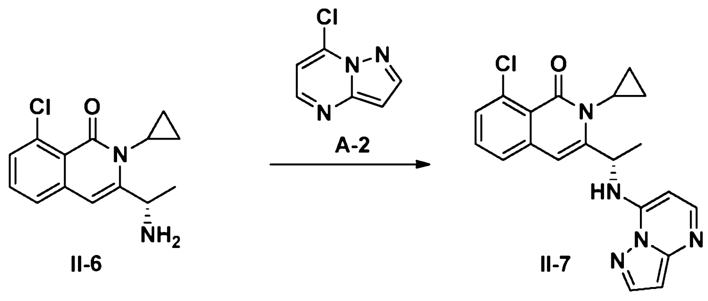
Example 82



[00831] Compound **II-5** was prepared from compound **II-2** according to the following procedure:

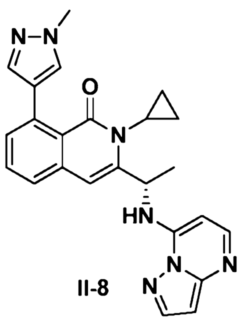
[00832] A mixture of (S)-8-chloro-2-phenyl-3-(1-(pyrazolo[1,5-a]pyrimidin-7-ylamino)ethyl)isoquinolin-1(2H)-one **II-2** (66 mg, 0.158 mmol, 1.0 eq), 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (66 mg, 0.316 mmol, 2.0 eq), $PdCl_2$(dppf)(13 mg, 0.016 mmol, 0.1 eq) and Na_2CO_3(84 mg, 0.79 mmol, 5.0 eq) was suspended in a mixture of N,N-dimethylacetamide (5 mL) and water (2 mL). The resulting mixture was degassed and back-filled with argon three times and stirred at 80 °C under argon overnight. The mixture was concentrated *in vacuo* and the residue was purified by flash column chromatography on silica gel (1-5% MeOH-DCM) to afford the product, (S)-8-(1-methyl-1H-pyrazol-4-yl)-2-phenyl-3-(1-(pyrazolo[1,5-a]pyrimidin-7-ylamino)ethyl)isoquinolin-1(2H)-one **II-5** (43 mg, 60% yield). ESI-MS *m/z*: 462.2 $[M+H]^+$.

Example 83



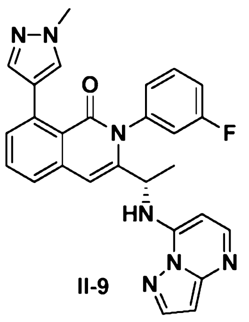
[00833] Amine **II-6** was prepared using Method E and then coupled with (**A-2**) using Method G to provide compound **II-7**. ESI-MS *m/z*: 380.2 $[M+H]^+$.

Example 84



[00834] Compound **II-8** was prepared from compound **II-7** in analogous fashion to compound **II-5** in Example 82. ESI-MS *m/z*: 426.2 $[M+H]^+$.

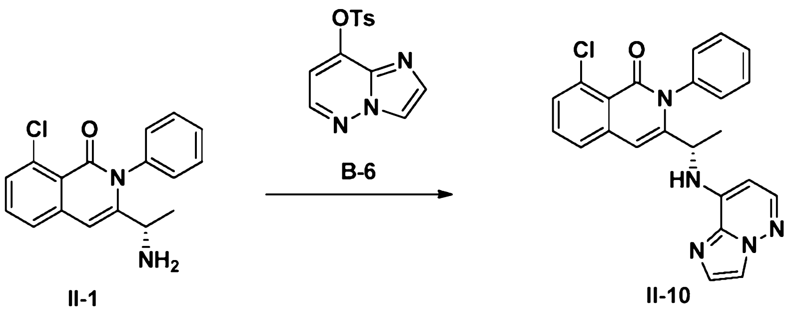
Example 85



II-9

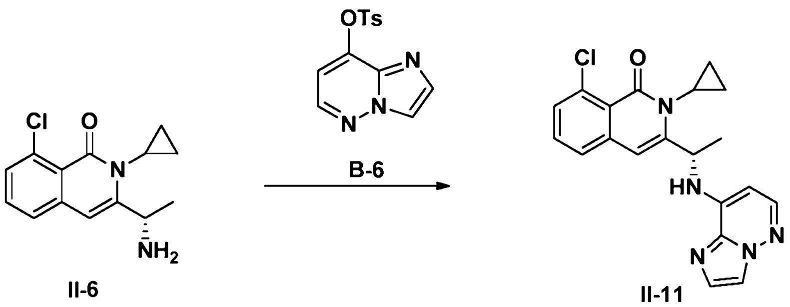
[00835] Compound **II-9** was prepared from compound **II-4** in analogous fashion to compound **II-5** in Example 82. ESI-MS *m/z*: 480.2 $[M+H]^+$.

Example 86



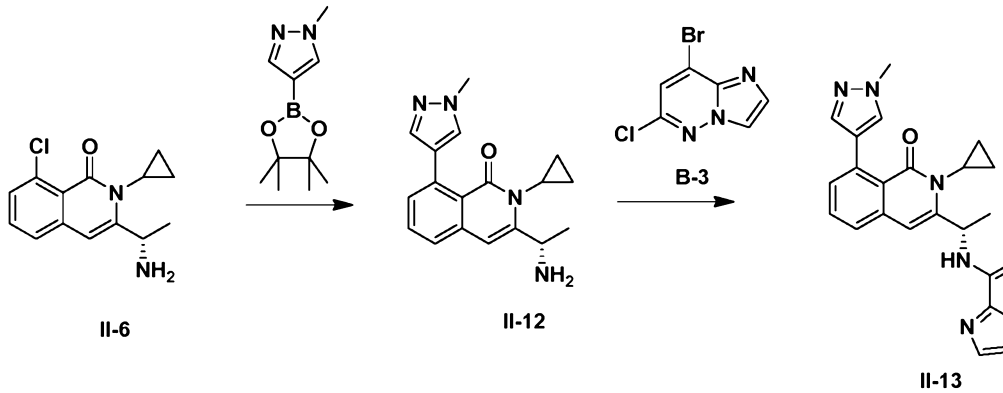
[00836] Intermediate imidazo[1,2-b]pyridazin-8-yl 4-methylbenzenesulfonate (**B-6**) was prepared according to Method B. Amine **II-1** was then coupled to (**B-6**) using Method G to provide compound **II-10**. ESI-MS *m/z*: 416.2 $[M+H]^+$.

Example 87



[00837] Amine **II-6** was prepared using Method E and then coupled with (**B-6**) using Method G to provide compound **II-11**. ESI-MS *m/z*: 380.2 $[M+H]^+$.

Example 88

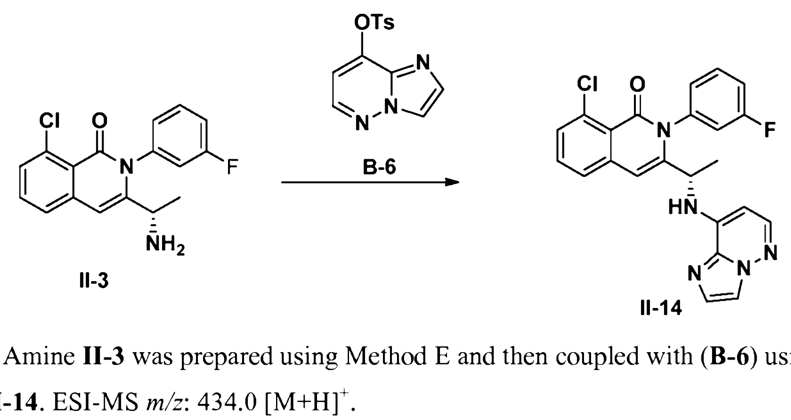


[00838] Amine **II-6** was prepared using Method E. Amine **II-12** was coupled with (**B-3**) using Method G to provide compound **II-13**. ESI-MS *m/z*: 460.2 [M+H]$^+$.

[00839] Amine **II-12** was prepared from **II-6** according to the following procedure:

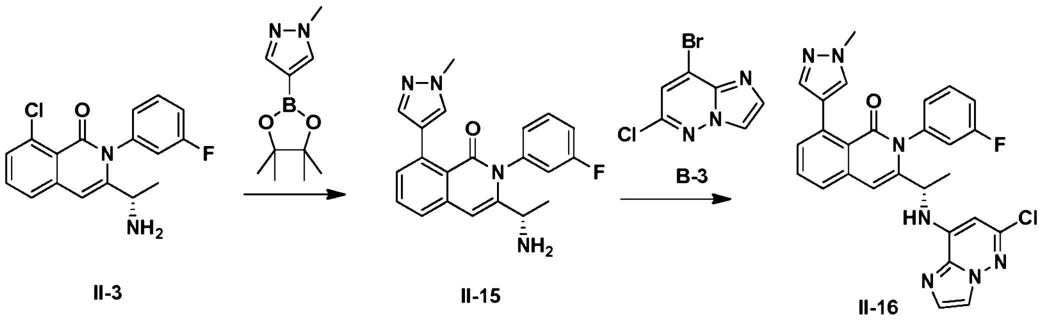
[00840] To a mixture of (S)-3-(1-aminoethyl)-8-chloro-2-cyclopropylisoquinolin-1(2H)-one **II-6** (878 mg, 3.35 mmol, 1.0 eq) and 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (815 mg, 3.92 mmol, 1.2 eq) in anhydrous DMA (10 mL) in a sealed tube, $PdCl_2$(dppf) (219 mg, 0.27 mmol, 0.08eq) and aqueous Na_2CO_3 solution (1 M, 10.0 mL, 10.0 mmol, 3.0 eq) were added and the resulting mixture was stirred at 120 °C for 3 h. The reaction mixture was allowed to cool to RT, quenched with water, and then extracted with ethyl acetate (200 mL x 3). The combined organic layers were washed with brine, dried over Na_2SO_4 and filtered. The filtrate was concentrated *in vacuo* and the residue was purified by ISCO (silica gel cartridge, 0-8% MeOH-DCM) to afford the product, (S)-3-(1-aminoethyl)-2-cyclopropyl-8-(1-methyl-1H-pyrazol-4-yl)isoquinolin-1(2H)-one **II-12** as a pink/magenta solid. ESI-MS *m/z*: 309.2 [M+H]$^+$.

Example 89



[00841] Amine **II-3** was prepared using Method E and then coupled with (**B-6**) using Method G to provide compound **II-14**. ESI-MS *m/z*: 434.0 [M+H]$^+$.

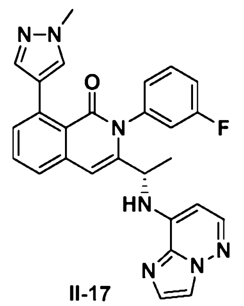
Example 90



II-3 II-15 II-16

[00842] Compound **II-16** was prepared from compound **II-15** in analogous fashion to compound **II-13** in Example 88. ESI-MS *m/z*: 514.0 $[M+H]^+$.

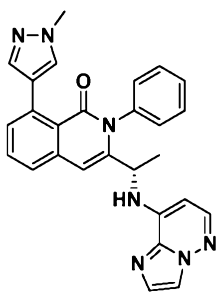
Example 91



II-17

[00843] Compound **II-17** was prepared from compound **II-14** in analogous fashion to compound **II-5** in Example 82. ESI-MS *m/z*: 480.2 $[M+H]^+$.

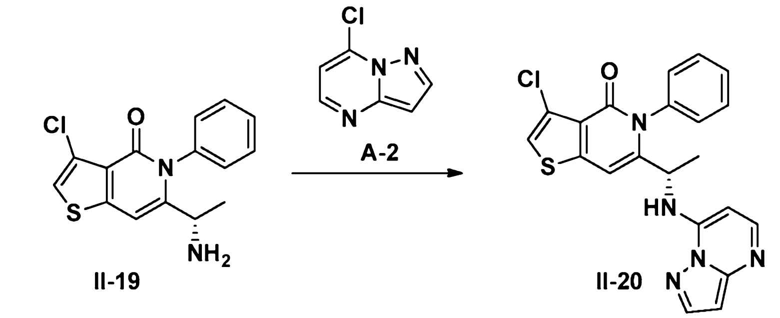
Example 92



II-18

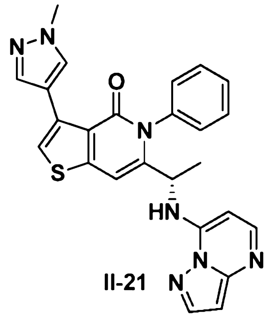
[00844] Compound **II-18** was prepared from compound **II-10** in analogous fashion to compound **II-5** in Example 82. ESI-MS *m/z*: 462.2 $[M+H]^+$.

Example 93



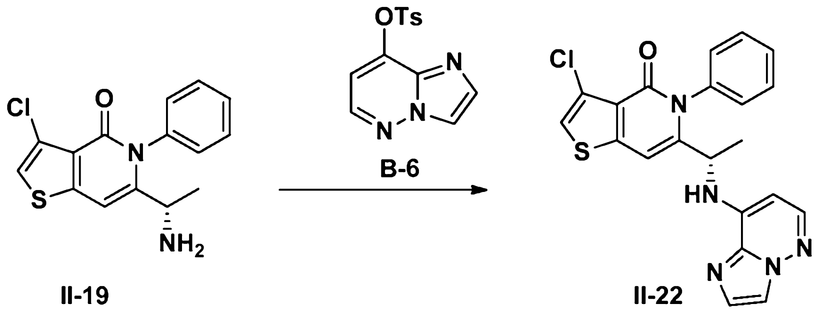
[00845] Amine **II-19** was prepared using Method F and then coupled with (**A-2**) using Method G to provide compound **II-20**. ESI-MS *m/z*: 422.0 $[M+H]^+$.

Example 94



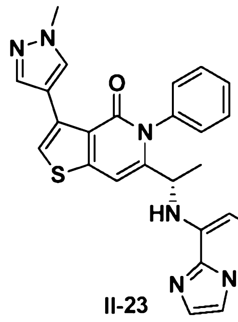
[00846] Compound **II-21** was prepared from compound **II-20** in analogous fashion to compound **II-5** in Example 82. ESI-MS *m/z*: 468.2 $[M+H]^+$.

Example 95



[00847] Amine **II-19** was coupled with (**B-6**) using Method G to provide compound **II-22**. ESI-MS *m/z*: 422.0 $[M+H]^+$.

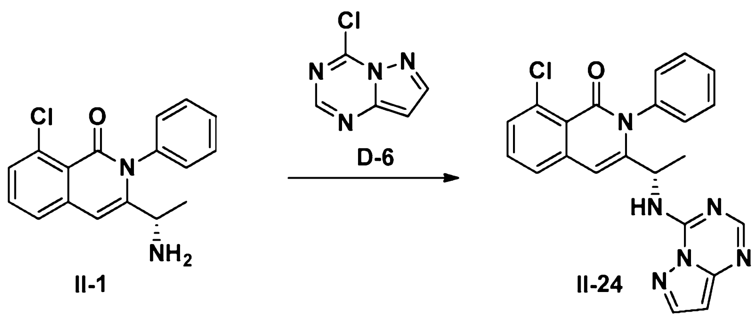
Example 96



II-23

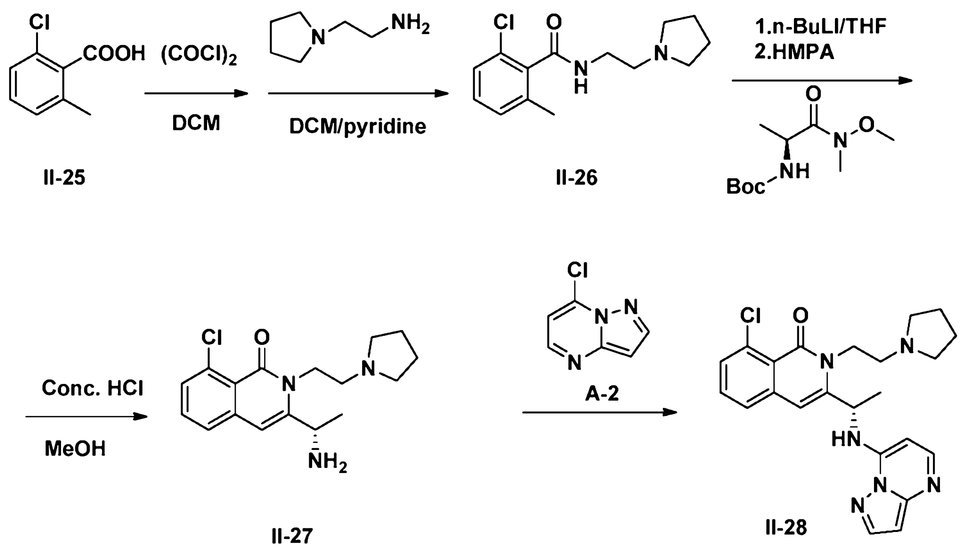
[00848] Compound **II-23** was prepared from compound **II-22** in analogous fashion to compound **II-5** in Example 82. ESI-MS *m/z*: 468.2 $[M+H]^+$.

Example 97



[00849] Amine **II-1** was coupled with (**D-6**) using Method G to provide compound **II-24**. ESI-MS *m/z*: 417.0 $[M+H]^+$.

Example 98



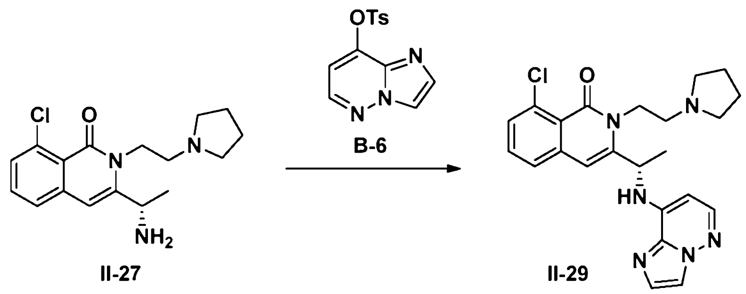
[00850] Compound **II-28** was prepared in 4 steps according to the following procedures:

[00851] Compound **II-26** was prepared from **II-25** in analogous fashion to (**E-2**) in Method E except that 2-(pyrrolidin-1-yl)ethanamine was used in place of aniline and pyridine was used as a base in place of triethylamine . Compound **II-26** was converted to **II-27** according to the following procedure:

[00852] To a mixture of 2-chloro-6-methyl-N-(2-(pyrrolidin-1-yl)ethyl)benzamide **II-26** (1.33 g, 5.0 mmol, 1.0 eq) and HMPA (0.87 mL, 5.0 mmol, 1.0 eq) in THF (12.5 mL) at -60 °C under argon, n-butyllithium solution (2.5 M in hexanes, 5.0 mL, 12.5 mmol, 2.5 eq) was added dropwise while keeping the temperature below -60 °C. The resulting mixture was stirred between -70 °C and -60 °C for 30 min. To this mixture, (S)-tert-butyl 1-(methoxy(methyl)amino)-1-oxopropan-2-ylcarbamate (1.39 g, 6.0 mmol, 1.2 eq) was added quickly. The resulting mixture was allowed to slowly warm to RT (over 1 h) and then stirred at RT for an additional 2 h. The reaction mixture was cooled to 0 °C, quenched with water (5.0 mL), and then acidified with aqueous HCl (5 M) to adjust the pH to 5-6. The mixture was concentrated *in vacuo*. The residue was suspended in a mixture of MeOH (20 mL) and H_2O (5.0 mL), concentrated HCl (10.0 mL) was added and the resulting mixture was stirred at reflux for 2 h. The mixture was cooled to -5 °C and basified with saturated aqueous NH_4OH to adjust the pH to 8-9. The precipitate was filtered off and the filtrate was extracted with DCM (20 mL x 3). The combined organic layers were dried over anhydrous Na_2SO_4 and filtered. The filtrate was concentrated *in vacuo* and the residue was purified by flash column chromatography on silica gel (1-10% MeOH-DCM) to afford the product, (S)-3-(1-aminoethyl)-8-chloro-2-(2-(pyrrolidin-1-yl)ethyl)isoquinolin-1(2H)-one **II-27**)as a yellow solid.

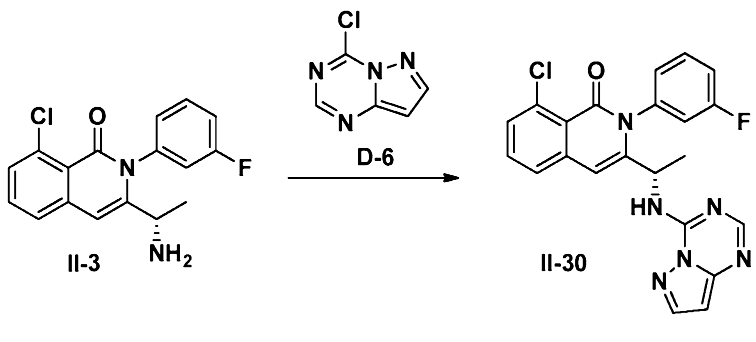
[00853] Compound **II-27** was then coupled with (**A-2**) using Method G to provide compound **II-28**. ESI-MS *m/z*: 437.2 [M+H]$^+$.

Example 99



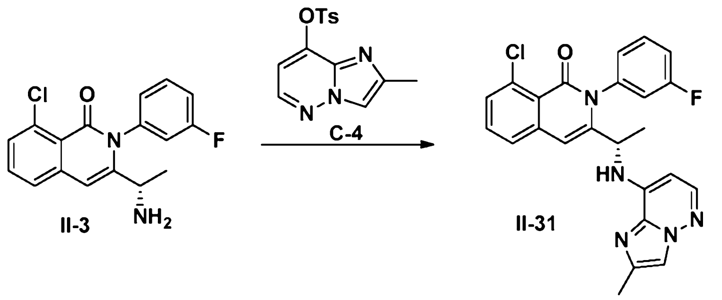
[00854] Amine **II-27** was coupled with (**B-6**) using Method G to provide compound **II-29**. ESI-MS *m/z*: 437.2 [M+H]$^+$.

Example 100



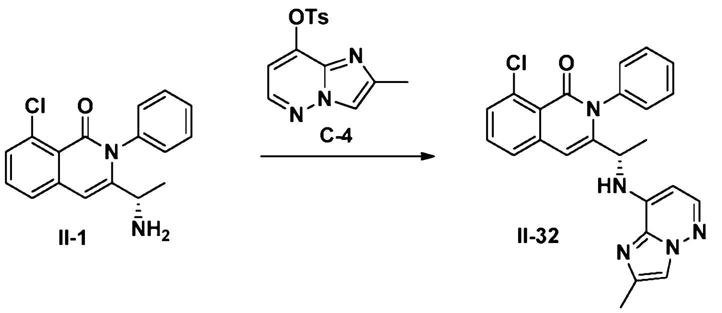
[00855] Amine **II-3** was coupled with (**D-6**) using Method G to provide compound **II-30**. ESI-MS *m/z*: 435.0 $[M+H]^+$.

Example 101



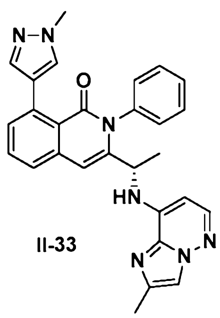
[00856] Amine **II-3** was coupled with (**C-4**) using Method G to provide compound **II-31**. ESI-MS *m/z*: 448.2 $[M+H]^+$.

Example 102



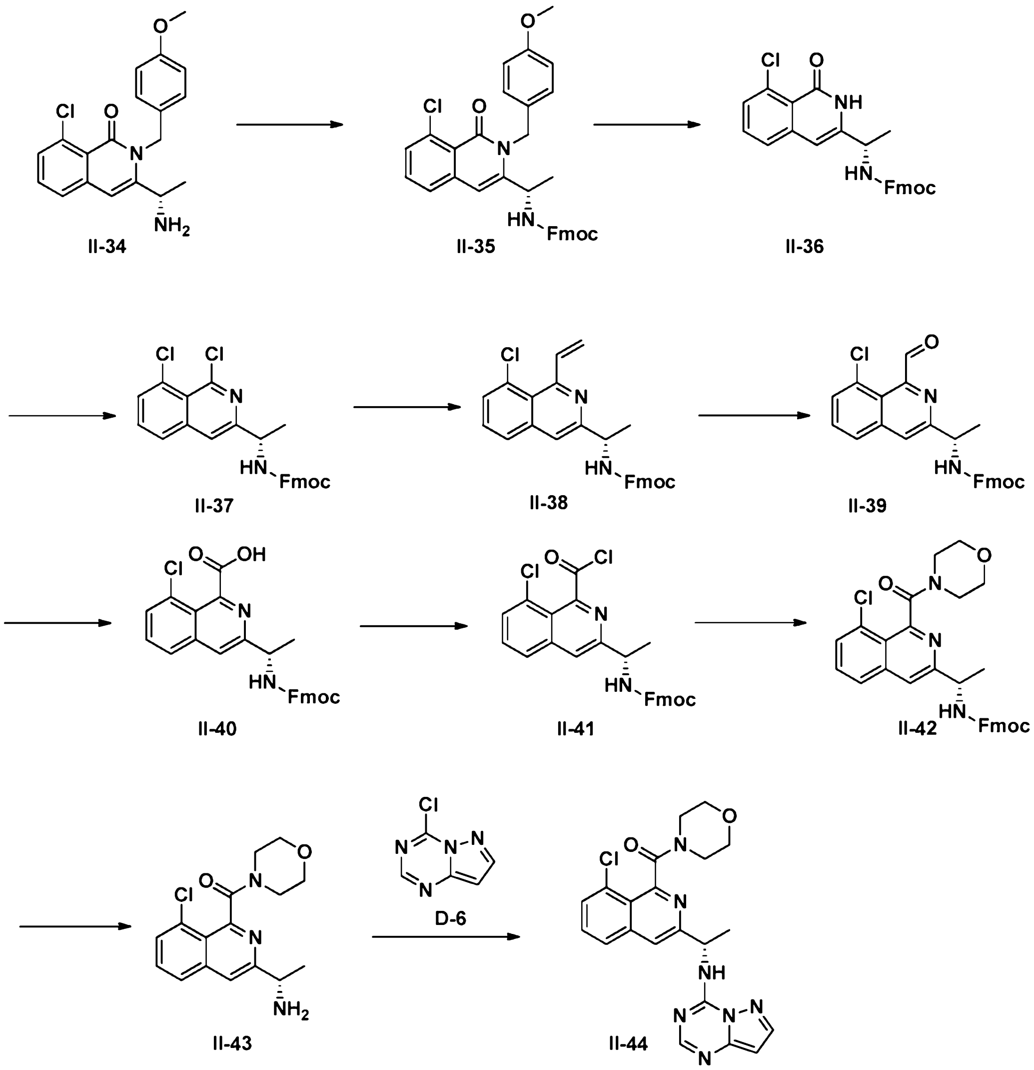
[00857] Amine **II-1** was coupled with (**C-4**) using Method G to provide compound **II-32**. ESI-MS *m/z*: 430.2 $[M+H]^+$.

Example 103



[00858] Compound **II-33** was prepared from compound **II-32** in analogous fashion to compound **II-5** in Example 82. ESI-MS *m/z*: 476.2 $[M+H]^+$.

Example 104



[00859] Compound **II-44** was prepared according to the following procedures:

[00860] Compound **II-34** was prepared according to Method E. To a stirred mixture of **II-34** (10.0 mmol, 1.0 eq) in DCM (20 mL), saturated aqueous $NaHCO_3$ solution (2.8 mL) was added. The mixture was cooled to 0°C and 9-fluorenylmethyl chloroformate (10.5 mmol, 1.05 eq) was added in one portion. The resulting mixture was allowed to warm to RT and stirred at RT for 1 h. The organic layers were separated, washed with water (50 mL x 2), dried over anhydrous $MgSO_4$ and filtered. The filtrate was concentrated *in vacuo* to afford the product **II-35**.

[00861] Compound **II-35** (10.0 mmol, 1.0 eq) was then dissolved in TFA (25 mL) and the resulting mixture was stirred at reflux for 1 h. The mixture was allowed to cool to RT and concentrated *in vacuo* to remove TFA. The resulting brown oil residue was partitioned between DCM (50 mL) and saturated aqueous $NaHCO_3$ (50 mL) solution. The organic layer was washed with water (20 mL x 2), dried over anhydrous $MgSO_4$ and filtered. The filtrate was concentrated *in vacuo* to afford the product **II-36**.

[00862] A mixture of compound **II-36** (45.0 mmol) and DMF (0.3 mL) in $SOCl_2$ (100 mL) was stirred at reflux for 2 h. The mixture was allowed to cool to RT and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel to afford the product **II-37**.

[00863] To a stirred mixture of **II-37** (5.4 mmol, 1 eq), $Pd(OAc)_2$ (363 mg, 1.62 mmol, 0.3 eq) and PPh_3 (846 mg, 3.24 mol, 0.6 eq) in THF (50 mL) at RT, tributyl(vinyl)tin (1.97 g, 5.94 mmol, 1.1 eq) was added and the resulting mixture was stirred at reflux overnight. The mixture was allowed to cool to RT and filtered through silica gel (10 g). The filtrate was concentrated *in vacuo* and the residue was purified by flash column chromatography on silica gel (1-5% MeOH-DCM) to afford the product **II-38**.

[00864] To a stirred mixture of **II-38** (7.6 mmol, 1 eq) in a mixture of 1,4-dioxane (40 mL) and H_2O (40 mL) at RT, osmium tetraoxide (5 mg) was added and the resulting mixture was stirred at RT for 30 min. To this mixture, sodium periodate (3.3 g, 15.2 mmol, 2 eq) was added and the resulting mixture was stirred at RT overnight. The reaction mixture was filtered through silica gel (10 g). The filtrate was extracted with DCM (3 x 60 mL), washed with brine, dried over Na_2SO_4 and filtered. The filtrate was concentrated *in vacuo* and the residue was purified by flash column chromatography on silica gel (1-5% MeOH-DCM) to afford the aldehyde **II-39**.

[00865] To a solution of compound **II-39** (3.53 mmol, 1 eq) in DMF (40 mL) at RT, oxone (6.5 g, 10.59 mmol, 3 eq) was slowly added and the resulting mixture was stirred at RT overnight. The reaction mixture was poured into water (50 mL) and neutralized with concentrated ammonium hydroxide to adjust the pH value to 7-8. The mixture was stirred at RT for 30 min and then extracted with ethyl acetate (3 x 50 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and filtered. The filtrate was concentrated *in vacuo* and the residue was purified by flash column chromatography on silica gel (1-5% MeOH -DCM) to afford the carboxylic acid **II-40**.

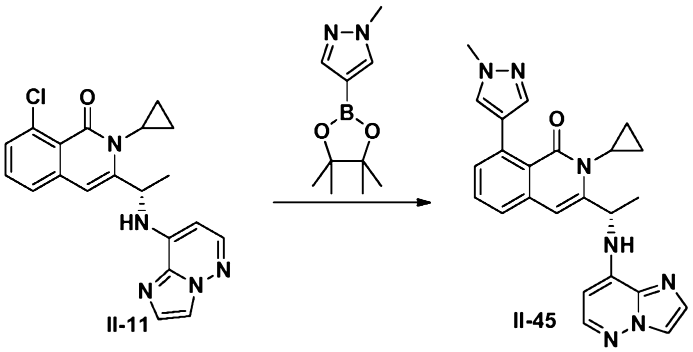
[00866] To a solution of compound **II-40** (0.327 mol, 1 eq) and DMF (0.1 mL) in DCM (10 mL), oxalyl chloride (83.1 mg, 0.654 mmol, 2 eq) was added and the resulting mixture was stirred at RT for 1 h. The mixture was concentrated *in vacuo* to afford the acid chloride **II-41** as a yellow oil. The product obtained was used directly in the next step without purification.

[00867] To a solution of morpholine (34 mg, 0.392 mmol, 1.3 eq) and triethylamine (100 mg, 0.981 mol, 3 eq) in DCM (20 mL), acid chloride **II-41** was added at RT. The resulting mixture was stirred at RT for 1. The reaction mixture was poured into water (50 mL) and extracted with DCM (3 x 50 mL). The combined organic layer was washed with brine, dried over Na_2SO_4 and filtered. The filtrate was concentrated *in vacuo* and the residue was purified by flash column chromatography on silica gel (1-5% MeOH-DCM) to afford the amide **II-42**.

[00868] To a stirred mixture of **II-42** (1.76 mmol, 1 eq) in EtOH (50 mL) at RT, morpholine (3.05 g, 35.2 mmol, 20 eq) was added and the resulting mixture was stirred at reflux for 4 h. The mixture was allowed to cool to RT and then concentrated *in* vacuo. The residue was purified by flash column chromatography on silica gel (1-10% MeOH-DCM) to afford the amine **II-43**.

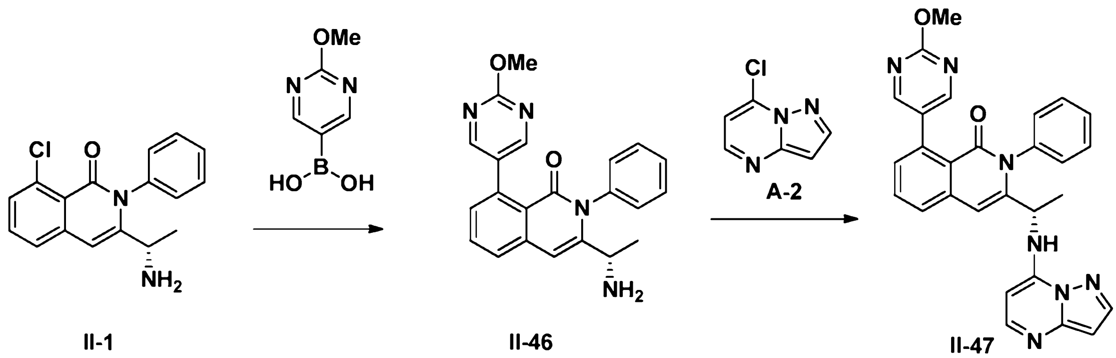
[00869] Amine **II-43** was then coupled with (**D-6**) using Method G to provide compound **II-44**. ESI-MS *m/z*: 438.2 $[M+H]^+$.

Example 105



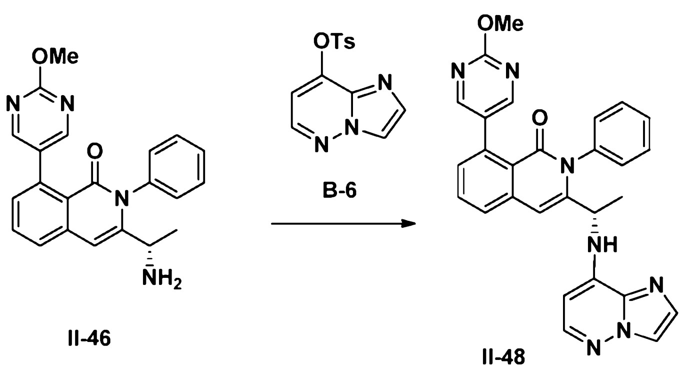
[00870] Compound **II-45** was prepared from compound **II-11** in analogous fashion to compound **II-5** in Example 82. ESI-MS *m/z*: 426.2 $[M+H]^+$.

Example 106



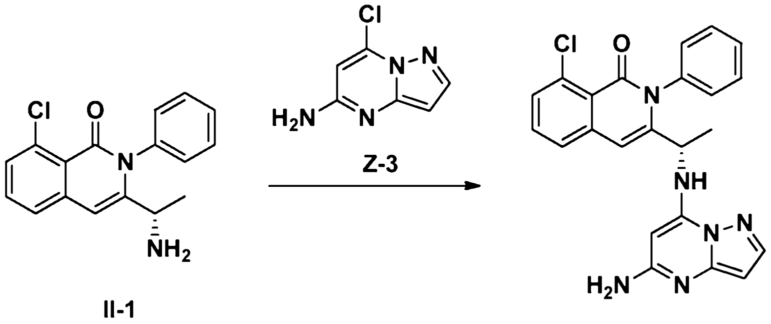
[00871] Compound **II-46** was prepared from compound **II-1** in analogous fashion to compound **II-12** in Example 88 except that 2-methoxypyrimidin-5-ylboronic acid was used in place of 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole. Compound **II-46** was then coupled to compound **A-2** to provide compound **II-47** according to Method G. ESI-MS *m/z*: 490.2 $[M+H]^+$.

Example 107



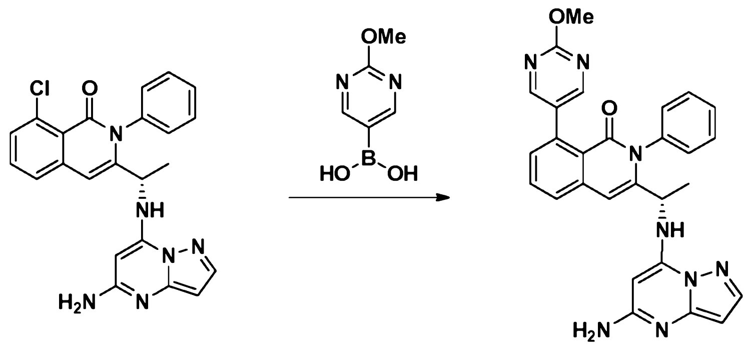
[00872] Compound **II-46** was coupled with **B-6** to provide compound **II-48** according to Method G. ESI-MS *m/z*: 490.2 [M+H]$^+$.

Example 108



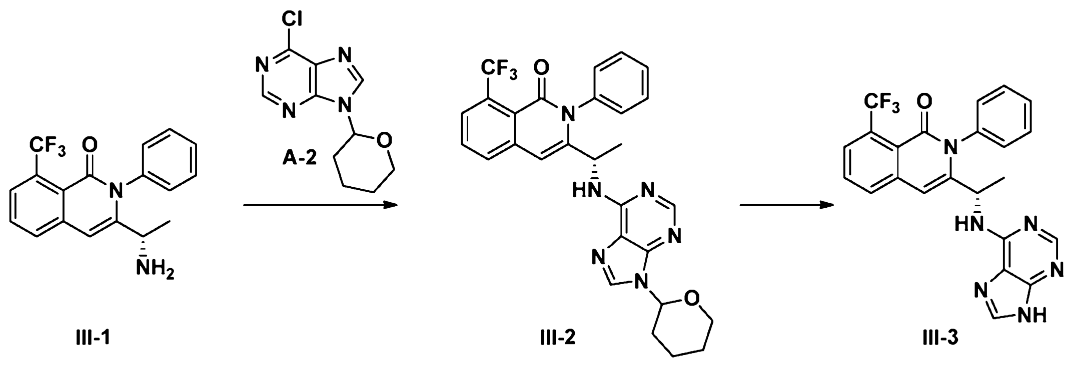
[00873] Compound **II-49** was prepared by coupling compound **Z-3** to compound **II-1** according to Method G. ESI-MS *m/z*: 431.2 [M+H]$^+$.

Example 109



[00874] Compound **II-50** was prepared from compound **II-49** in analogous fashion to compound **II-5** in Example 82 except that 2-methoxypyrimidin-5-ylboronic acid was used in place of 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole. ESI-MS *m/z*: 505.2 [M+H]$^+$.

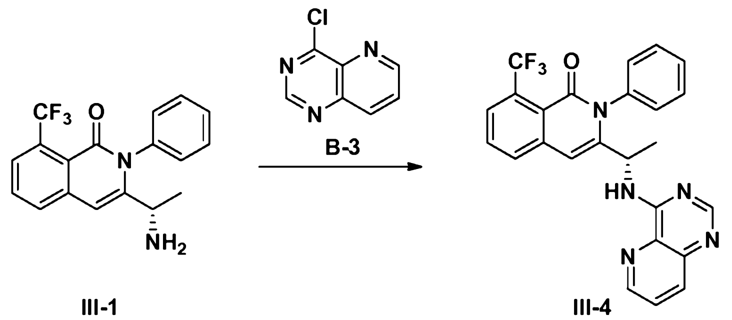
Example 110



[00875] Amine **III-1** was prepared according to Method Q. Compound **III-1** was then converted to compound **III-2** using Method S. The THP protecting group was then removed according to the following general procedure:

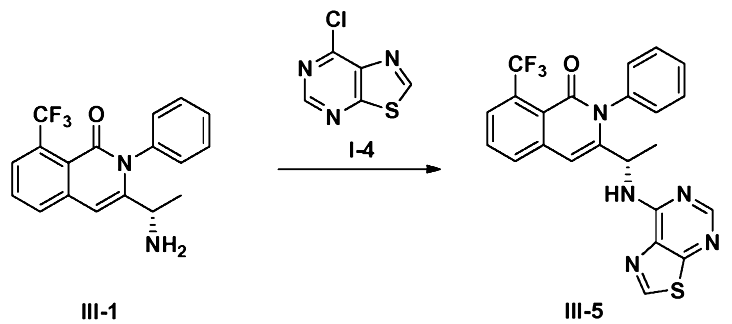
[00876] To a mixture of compound **III-2** in ethanol (4 vol)/water (2 vol), concentrated HCl solution (2 vol) was added and the resulting mixture was stirred at RT for 1 h. The resulting mixture was diluted with cold water, basified with saturated aqueous $NaHCO_3$ to adjust the pH to 8-9 and then extracted with DCM (3 x 20 vol). The combined organic layers were washed with brine, dried over Na_2SO_4 and filtered. The filtrate was concentrated *in vacuo*. The residue purified by flash column chromatography on silica gel eluting with a mixture solvent of MeOH and DCM to afford compound **III-3**. ESI-MS *m/z*: 451.0[M+H]$^+$.

Example 111



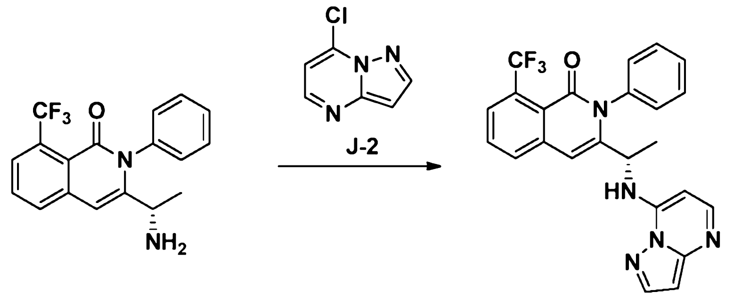
[00877] Compound **III-4** was prepared by coupling amine **III-1** and (**B-3**) according to Method Q. ESI-MS *m/z*: 462.0 [M+H]$^+$.

Example 112



[00878] Compound **III-5** was prepared by coupling amine **III-1** and (**I-4**) according to Method S. ESI-MS *m/z*: 468.0 [M+H]$^+$.

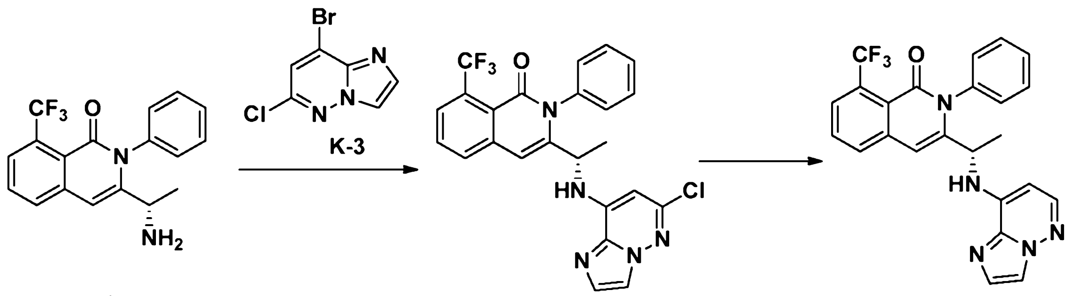
Example 113



III-1 III-6

[00879] Compound **III-6** was prepared by coupling amine **III-1** and (**J-2**) according to Method S. ESI-MS *m/z*: 450.2 $[M+H]^+$.

Example 114

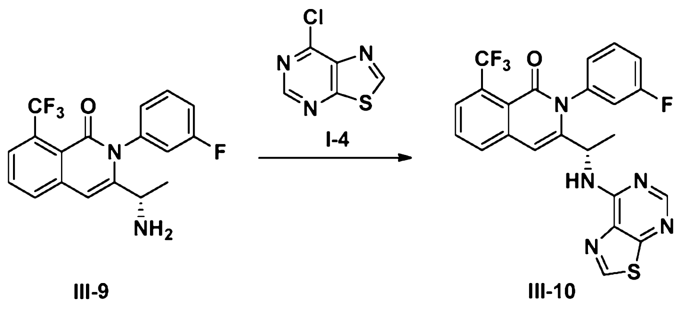


III-1 III-7 III-8

[00880] Compound **III-7** was prepared by coupling amine **III-1** and (**K-3**) according to Method S. Compound **8** was then prepared according to the following procedure:

[00881] To a suspension of (S)-3-(1-(6-chloroimidazo[1,2-b]pyridazin-8-ylamino)ethyl)-2-phenyl-8-(trifluoromethyl)isoquinolin-1(2H)-one **III-7** (50 mg, 0.104 mmol, 1.0 eq) in MeOH (20 mL), palladium on carbon (10%, 17 mg) and triethylamine (0.1 mL, 0.72 mmol, 6.9 eq) were added. The resulting mixture was degassed and back-filled with hydrogen (three cycles), and then stirred at RT under hydrogen overnight. The mixture was filtered and the filtrate was concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (5-10% ethyl acetate-petroether) to afford the product, (S)-3-(1-(imidazo[1,2-b]pyridazin-8-ylamino)ethyl)-2-phenyl-8-(trifluoromethyl)isoquinolin-1(2H)-one **III-8**. ESI-MS *m/z*: 450.2 $[M+H]^+$.

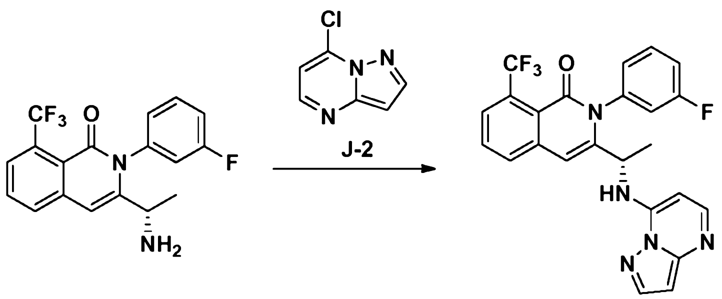
Example 115



III-9 III-10

[00882] Amine **III-9** was prepared according to Method Q. Compound **III-10** was then prepared by coupling compound **III-9** with (**I-4**) using Method S. ESI-MS *m/z*: 486.0 [M+H]$^+$.

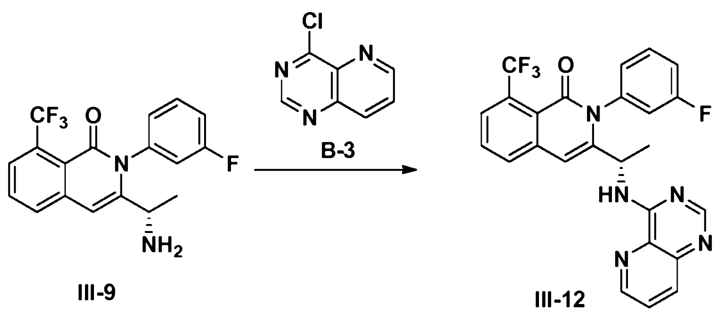
Example 116



III-9 III-11

[00883] Compound **III-11** was prepared by coupling amine **III-9** and (**J-2**) according to Method S. ESI-MS *m/z*: 468.2 [M+H]$^+$.

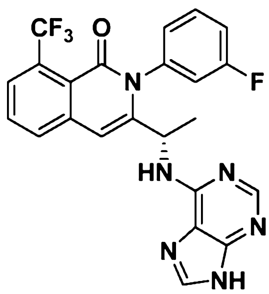
Example 117



III-9 III-12

[00884] Compound **III-12** was prepared by coupling amine **III-9** and (**B-3**) according to Method S. ESI-MS *m/z*: 480.2 [M+H]$^+$.

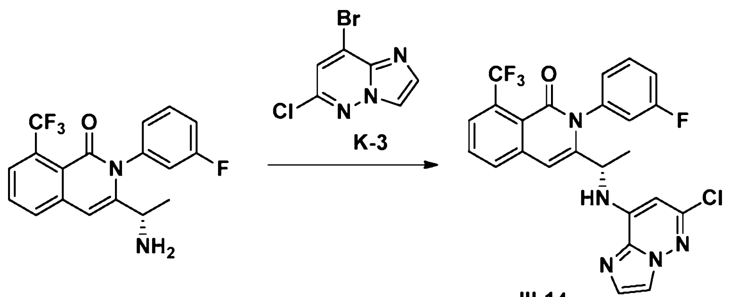
Example 118



III-13

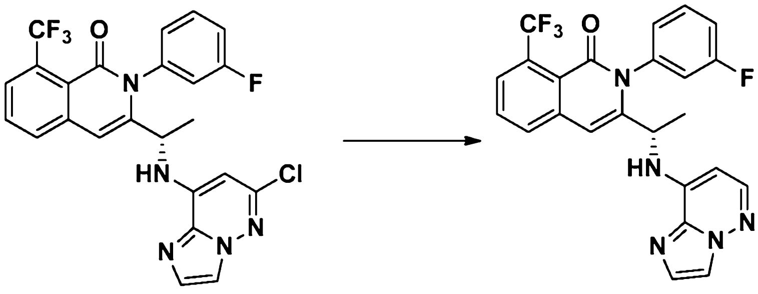
[00885] Compound **III-13** was prepared in analogous fashion to compound **III-3** in Example 75 except that amine **III-9** was used in place of amine **III-1**. ESI-MS *m/z*: 469.0 [M+H]$^+$.

Example 119



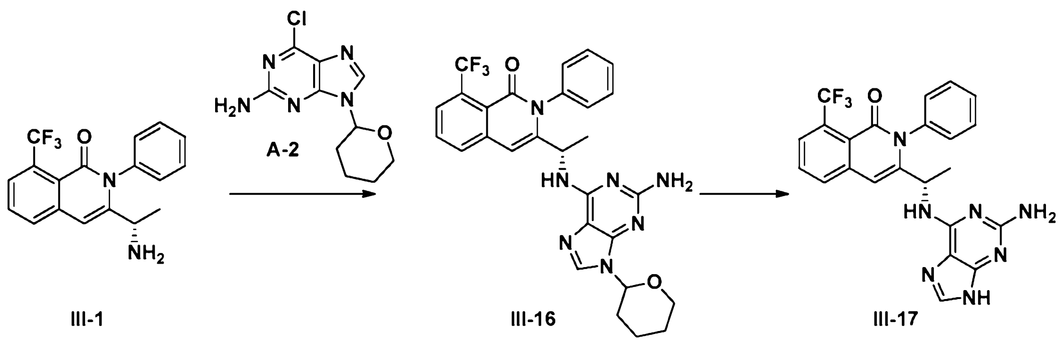
[00886] Compound **III-14** was prepared by coupling amine **III-9** and (**K-3**) according to Method S. ESI-MS *m/z*: 502.0 [M+H]$^+$.

Example 120



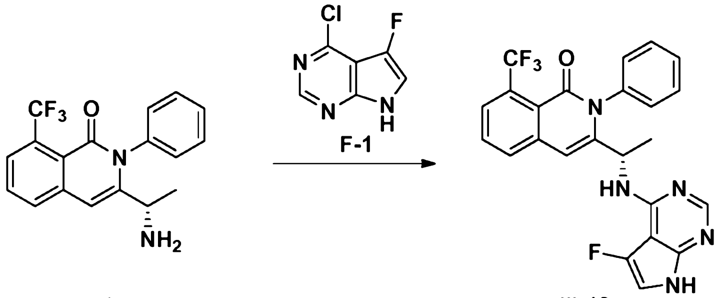
[00887] Compound **III-15** was prepared from compound **III-14** using the analogous procedure for compound **III-8** in Example 79. ESI-MS *m/z*: 468.2 [M+H]$^+$.

Example 121



[00888] Compound **III-16** was prepared by coupling amine **III-1** and (**A-2**) according to Method S. This compound **III-16** was then converted to compound **III-17** according to the analogous procedure for compound **III-3** in Example 75. ESI-MS *m/z*: 466.0 [M+H]$^+$.

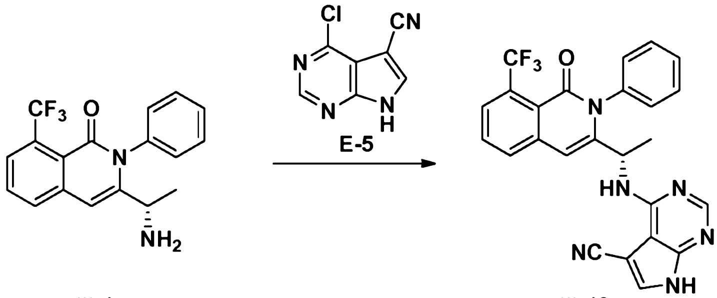
Example 122



III-1 III-18

[00889] Compound **III-18** was prepared by coupling amine **III-1** and (**F-1**) according to Method S. ESI-MS *m/z*: 468.2 [M+H]$^+$.

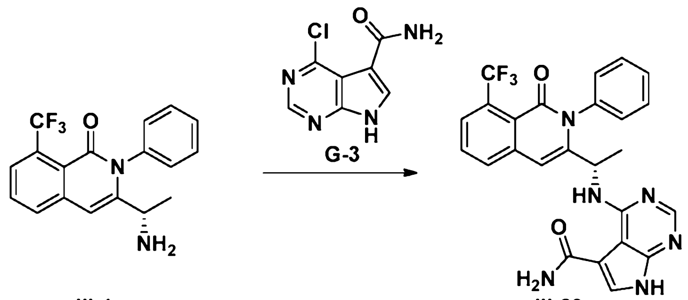
Example 123



III-1 III-19

[00890] Compound **III-19** was prepared by coupling amine **III-1** and (**E-5**) according to Method S. ESI-MS *m/z*: 475.0 [M+H]$^+$.

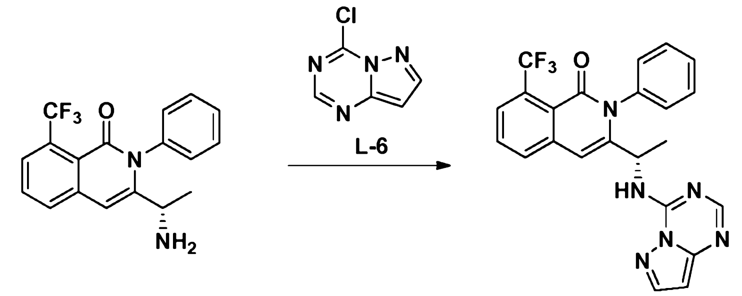
Example 124



III-1 III-20

[00891] Compound **III-20** was prepared by coupling amine **III-1** and (**G-3**) according to Method S. ESI-MS *m/z*: 493.2 [M+H]$^+$.

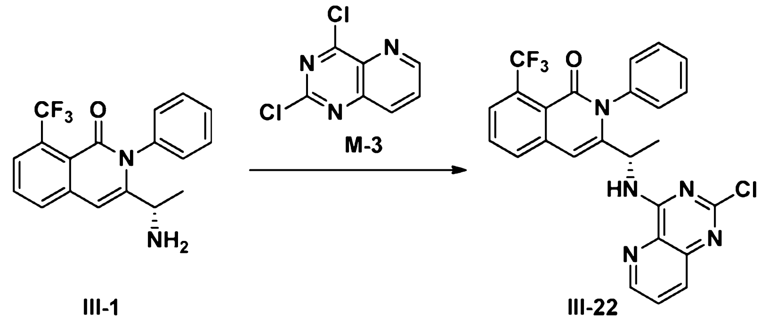
Example 125



III-1 III-21

[00892] Compound **III-21** was prepared by coupling amine **III-1** and (**L-6**) according to Method S. ESI-MS *m/z*: 451.2 [M+H]$^+$.

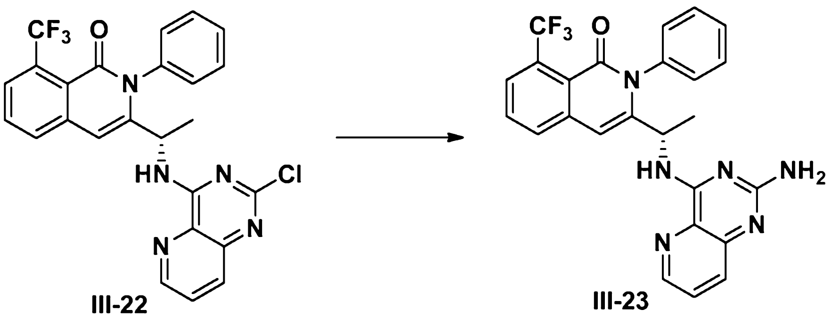
Example 126



III-1 III-22

[00893] Compound **III-22** was prepared by coupling amine **III-1** and (**M-3**) according to Method S. ESI-MS *m/z*: 496.2 [M+H]$^+$.

Example 127

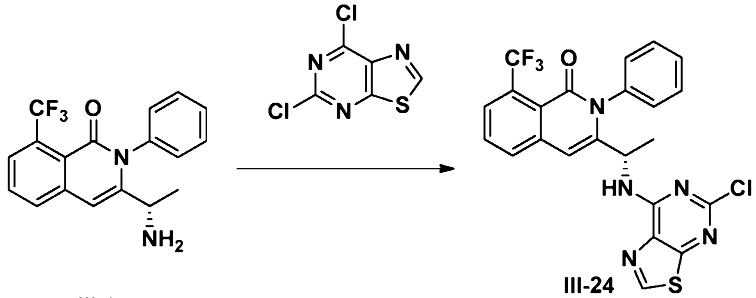


III-22 III-23

[00894] Compound **III-23** was prepared from **III-22** according to the following procedure:

[00895] Compound **III-22** (0.11 mmol, 1.0 eq) was suspended in ammonium hydroxide (10-35% solution, 20 mL) in a sealed tube and the resulting mixture was stirred at 140 °C overnight. The mixture was allowed to cool to RT and then extracted with DCM (3 x 15 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and filtered. The filtrate was concentrated *in vacuo* and the residue was purified by column chromatography on silica gel (1-2% MeOH-DCM) to afford compound **III-23**. ESI-MS *m/z*: 477.2 [M+H]$^+$.

Example 128

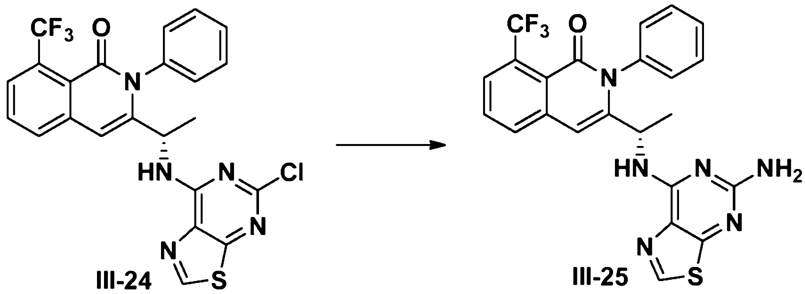


III-1

III-24

[00896] Compound **III-24** was prepared by coupling amine **III-1** and commercially available 5,7-dichlorothiazolo[5,4-d]pyrimidine according to Method S. ESI-MS *m/z*: 502.0 [M+H]$^{+}$.

Example 129

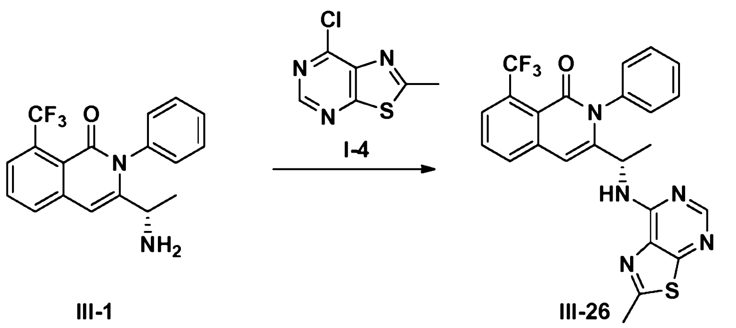


III-24

III-25

[00897] Compound **III-25** was prepared from compound **III-24** in analogous fashion to compound **III-23** in Example 92. ESI-MS *m/z*: 473.2 [M+H]$^{+}$.

Example 130

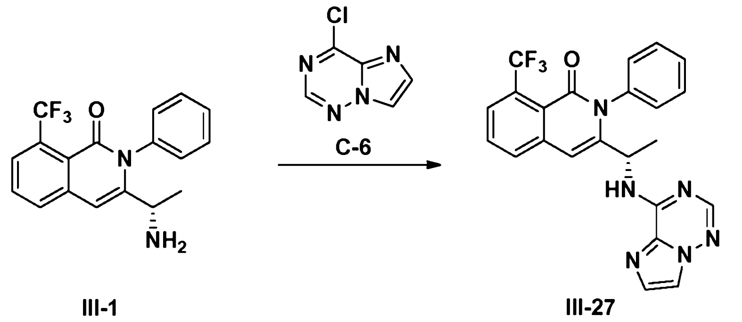


III-1

III-26

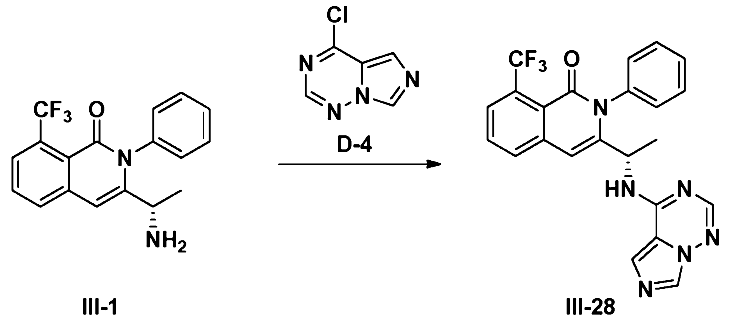
[00898] Compound **III-26** was prepared by coupling amine **III-1** and (**I-4**) according to Method S. ESI-MS *m/z*: 482.0 [M+H]$^{+}$.

Example 131



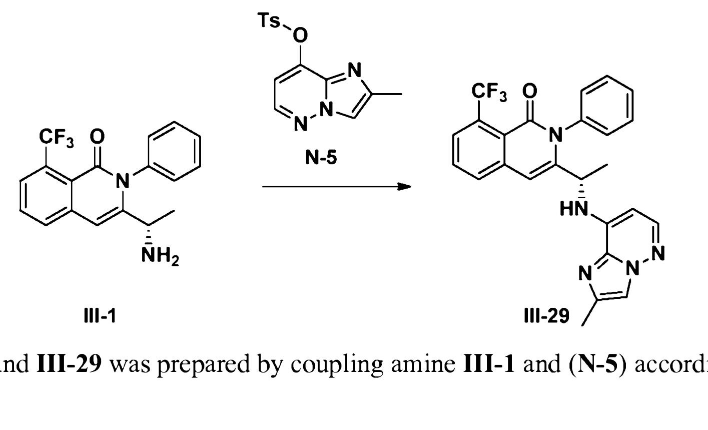
[00899] Compound **III-27** was prepared by coupling amine **III-1** and (**C-6**) according to Method S. ESI-MS *m/z*: 451.2 $[M+H]^+$.

Example 132



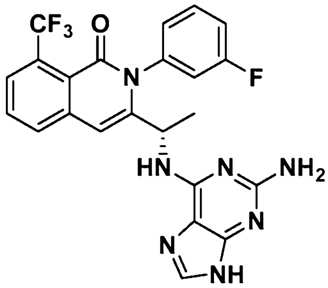
[00900] Compound **III-28** was prepared by coupling amine **III-1** and (**D-4**) according to Method S. ESI-MS *m/z*: 451.2 $[M+H]^+$.

Example 133



[00901] Compound **III-29** was prepared by coupling amine **III-1** and (**N-5**) according to Method S. ESI-MS *m/z*: 464.0 $[M+H]^+$.

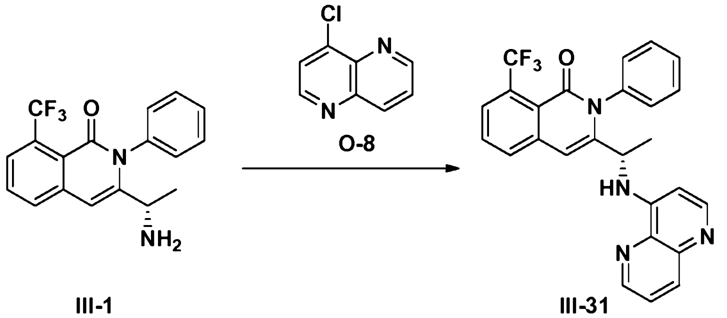
Example 134



III-30

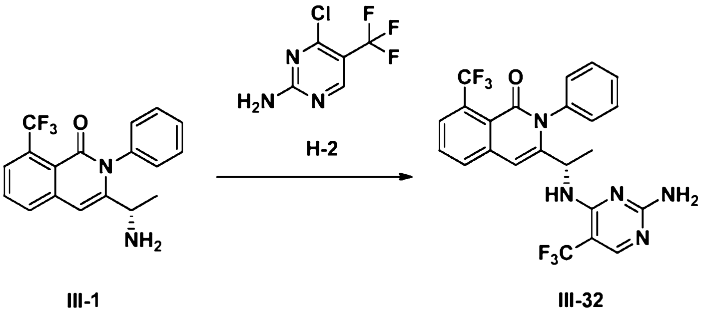
[00902] Compound **III-30** was prepared in analogous fashion to compound **III-17** in Example 88 except that amine **III-9** was used in place of amine **III-1** as starting material. ESI-MS *m/z*: 484.2 $[M+H]^+$.

Example 135



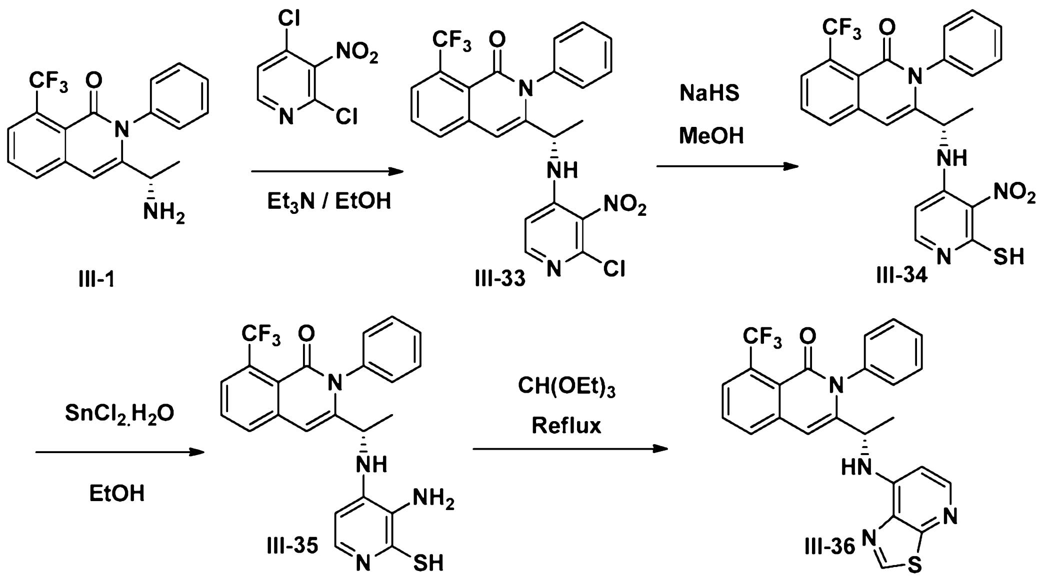
[00903] Compound **III-31** was prepared by coupling amine **III-1** and (**O-8**) according to Method S except that N,N-diisopropylethylamine was used in place of triethylamine. ESI-MS *m/z*: 461.2 $[M+H]^+$.

Example 136



[00904] Compound **III-32** was prepared by coupling amine **III-1** and (**H-2**) according to Method S. ESI-MS *m/z*: 494.0 $[M+H]^+$.

Example 137



[00905] Compound **III-36** was prepared from amine **III-1** according to the following procedures:

[00906] To a mixture of (S)-3-(1-aminoethyl)-2-phenyl-8-(trifluoromethyl)isoquinolin-1(2H)-one **III-1** (1.0 g, 3.0 mmol, 1.0 eq) and 2,4-dichloro-3-nitropyridine (578 mg, 3.0 mmol, 1.0 eq) in EtOH (10 mL), triethylamine (608 mg, 6.0 mmol, 2.0 eq) was added and the resulting mixture was stirred at reflux overnight. The mixture was allowed to cool to RT and then concentrated *in vacuo*. The resultant residue was purified by flash column chromatography on silica gel (1% MeOH-DCM) to afford the product, (S)-3-(1-(2-chloro-3-nitropyridin-4-ylamino) ethyl)-2-phenyl-8-(trifluoromethyl) isoquinolin-1 (2H)-one **III-33**.

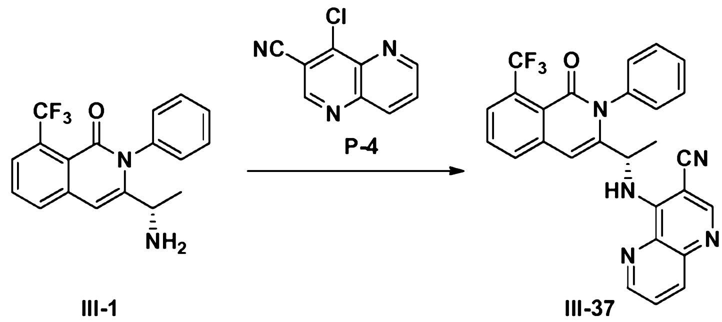
[00907] To a solution of (S)-3-(1-(2-chloro-3-nitropyridin-4-ylamino)ethyl)-2-phenyl-8-(trifluoromethyl) isoquinolin-1 (2H)-one **III-33** (500 mg, 1.0 mmol, 1eq) in MeOH (10 mL), sodium hydrosulphide (69 g, 1.29 mmol, 1.2 eq) was added and the resulting mixture was stirred at reflux for 2 h. The mixture was allowed to cool to RT and then concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (2-3% MeOH-DCM) to afford the product, (S)-3-(1-(2-mercapto-3-nitropyridin-4-ylamino) ethyl)-2-phenyl-8-(trifluoromethyl)isoquinolin-1(2H)-one **III-34**.

[00908] A mixture of (S)-3-(1-(2-mercapto-3-nitropyridin-4-ylamino) ethyl)-2-phenyl-8-(trifluoro methyl)isoquinolin-1(2H)-one **III-34** (120 mg, 0.247 mmmol, 1.0 eq) and stannous chloride dihydrate (297 mg, 1.32 mmol, 5.3 eq) in EtOH (5 mL) was stirred at refluxed for 2 h. The resulting mixture was cooled to RT and concentrated *in vacuo*. The residue was suspended in water (5 mL), neutralized with saturated $NaHCO_3$ solution to adjust the pH to 7-8 and then extracted with ethyl acetate (5 mL × 3). The combined organic layers were washed with brine, dried over Na_2SO_4 and filtered. The filtrate was concentrated *in vacuo* to afford the product, (S)-3-(1-(3-amino-2-mercaptopyridin-4-ylamino) ethyl)-2-phenyl-8-(trifluoromethyl)isoquinolin-1(2H)-one **III-35**.

[00909] A mixture of (S)-3-(1-(3-amino-2-mercaptopyridin-4-ylamino)ethyl)-2-phenyl-8-(trifluoro methyl)isoquinolin-1(2H)-one **III-35** (80 mg, 0.175 mmol, 1.0 eq) in triethyl orthoformate (180 mL) was stirred at

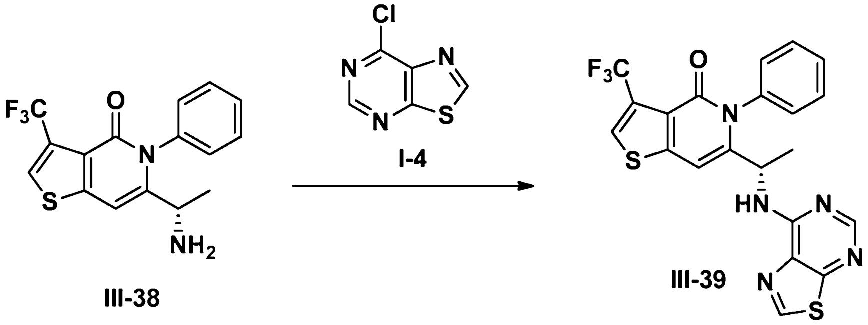
reflux for 2 h. The reaction mixture was allowed to cool to RT and then concentrated *in vacuo.* The residue was purified by flash column chromatography on silica gel (1-2% MeOH-DCM) to afford the product, (S)-2-phenyl-3-(1-(thiazolo[5,4-b]pyridin-7-ylamino)ethyl)-8-(trifluoromethyl)isoquinolin-1(2H)-one **III-36**. ESI-MS *m/z*: 467.0 $[M+H]^+$.

Example 138



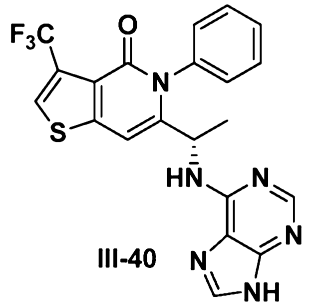
[00910] Compound **III-37** was prepared by coupling amine **III-1** and (**P-4**) according to Method S. ESI-MS *m/z*: 486.2 $[M+H]^+$.

Example 139



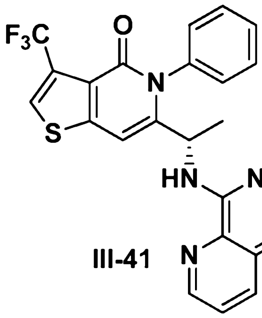
[00911] Amine **III-38** was prepared according to Method R. Compound **III-39** was then prepared by coupling amine **III-38** and (**I-4**) according to Method S. ESI-MS *m/z*: 474.0 $[M+H]^+$.

Example 140



[00912] Compound **III-40** was prepared from amine **III-38** in analogous fashion to compound **III-3** in Example 75. ESI-MS *m/z*: 457.0 $[M+H]^+$.

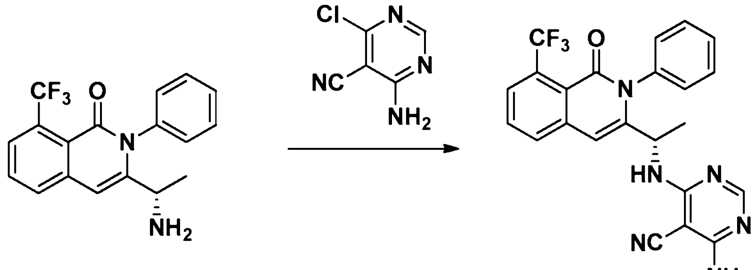
Example 141



III-41

[00913] Compound **III-41** was prepared from amine **III-38** and (**B-3**) according to Method S. ESI-MS *m/z*: 468.0 $[M+H]^+$.

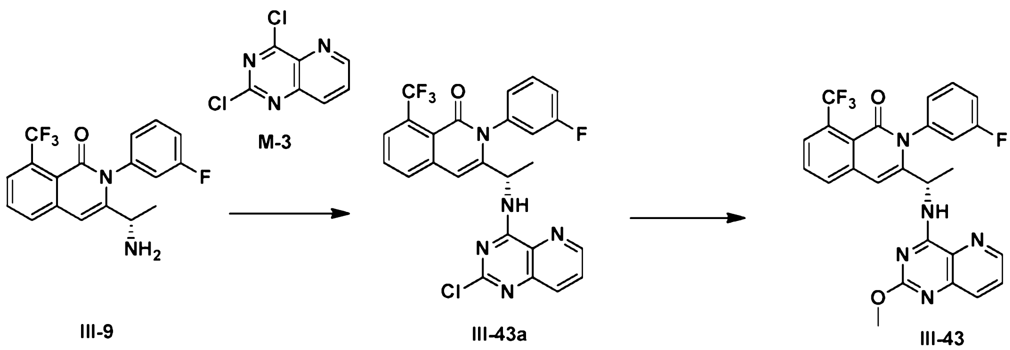
Example 142



III-1 III-42

[00914] Compound **III-42** was prepared by coupling amine **III-1** and commercially available 4-amino-6-chloropyrimidine-5-carbonitrile according to Method S. ESI-MS *m/z*: 451.2 $[M+H]^+$.

Example 143



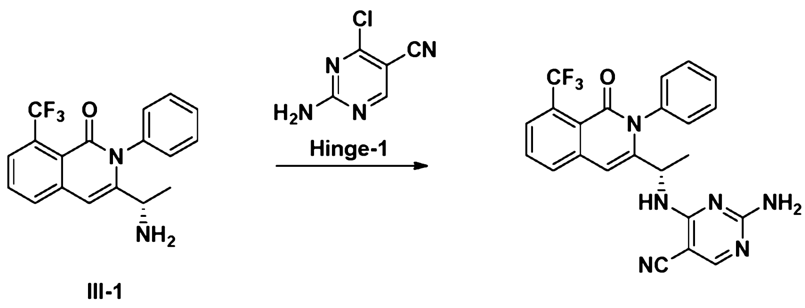
III-9 M-3 III-43a III-43

[00915] Amine **III-9** was prepared according to Method Q. Compound **III-43a** was prepared from amine **III-9** and **M-3** according to Method S. Compound **III-43a** was converted to **III-43** according to the following procedure:

[00916] To a stirred solution of quinolinone **III-43a** (0.1 mmol, 1.0 eq) in THF (10 mL) at RT, sodium methoxide (0.2 mmol, 2 eq) was added and the resulting mixture was stirred at reflux for 1-2 h. The mixture was

allowed to cool to RT and then extracted with DCM (15 mL x 3). The combined organic layers were washed with brine, dried over Na_2SO_4 and filtered. The filtrate was concentrated *in vacuo* and the residue was purified by column chromatography on silica gel (1-2% MeOH/DCM) to afford compound **III-43**. ESI-MS *m/z*: 510.2 $[M+H]^+$.

Example 144

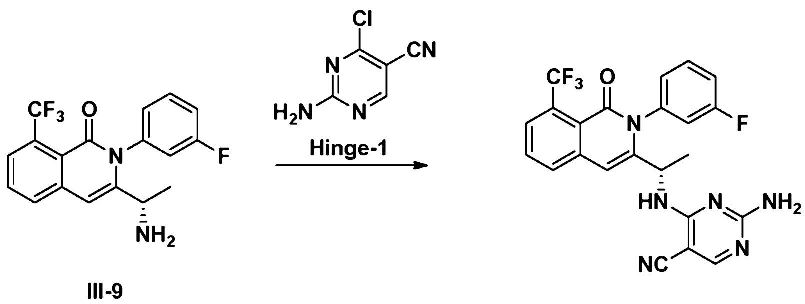


III-1

III-44

[00917] Compound **III-44** was prepared from amine **III-1** and 2-amino-4-chloropyrimidine-5-carbonitrile (**Hinge-1**) according to Method S. ESI-MS *m/z*: 451.2 $[M+H]^+$.

Example 145

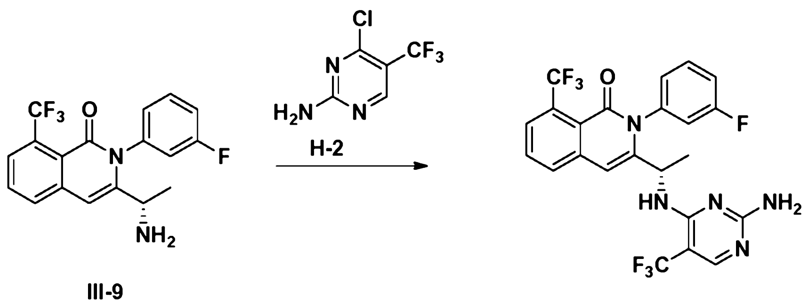


III-9

III-45

[00918] Compound **III-45** was prepared from amine **III-9** and 2-amino-4-chloropyrimidine-5-carbonitrile (**Hinge-1**) according to Method S. ESI-MS *m/z*: 469.2 $[M+H]^+$.

Example 146

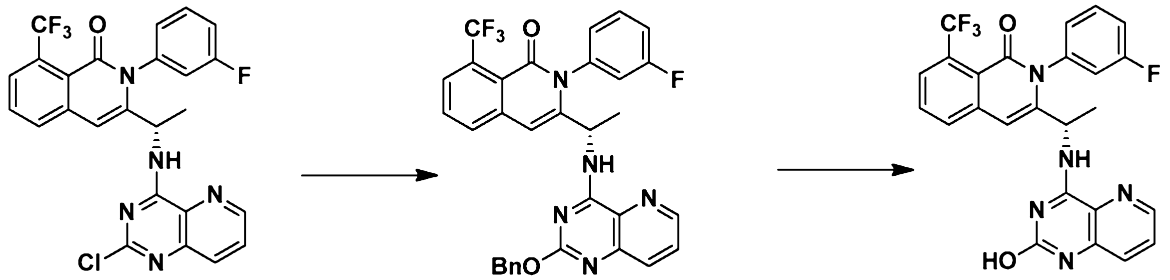


III-9

III-46

[00919] Compound **III-46** was prepared from amine **III-9** and 4-chloro-5-(trifluoromethyl)pyrimidin-2-amine (**H-2**) according to Method S. ESI-MS *m/z*: 512.0 $[M+H]^+$.

Example 147

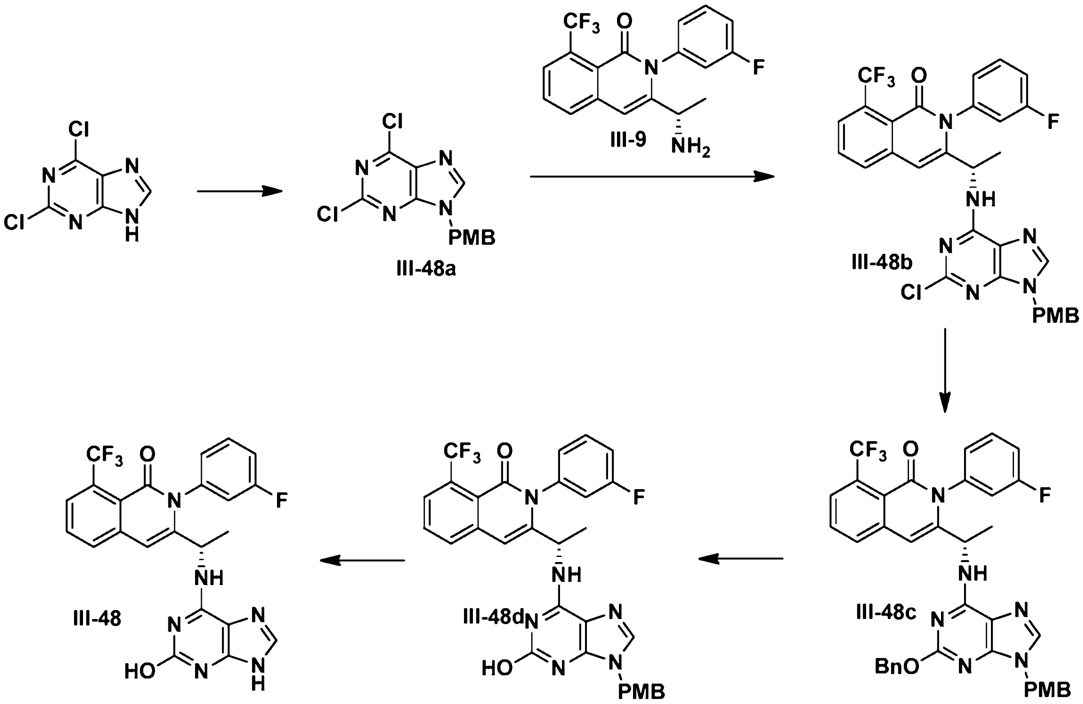


III-43a III-47a III-47

[00920] Compound **III-43a** was converted to compound **III-47a** in analogous fashion to compound **III-43** in Example 143 except that sodium benzyloxide was used in place of sodium methoxide. Compound **III-47** was prepared from **III-47a** according to the following procedure:

[00921] To a solution of **III-47a** (280 mg, 0.478 mmol) in MeOH (30 mL) at RT, Pd/C (150 mg, 10%) was added and the resulting mixture was stirred under hydrogen overnight. The mixture was filtered and the filtrate was concentrated *in vacuo* to afford compound **III-47**. ESI-MS *m/z*: 496.1 $[M+H]^+$.

Example 148

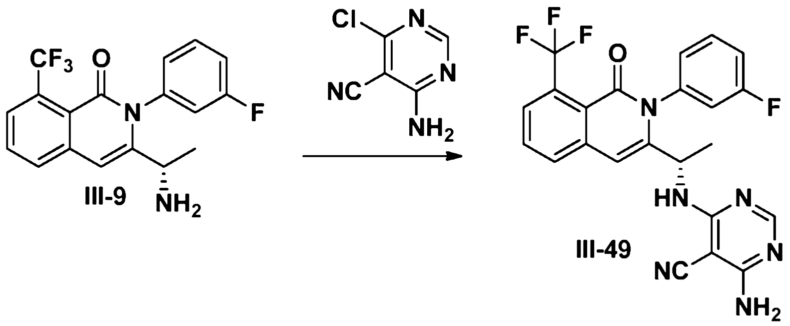


[00922] Compound **III-48** was prepared in five steps from 2,6-dichloro-9H-purine according to the following procedure: 2,6-dichloro-9H-purine (10 mmol, 1.0 equiv) was dissolved in 30 mL N,N-dimethylformamide. Sodium hydride (11 mmol, 1.1 equiv) was added portion-wise at 0 °C and stirred for 10 minutes, after which p-methoxylbenzyl chloride (11 mmol, 1.1 equiv) was added and the reaction was allowed to

stir at room temperature overnight. The reaction was then transferred to a separatory funnel with excess ethyl acetate and water. The water layer was then extracted with ethyl acetate (3 x 200 mL), dried over Na_2SO_4, and concentrated. The mixture was purified by silica gel chromatography, eluting with 10% ethyl acetate/diethyl ether , to provide **III-48a**.

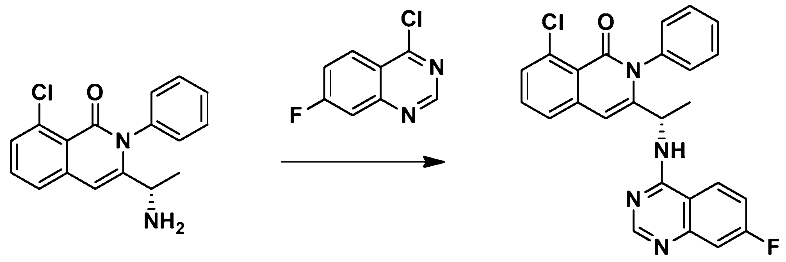
[00923] **III-48a** was then couped to compound **III-9** using Method S to afford compound **III-48b**. Compound **III-48b** was then converted to compound **III-48c** in analogous fashion to compound **III-43** in Example 143 except that sodium benzyloxide was used in place of sodium methoxide. Compound **III-48c** was then deprotected using analogous conditions as **III-47** in Example 147 to provide **III-48d**. Compound **III-48d** was then further deprotected to provide **III-48** according the the following procedure: Compound **III-48d** was dissolved in excess TFA and allowed to stir at reflux for 5h, after which it was concentrated *in vacuo*. The residue was resuspended in saturated $NaHCO_3$ and transferred to a separatory funnel where it was extracted with methylene chloride (2 x 200 mL). The organic layers were combined, concentrated and purified using flash silica gel chromatography (7.5:1 methylene chloride/methanol) to provide **III-48**. ESI-MS *m/z*: 485.2 $[M+H]^+$.

Example 149



[00924] Compound **III-49** was prepared from amine **III-9** and 4-amino-6-chloropyrimidine-5-carbonitrile according to Method S. ESI-MS *m/z*: 469.0 $[M+H]^+$.

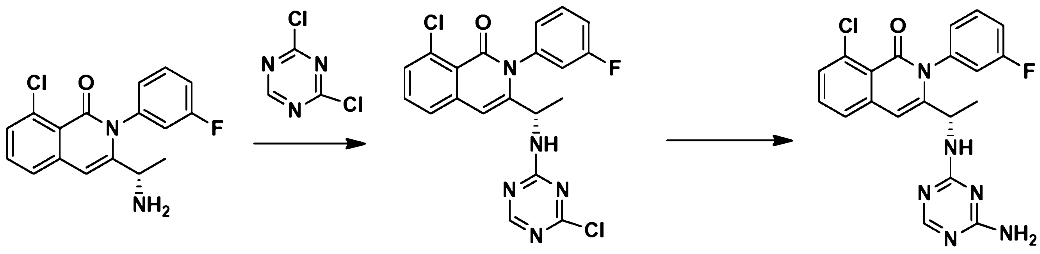
Example 150



I-1 **IV-1**

[00925] 4-Chloro-7-fluoroquinazoline was coupled with amine **I-1** using Method I to afford compound **IV-1**. ESI-MS *m/z*: 445.2 $[M+H]^+$.

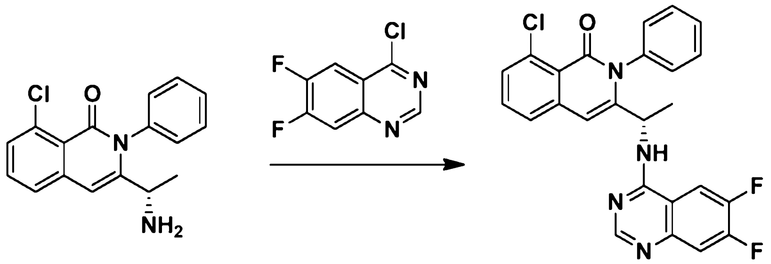
Example 151



IV-2a IV-2b IV-2

[00926] Amine **IV-2a** was prepared using Method E. It was then coupled with 2,4-dichloro-1,3,5-triazine using Method I to provide compound **IV-2b**. Compound **IV-2b** was converted to compound **IV-2** according to the following procedure: Compound **IV-2b** (71 mg, 0.16 mmol) was suspended in ammonium hydroxide (30 mL) in a sealed tube and the resulting mixture was stirred at 140 °C overnight. The mixture was allowed to cool to RT and then extracted with DCM (15 mL x 3). The combined organic layers were washed with brine, dried over Na_2SO_4 and filtered. The filtrate was concentrated *in vacuo* and the residue was purified by column chromatography on silica gel (1-2% MeOH/DCM) to afford compound **IV-2** (20 mg, 29% yield). ESI-MS *m/z*: 411.0 $[M+H]^+$.

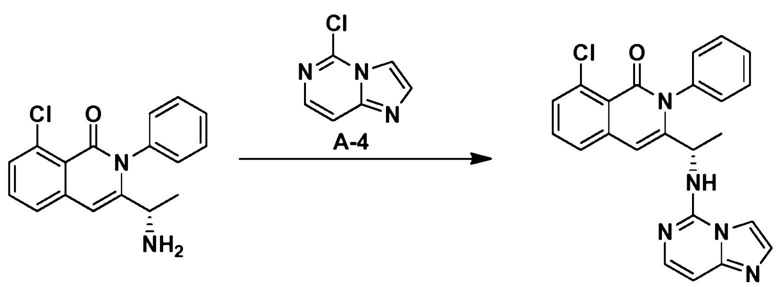
Example 152



I-1 IV-3

[00927] 4-Chloro-6,7-difluoroquinazolinewas coupled with amine **I-1** using Method I to afford compound **IV-3**. ESI-MS *m/z*: 463.2 $[M+H]^+$.

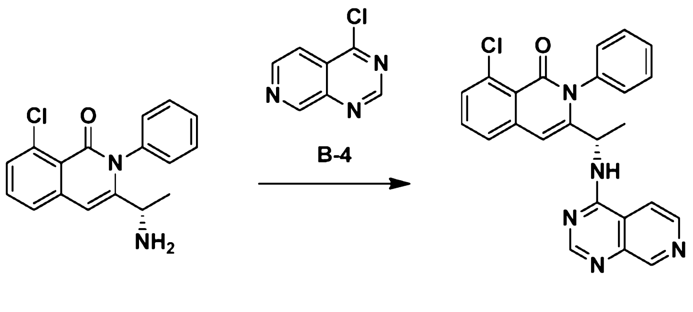
Example 153



I-1 IV-4

[00928] Amine **I-1** was prepared using Method E. It was then coupled with compound (**A-4**) using Method I to provide compound **IV-4**. ESI-MS *m/z*: 416.1 $[M+H]^+$.

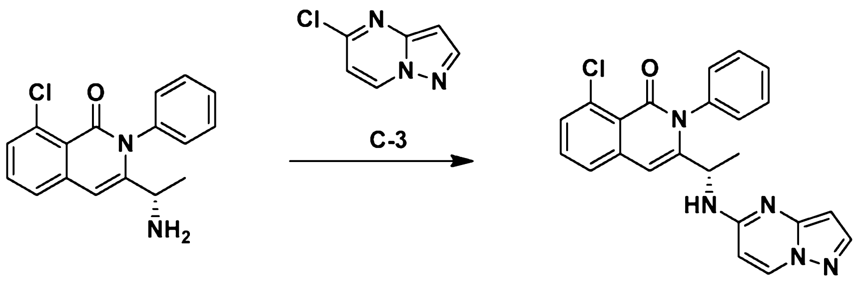
Example 154



I-1 IV-5

[00929] Compound **B-4** was coupled with amine **I-1** using Method I to afford compound **IV-5**. ESI-MS *m/z*: 428.2 $[M+H]^+$.

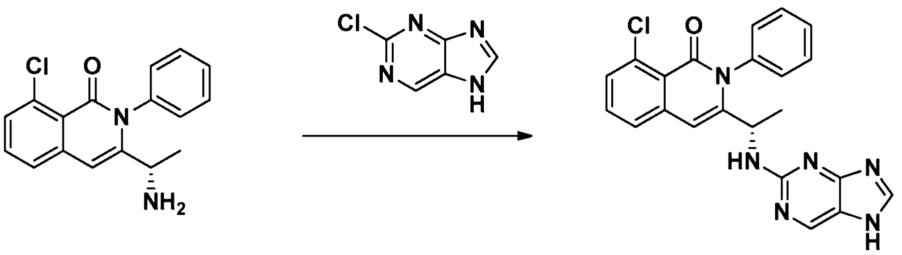
Example 155



I-1 IV-6

[00930] Compound **C-3** was coupled with amine **I-1** using Method I to afford compound **IV-6**. ESI-MS *m/z*: 416.2 $[M+H]^+$.

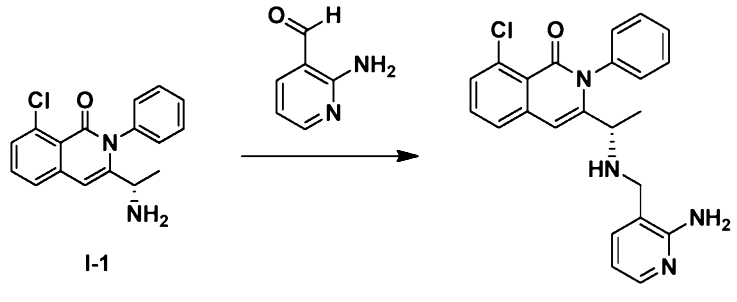
Example 156



I-1 IV-7

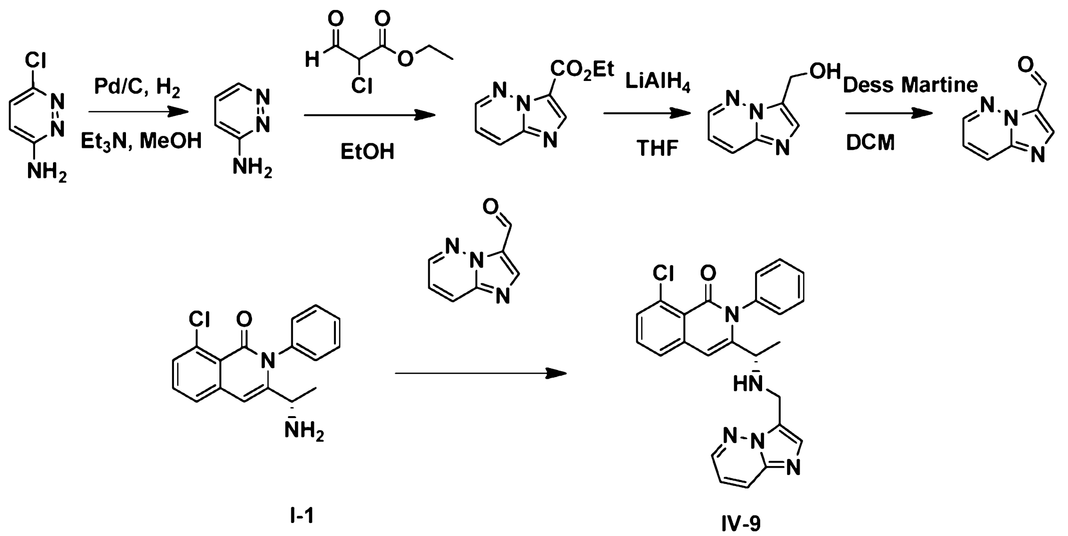
[00931] Compound **IV-7** was prepared from amine **I-1** by coupling to 2-chloro-7*H*-purine using Method I. ESI-MS *m/z*: 417.2 $[M+H]^+$.

Example 157



[00932] Compound **IV-8** was prepared from amine **I-1** and commercially available 2-aminonicotinaldehyde according to the following procedure: To a stirred mixture of compound **I-1** (150 mg, 0.5 mmol) and 2-aminonicotinaldehyde (37 mg, 0.6 mmol) in MeOH (5 mL), acetic acid (0.2 mL) and $NaBH_3CN$ (79 mg, 1.25 mmol) were added sequentially. The resulting mixture was stirred at RT for 16 h and LC-MS showed about 60% conversion. Additional amounts of 2-aminonicotinaldehyde (18 mg, 0.3 mmol) and $NaBH_3CN$ (40 mg, 0.62 mmol) were added and the resulting mixture was stirred for 16 h. The reaction was quenched by aqueous $NaHCO_3$ solution, and then extracted with ethyl acetate. The combined organic layer was washed with brine, dried over Na_2SO_4 and filtered. The filtrate was concentrated in vacuo and the residue was purified by ISCO (12 g silica gel cartridge, 0-10% MeOH/DCM) to afford compound **IV-8** (65 mg, 32% yield). ESI-MS *m/z*: 405.0 $[M+H]^+$.

Example 158



[00933] To a stirred solution of 6-chloropyridazin-3-amine (12.9 g, 0.1 mol) and triethylamine (11.2 g, 0.11 mmol) in MeOH (20 mL), Pd/C (10%, 1.3 g) was added. The resulting mixture was degassed and back-filled with hydrogen (three cycles) and then stirred at RT under hydrogen atmosphere for 18 h. The resulting mixture was filtered and the filtrate was concentrated *in vacuo* to afford pyridazin-3-amine, which was used in the next step without further purification.

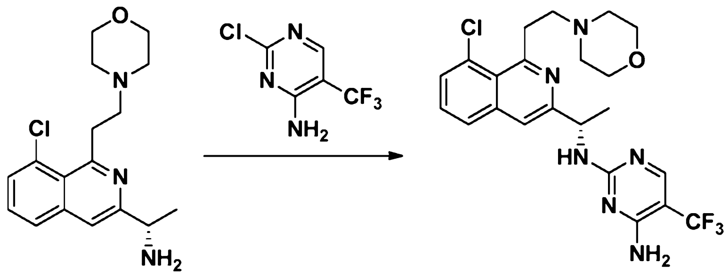
[00934] A mixture of pyridazin-3-amine (9.51 g, 0.1 mol) and 2- ethyl 2-chloro-3-oxopropanoate (22.5 g, 0.15 mol) in EtOH (20 mL) was stirred at reflux overnight. The mixture was allowed to cool to RT and concentrated *in vacuo* to remove EtOH. The residue was partitioned between water (100 mL) and ethyl acetate (100 mL). The organic layer was separated. The aqueous layer was extracted with ethyl acetate (2 x 50 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and filtered. The filtrate was concentrated *in vacuo*. The residue was slurried in isopropyl ether (50 mL) with stirring for 30 min, collected by filtration and dried *in vacuo* to afford ethyl imidazo[1,2-b]pyridazine-3-carboxylate (7.8 g, 40.8% yield).

[00935] To a solution of ethyl imidazo[1,2-b]pyridazine-3-carboxylate (1.91 g, 10 mmol) in anhydrous THF (20 mL), lithium aluminium hydride (1.34 g, 35 mmol) was added in portions over 15 min. After stirring at RT for 16 h, the mixture was quenched with ice-water (20 mL) and then extracted with ethyl acetate (30 mL × 2). The combined organic layers were washed with brine, dried over Na_2SO_4 then filtered. The filtrate was concentrated *in vacuo* to afford imidazo[1,2-b]pyridazin-3-ylmethanol (0.85 g, 57% yield).

[00936] A mixture of imidazo[1,2-b]pyridazin-3-ylmethanol (45 mg, 0.3 mmol) and Dess-Martin periodinane (130 mg, 0.3 mmol) in anhydrous DCM (5 mL) were stirred at RT overnight. The recation mixture was quenched with water (5 mL). The organic layer was separated, dried over $MgSO_4$ and filtered. The filtrate was concentrated *in vacuo* to afford imidazo[1,2-b]pyridazine-3-carbaldehyde (40 mg, 90.7% yield).

[00937] To a stirred mixture of compound **I-1** (60 mg, 0.2 mmol) and imidazo[1,2-b]pyridazine-3-carbaldehyde (30 mg, 0.2 mmol) in DCM (5 mL), acetic acid (24 mg, 0.4 mmol) and triacetoxyborohydride (85 mg, 0.42 mmol) were added respectively. After stirring at RT for 2 h, the mixture was quenched with water (10 mL). The organic layer was separated, dried over $MgSO_4$ and filtered. The filtrate was concentrated *in vacuo* to afford (S)-8-chloro-3-(1-(imidazo[1,2-b]pyridazin-3-ylmethylamino)ethyl)-2-phenylisoquinolin-1(2H)-one (**IV-9**) (75 mg, 87.2% yield). ESI-MS *m/z*: 430.2 $[M+H]^+$.

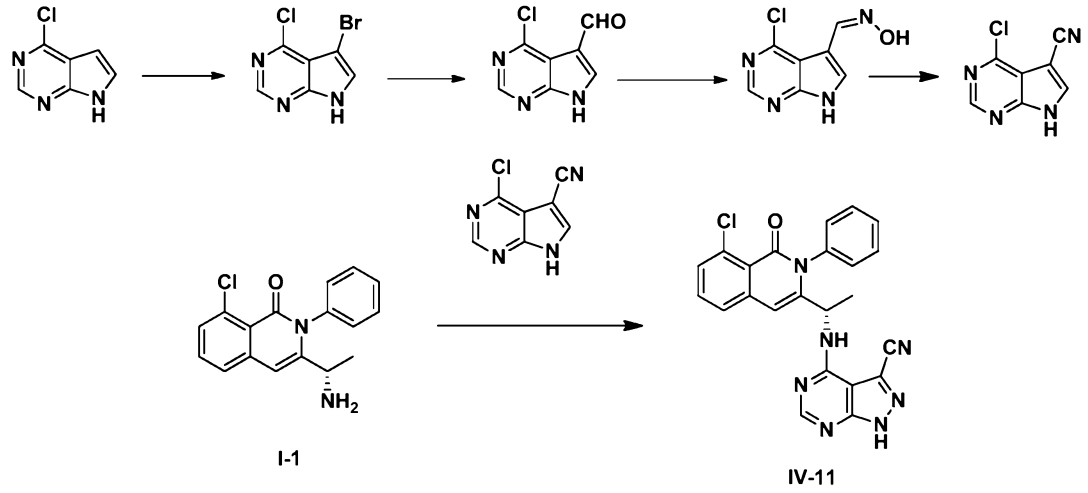
Example 159



IV-10a IV-10

[00938] Compound **IV-10a** was coupled with 2-chloro-5-(trifluoromethyl)pyrimidin-4-amine using Method I to afford compound **IV-10**. ESI-MS *m/z*: 481.2 $[M+H]^+$.

Example 160



[00939] To a suspension of 4-chloro-7H-pyrrolo[2,3-d]pyrimidine (3.99 g, 26.0 mmol, 1.0 eq) in dry DCM (150 mL) under argon, N-bromosuccinimide (6.02 g, 33.8 mmol, 1.3 eq) was added and the resulting mixture was stirred at RT for 3 h. The reaction mixture was diluted with MeOH (30 mL) and then concentrated *in vacuo* to yield a slight brown solid. The residue was triturated with H_2O (150 mL). The solid was collected by filtration and then re-crystallized in MeOH to afford 5-bromo-4-chloro-7H-pyrrolo[2,3-d] pyrimidine (4.0 g, 66% yield).

[00940] To a solution of 5-bromo-4-chloro-7H-pyrrolo[2,3-d]pyrimidine (2.33 g, 10.0 mmol, 1.0 eq) in anhydrous THF (100 mL) at -78 °C under argon, n-BuLi solution (2.5 M in THF, 8.8 mL, 22.0 mmol, 2.2 eq) was added dropwise (over 10 min). The resulting mixture was stirred at -78 °C for 1h and then DMF (2.0 g, 11.0 mmol, 1.1 eq) was added dropwise (over 10 min). The mixture was stirred at -78 °C for an additional 30 min and then stirred at RT overnight. The reaction mixture was quenched with H_2O (50 mL) and then concentrated *in vacuo*. The residue was triturated with saturated aqueous NH_4Cl solution. The solid was collected by filtration, rinsed with ethyl acetate, and dried *in vacuo* to afford 4-chloro-7H-pyrrolo[2,3-d]pyrimidine-5-carbaldehyde (1.17 g, 65% yield).

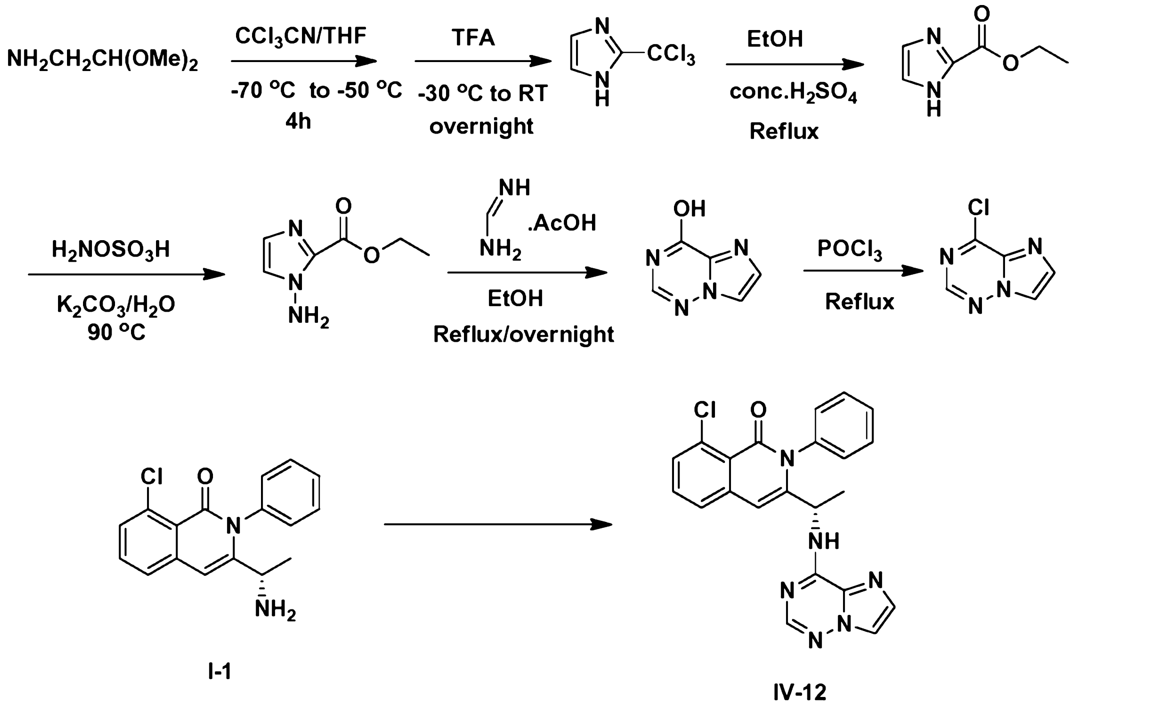
[00941] To a suspension of 4-chloro-7H-pyrrolo[2,3-d]pyrimidine-5-carbaldehyde (1.17 g, 6.47 mmol, 1.0 eq) and hydroxylamine hydrochloride (0.54 g, 7.77 mmol, 1.2 eq) in EtOH (25 mL), aqueous NaOH solution (0.31 g, 7.77 mmol, 1.2 eq) in H_2O (4 mL) was added dropwise. The resulting mixture was stirred at RT for 30 min and then was diluted with a sufficient amount of EtOH to allow stirring for additional 30 min. The solid was collected by filtration, rinsed with H_2O and dried *in vacuo* to afford 4-chloro-7H-pyrrolo[2,3-d]pyrimidine-5-carbaldehyde oxime (0.89 g, 70% yield) as a mixture of isomers. ESI-MS *m/z*: 194.8 $[M-H]^-$.

[00942] To a suspension of 4-chloro-7H-pyrrolo[2,3-d]pyrimidine-5-carbaldehyde oxime (865 mg, 4.40 mmol, 1.0 eq) in DCM (20 mL), thionyl chloride (3.1 mL, 43.7 mmol, 10.0 eq) was added and the resulting mixture was stirred at RT overnight. The reaction mixture was concentrated *in vacuo*. The residue was suspended in water (60 mL) and saturated aqueous $NaHCO_3$ was added to adjust the pH to 4. The solid was collected by filtration, rinsed with water followed by ethyl acetate to afford the first batch of product. The filtrate was then extracted with ethyl acetate (50 mL x 3). The combined organic layer was washed with brine, dried over Na_2SO_4 and filtered. The

filtrate was concentrated *in vacuo* and the residue was combined with the above-obtained solid. The crude product was then re-crystallized in ethyl acetate/hexanes (1:1) and dried *in vacuo* to afford 4-chloro-7H-pyrrolo[2,3-d]pyrimidine-5-carbonitrile (763 mg, 97% yield). ESI-MS *m/z*: 178.8 $[M+H]^+$, 176.8 $[M-H]^-$.

[00943] 4-Chloro-7H-pyrrolo[2,3-d]pyrimidine-5-carbonitrile was coupled with amine **I-1** using Method I to afford compound **IV-11**. ESI-MS *m/z*: 4420.2 $[M-H]^-$.

Example 161



[00944] To a stirred solution of trichloroacetonitrile (28.8 g, 200 mmol, 1 eq) in anhydrous THF (70 mL) at -60 °C under an argon atmosphere, 2,2-dimethoxyethanamine (21.8 mL, 200 mmol, 1.0 eq) was added dropwwase over 5 min. The resulting mixture was allowed to warm to RT and stirred at RT for 4 h. The mixture was concentrated *in vacuo* and the residue was added in portions to a stirred solution of trifluoroacetic acid (100 mL) at -30 °C under argon. The resulting mixture was then stirred from -30 °C to RT overnight. The reaction mixture was concentrated *in vacuo* to afford 2-(trichloromethyl)-1H-imidazole. The crude product was used in the next step without further purification.

[00945] The above-obtained residue was dissolved in EtOH (300 mL). To this solution, conc. H_2SO_4 (98%, 30 mL, 522 mmol, 2.76 eq) was added dropwise while keeping the reaction temperature below 25 °C. The resulting mixture was stirred at reflux for 7 h and then stirred at RT overnight. The mixture was concentrated *in vacuo* to remove EtOH. The resulting suspension was diluted with ice-water (200 mL) and neutralized with concentrated ammonium hydroxide to adjust the pH to 5-6 while keeping the temperature below 5 °C. The solid was collected by filtration, rinsed with water (10 mL x 3), and dried *in vacuo* to afford the first batch of crude product (10 g). The filtrate was extracted with ethyl acetate (200 mL x 2). The combined organic layer was washed with brine, dried over Na_2SO_4 and filtered. The filtrate was concentrated *in vacuo*. The resulting residue was

combined with the first batch crude product and then re-crystallized in isopropyl ether to afford ethyl 1H-imidazole-2-carboxylate (18 g, 64.3% yield).

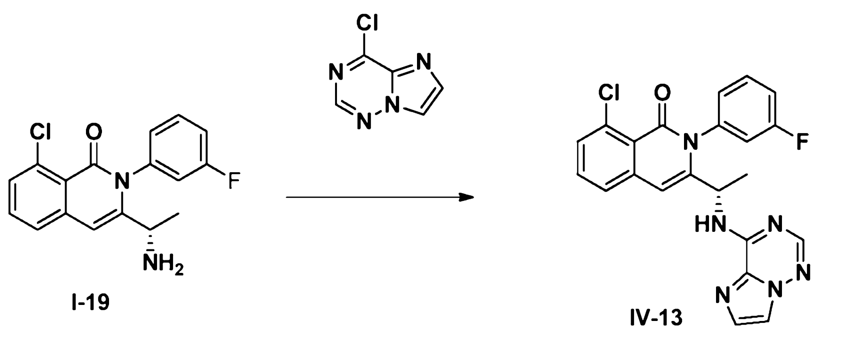
[00946] To a stirred solution of hydroxylamine-o-sulfonic acid (26.64 g, 235.8 mmol, 3.0 eq) in H_2O (17 mL) at 0 °C, ethyl 1H-imidazole-2-carboxylate (11.0 g, 78.6 mmol, 1.0 eq) was added and the resulting mixture was stirred at 90 °C for 30 min. The mixture was cooled to RT and K_2CO_3 (3.6 g, 26.2 mmol, 1.0 eq) was added in portions. The resulting mixture was stirred at RT overnight, filtered and rinsed with H_2O (10 mL x 3). The filtrate was extracted with ethyl acetate (50 mL x 5). The combined organic layer was washed with brine, dried over Na_2SO_4 and filtered. The filtrate was evaporated *in vacuo* and the residue was purified by flash column chromatography on silica gel (1% MeOH in DCM) to afford ethyl 1-amino-1H-imidazole-2-carboxylate (800 mg, 6.5 % yield). ESI-MS *m/z*: 156.1 $[M+H]^+$.

[00947] A mixture of ethyl 1-amino-1H-imidazole-2-carboxylate (800 mg, 5.16 mmol, 1.0 eq) and formamidine acetate (2.68 g, 25.78 mmol, 5.0 eq) in EtOH (100 mL) was stirred at reflux overnight. The resulting mixture was cooled to RT. The solid was collected by filtration, rinsed with EtOH (3 x 2 mL) and petroleum ether (2 mL× 3), and then dried *in vacuo* to afford imidazo[1,2-f][1,2,4]triazin-4-ol (400 mg, 50.2% yield).

[00948] Imidazo[1,2-f][1,2,4]triazin-4-ol (400 mg, 2.94 mmol, 1.0 eq) was dissolved in $POCl_3$ (10 mL, 109.2 mmol, 37.1 eq) and the resulting mixture was stirred at reflux for 2 h. The mixture was concentrated *in vacuo* to remove $POCl_3$. The residue was poured into ice water (30 mL) and neutralized with saturated aqueous $NaHCO_3$ solution to adjust the pH to 6-7 while keeping the temperature below 5 °C. The mixture was extracted with ethyl acetate (30 mL x 4). The combined organic layer was washed with brine, dried over Na_2SO_4 and filtered. The filtrate was concentrated *in vacuo* and the residue was purified by flash column chromatography on silica gel (16% ethyl acetate in petro ether) to afford 4-chloroimidazo[1,2-f][1,2,4]triazine (300 mg, 66.0 % yield).

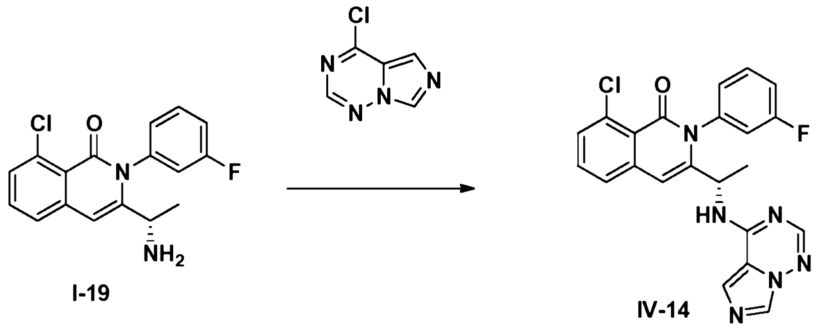
[00949] 4-Chloroimidazo[1,2-f][1,2,4]triazine was coupled with amine **I-1** using Method I to afford compound **IV-12**. ESI-MS *m/z*: 417.2 $[M+H]^+$.

Example 162



[00950] 4-Chloroimidazo[1,2-f][1,2,4]triazine was coupled with amine **I-19** using Method I to afford compound **IV-13**. ESI-MS *m/z*: 435.0 $[M+H]^+$.

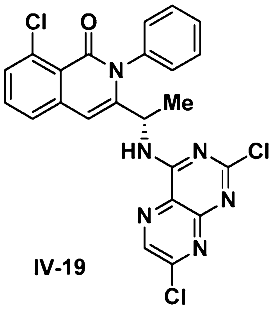
Example 163



I-19 IV-14

[00951] 4-Chloroimidazo[5,1-f][1,2,4]triazine was coupled with amine **I-19** using Method I to afford compound **IV-14**. ESI-MS *m/z*: 435.0 $[M+H]^+$.

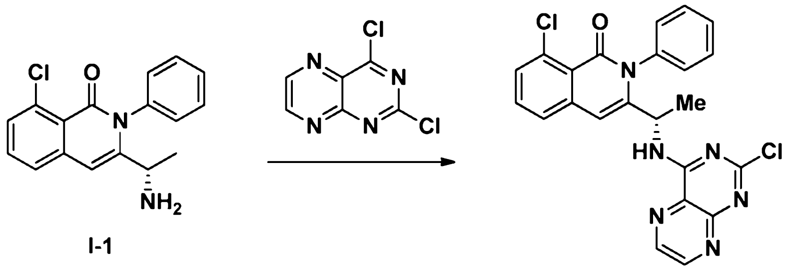
Example 164



IV-19

[00952] Compound **IV-19** was isolated as a byproduct of the coupling reaction to provide compound **IV-20**. ESI-MS *m/z*: 499.12 $[M+H]^+$.

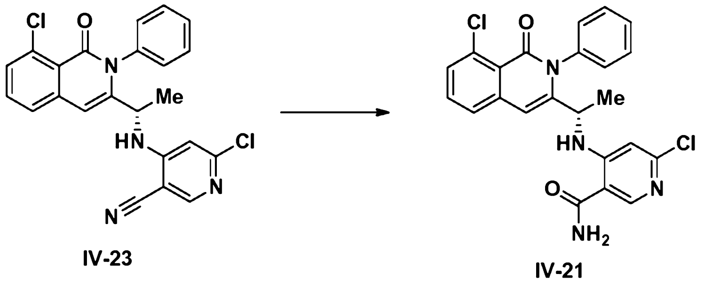
Example 165



I-1 IV-20

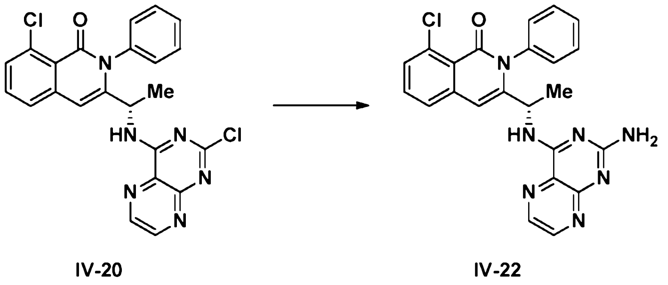
[00953] Amine **I-1** (300 mg, 1.0 equiv) was dissoved in dioxane (5 mL). 2,4-Dichloropteridine (1.5 equiv) and diisopropylethyl amine were dissolved in 5 mL dioxance and added slowly to amine **I-1**. The reaction was heated to 60 °C for 72h after which point there was no starting material by LC/MS analysis. The reaction was transferred to a separatory funnel with excess dichloromethane. The organic layer was washed with saturated sodium bicarbonate (2x), brine (1x) and water (1x), dried over sodium sulfate and concentrated to provide crude material which was purified using flash silica gel chromatography (gradient of 50-100% ethyl acetate/hexanes) to provide cmpound **IV-20**. ESI-MS *m/z*: 463.13 $[M+H]^+$.

Example 166



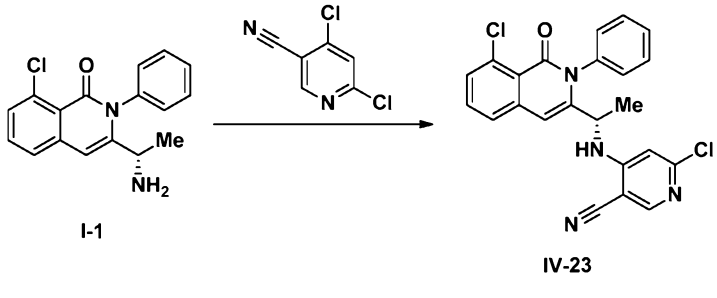
[00954] A 35 mL heavy-walled tube with PTFE stopper and PTFE-jacketed-silicone o-ring seal was charged with isoquinolinone **IV-23** (0.23 mmol) and 1,4-dioxane (10 mL). The suspension was treated with ammonium hydroxide solution (10 mL), and the tube sealed tightly and placed in a 110 °C bath overnight. After cooling, LC/MS showed a mixture of products and < 10% remaining starting material. The reaction mixture was dilluted with 2 volumes of brine after which a solid is formed that was collected via vacuum filtration to provide amide **IV-21**. ESI-MS *m/z*: 453.17 $[M+H]^+$.

Example 167



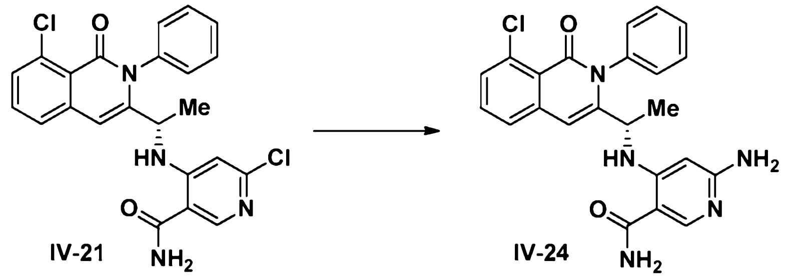
[00955] A 35 mL heavy-walled tube with PTFE stopper and PTFE-jacketed-silicone o-ring seal was charged with isoquinolinone **IV-20** (243 mg, 0.52 mmol) and 1,4-dioxane (10 mL). The suspension was treated with ammonium hydroxide solution (10 mL), and the tube sealed tightly and placed in a 140 °C bath overnight. After cooling, LC/MS showed complete conversion and the reaction mixture was transferred to a larger flask using 1-2 mLs of MeOH, then diluted with 2 volumes of brine. After stirring about 1h, the resulting precipitate was collected by filtration, washing with water. The product cake was dried *in vacuo* to give compound **IV-22** as a tan powder. ESI-MS *m/z*: 444.20 $[M+H]^+$.

Example 168



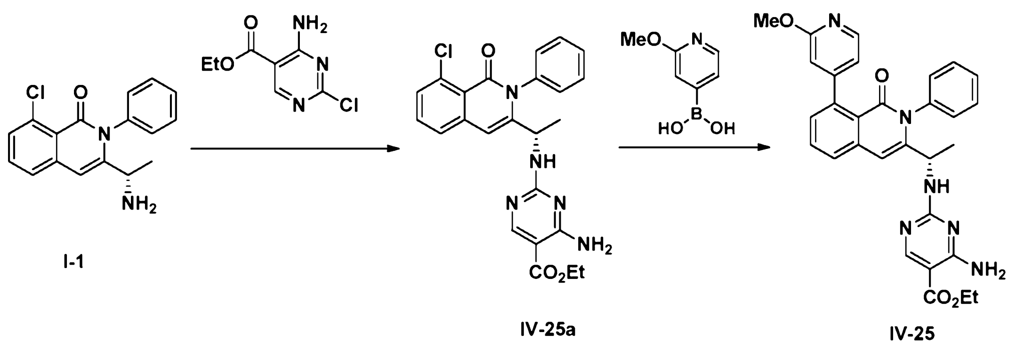
[00956] Compound **I-1** was reacted with 4,6-dichloronicotinonitrile according to Method I to provide compound **IV-23**. ESI-MS *m/z*: 435.11 $[M+H]^+$.

Example 169



[00957] A 35 mL heavy-walled tube with PTFE stopper and PTFE-jacketed-silicone o-ring seal was charged with isoquinolinone **IV-21** (0.14 mmol) and 1,4-dioxane (4 mL). The suspension was treated with ammonium hydroxide solution (30%, 5 mL), and the tube sealed tightly and placed in a 150 °C bath for 3d. The mixture was then recharged with 5 mL of ammonium hydroxide (30%, 5mL) and heated for 24 additional hours at 170 °C. The reaction mixture transferred to a separtory funnel with excess methylene chloride. The organic layer was washed with brine (1x) and water (1x), dried over Na_2SO_4 and concentrated to provide material which is 85% of compound **IV-24** and 15% of starting material which was used directly for biochemical profiling. ESI-MS *m/z*: 434.18 $[M+H]^+$.

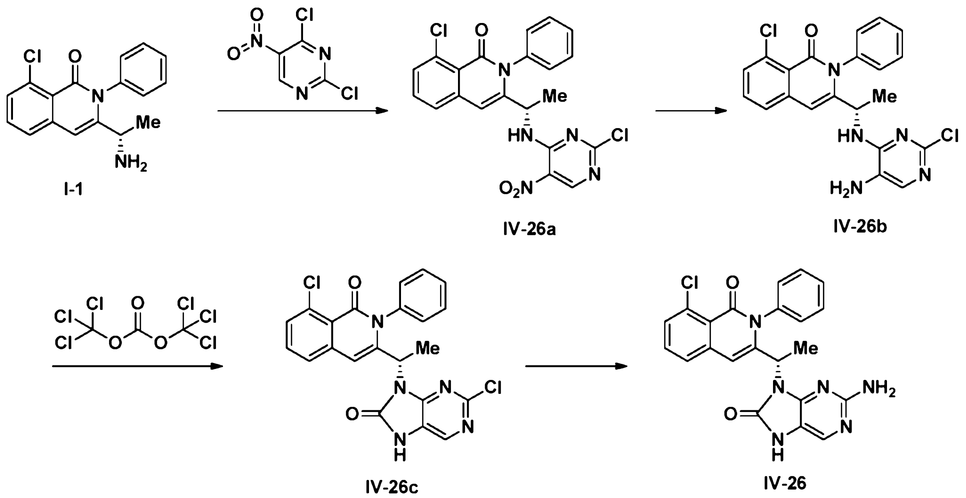
Example 170



[00958] Compound **IV-25a** was prepared from compound **I-1** by coupling to ethyl 4-amino-2-chloropyrimidine-5-carboxylate using Method I. Compound **IV-25a** was then converted to compound **IV-25** according to the following procedure: The mixture of compound **IV-25a** (300 mg, 0.65 mmol) and 2-methoxypyridin-4-yl)boronic acid (149 mg, 0.98 mmol) in 1,4-dioxane:water (3:1, 12 mL) was degassed and backfilled with argon (three cycles). To this mixture, 2-dicyclohexylphosphino-2',6'-diisopropoxybiphenyl (121 mg, 0.26 mmol), palladium(II) acetate (29 mg, 0.13 mmol), and Na_2CO_3 (207 mg, 1.95 mmol) were added sequentially. The resulting mixture was degassed and backfilled with argon (three cycles), and then stirred at 120 °C for 3 h. The mixture was allowed to cool to RT, and then partitioned between ethyl acetate and water. The organic layer was washed with brine, dried over Na_2SO_4 and filtered. The filtrate was concentrated *in vacuo* and the residue

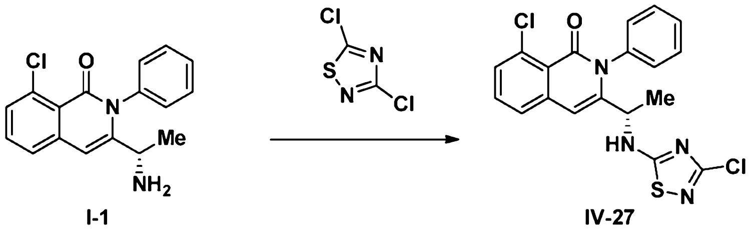
was purified by ISCO column chromatography (silica gel cartridge, 0-10% MeOH/DCM) to afford compound **IV-25** (160 mg, 46% yield). ESI-MS *m/z*: 537.2 $[M+H]^+$.

Example 171



[00959] Compound **I-1** was reacted with 2,4-dichloro-5-nitropyrimidine according to Method I to provide compound **IV-26a**. Compound **IV-26a** was then converted to compound **IV-26** in 3 steps according to the following procedures: Compound **IV-26a** (450 mg, 1.0 equiv) was dissoved in 30 mL of methanol and purged with N_2. Palladium on carbon (1.0 equiv) was added and the reaction was flushed with H_2. The reaction was kept under an atmosphere of H_2 using a ballon and stirred at room temperature for 12h after which it was filtered through celite and washed with excess methanol. The solution was concentrated to provide amine **IV-26b** which was used directly in the next step. Compound **IV-26b** (68 mg, 1.0 equiv) was dissolved in tetrahydrofuran (5 mL). Triphosgene was added (1.2 equiv), follwed by triethylamine (3.0 equiv) and the reaction was heated to 50 °C for 16h. The reaction was cooled and transferred to a separatory funnel with excess ethyl acetate. The organic layer was washed with brine (1x), dried over Na_2SO_4 and concentrated under vacuum to provide crude material that was purified using CombiFlash silica gel chromatography (60% ethyl acetate/hexanes) to provide compound **IV-26c**. Compound **IV-26c** was then added to a sealed tube (0.08 mmol) and dissolved in 1 mL dioxane. Ammonium hydoxide (30%, 4 mL) was added and the reaction was sealed and heated to 160 °C for 24h after which it was recharged with 3 mL additional ammonium hydroxide and heated for 24 additional hours. The reaction was cooled, concentrated and purified via HPLC purificaiton to provide compound **IV-26**. ESI-MS *m/z*: 433.1 $[M+H]^+$.

Example 172



[00960] A solution of dichlorothiadiazole (250 mg, 1.62 mmol, 1.1 eq.) in THF (4 mL) was treated dropwise with a solution of amine **I-1** (440 mg, 1.47 mmol, 1 eq.) and triethylamine (250 uL, 1.6 mmol, 1.1 eq.) in THF (6 mL). The reaction was monitored by LC/MS and allowed to proceed for 5d, at which point most of the material appeared to be converted and the reaction mixture was diluted with DCM, 2-3g of silica gel added, and concentrated *in vacuo*. Purification of this material by flash chromatography (gradient of 30-100% ethyl acetate/hexanes) afforded compound **IV-27** as a white solid (540 mg, 88% yield). ESI-MS *m/z*: 417.11 $[M+H]^+$.

Table 3. *In Vitro* IC_{50} data for selected compounds.

IC_{50} (nM)	Greater than 10 μM	Greater than 1 μM to 10 μM	1 μM to 100 nM	Less than 100 nM

IC$_{50}$ (nM)	Greater than 10 μM	Greater than 1 μM to 10 μM	1 μM to 100 nM	Less than 100 nM
PI3K δ	**I-53, I-54, I-55, I-62, I-71, I-72, I-77, III-26, III-29, III-37, III-43, III-47, III-48, IV-1, IV-3, IV-4, IV-5, IV-6, IV-8, IV-10, IV-25, IV-26, IV-27**	**I-30, I-46, I-52, I-68, I-99, I-100, I-102, II-13, II-28, II-29, II-31, II-32, II-33, III-22, III-28, IV-7, IV-9, IV-14, IV-19, IV-20, IV-23**	**I-6, I-27, I-35, I-37, I-39, I-93, I-95, I-98, I-101, I-106, II-16, II-21, II-23, II-44, III-14, III-40, IV-2, IV-21, IV-22**	**I-2, I-4, I-14, I-16, I-18, I-20, I-21, I-23, I-24, I-25, I-29, I-33, I-36, I-38, I-40, I-41, I-42, I-43, I-44, I-45, I-47, I-48, I-49, I-50, I-51, I-57, I-58, I-59, I-63, I-65, I-70, I-73, I-74, I-75, I-76, I-78, I-79, I-80, I-81, I-82, I-83, I-84, I-85, I-86, I-87, I-88, I-89, I-90, I-91, I-92, I-94, I-96, I-97, I-103, II-2, II-4, II-5, II-7, II-8, II-9, II-10, II-11, II-14, II-17, II-18, II-20, II-22, II-24, II-30, II-45, II-47, II-48, II-49, II-50, III-3, III-4, III-5, III-6, III-8, III-10, III-11, III-12, III-13, III-15, III-17, III-18, III-19, III-20, III-21, III-23, III-24, III-25, III-27, III-30, III-31, III-32, III-36, III-39, III-41, III-42, III-44, III-45, III-46, III-49, IV-11, IV-12, IV-13, IV-24**

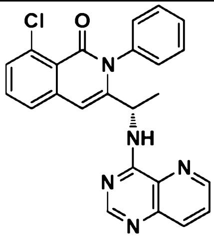
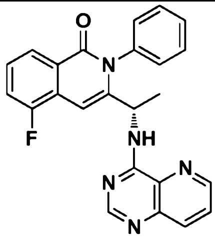
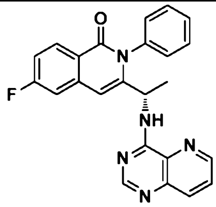
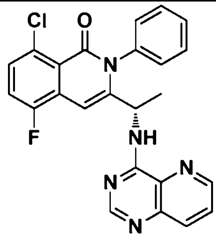
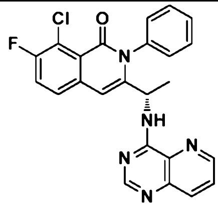
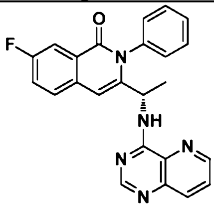
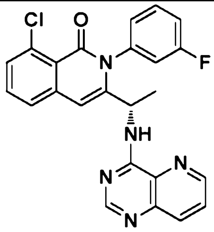
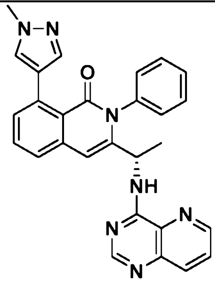
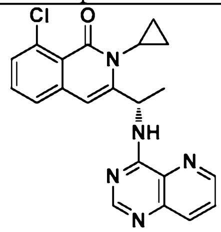
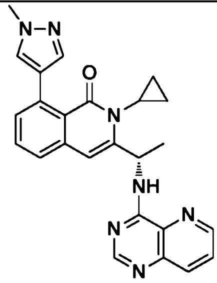
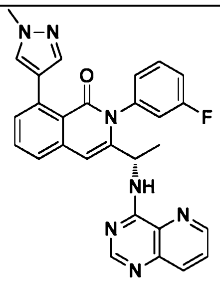
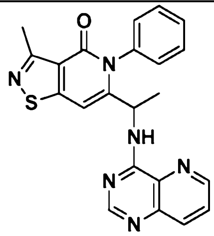
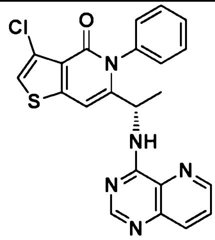
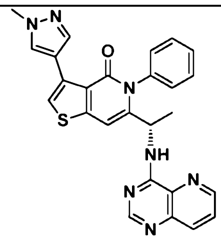
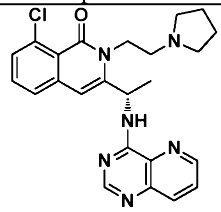
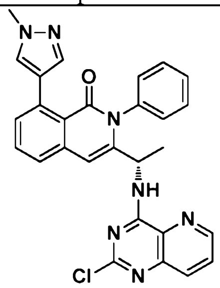
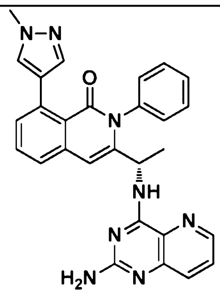
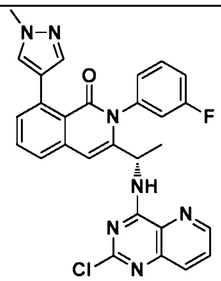
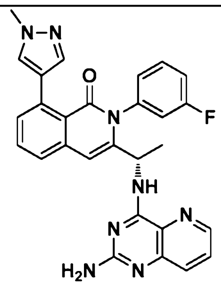
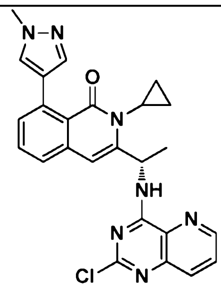
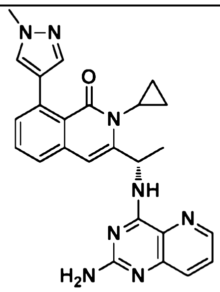
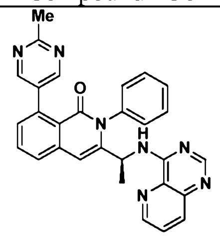
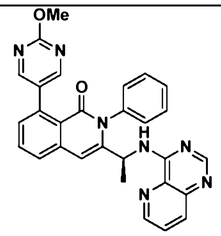
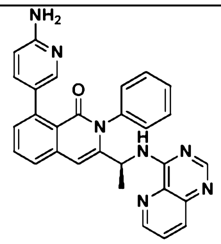
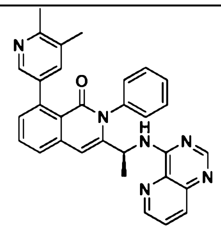
IC$_{50}$ (nM)	Greater than 10 μM	Greater than 1 μM to 10 μM	1 μM to 100 nM	Less than 100 nM
PI3K γ	**I-68, I-71, I-72, I-77, I-99, II-28, II-29, III-28, III-47, III-48, IV-1, IV-3, IV-4, IV-5, IV-6, IV-7, IV-8, IV-9, IV-10, IV-14, IV-19, IV-23, IV-25, IV-26, IV-27**	**I-6, I-27, I-46, I-53, I-54, I-55, I-100, I-106, II-8, II-13, II-31, II-32, II-33, II-44, III-14, III-26, III-29, III-37, III-40, III-41, III-43, IV-2, IV-20**	**I-33, I-37, I-39, I-44, I-62, I-65, I-73, I-93, I-97, I-98, I-102, II-7, II-9, II-11, II-16, II-21, II-23, II-30, II-45, II-47, II-48, II-50, III-22, IV-21**	**I-2, I-4, I-14, I-16, I-18, I-20, I-21, I-23, I-24, I-25, I-29, I-30, I-35, I-36, I-38, I-40, I-41, I-42, I-43, I-45, I-47, I-48, I-49, I-50, I-51, I-52, I-57, I-58, I-59, I-63, I-70, I-74, I-75, I-76, I-78, I-79, I-80, I-81, I-82, I-83, I-84, I-85, I-86, I-87, I-88, I-89, I-90, I-91, I-92, I-94, I-95, I-96, I-101, I-103, II-2, II-4, II-5, II-10, II-14, II-17, II-18, II-20, II-22, II-24, II-49, III-3, III-4, III-5, III-6, III-8, III-10, III-11, III-12, III-13, III-15, III-17, III-18, III-19, III-20, III-21, III-23, III-24, III-25, III-27, III-30, III-31, III-32, III-36, III-39, III-42, III-44, III-45, III-46, III-49, IV-11, IV-12, IV-13, IV-22, IV-24**

IC_{50} (nM)	Greater than 10 μM	Greater than 1 μM to 10 μM	1 μM to 100 nM	Less than 100 nM
PI3K α	**I-27, I-30, I-33, I-35, I-37, I-39, I-41, I-42, I-46, I-52, I-53, I-54, I-55, I-57, I-59, I-62, I-65, I-68, I-71, I-72, I-77, I-78, I-93, I-95, I-97, I-98, I-99, I-100, I-101, I-102, II-13, II-16, II-21, II-23, II-28, II-29, II-30, II-31, II-32, II-33, II-44, II-47, II-49, II-50, III-11, III-14, III-19, III-21, III-22, III-24, III-26, III-28, III-29, III-31, III-32, III-37, III-41, III-42, III-43, III-46, III-47, III-48, IV-1, IV-2, IV-3, IV-4, IV-5, IV-6, IV-7, IV-8, IV-9, IV-10, IV-11, IV-14, IV-19, IV-20, IV-21, IV-22, IV-23, IV-25, IV-26, IV-27**	**I-2, I-4, I-6, I-18, I-21, I-24, I-25, I-29, I-36, I-38, I-43, I-44, I-47, I-48, I-49, I-50, I-51, I-70, I-73, I-74, I-79, I-80, I-84, I-86, I-87, I-89, I-91, I-96, I-106, II-2, II-4, II-5, II-7, II-8, II-9, II-11, II-14, II-17, II-18, II-20, II-22, II-24, II-45, II-48, III-3, III-4, III-6, III-8, III-10, III-12, III-13, III-15, III-18, III-20, III-23, III-25, III-27, III-30, III-36, III-39, III-44, III-45, III-49, IV-12, IV-13**	**I-14, I-16, I-20, I-23, I-40, I-45, I-58, I-63, I-75, I-76, I-81, I-82, I-83, I-85, I-88, I-90, I-92, I-94, I-103, II-10, III-5, III-17, III-40, IV-24**	

IC_{50} (nM)	Greater than 10 μM	Greater than 1 μM to 10 μM	1 μM to 100 nM	Less than 100 nM
PI3K β	**I-6, I-21, I-25, I-27, I-30, I-35, I-36, I-37, I-38, I-39, I-41, I-42, I-43, I-44, I-45, I-46, I-47, I-48, I-52, I-53, I-54, I-55, I-57, I-59, I-62, I-68, I-71, I-72, I-73, I-77, I-78, I-80, I-84, I-86, I-87, I-89, I-91, I-95, I-97, I-98, I-99, I-100, I-101, I-102, II-9, II-13, II-16, II-17, II-21, II-23, II-31, II-32, II-33, II-47, II-48, II-50, III-14, III-22, III-26, III-28, III-29, III-37, III-41, III-42, III-43, III-47, III-48, IV-1, IV-2, IV-3, IV-4, IV-5, IV-6, IV-7, IV-8, IV-9, IV-10, IV-14, IV-19, IV-20, IV-21, IV-23, IV-25, IV-26, IV-27**	**I-4, I-18, I-24, I-40, I-50, I-51, I-58, I-65, I-63, I-70, I-74, I-75, I-76, I-79, I-81, I-82, I-85, I-88, I-93, I-94, I-96, I-106, II-4, II-5, II-8, II-18, II-28, II-29, II-30, II-44, II-45, II-49, III-11, III-12, III-13, III-15, III-18, III-21, III-24, III-25, III-31, III-32, III-46, IV-11, IV-13, IV-22**	**I-2, I-14, I-16, I-20, I-29, I-33, I-49, I-83, I-90, II-2, II-7, II-11, II-14, II-20, II-22, II-24, III-3, III-4, III-6, III-8, III-10, III-19, III-20, III-23, III-27, III-30, III-36, III-39, III-40, III-44, III-45, III-49, IV-12**	**I-23, I-92, I-103, II-10, III-5, III-17, IV-24**

IC_{50} (nM)	Greater than 10 μM	Greater than 1 μM to 10 μM	1 μM to 100 nM	Less than 100 nM
B cell proliferation EC_{50} (nM)		**I-99, I-100**	**I-6, I-27, I-52, I-95, I-98, III-46**	**I-2, I-4, I-14, I-16, I-18, I-20, I-21, I-23, I-24, I-25, I-33, I-38, I-40, I-41, I-42, I-43, I-48, I-49, I-50, I-51, I-57, I-58, I-59, I-63, I-70, I-73, I-74, I-75, I-76, I-78, I-79, I-80, I-81, I-82, I-83, I-84, I-85, I-86, I-87, I-88, I-89, I-90, I-91, I-96, I-97, I-101, II-2, II-4, II-5, II-7, II-9, II-10, II-11, II-14, II-17, II-18, II-30, II-45, II-49, II-50, III-3, III-4, III-5, III-6, III-8, III-10, III-11, III-12, III-13, III-15, III-17, III-27, III-30, III-31, III-36, III-39, III-41, III-42, III-44, III-45, III-49, IV-2, IV-11, IV-22, IV-24**

Table 4. Structures of the Compounds for the IC_{50} results described in Table 3 above.

Structure				
 Compound I-**2**	 Compound I-**4**	 Compound I-**6**	 Compound I-**14**	 Compound I-**16**
 Compound I-**18**	 Compound I-**20**	 Compound I-**21**	 Compound I-**23**	 Compound I-**24**
 Compound I-**25**	 Compound I-**27**	 Compound I-**29**	 Compound I-**30**	 Compound I-**33**
 Compound I-**35**	 Compound I-**36**	 Compound I-**37**	 Compound I-**38**	 Compound I-**39**
 Compound I-**40**	 Compound I-**41**	 Compound I-**42**	 Compound I-**43**	 Compound I-**44**

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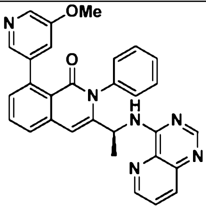
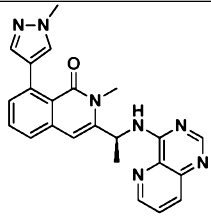
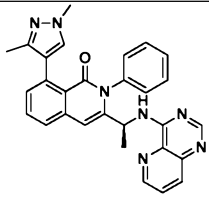
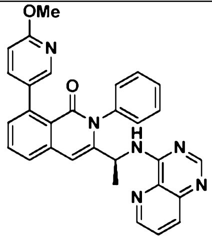
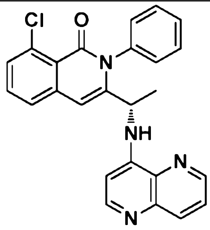
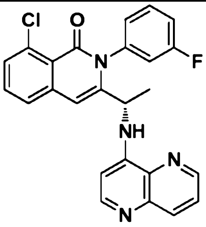
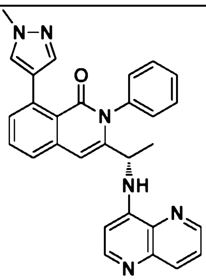
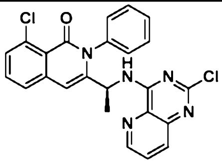
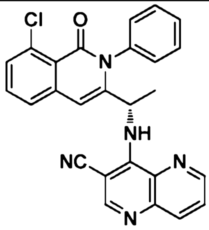
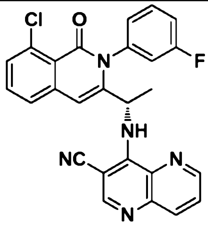
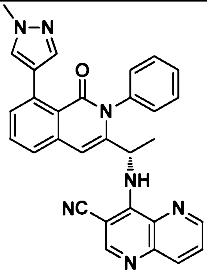
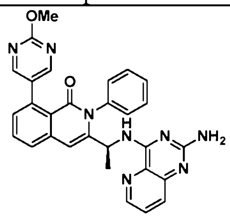
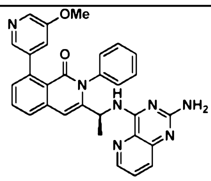
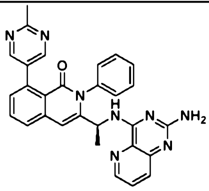
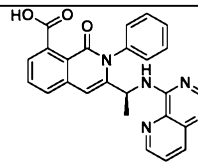
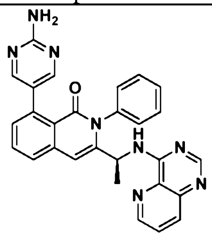
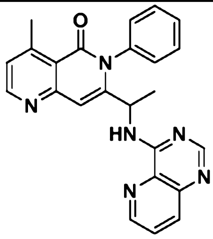
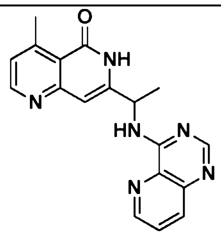
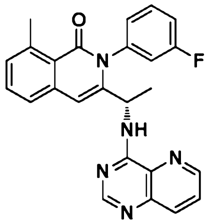
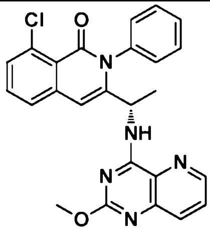
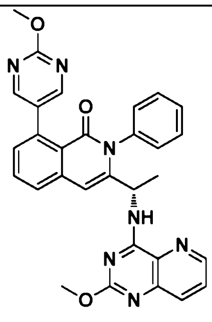
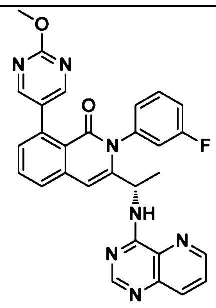
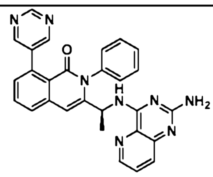
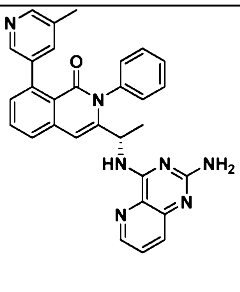
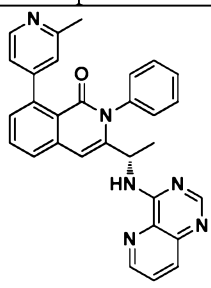
 Compound I-**45**	 Compound I-**46**	 Compound I-**47**	 Compound I-**48**	 Compound I-**49**
 Compound I-**50**	 Compound I-**51**	 Compound I-**52**	 Compound I-**53**	 Compound I-**54**
 Compound I-**55**	 Compound I-**57**	 Compound I-**58**	 Compound I-**59**	 Compound I-**62**
 Compound I-**63**	 Compound I-**65**	 Compound I-**68**	 Compound I-**70**	 Compound I-**71**
 Compound I-**72**	 Compound I-**73**	 Compound I-**74**	 Compound I-**75**	 Compound I-**76**

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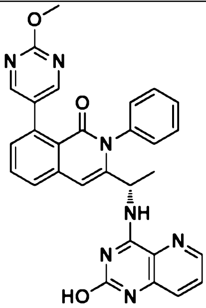
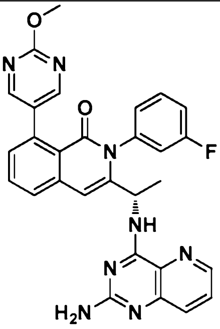
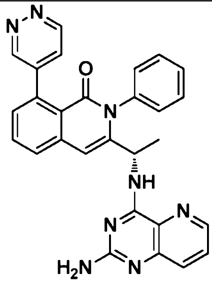
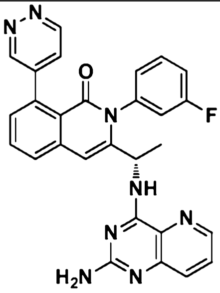
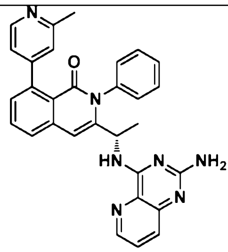
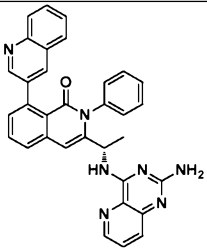
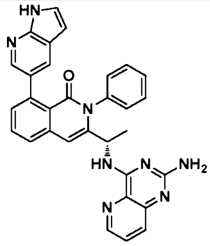
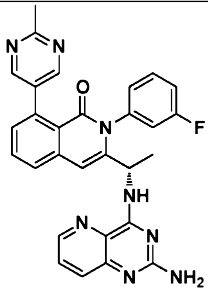
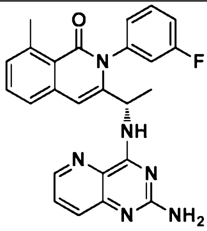
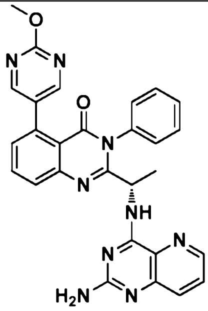
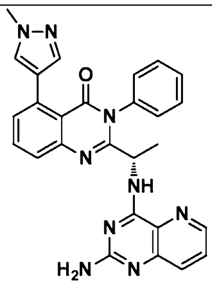
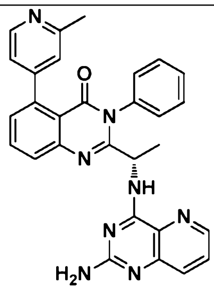
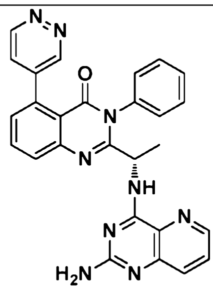
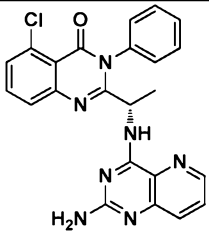
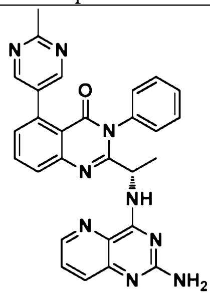
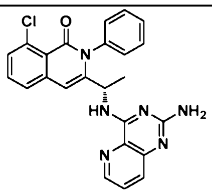
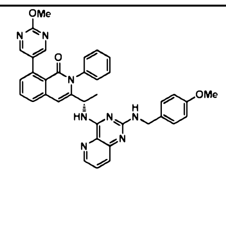
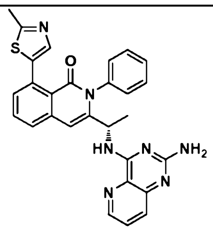
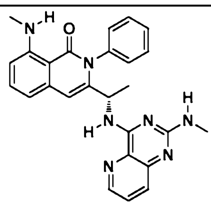
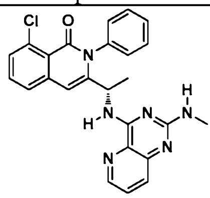
 Compound I-**77**	 Compound I-**78**	 Compound I-**79**	 Compound I-**80**	 Compound I-**81**
 Compound I-**82**	 Compound I-**83**	 Compound I-**84**	 Compound I-**85**	 Compound I-**86**
 Compound I-**87**	 Compound I-**88**	 Compound I-**89**	 Compound I-**90**	 Compound I-**91**
 Compound I-**92**	 Compound I-**93**	 Compound I-**94**	 Compound I-**95**	 Compound I-**96**

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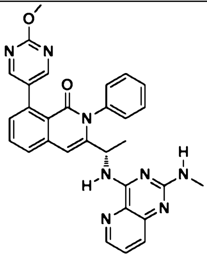
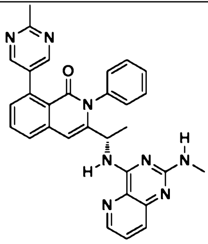
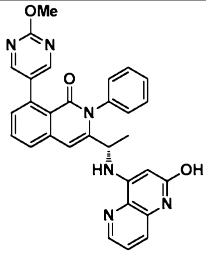
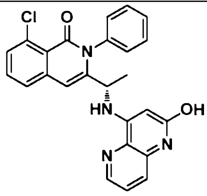
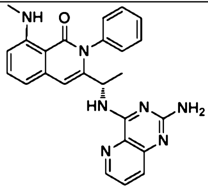
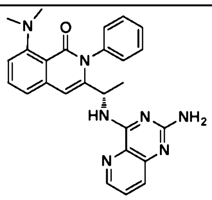
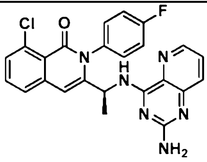
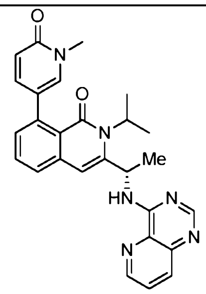
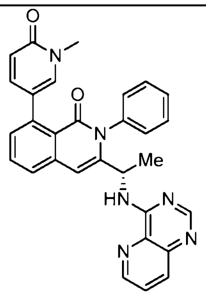
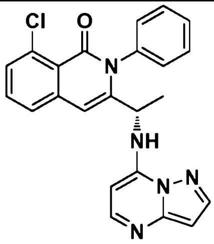
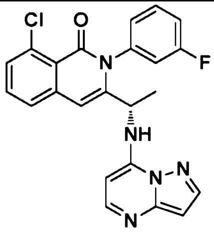
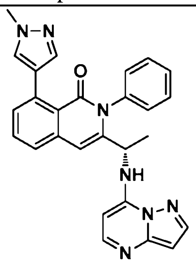
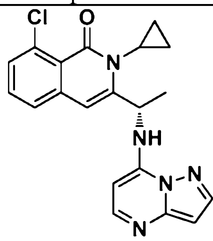
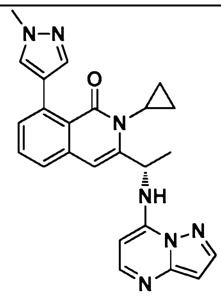
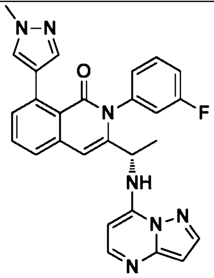
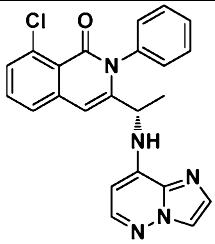
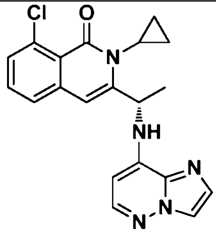
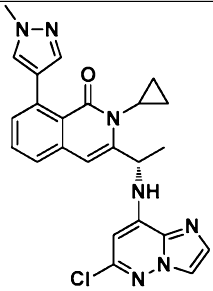
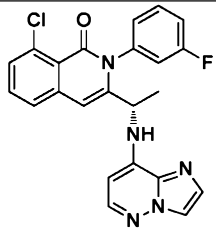
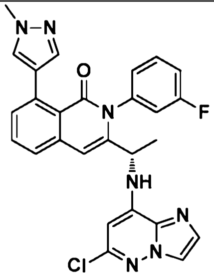
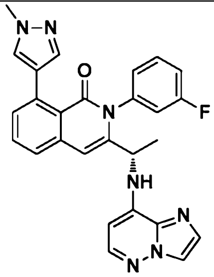
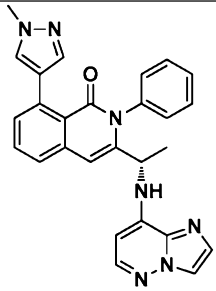
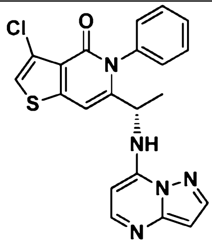
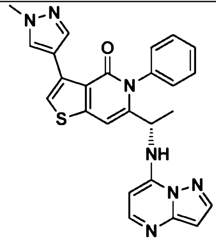
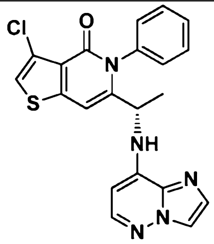
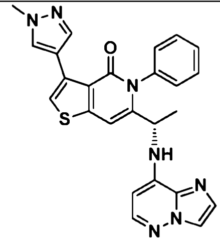
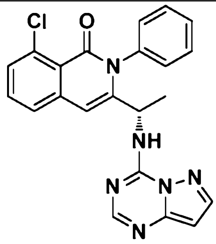
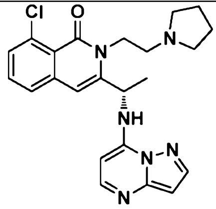
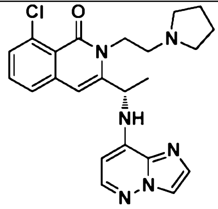
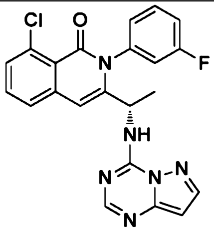
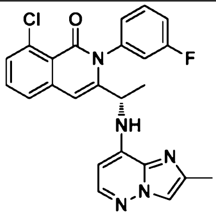
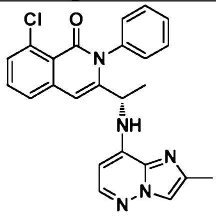
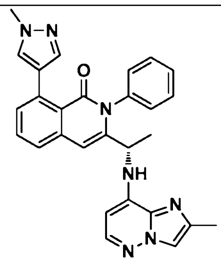
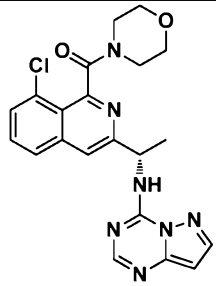
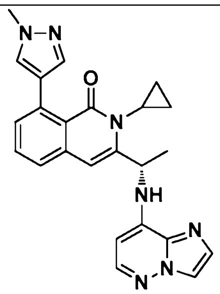
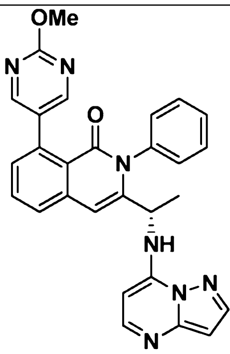
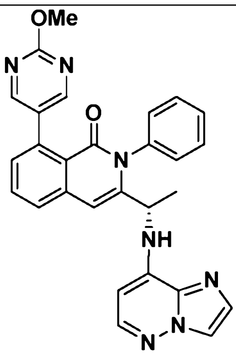
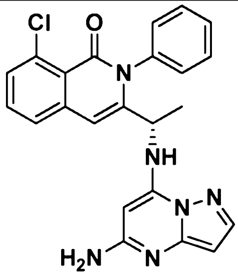
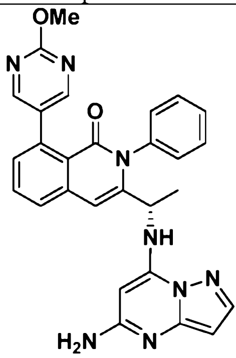
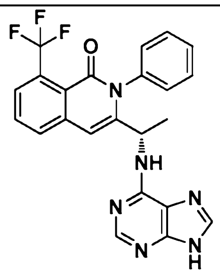
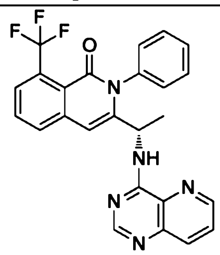
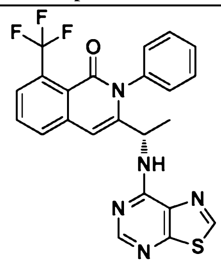
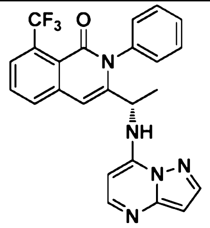
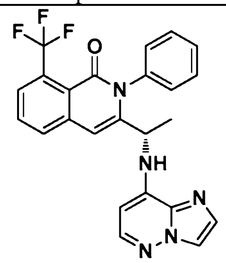
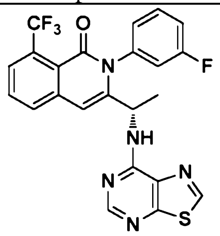
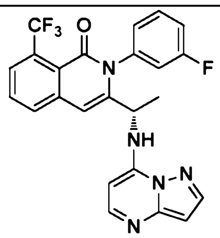
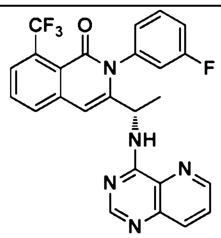
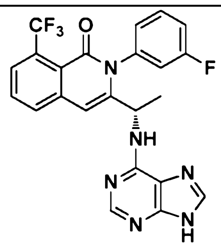
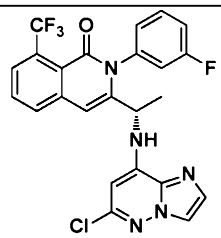
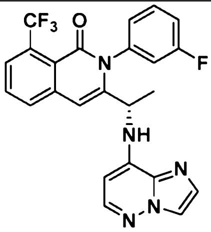
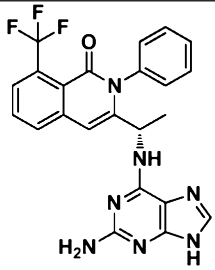
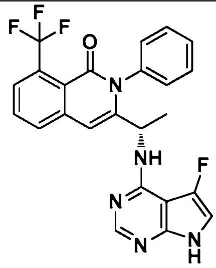
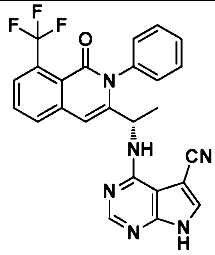
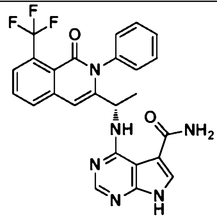
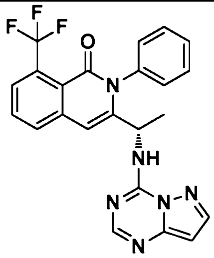
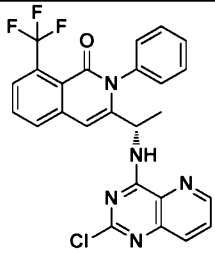
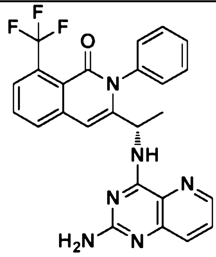
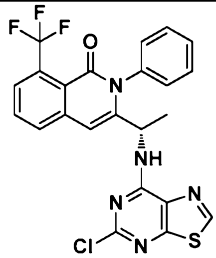
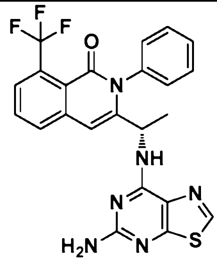
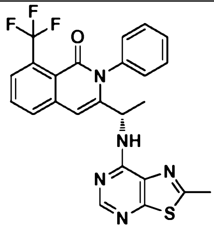
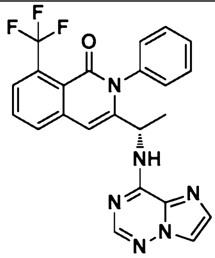
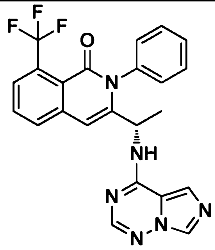
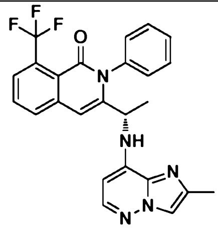
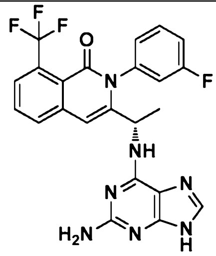
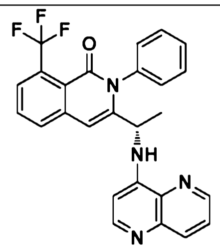
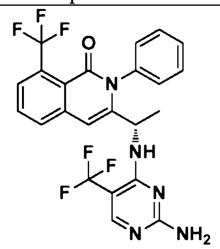
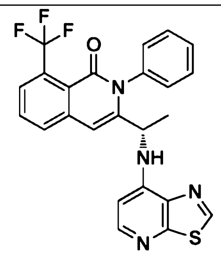
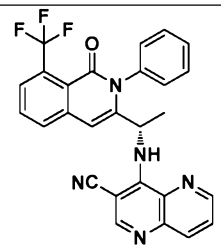
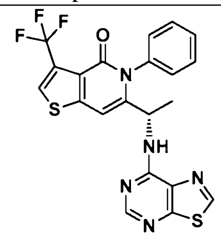
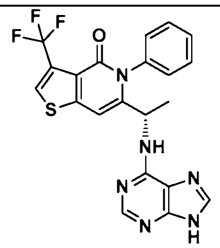
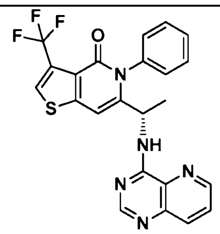
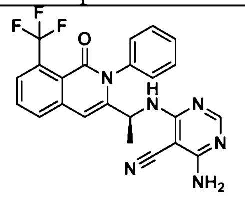
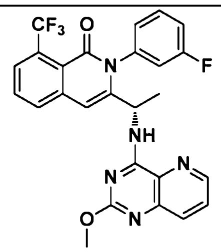
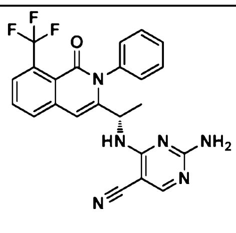
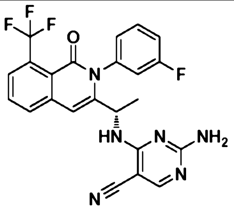
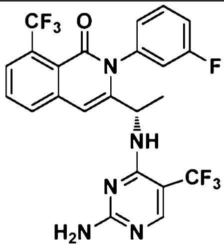
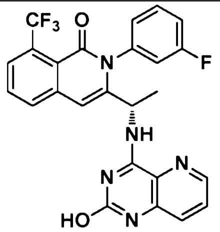
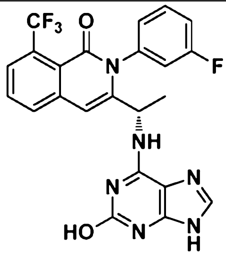
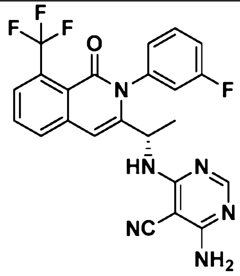
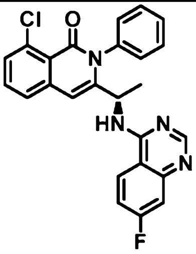
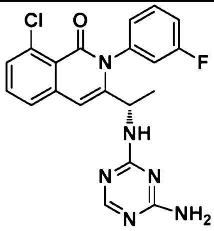
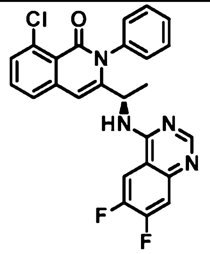
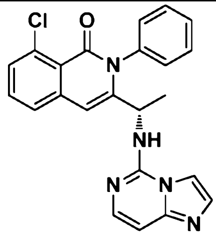
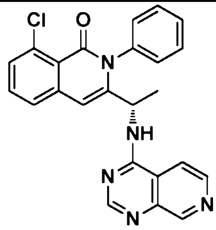
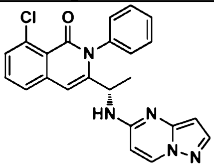
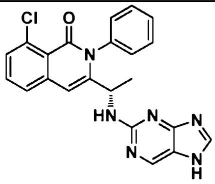
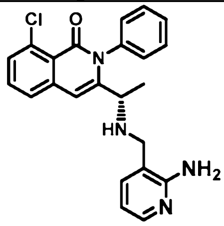
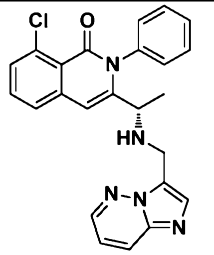
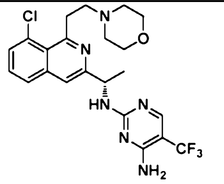
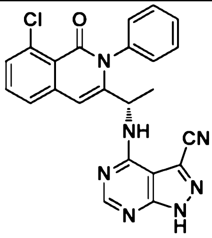
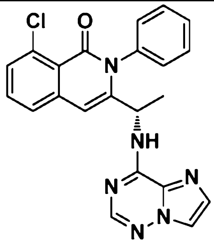
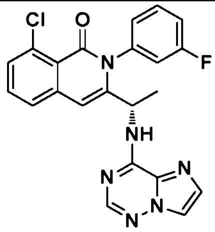
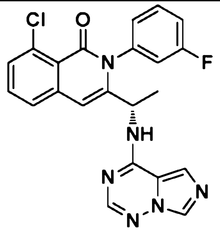
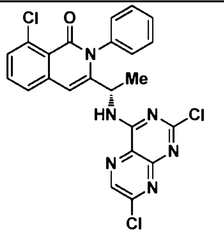
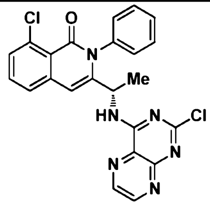
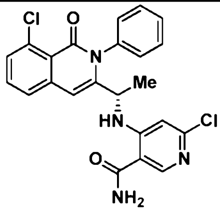
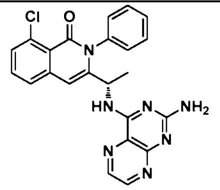
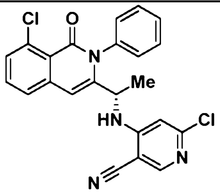
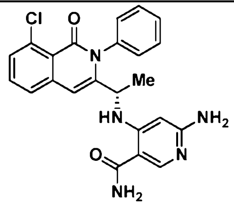
 Compound I-**97**	 Compound I-**98**	 Compound I-**99**	 Compound I-**100**	 Compound I-**101**
 Compound I-**102**	 Compound I-**103**	 Compound **I-106**	 Compound **I-107**	
 Compound II-**2**	 Compound II-**4**	 Compound II-**5**	 Compound II-**7**	 Compound II-**8**
 Compound II-**9**	 Compound II-**10**	 Compound II-**11**	 Compound II-**13**	 Compound II-**14**
 Compound II-**16**	 Compound II-**17**	 Compound II-**18**	 Compound II-**20**	 Compound II-**21**

Structure				
 Compound II-**22**	 Compound II-**23**	 Compound II-**24**	 Compound II-**28**	 Compound II-**29**
 Compound II-**30**	 Compound II-**31**	 Compound II-**32**	 Compound II-**33**	 Compound II-**44**
 Compound II-**45**	 Compound **II-47**	 Compound **II-48**	 Compound **II-49**	 Compound **II-50**
 Compound III-**3**	 Compound III-**4**	 Compound III-**5**	 Compound III-**6**	 Compound III-**8**
 Compound III-**10**	 Compound III-**11**	 Compound III-**12**	 Compound III-**13**	 Compound III-**14**

Structure				
 Compound III-**15**	 Compound III-**17**	 Compound III-**18**	 Compound III-**19**	 Compound III-**20**
 Compound III-**21**	 Compound III-**22**	 Compound III-**23**	 Compound III-**24**	 Compound III-**25**
 Compound III-**26**	 Compound III-**27**	 Compound III-**28**	 Compound III-**29**	 Compound III-**30**
 Compound III-**31**	 Compound III-**32**	 Compound III-**36**	 Compound III-**37**	 Compound III-**39**
 Compound III-**40**	 Compound III-**41**	 Compound III-**42**	 Compound III-**43**	 Compound III-**44**

Structure				
 Compound III-**45**	 Compound III-**46**	 Compound III-**47**	 Compound **III-48**	 Compound **III-49**
 Compound **IV-1**	 Compound **IV-2**	 Compound **IV-3**	 Compound **IV-4**	 Compound **IV-5**
 Compound **IV-6**	 Compound **IV-7**	 Compound **IV-8**	 Compound **IV-9**	 Compound **IV-10**
 Compound **IV-11**	 Compound **IV-12**	 Compound **IV-13**	 Compound **IV-14**	 Compound **IV-19**
 Compound **IV-20**	 Compound **IV-21**	 Compound **IV-22**	 Compound **IV-23**	 Compound **IV-24**

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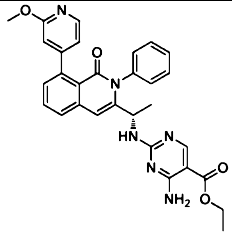
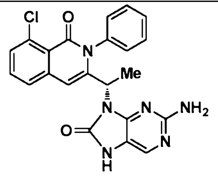
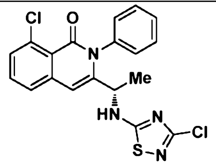
 Compound **IV-25**	 Compound **IV-26**	 Compound **IV-27**		

Biological Activity Assessment

[00961] A PI3-Kinase HTRF® assay kit (cat No. 33-016) purchased from Millipore Corporation was used to screen compounds provided herein. This assay used specific, high affinity binding of the GRP1 pleckstrin homology (PH) domain to PIP3, the product of a Class 1A or 1B PI3 Kinase acting on its physiological substrate PIP2. During the detection phase of the assay, a complex was generated between the GST-tagged PH domain and biotinylated short chain PIP3. The biotinylated PIP3 and the GST-tagged PH domain recruited fluorophores (Streptavidin-Allophycocyanin and Europium-labeled anti-GST respectively) to form the fluorescence resonance energy transfer (FRET) architecture, generating a stable time-resolved FRET signal. The FRET complex was disrupted in a competitive manner by non-biotinylated PIP3, a product formed in the PI3 Kinase assay.

[00962] PI3 Kinase α, β, γ and δ activity was assayed using the PI3 Kinase HTRF® assay kit (catalogue No. 33-016) purchased from Millipore Corporation. Purified recombinant PI3Kα (catalogue No. 14-602-K), PI3Kβ (catalogue No. 14-603-K), PI3Kγ (catalogue No. 14-558-K) and PI3Kδ (catalogue No. 14-604-K) were obtained from Millipore Corporation. Purified recombinant PI3K enzyme was used to catalyze the phosphorylation of phosphatidylinositol 4,5-bisphosphate (PIP2 at 10 μM) to phosphatidylinositol 3,4,5-trisphosphate (PIP3) in the presence of 10 μM ATP. The assay was carried out in 384-well format and detected using a Perkin Elmer EnVision Xcite Multilabel Reader. Emission ratios were converted into percent inhibitions and imported into GraphPad Prism software. The concentration necessary to achieve inhibition of enzyme activity by 50% (IC_{50}) was calculated using concentrations ranging from 20 μM to 0.1 nM (12-point curve). IC_{50} values were determined using a nonlinear regression model available in GraphPad Prism 5.

Example 173: Chemical Stability

[00963] The chemical stability of one or more subject compounds is determined according to standard procedures known in the art. The following details an exemplary procedure for ascertaining chemical stability of a subject compound. The default buffer used for the chemical stability assay is phosphate-buffered saline (PBS) at pH 7.4; other suitable buffers can be used. A subject compound is added from a 100 μM stock solution to an aliquot of PBS (in duplicate) to give a final assay volume of 400 μL, containing 5 μM test compound and 1% DMSO (for half-life determination a total sample volume of 700 μL is prepared). Reactions are incubated, with shaking, for 24 hours at 37ºC; for half-life determination samples are incubated for 0, 2, 4, 6, and 24 hours. Reactions are stopped by adding immediately 100 μL of the incubation mixture to 100 μL of acetonitrile and

vortexing for 5 minutes. The samples are then stored at -20°C until analysis by HPLC-MS/MS. Where desired, a control compound or a reference compound such as chlorambucil (5 μM) is tested simultaneously with a subject compound of interest, as this compound is largely hydrolyzed over the course of 24 hours. Samples are analyzed via (RP)HPLC-MS/MS using selected reaction monitoring (SRM). The HPLC conditions consist of a binary LC pump with autosampler, a mixed-mode, C12, 2 x 20 mm column, and a gradient program. Peak areas corresponding to the analytes are recorded by HPLC-MS/MS. The ratio of the parent compound remaining after 24 hours relative to the amount remaining at time zero, expressed as percent, is reported as chemical stability. In case of half-life determination, the half-life is estimated from the slope of the initial linear range of the logarithmic curve of compound remaining (%) vs. time, assuming first order kinetics.

Example 174: Expression and Inhibition Assays of p110α/p85α, p110β/p85α, p110δ/p85α, and p110γ:

[00964] Class I PI3-Ks can be either purchased (p110α/p85α, p110β/p85α, p110δ/p85α from Upstate, and p110γ from Sigma) or expressed as previously described (Knight et al., 2004). IC_{50} values are measured using either a standard TLC assay for lipid kinase activity (described below) or a high-throughput membrane capture assay. Kinase reactions are performed by preparing a reaction mixture containing kinase, inhibitor (2% DMSO final concentration), buffer (25 mM HEPES, pH 7.4, 10 mM MgCl2), and freshly sonicated phosphatidylinositol (100 μg/ml). Reactions are initiated by the addition of ATP containing 10 μCi of γ-32P-ATP to a final concentration of 10 or 100 μM and allowed to proceed for 5 minutes at room temperature. For TLC analysis, reactions are then terminated by the addition of 105 μl 1N HCl followed by 160 μl $CHCl_3$:MeOH (1:1). The biphasic mixture is vortexed, briefly centrifuged, and the organic phase is transferred to a new tube using a gel loading pipette tip precoated with $CHCl_3$. This extract is spotted on TLC plates and developed for 3 – 4 hours in a 65:35 solution of n-propanol:1M acetic acid. The TLC plates are then dried, exposed to a phosphorimager screen (Storm, Amersham), and quantitated. For each compound, kinase activity is measured at 10 – 12 inhibitor concentrations representing two-fold dilutions from the highest concentration tested (typically, 200 μM). For compounds showing significant activity, IC_{50} determinations are repeated two to four times, and the reported value is the average of these independent measurements.

[00965] Other commercial kits or systems for assaying PI3-K activities are available. The commercially available kits or systems can be used to screen for inhibitors and/or agonists of PI3-Ks including, but not limited to, PI 3-Kinase α, β, δ, and γ. An exemplary system is PI 3-Kinase (human) HTRF™ Assay from Upstate. The assay can be carried out according to the procedures suggested by the manufacturer. Briefly, the assay is a time resolved FRET assay that indirectly measures PIP3 product formed by the activity of a PI3-K. The kinase reaction is performed in a microtiter plate (*e.g.,* a 384 well microtiter plate). The total reaction volume is approximately 20 μl per well. In the first step, each well receives 2 μl of test compound in 20% dimethylsulphoxide resulting in a 2% DMSO final concentration. Next, approximately 14.5 μl of a kinase/PIP2 mixture (diluted in 1X reaction buffer) is added per well for a final concentration of 0.25-0.3 μg/ml kinase and 10 μM PIP2. The plate is sealed and incubated for 15 minutes at room temperature. To start the reaction, 3.5 μl of ATP (diluted in 1X reaction buffer) is added per well for a final concentration of 10 μM ATP. The plate is sealed and incubated for 1

hour at room temperature. The reaction is stopped by adding 5 µl of Stop Solution per well and then 5 µl of Detection Mix is added per well. The plate is sealed, incubated for 1 hour at room temperature, and then read on an appropriate plate reader. Data is analyzed and IC_{50}s are generated using GraphPad Prism 5.

Example 175: B Cell Activation and Proliferation Assay

[00966] The ability of one or more subject compounds to inhibit B cell activitation and proliferation is determined according to standard procedures known in the art. For example, an *in vitro* cellular proliferation assay is established that measures the metabolic activity of live cells. The assay is performed in a 96 well microtiter plate using Alamar Blue reduction. Balb/c splenic B cells are purified over a Ficoll-Paque™ PLUS gradient followed by magnetic cell separation using a MACS B cell Isolation Kit (Miletenyi). Cells are plated in 90 µl at 50,000 cells/well in B Cell Media (RPMI + 10% FBS + Penn/Strep + 50 µM bME + 5 mM HEPES). A compound provided herein is diluted in B Cell Media and added in a 10 µl volume. Plates are incubated for 30 min at 37 °C and 5% CO_2 (0.2% DMSO final concentration). A 50 µl B cell stimulation cocktail is then added containing either 10 µg/ml LPS or 5 µg/ml F(ab')2 Donkey anti-mouse IgM plus 2ng/ml recombinant mouse IL4 in B Cell Media. Plates are incubated for 72 hours at 37 ^{0}C and 5% CO_2. A volume of 15 µL of Alamar Blue reagent is added to each well and plates are incubated for 5 hours at 37 ^{0}C and 5% CO_2. Alamar Blue fluoresce is read at 560Ex/590Em, and IC_{50} or EC_{50} values are calculated using GraphPad Prism 5.

Example 176: Tumor Cell Line Proliferation Assay

[00967] The ability of one or more subject compounds to inhibit tumor cell line proliferation can be determined according to standard procedures known in the art. For instance, an *in vitro* cellular proliferation assay can be performed to measure the metabolic activity of live cells. The assay is performed in a 96 well microtiter plate using Alamar Blue reduction. Human tumor cell lines are obtained from ATCC (*e.g.,* MCF7, U-87 MG, MDA-MB-468, PC-3), grown to confluency in T75 flasks, trypsinized with 0.25% trypsin, washed one time with Tumor Cell Media (DMEM + 10%FBS), and plated in 90 µl at 5,000 cells/well in Tumor Cell Media. A compound provided herein is diluted in Tumor Cell Media and added in a 10 µl volume. Plates are incubated for 72 hours at 37 ^{0}C and 5% CO_2. A volume of 10 µL of Alamar Blue reagent is added to each well and plates are incubated for 3 hours at 37 ^{0}C and 5% CO_2. Alamar Blue fluoresce is read at 560Ex/590Em, and IC_{50} values are calculated using GraphPad Prism 5.

Example 177: Antitumor Activity *in vivo*

[00968] The compounds described herein can be evaluated in a panel of human and murine tumor models.

<u>Paclitaxel-refractory Tumor Models</u>

1. Clinically-derived Ovarian Carcinoma Model.

[00969] This tumor model is established from a tumor biopsy of an ovarian cancer patient. Tumor biopsy is taken from the patient. The compounds described herein are administered to nude mice bearing staged tumors using an every 2 days x 5 schedule.

2. A2780Tax Human Ovarian Carcinoma Xenograft (Mutated Tubulin).

[00970] A2780Tax is a paclitaxel-resistant human ovarian carcinoma model. It is derived from the sensitive parent A2780 line by co-incubation of cells with paclitaxel and verapamil, an MDR-reversal agent. Its resistance mechanism has been shown to be non-MDR related and is attributed to a mutation in the gene encoding the beta-tubulin protein. The compounds described herein can be administered to mice bearing staged tumors on an every 2 days x 5 schedule.

3. HCT116/VM46 Human Colon Carcinoma Xenograft (Multi-Drug Resistant).

[00971] HCT116/VM46 is an MDR-resistant colon carcinoma developed from the sensitive HCT116 parent line. *In vivo*, grown in nude mice, HCT116/VM46 has consistently demonstrated high resistance to paclitaxel. The compounds described herein can be administered to mice bearing staged tumors on an every 2 days x 5 schedule.

4. M5076 Murine Sarcoma Model

[00972] M5076 is a mouse fibrosarcoma that is inherently refractory to paclitaxel *in vivo*. The compounds described herein can be administered to mice bearing staged tumors on an every 2 days x 5 schedule.

[00973] One or more compounds as provided herein can be used in combination other therapeutic agents *in vivo* in the multidrug resistant human colon carcinoma xenografts HCT/VM46 or any other model known in the art including those described herein.

Example 178: Microsome stability assay

[00974] The stability of one or more subject compounds is determined according to standard procedures known in the art. For example, stability of one or more subject compounds is established by an *in vitro* assay. For example, an *in vitro* microsome stability assay is established that measures stability of one or more subject compounds when reacting with mouse, rat or human microsomes from liver. The microsome reaction with compounds is performed in 1.5 mL Eppendorf tube. Each tube contains 0.1 μL of 10.0 mg/ml NADPH; 75 μL of 20.0 mg/ml mouse, rat or human liver microsome; 0.4 μL of 0.2 M phosphate buffer, and 425 μL of ddH_2O. Negative control (without NADPH) tube contains 75 μL of 20.0 mg/ml mouse, rat or human liver microsome; 0.4 μL of 0.2 M phosphate buffer, and 525 μL of ddH_2O. The reaction is started by adding 1.0 μL of 10.0 mM tested compound. The reaction tubes are incubated at 37°C. 100 μL sample is collected into new Eppendorf tube containing 300 μL cold methanol at 0, 5, 10, 15, 30 and 60 minutes of reaction. Samples are centrifuged at 15,000 rpm to remove protein. Supernatant of centrifuged sample is transferred to new tube. Concentration of stable compound after reaction with microsome in the supernatant is measured by Liquid Chromatography/Mass Spectrometry (LC-MS).

Example 179: Plasma stability assay

[00975] The stability of one or more subject compounds in plasma is determined according to standard procedures known in the art. *See, e.g., Rapid Commun. Mass Spectrom.*, 10: 1019-1026. The following procedure is an HPLC-MS/MS assay using human plasma; other species including monkey, dog, rat, and mouse are also available. Frozen, heparinized human plasma is thawed in a cold water bath and spun for 10 minutes at 2000 rpm at 4 ºC prior to use. A subject compound is added from a 400 μM stock solution to an aliquot of pre-warmed plasma to give a final assay volume of 400 μL (or 800 μL for half-life determination), containing 5 μM test compound and 0.5 % DMSO. Reactions are incubated, with shaking, for 0 minutes and 60 minutes at 37 ºC, or for 0, 15, 30, 45 and 60 minutes at 37 C for half life determination. Reactions are stopped by transferring 50 μL of the incubation mixture to 200 μL of ice-cold acetonitrile and mixed by shaking for 5 minutes. The samples are centrifuged at 6000 x g for 15 minutes at 4ºC and 120 μL of supernatant removed into clean tubes. The samples are then evaporated to dryness and submitted for analysis by HPLC-MS/MS.

[00976] In one embodiment, one or more control or reference compounds (5 μM) are tested simultaneously with the test compounds: one compound, propoxycaine, with low plasma stability and another compound, propantheline, with intermediate plasma stability.

[00977] Samples are reconstituted in acetonitrile/methanol/water (1/1/2, v/v/v) and analyzed via (RP)HPLC-MS/MS using selected reaction monitoring (SRM). The HPLC conditions consist of a binary LC pump with autosampler, a mixed-mode, C12, 2 x 20 mm column, and a gradient program. Peak areas corresponding to the analytes are recorded by HPLC-MS/MS. The ratio of the parent compound remaining after 60 minutes relative to the amount remaining at time zero, expressed as percent, is reported as plasma stability. In case of half-life determination, the half-life is estimated from the slope of the initial linear range of the logarithmic curve of compound remaining (%) vs. time, assuming first order kinetics.

Example 180: Kinase Signaling in Blood

[00978] PI3K/ Akt /mTor signaling is measured in blood cells using the phosflow method (*Methods Enzymol.* (2007) 434:131-54). This method is by nature a single cell assay so that cellular heterogeneity can be detected rather than population averages. This allows concurrent dinstinction of signaling states in different populations defined by other markers. Phosflow is also highly quantitative. To test the effects of one or more compounds provided herein, unfractionated splenocytes, or peripheral blood mononuclear cells are stimulated with anti-CD3 to initiate T-cell receptor signaling. The cells are then fixed and stained for surface markers and intracellular phosphoproteins. Inhibitors provided herein inhibit anti-CD3 mediated phosphorylation of Akt -S473 and S6, whereas rapamycin inhibits S6 phosphorylation and enhances Akt phosphorylation under the conditions tested.

[00979] Similarly, aliquots of whole blood are incubated for 15 minutes with vehicle (*e.g.,* 0.1% DMSO) or kinase inhibitors at various concentrations, before addition of stimuli to crosslink the T cell receptor (TCR) (anti-CD3 with secondary antibody) or the B cell receptor (BCR) using anti-kappa light chain antibody (Fab'2 fragments). After approximately 5 and 15 minutes, samples are fixed (*e.g.,* with cold 4% paraformaldehyde)

and used for phosflow. Surface staining is used to distinguish T and B cells using antibodies directed to cell surface markers that are known to the art. The level of phosphorylation of kinase substrates such as Akt and S6 are then measured by incubating the fixed cells with labeled antibodies specific to the phosphorylated isoforms of these proteins. The population of cells are then analyzed by flow cytometry.

Example 181: Colony Formation Assay

[00980] Murine bone marrow cells freshly transformed with a p190 BCR-Abl retrovirus (herein referred to as p190 transduced cells) are plated in the presence of various drug combinations in M3630 methylcellulose media for about 7 days with recombinant human IL-7 in about 30% serum, and the number of colonies formed is counted by visual examination under a microscope.

[00981] Alternatively, human peripheral blood mononuclear cells are obtained from Philadelphia chromosome positive (Ph+) and negative (Ph-) patients upon initial diagnosis or relapse. Live cells are isolated and enriched for CD19+ CD34+ B cell progenitors. After overnight liquid culture, cells are plated in methocult GF+ H4435, Stem Cell Technologies) supplemented with cytokines (IL-3, IL-6, IL-7, G-CSF, GM-CSF, CF, Flt3 ligand, and erythropoietin) and various concentrations of known chemotherapeutic agents in combination with either compounds of the present disclosure. Colonies are counted by microscopy 12-14 days later. This method can be used to test for evidence of additive or synergistic activity.

Example 182: *In Vivo* Effect of Kinase Inhibitors on Leukemic Cells

[00982] Female recipient mice are lethally irradiated from a γ source in two doses about 4 hr apart, with approximately 5Gy each. About 1 hr after the second radiation dose, mice are injected i.v. with about $1x10^6$ leukemic cells (*e.g.*, Ph+ human or murine cells, or p190 transduced bone marrow cells). These cells are administered together with a radioprotective dose of about $5x10^6$ normal bone marrow cells from 3-5 week old donor mice. Recipients are given antibiotics in the water and monitored daily. Mice who become sick after about 14 days are euthanized and lymphoid organs are harvested for analysis. Kinase inhibitor treatment begins about 10 days after leukemic cell injection and continues daily until the mice become sick or a maximum of approximately 35 days post-transplant. Inhibitors are given by oral lavage.

[00983] Peripheral blood cells are collected approximately on day 10 (pre-treatment) and upon euthanization (post treatment), contacted with labeled anti-hCD4 antibodies and counted by flow cytometry. This method can be used to demonstrate that the synergistic effect of one or more compounds provided herein in combination with known chemotherapeutic agents can reduce leukemic blood cell counts as compared to treatment with known chemotherapeutic agents (*e.g.*, Gleevec) alone under the conditions tested.

Example 183: Treatment of Lupus Disease Model Mice

[00984] Mice lacking the inhibitory receptor FcγRIIb that opposes PI3K signaling in B cells develop lupus with high penetrance. FcγRIIb knockout mice (R2KO, Jackson Labs) are considered a valid model of the

human disease as some lupus patients show decreased expression or function of FcγRIIb (S. Bolland and J.V. Ravtech 2000. *Immunity* 12:277-285).

[00985] The R2KO mice develop lupus-like disease with anti-nuclear antibodies, glomerulonephritis and proteinurea within about 4-6 months of age. For these experiments, the rapamycin analogue RAD001 (available from LC Laboratories) is used as a benchmark compound, and administered orally. This compound has been shown to ameliorate lupus symptoms in the B6.Sle1z.Sle3z model (T. Wu et al. *J. Clin Invest*. 117:2186-2196).

[00986] The NZB/W F1 mice spontaniously develop a systemic autoimmune disease with that is a model of lupus. The mice are treated starting at 20 weeks of age for a profilactic model and at 23 weeks of age for a therapeutic model. Blood and urine samples are obtained at approximately throughout the testing period, and tested for antinuclear antibodies (in dilutions of serum) or protein concentration (in urine). Serum is also tested for anti-ssDNA and anti-dsDNA antibodies by ELISA.. Glomerulonephritis is assessed in kidney sections stained with H&E at the end of the study, or survival can be an endpoint. For example, tThe proteozome inhibitor Bortezimib is effective at blocking disease in the NZB/W model in both the profilactic and therapeuctic model with reductions in auto-antibody production, kidney damage, and improvements in survival (*Nature Medicine* 14, 748 - 755 (2008)).

[00987] Lupus disease model mice such as R2KO, BXSB or MLR/lpr are treated at about 2 months old, approximately for about two months. Mice are given doses of: vehicle, RAD001 at about 10 mg/kg, or compounds provided herein at approximately 1 mg/kg to about 500 mg/kg. Blood and urine samples are obtained at approximately throughout the testing period, and tested for antinuclear antibodies (in dilutions of serum) or protein concentration (in urine). Serum is also tested for anti-ssDNA and anti-dsDNA antibodies by ELISA. Animals are euthanized at day 60 and tissues harvested for measuring spleen weight and kidney disease. Glomerulonephritis is assessed in kidney sections stained with H&E. Other animals are studied for about two months after cessation of treatment, using the same endpoints.

[00988] This established art model can be employed to demonstrate that the kinase inhibitors provided herein can suppress or delay the onset of lupus symptoms in lupus disease model mice.

Example 184: Murine Bone Marrow Transplant Assay

[00989] Female recipient mice are lethally irradiated from a γ ray source. About 1hr after the radiation dose, mice are injected with about 1x106 leukemic cells from early passage p190 transduced cultures (*e.g.*, as described in *Cancer Genet Cytogenet*. 2005 Aug;161(1):51-6) . These cells are administered together with a radioprotective dose of approximately $5x10^6$ normal bone marrow cells from 3-5wk old donor mice. Recipients are given antibiotics in the water and monitored daily. Mice who become sick after about 14 days are euthanized and lymphoid organs harvested for flow cytometry and/or magnetic enrichment. Treatment begins on approximately day 10 and continues daily until mice become sick, or after a maximum of about 35 days post-transplant. Drugs are given by oral gavage (p.o.). In a pilot experiment a dose of chemotherapeutic that is not curative but delays leukemia onset by about one week or less is identified; controls are vehicle-treated or treated with chemotherapeutic agent, previously shown to delay but not cure leukemogenesis in this model (*e.g.*, imatinib at about 70mg/kg twice daily). For the first phase p190 cells that express eGFP are used, and postmortem analysis is limited to enumeration of the

percentage of leukemic cells in bone marrow, spleen and lymph node (LN) by flow cytometry. In the second phase, p190 cells that express a tailless form of human CD4 are used and the postmortem analysis includes magnetic sorting of hCD4+ cells from spleen followed by immunoblot analysis of key signaling endpoints: p Akt -T308 and S473; pS6 and p4EBP-1. As controls for immunoblot detection, sorted cells are incubated in the presence or absence of kinase inhibitors of the present disclosure inhibitors before lysis. Optionally, "phosflow" is used to detect p Akt -S473 and pS6-S235/236 in hCD4-gated cells without prior sorting. These signaling studies are particularly useful if, for example, drug-treated mice have not developed clinical leukemia at the 35 day time point. Kaplan-Meier plots of survival are generated and statistical analysis done according to methods known in the art. Results from p190 cells are analyzed separated as well as cumulatively.

[00990] Samples of peripheral blood (100-200μl) are obtained weekly from all mice, starting on day 10 immediately prior to commencing treatment. Plasma is used for measuring drug concentrations, and cells are analyzed for leukemia markers (eGFP or hCD4) and signaling biomarkers as described herein.

[00991] This general assay known in the art can be used to demonstrate that effective therapeutic doses of the compounds provided herein can be used for inhibiting the proliferation of leukemic cells.

Example 185: Matrigel Plug Angiogenesis Assay

[00992] Matrigel containing test compounds are injected subcutaneously or intraocularly, where it solidifies to form a plug. The plug is recovered after 7–21 days in the animal and examined histologically to determine the extent to which blood vessels have entered it. Angiogenesis is measured by quantification of the vessels in histologic sections. Alternatively, fluorescence measurement of plasma volume is performed using fluorescein isothiocyanate (FITC)-labeled dextran 150. The results are expected to indicate one or more compounds provided herein that inhibit angiogenesis and are thus expected to be useful in treating ocular disorders related to aberrant angiogenesis and/or vascular permeability.

Example 186: Corneal Angiogenesis Assay

[00993] A pocket is made in the cornea, and a plug containing an angiogenesis inducing formulation (*e.g.,* VEGF, FGF, or tumor cells), when introduced into this pocket, elicits the ingrowth of new vessels from the peripheral limbal vasculature. Slow-release materials such as ELVAX (ethylene vinyl copolymer) or Hydron are used to introduce angiogenesis inducing substances into the corneal pocket. Alternatively, a sponge material is used.

[00994] The effect of putative inhibitors on the locally induced (*e.g.,* sponge implant) angiogenic reaction in the cornea (*e.g.,* by FGF, VEGF, or tumor cells). The test compound is administered orally, systemically, or directly to the eye. Systemic administration is by bolus injection or, more effectively, by use of a sustained-release method such as implantation of osmotic pumps loaded with the test inhibitor. Administration to the eye is by any of the methods described herein including, but not limited to eye drops, topical administration of a cream, emulsion, or gel, intravitreal injection.

[00995] The vascular response is monitored by direct observation throughout the course of the experiment using a stereomicroscope in mice. Definitive visualization of the corneal vasculature is achieved by

administration of fluorochrome-labeled high-molecular weight dextran. Quantification is performed by measuring the area of vessel penetration, the progress of vessels toward the angiogenic stimulus over time, or in the case of fluorescence, histogram analysis or pixel counts above a specific (background) threshold.

[00996] The results can indicate one or more compounds provided herein inhibit angiogenesis and thus can be useful in treating ocular disorders related to aberrant angiogenesis and/or vascular permeability.

Example 187: Microtiter-plate Angiogenesis Assay

[00997] The assay plate is prepared by placing a collagen plug in the bottom of each well with 5-10 cell spheroids per collagen plug each spheroid containing 400-500 cells. Each collagen plug is covered with 1100 µl of storage medium per well and stored for future use (1-3 days at 37°C, 5% CO_2). The plate is sealed with sealing. Test compounds are dissolved in 200 µl assay medium with at least one well including a VEGF positive control and at least one well without VEGF or test compound as a negative control. The assay plate is removed from the incubator and storage medium is carefully pipeted away. Assay medium containing the test compounds are pipeted onto the collagen plug. The plug is placed in a humidified incubator for (37°C, 5% CO_2) 24-48 hours. Angiogenesis is quantified by counting the number of sprouts, measuring average sprout length, or determining cumulative sprout length. The assay can be preserved for later analysis by removing the assay medium, adding 1ml of 10% paraformaldehyde in Hanks BSS per well, and storing at 4°C. The results are expected to identify compounds that inhibit angiogenesis in various cell types tested, including cells of ocular origin.

Example 188: Combination use of PI3K-δ inhibitors and agents that inhibit IgE production or activity

[00998] The compounds as provided herein can present synergistic or additive efficacy when administered in combination with agents that inhibit IgE production or activity. Agents that inhibit IgE production include, for example, one or more of TEI-9874, 2-(4-(6-cyclohexyloxy-2-naphtyloxy)phenylacetamide)benzoic acid, rapamycin, rapamycin analogs (*i.e.,* rapalogs), TORC1 inhibitors, TORC2 inhibitors, and any other compounds that inhibit mTORC1 and mTORC2. Agents that inhibit IgE activity include, for example, anti-IgE antibodies such as Omalizumab and TNX-901.

[00999] One or more of the subject compounds capable of inhibiting PI3K-δ can be efficacious in treatment of autoimmune and inflammatory disorders (AIID), for example, rheumatoid arthritis. If any of the compounds causes an undesired level of IgE production, one can choose to administer it in combination with an agent that inhibits IgE production or IgE activity. Additionally, the administration of PI3K-δ or PI3K-δ/γ inhibitors as provided herein in combination with inhibitors of mTOR can also exhibit synergy through enhanced inhibition of the PI3K pathway. Various *in vivo* and *in vitro* models can be used to establish the effect of such combination treatment on AIID including, but not limited to (a) *in vitro* B-cell antibody production assay, (b) *in vivo* TNP assay, and (c) rodent collagen induced arthritis model.

(a) B-cell Assay

[001000] Mice are euthanized, and the spleens are removed and dispersed through a nylon mesh to generate a single-cell suspension. The splenocytes are washed (following removal of erythrocytes by osmotic shock)

and incubated with anti-CD43 and anti-Mac-1 antibody-conjugated microbeads (Miltenyi Biotec). The bead-bound cells are separated from unbound cells using a magnetic cell sorter. The magnetized column retains the unwanted cells and the resting B cells are collected in the flow-through. Purified B-cells are stimulated with lipopolysaccharide or an anti-CD40 antibody and interleukin 4. Stimulated B-cells are treated with vehicle alone or with PI3K-δ inhibitors as provided herein with and without mTOR inhibitors such as rapamycin, rapalogs, or mTORC1/C2 inhibitors. The results are expected to show that in the presence of mTOR inhibitors (*e.g.,* rapamycin) alone, there is little to no substantial effect on IgG and IgE response. However, in the presence of PI3K-δ and mTOR inhibitors, the B-cells are expected to exhibit a decreased IgG response as compared to the B-cells treated with vehicle alone, and the B-cells are expected to exhibit a decreased IgE response as compared to the response from B-cells treated with PI3K-δ inhibitors alone.

(b) TNP Assay

[001001] Mice are immunized with TNP-Ficoll or TNP-KHL and treated with: vehicle, a PI3K-δ inhibitor, an mTOR inhibitor, for example rapamycin, or a PI3K-δ inhibitor in combination with an mTOR inhibitor such as rapamycin. Antigen-specific serum IgE is measured by ELISA using TNP-BSA coated plates and isotype specific labeled antibodies. It is expected that mice treated with an mTOR inhibitor alone exhibit little or no substantial effect on antigen specific IgG3 response and no statistically significant elevation in IgE response as compared to the vehicle control. It is also expected that mice treated with both PI3K-δ inhibitor and mTOR inhibitor exhibit a reduction in antigen specific IgG3 response as compared to the mice treated with vehicle alone. Additionally, the mice treated with both PI3K-δ inhibitor and mTOR inhibitor exhibit a decrease in IgE response as compared to the mice treated with PI3K-δ inhibitor alone.

(c) Rat Collagen Induced Arthritis Model

[001002] Female Lewis rats are anesthetized and given collagen injections prepared and administered as described previously on day 0. On day 6, animals are anesthetized and given a second collagen injection. Caliper measurements of normal (pre-disease) right and left ankle joints are performed on day 9. On days 10-11, arthritis typically occurs and rats are randomized into treatment groups. Randomization is performed after ankle joint swelling is obviously established and there is good evidence of bilateral disease.

[001003] After an animal is selected for enrollment in the study, treatment is initiated. Animals are given vehicle, PI3K-δ inhibitor, or PI3K-δ inhibitor in combination with rapamycin. Dosing is administered on days 1-6. Rats are weighed on days 1-7 following establishment of arthritis and caliper measurements of ankles taken every day. Final body weights are taken on day 7 and animals are euthanized.

[001004] The combination treatment using a compound as provided herein and rapamycin can provide greater efficacy than treatment with PI3K-δ inhibitor alone.

[001005] Certain compounds provided herein (*e.g.*, Compounds **I-21**, **I-86**, **I-87**, **I-91**, and **III-13**) were tested in the rat Collagen Induced Arthritis Model using procedures substantially similar to those described above, and all of the tested compounds demonstrated EC_{50} values of less than 50 mg/kg.

Example 189: Delayed Type Hypersensitivity Model

[001006] DTH was induced by sensitizing 60 BALB/c male mice on day 0 and day 1 with a solution of 0.05% 2,4 dinitrofluorobenzene (DNFB) in a 4:1 acetone/olive oil mixture. Mice were gently restrained while 20 µL of solution was applied to the hind foot pads of each mouse. The hind foot pads of the mice were used as they represent an anatomical site that can be easily isolated and immobilized without anesthesia. On day 5, mice were administered a single dose of vehicle, a compound provided herein at 10, 3, 1, or 0.3 mg/kg, or dexamethasone at a dose of 5 mg/kg by oral gavage. Thirty minutes later mice were anaesthetized, and a solution of 0.25% DNFB in a 4:1 acetone/olive oil solution was applied to the left inner and outer ear surface. This application resulted in the induction of swelling to the left ear and under these conditions, all animals responded to this treatment with ear swelling. A vehicle control solution of 4:1 acetone/olive oil was applied to the right inner and outer ear. Twenty four hours later, mice were anaesthetized, and measurements of the left and right ear were taken using a digital micrometer. The difference between the two ears was recorded as the amount of swelling induced by the challenge of DNFB. Drug treatment groups were compared to vehicle control to generate the percent reduction in ear swelling. Dexamethasone is routinely used as a positive control as it has broad anti-inflammatory activity.

Example 190: Peptidoglycan-Polysaccharide rat Arthritic Model

(a) *Systemic arthritis model*

[001007] All injections are performed under anesthesia. 60 female Lewis rats (150-170) are anesthetized by inhalation isoflurane using a small animal anesthesia machine. The animals are placed in the induction chamber until anesthetized by delivery of 4-5% isoflurane in O_2 and then held in that state using a nose cone on the procedure table. Maintenance level of isoflurane is at 1-2%. Animals are injected intraperitoneally (i.p.) with a single injection of purified PG-PS 10S Group A, D58 strain (concentration 25µg/g of bodyweight) suspended in sterile 0.85% saline. Each animal receives a total volume of 500 microliters administered in the lower left quadrant of the abdomen using a 1 milliliter syringe with a 23 gauge needle. Placement of the needle is critical to avoid injecting the PG-PS 10S into either the stomach or caecum. Animals are under continuous observation until fully recovered from anesthesia and moving about the cage. An acute response of a sharp increase in ankle measurement, typically 20% above baseline measurement can peak in 3-5 days post injection. Treatment with test compounds can be PO, SC, IV or IP. Rats are dosed no more than two times in a 24 hour time span. Treatment can begin on day 0 or any day after that through day 30. The animals are weighed on days 0, 1, 2, 3, 4, 5, 6, 7 and beginning again on day 12 – 30 or until the study is terminated. Paw/ankle diameter is measured with a digital caliper on the left and right side on day 0 prior to injection and again on day 1, 2, 3, 4, 5, 6 and 7. On day 12, measurements begin again and continue on through day 30. At this time, animals can be anesthetized with isoflurane, as described above, and terminal blood samples can be obtained by tail vein draws for the evaluation of the compound blood levels, clinical chemistry or hematology parameters. Animals are them euthanized with carbon dioxide overdose. A thoracotomy can be conducted as a means of death verification.

(b) Monoarticular arthritis model

[001008] All injections are performed under anesthesia. 60 female Lewis rats (150-170) are anesthetized by inhalation isoflurane using a small animal anesthesia machine. The animals are placed in the induction chamber until anesthetized by delivery of 4-5% isoflurane in O_2 and then held in that state using a nose cone on the procedure table. Maintenance level of isoflurane is at 1-2%. Animals are injected intra-articular (i.a.) with a single injection of purified PG-PS 100P Group A, D58 strain (concentration 500ug/mL) suspended in sterile 0.85% saline. Each rat receives a total volume of 10 microliters administered into the tibiotalar joint space using a 1 milliliter syringe with a 27 gauge needle. Animals are under continuous observation until fully recovered from anesthesia and moving about the cage. Animals that respond 2-3 days later with a sharp increase in ankle measurement, typically 20% above baseline measurement on the initial i.a. injection, are included in the study. On day 14, all responders are anesthetized again using the procedure previously described. Animals receive an intravenous (I.V.) injection of PG-PS (concentration 250uL/mL). Each rat receives a total volume of 400 microliters administered slowly into the lateral tail vein using a 1 milliliter syringe with a 27 gauge needle. Baseline ankle measurements are measured prior to IV injection and continue through the course of inflammation or out to day 10. Treatment with test compounds will be PO, SC, IV or IP. Rats are dosed no more than two times in a 24 hour time span. Treatment can begin on day 0 or any day after that through day 24. The animals are weighed on days 0, 1, 2, 3, 4, 5, and beginning again on day 14 – 24 or until the study is terminated. Paw/ankle diameter is measured with a digital caliper on the left and right side on day 0 prior to injection and again on day 1, 2, 3, 4, 5, and beginning again on day 14 – 24 or until the study is terminated. At this time, animals can be anesthetized with isoflurane, as described above, and terminal blood samples can be obtained by tail vein draws for the evaluation of the compound blood levels, clinical chemistry or hematology parameters. Animals are them euthanized with carbon dioxide overdose. A thoracotomy can be conducted as a means of death verification.

Example 191: Mice Models for Asthma

[001009] Efficacy of a compound provided herein in treating, preventing and/or managing asthma can be assessed using an conventional animal models including various mice models described in, for example, Nials *et al.*, *Dis Model Mech.* 1(4-5): 213-220 (2008).

(a) Acute Allergen Challenge Models

[001010] Several models are known in the art and any of such models can be used. Although various allergens can be used to induce asthma-like conditions, the principle is consistent throughout the methods. Briefly, asthma-like conditions are induced through multiple systemic administration of the allergen (*e.g.*, ova, house dust mite extracts and cockroach extracts) in the presence of an adjuvant such as aluminum hydroxide. Alternatively, an adjuvant-free system can be used, but it usually requires a higher number of exposures to achieve suitable sensitization. Once induced, animals exhibit many key features of clinical asthma such as: elevated levels of IgE; airway inflammation; goblet cell hyperplasia; epithelial hypertrophy; AHR ro specific stimuli; and early and late phase bronchoconstriction. Potential efficacy of a compound thus can be assessed by determining whether one or more of these clinical features are reversed or mitigated.

(b) Chronic Allergen Challenge Models

[001011] Chronic allergen challenge models aim to reproduce more of the features of the clinical asthma, such as airway remodeling and persistent AHR, than acute challenge models. While allergens similar to those used in acute allergen challenge models can be used, in chronic allergen challenge models, animals are subjected to repeated exposure of the airways to low levels of allergen for a period of up to 12 weeks. Once induced, animals exhibit key features of human asthma such as: allergen-dependent sensitization; a Th2-dependent allergic inflammation characterized by eosinophillic influx into the airway mucosa; AHR; and airway remodeling as evidenced by goblet cell hyperplasia, epithelial hypertrophy, subepithelial or peribronchiolar fibrosis. Potential efficacy of a compound thus can be assessed by determining whether one or more of these clinical features are reversed or mitigated.

Example 192: Models for Psoriasis

[001012] Efficacy of a compound provided herein in treating, preventing and/or managing psoriasis can be assessed using an conventional animal models including various animal models described in, for example, Boehncke *et al.*, *Clinics in Dermatology*, 25: 596-605 (2007).

[001013] As an example, the mouse model based on adoptive transfer of $CD4^{+}CD45RB^{hi}$ T cells described in Hong *et al.*, *J. Immunol.*, 162: 7480-7491 (1999) can be made. Briefly, female BALB/cBY (donor) and C.B.-17/Prkdc scid/scid (recipient) mice are housed in a specific pathogen-free environment and are used between 6 and 8 weeks of age. $CD4^{+}$ T cells are enriched from BALB/cBy splenocytes using a mouse CD4 enrichment kit. The cells are then labeled with PE-conjugated anti-CD4, FITC-conjugated anti-CD45RB, and APC-conjugated anti-CD25 antibodies. Cells are sorted using a cell sorter. $CD4^{+}CD45RB^{hi}CD25$ cells are collected. Cells are resuspended in saline and $4x10^{8}$ cells/mouse are injected i.p. into C.B.-17/Prkdc scid/scid mice. Mice may be dosed with LPS, cytokines, or antibodies as necessary. Mice are monitored for external signs of skin lesions twice each week. After the termination, ear, back skin, lymph nodes and spleen may be collected for further *ex vivo* studies.

Example 193: Models for Scleroderma

[001014] A compound's efficacy in treating scleroderma can be tested using animal models. An exemplary animal model is a mouse model for scleroderma induced by repeated local injections of bleomycin ("BLM") described, for example, in Yamamoto *et al.*, *J Invest Dermatol* 112: 456-462 (1999), the entirety of which is incorporated herein by reference. This mouse model provides dermal sclerosis that closely resembles systemic sclerosis both histologically and biochemically. The sclerotic changes observed in the model include, but are not limited to: thickened and homogenous collagen bundles and cellular filtrates; gradual increase in number of mast cells; degranulation of mast cells; elevated histamine release; increase in hydroxyproline in skin; presence of anti-nuclear antibody in serum; and strong expression of transforming growth factor β-2 mRNA. Therefore, efficacy of a compound in treating scleroderma can be assessed by monitoring the lessening of one or more of these changes.

[001015] Briefly, the following exemplary procedures can be used to generate the mouse model for scleroderma: Specific pathogen-free, female BALB/C mice and C3H mice of 6 weeks old, weighing about 20 g, are purchased and maintained with food and water ad libitum. BLM is dissolved in PBS at differing concentrations and

sterilized with filtration. Aliquots of each concentration of BLM or PBS are injected subcutaneously into the shaved back of the mice daily for 1-4 weeks with a needle. Alternatively, mice are injected every other day.

[001016] Histolopathological and biochemical changes induced can be assessed using any methods commonly practiced in the field. For example, histopathological changes can be assessed using a standard avidine-biotin peroxidase technique with anti-L3T4 monoclonal antibody, anti-Lyt2 monoclonal antibody, anti-mouse pan-tissue-fixed macrophage antibody, anti-stem cell factor monoclonal antibody, anti-transforming growth factor-β polyclonal antibody, and anti-decorin antibody. Cytokine expression of cellular infiltrates can be assessed by using several anti-cytokine antibodies. Hydroxyproline level can be assessed by hydrolyzing skin pieces with hydrochloric acid, neutralizing with sodium hydroxide, and colorimetrically assessing the hydrolates at 560 nm with p-dimethylaminobenzaldehyde. Pepsin-resistant collagen can be assessed by treating collagen sample extracted from biopsied tissues and analyzing by polyacrylamide stacking gel electrophoresis. Mast cells can be identified by toluidine blue, and cells containing matachromatic granules can be counted under high magnification of a light microscope. Serum levels of various cytokines can be assessed by enzyme-linked immunosorbent assay, and mRNA levels of the cytokines can be assessed by reverse-transcriptase polymerase chain reaction. Autoantibodies in serum can be detected using 3T3 fibroblasts as the substrate for the screening.

Example 194: Models for Myositis

[001017] A compound's efficacy in treating myositis (*e.g.*, dermatomyositis) can be tested using animal models known in the art. One such example is the familial canine dermatomyositis model described in Hargis *et al.*, *AJP* 120(2): 323-325 (1985). Another example is the rabbit myosin induced mouse model described in Phyanagi *et al.*, *Arthritis & Rheumatism*, 60(10): 3118-3127 (2009).

[001018] Briefly, 5-week old male SJL/J mice are used. Purified myosin from rabbit skeletal muscle (6.6 mg/ml) is emulsified with an equal amount of Freund's complete adjuvant and 3.3 mg/ml *Mycobacterium butyricum*. The mice are immunized repeatedly with emulsified rabbit myosin. Once myositis is induced, inflammatory cell filtration and necrotic muscle fiber should be evident in the model. In the muscles of animals, $CD4^+$ T cells are mainly located in the perimysum and $CD8^+$ T cells are mainly located in the endomysium and surround non-necrotic muscle fibers. TNFα, IFNγ and perforin are up-regulated and intercellular adhesion molecule 1 is increased in the muscles.

[001019] To assess the efficacy of a compound, following administration of the compound through adequate route at specified dose, the mice are killed and muscle tissues are harvested. The muscle tissue is immediately frozen in chilled isopentane precooled in liquid nitrogen, and then cryostat sections are prepared. The sections are stained with hematoxylin and eosin for counting of number of infiltrated cells. Three sections from each mouse are prepared and photomicrographs are obtained. For immunohistochemical tests, cryostat sections of muscle are dried and fixed in cold acetone at -20°C. The slides are rehydrated in PBS, and then endogeneous peroxide activity is blocked by incubation in 1% hydrogen peroxide. The sections are incubated overnight with rat anti-mouse CD4 monoclonal antibody, rat anti-mouse CD8 monoclonal antibody, rat anti-mouse F4/80 monoclonal antibody or normal rat IgG in antibody diluent. The samples are washed with PBS and incubated with biotin-

conjugated rabbit anti-rat IgG pretreated with 5% normal mouse serum. After washing with PBS, the samples are incubated with streptavidin-horseradish peroxidase. After washing PBS, diaminobenzidine is used for visualization.

Example 195: Models for Sjögren Syndrome

[001020] A compound's efficacy in treating Sjögren's syndrome can be tested using animal models known in the art, for example, those described in Chiorini *et al.*, *Journal of Autoimmunity* 33: 190-196 (2009). Examples include: mouse model spontaneously developed in first filial generation of NZB mice crossed to NZW mice (*see*, *e.g.*, Jonsson *et al.*, *Clin Immunol Immunopathol* 42: 93-101 (1987); mouse model induced by i.p. injection of incomplete Freund's adjuvant (*id.*; Deshmukh *et al.*, *J Oral Pathol Med* 38: 42-27 (2009)); NOD mouse models wherein Sjögren's phenotype is developed by specific genotypes (*see*, *e.g.*, Cha *et al.*, *Arthritis Rheum* 46: 1390-1398 (2002); Kong *et al.*, *Clin Exp Rheumatol* 16: 675-681 (1998); Podolin *et al.*, *J Exp Med* 178: 793-803 (1993); and Rasooly *et al.*, *Clin Immunol Immunopathol* 81: 287-292 (1996)); mouse model developed in spontaneous lpr mutation; mouse model developed in Id3 knock-out mice (*see*, *e.g.*, Li *et al.*, *Immunity* 21: 551-560 (2004)); mouse model developed in PI3K knock-out mice (*see*, *e.g.*, Oak *et al.*, *Proc Natl Acad Sci USA* 103: 16882-16887 (2006)); mouse model developed in BAFF over-expressing transgenic mice (*see*, *e.g.*, Groom *et al.*, *J Clin Invest* 109: 59-68 (2002)); mouse model induced by injection of Ro antigen into BALB/c mice (*see*, *e.g.*, Oh-Hora *et al.*, *Nat. Immunol* 9: 432-443 (2008)); mouse model induced by injection of carbonic anhydrase II (*see*, *e.g.*, Nishimori *et al.*, *J Immunol* 154: 4865-4873 (1995); mouse model developed in IL-14 over-expressing transgenic mice (*see*, *e.g.*, Shen *et al.*, *J Immunol* 177: 5676-5686 (2006)); and mouse model developed in IL-12 expressing transgenic mice (*see*, *e.g.*, McGrath-Morrow *et al.*, *Am J Physiol Lung Cell Mol Physiol* 291: L837-846 (2006)).

Example 196: Models for Immune Complex Mediated Disease

[001021] The Arthus reaction is a type 3 immune response to immune complexes, and thus, can be a mechanistic model supporting therapeutic hypothesis for immune complex mediated diseases such as rheumatoid arthritis, lupus and other autoimmune diseases. For example, PI3Kγ and δ deficient mice can be used as experimental models of the Arthus reaction and provide assessment of therapeutic potential of a compound as to the treatment of immune complex mediated diseases. The Arthus reaction can be induced using the following exemplary procedures as described in Konrad *et al.*, *Journal of Biological Chemistry* (2008 283(48): 33296-33303.

[001022] PI3Kγ- and PI3Kδ-deficient mice are maintained under dry barrier conditions. Mice are anesthetized with ketamine and xylazine, and the trachea is cannulated. Appropriate amount of protein G-purified anti-OVA IgG Ab is applied, and appropriate amount of OVA antigen is given intravenously. For PI3K blocking experiments, wortmanin is given intratracheally together with the application of anti-OVA igG. Mice are killed at 2-4 hours after initiation of inflammation, and desired follow up assessments can be performed using methods known in the art.

Example 197: Isoform-Selective Cellular Assays

(a) PI3Kδ Selective Assay

[001023] A compound's ability in selectively inhibiting PI3Kδ can be assessed using RAJI cells, *i.e.*, B lymphocyte cells derived from lymphoma patients. Briefly, serum-starved RAJI cells are stimulated with anti-human IgM, thereby causing signaling through the B-cell receptors, as described in, for example, He *et al.*, *Leukemia Research* (2009) 33: 798-802. B-cell receptor signaling is important for the activation, differentiation, and survival of B cells and certain B-cell derived cancers. Reduction of phospho-AKT is indicative of compounds that may inhibit B-cell proliferation and function in certain diseases. By monitoring the reduction of phospho-AKT in stimulated RAJI cells (using for example, phospho-AKT antibodies), a compound's potential efficacy in selectively inhibiting PI3Kδ can be assessed.

[001024] Certain compounds provided herein (*e.g.*, Compounds **I-21**, **I-86**, **I-87**, **I-91**, **I-106**, and **III-13**) were tested in RAJI cell model using procedures as described above. It was found that IC_{50} values for phospho-AKT are as follows: Compounds **I-21**, **I-86**, **I-87**, **I-91**, **I-106**, and **III-13** in the range of less than 100 nM.

(b) PI3Kγ Selective Assay

[001025] A compound's ability in selectively inhibiting PI3Kγ can be assessed using RAW264.7 macrophages. Briefly, serum-starved PAW264.7 cells are stimulated with a known GPCR agonist C5a. (*See*, *e.g.*, Camps *et al.*, *Nature Medicine* (2005) 11(9): 936- 943). Cells can be treated with test compounds prior to, simultaneously with, or subsequent to the stimulation by C5a. RAW 264.7 cells respond to the complement component fragment C5a through activation of the C5a receptor, and the C5a receptor activates macrophages and induces cell migration. Test compounds' ability to inhibit C5a-mediated AKT phosphorylation is indicative of selective inhibition of PI3Kγ. Thus, by monitoring the reduction of phospho-AKT in stimulated RAW 264.7 cells (using for example, phospho-AKT antibodies), a compound's potential efficacy in selectively inhibiting PI3Kγ can be assessed.

[001026] Certain compounds provided herein (*e.g.*, Compounds **I-21**, **I-86**, **I-87**, **I-91**, **I-106**, and **III-13**) were tested in RAW 264.7 cell model using procedures as described above. It was found that IC_{50} values for phospho-AKT are as follows: Compounds **I-86**, **I-87**, and **I-91** in the range of less than 100 nM; Compounds **I-21**, **I-106**, and **III-13** in the range of between 100 nM and 1 μM.

(c) PI3Kα Selective Assay

[001027] A compound's ability in selectively inhibiting PI3Kα can be assessed using SKOV-3 cells, *i.e.*, human ovarian carcinoma cell line. Briefly, SKOV-3 cells, in which mutant PI3Kα is constitutively active, can be treated with test compounds. Test compounds' ability to inhibit AKT phosphorylation in SKOV-3 cells, therefore, is indicative of selective inhibition of PI3Kα. Thus, by monitoring the reduction of phospho-AKT in SKOV-3 cells (using for example, phospho-AKT antibodies), a compound's potential efficacy in selectively inhibiting PI3Kα can be assessed.

[001028] Certain compounds provided herein (*e.g.*, Compounds **I-21**, **I-86**, **I-87**, **I-91**, and **III-13**) were tested in SKOV-3 cell model using procedures as described above. It was found that IC_{50} values for phospho-AKT

are as follows: Compound **I-87** in the range of between 100 nM and 1 μM; Compounds **I-21**, **I-86**, **I-91**, and **III-13** in the range of between 1 μM and 10 μM.

(d) PI3Kβ Selective Assay

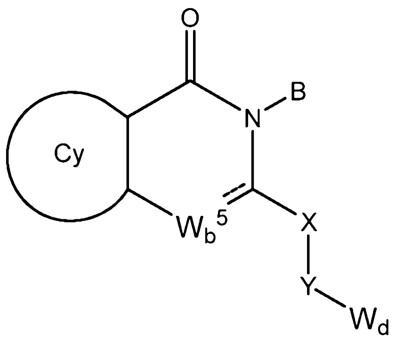
[001029] A compound's ability in selectively inhibiting PI3Kβ can be assessed using 786-O cells, *i.e.*, human kidney carcinoma cell line. Briefly, 786-O cells, in which PI3Kβ is constitutively active, can be treated with test compounds. Test compounds' ability to inhibit AKT phosphorylation in 786-O cells, therefore, is indicative of selective inhibition of PI3Kβ. Thus, by monitoring the reduction of phospho-AKT in 786-O cells (using for example, phospho-AKT antibodies), a compound's potential efficacy in selectively inhibiting PI3Kβ can be assessed.

[001030] Certain compounds provided herein (*e.g.*, Compounds **I-21**, **I-86**, **I-87**, **I-91**, and **III-13**) were tested in 786-O cell model using procedures as described above. It was found that IC_{50} values for phospho-AKT are as follows: Compounds **I-21**, **I-86**, **I-87**, **I-91**, and **III-13** in the range of between 1 μM and 10 μM.

CLAIMS

WHAT IS CLAIMED IS:

1. A compound of Formula (I):



Formula (I)

or an enantiomer, a mixture of enantiomers, or a mixture of two or more diastereomers thereof, or its pharmaceutically acceptable forms thereof, wherein

Cy is aryl or heteroaryl substituted by 0-1 occurrences of R^3 and 0-3 occurrences of R^5;

W_b^5 is CR^8, CHR^8, or N;

R^8 is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heteroalkyl, alkoxy, amido, amino, acyl, acyloxy, sulfonamido, halo, cyano, hydroxyl, or nitro;

B is hydrogen, alkyl, amino, heteroalkyl, cycloalkyl, heterocyclyl, heterocyclylalkyl, aryl or heteroaryl, each of which is substituted with 0-4 occurrences of R^2;

each R^2 is independently alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, alkoxy, amido, amino, acyl, acyloxy, alkoxycarbonyl, sulfonamido, halo, cyano, hydroxyl, nitro, phosphate, urea or carbonate;

X is absent or is $-(CH(R^9))_z-$;

Y is absent, -O-, -S-, -S(=O)-, $-S(=O)_2-$, $-N(R^9)-$, $-C(=O)-(CHR^9)_z-$, -C(=O)-, $-N(R^9)-C(=O)-$, or $-N(R^9)-C(=O)NH-$, $-N(R^9)C(R^9)_2-$, or $-C(=O)-N(R^9)-(CHR^9)_z$;

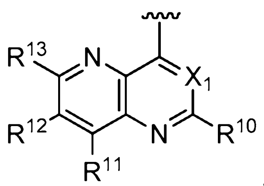
each z is independently an integer of 1, 2, 3, or 4;

wherein when W_b^5 is N, no more than one of X or Y is absent;

R^3 is alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, fluoroalkyl, heteroalkyl, alkoxy, amido, amino, acyl, acyloxy, sulfinyl, sulfonyl, sulfoxide, sulfone, sulfonamido, halo, cyano, heteroaryl, aryl, hydroxyl, or nitro; wherein each of the above substituents can be substituted with 0, 1, 2, or 3 R^{17};

each R^5 is independently alkyl, alkenyl, alkynyl, cycloalkyl, heteroalkyl, alkoxy, amido, amino, acyl, acyloxy, sulfonamido, halo, cyano, hydroxyl, or nitro;

each R^9 is independently hydrogen, alkyl, cycloalkyl, or heteroalkyl; and

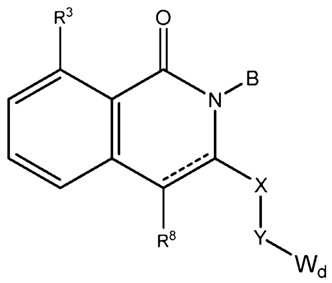
W_d is  , wherein X_1 is N or CR^{14};

wherein R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, and R^{17} are independently hydrogen, alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, alkoxy, heterocyclyloxy, amido, amino, acyl, acyloxy, alkoxycarbonyl, sulfonamido, halo, cyano, hydroxyl, nitro, phosphate, urea, carbonate, oxo, or NR′R″ wherein R′ and R″ are taken together with nitrogen to form a cyclic moiety.

2. The compound of claim 1, wherein Cy is aryl substituted with 0-1 occurrences of R^3 and 0-3 occurrences of R^5.

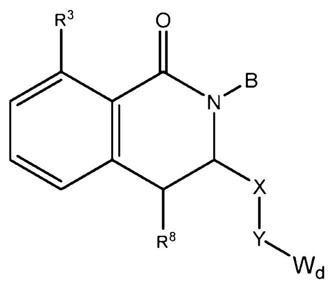
3. The compound of claim 2, wherein Cy is phenyl substituted with 1 occurrence of R^3 and 0 occurrences of R^5.

4. The compound of claim 3, wherein the compound of Formula (I) has a structure of Formula (II):

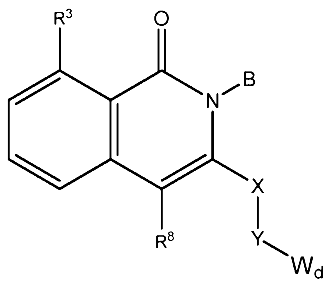


Formula (II).

5. The compound of claim 4, wherein the compound of Formula (II) has a structure of Formula (IIa) or (IIb):

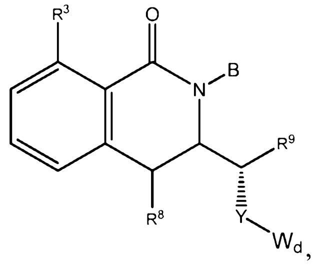


Formula (IIa) or

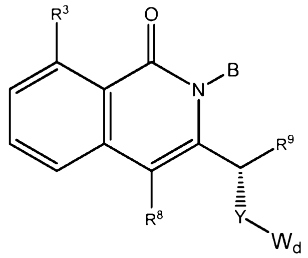


Formula (IIb).

6. The compound of claim 5, wherein the compound of Formula (II) has a structure of Formula (IIIa) or (IIIb):

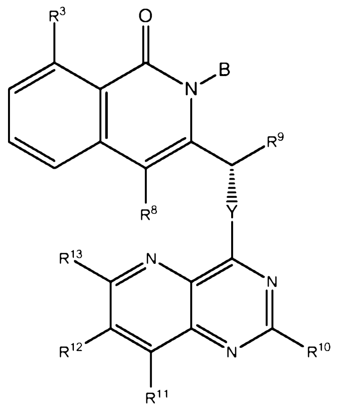


Formula (IIIa) or



Formula (IIIb).

7. The compound of claim 6, wherein the compound of Formula (II) has a structure of Formula (IIIb-1):



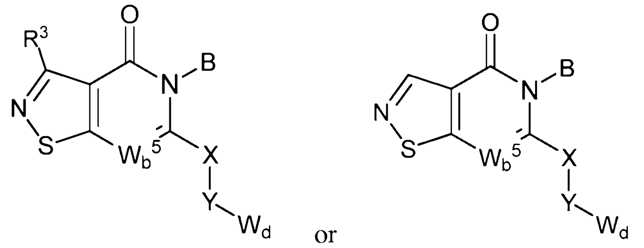
Formula (IIIb-1).

8. The compound of claim 1, wherein Cy is heteroaryl substituted with 0-1 occurrences of R^3 and 0-3 occurrences of R^5.

9. The compound of claim 8, wherein Cy is 5-membered heteroaryl substituted with 0-1 occurrences of R^3 and 0-3 occurrences of R^5.

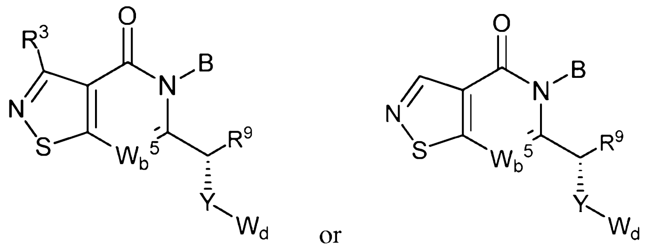
10. The compound of claim 9, wherein Cy is isothiazolyl substituted with 0-1 occurrences of R^3 and 0 occurrence of R^5.

11. The compound of claim 10, wherein the compound of Formula (I) has the structure of Formula (IVa) or Formula (IVb):



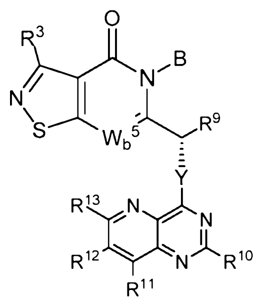
Formula (IVa) Formula (IVb).

12. The compound of claim 11, wherein the compound of Formula (IVa) or Formula (IVb) has the structure of Formula (Va) or Formula (Vb):



Formula (Va) Formula (Vb).

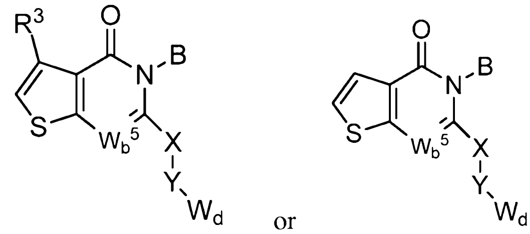
13. The compound of claim 12, wherein the compound of Formula (I) has a structure of Formula (Va-1):



Formula (Va-1).

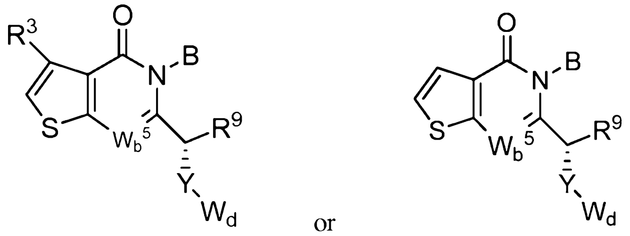
14. The compound of claim 9, wherein Cy is thiophenyl substituted with 0-1 occurrences of R^3 and 0 occurrence of R^5.

15. The compound of claim 14, wherein the compound of Formula (I) has the structure of Formula (VIa) or Formula (VIb):



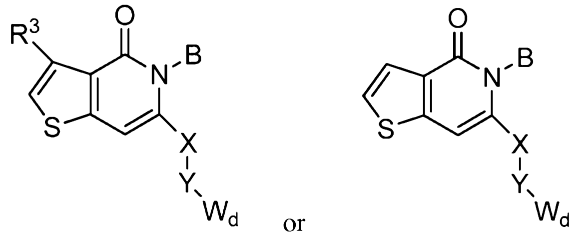
Formula (VIa) Formula (VIb).

16. The compound of claim 15, wherein the compound of Formula (VIa) or Formula (VIb) has the structure of Formula (VIIa) or (VIIb):



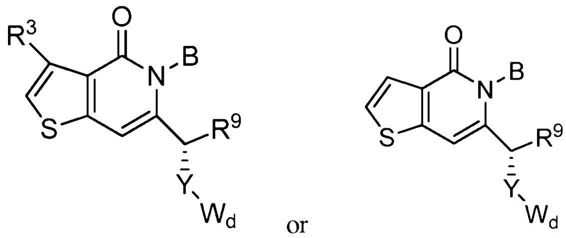
Formula (VIIa) Formula (VIIb).

17. The compound of claim 15, wherein the compound of Formula (VIa) or Formula (VIb) has the structure of Formula (VIIIa) or Formula (VIIIb):



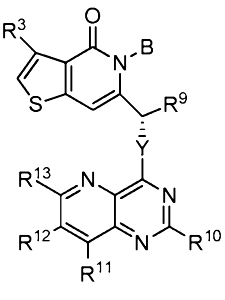
Formula (VIIIa) Formula (VIIIb).

18. The compound of claim 17, wherein the compound of Formula (VIIa) or Formula (VIIb) has the structure of Formula (IXa) or Formula (IXb):



Formula (IXa) Formula (IXb).

19. The compound of claim 18, wherein the compound of Formula (I) has a structure of Formula (IXa-1):



Formula (IXa-1).

20. The compound of any one of claims 1–19, wherein each R^5 is independently selected from CH_3, OCH_3, CF_3, and halo.

21. The compound of any one of claims 1–20, wherein R^3 is selected from alkyl, cycloalkyl, halo, aryl, and heteroaryl.

22. The compound of any one of claims 1–21, wherein R^3 is selected from methyl, chloro, and pyrazolo.

23. The compound of any one of claims 1–22, wherein B is aryl substituted with 0-3 occurrences of R^2.

24. The compound of any one of claims 1–23, wherein B is phenyl substituted with 0-3 occurrences of R^2.

25. The compound of any one of claims 1–24, wherein B is unsubstituted phenyl.

26. The compound of any one of claims 1–24, wherein B is phenyl substituted with 1 occurrence of R^2.

27. The compound of any one of claims 1–26, wherein R^2 is halo or alkyl.

28. The compound of any one of claims 1–22, wherein B is cycloalkyl.

29. The compound of any one of claims 1–22, wherein B is heterocyclyl.

30. The compound of any one of claims 1–29, wherein Y is absent, -O-, -NH(R^9)-, or -S(=O)$_2$-.

31. The compound of any one of claims 1–30, wherein X-Y is -CH_2-N(CH_3).

32. The compound of any one of claims 1–30, wherein X-Y is (S)-CH(CH_3)-NH-.

33. The compound of any one of claims 1–30, wherein X-Y is (R)-CH(CH_3)-NH-.

34. The compound of any one of claims 1–33, wherein X_1 is N.

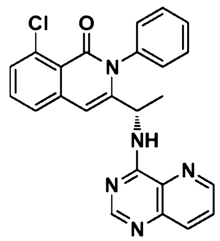
35. The compound of any one of claims 1–34, wherein R^{10}, R^{11}, R^{12}, and R^{13} are independently selected from hydrogen, alkyl, heteroalkyl, alkenyl, alkynyl, alkoxy, amido, amino, acyl, acyloxy, alkoxycarbonyl, sulfonamido, halo, cyano, and hydroxyl.

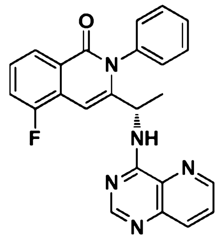
36. The compound of any one of claims 1–35, wherein R^{10}, R^{11}, R^{12}, and R^{13} are independently selected from hydrogen, amino, and chloro.

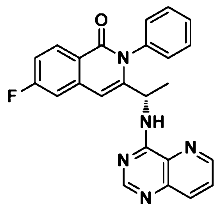
37. The compound of any one of claims 1–36, wherein R^{10} is selected from amino and chloro.

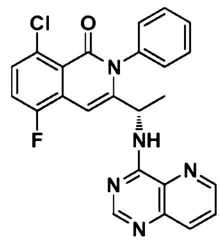
38. The compound of any one of claims 1–37, wherein R^8 is hydrogen.

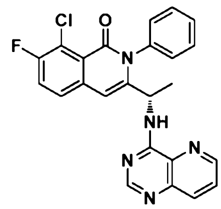
39. The compound of claim 1, wherein the compound is


Compound I-**2**,


Compound I-**4**,


Compound I-**6**,


Compound I-**14**,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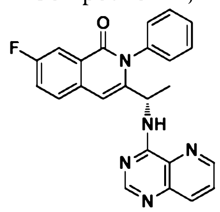
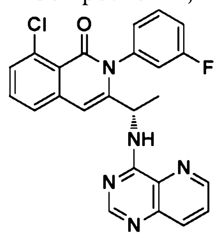
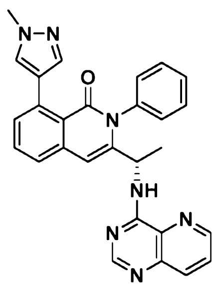

Compound I-**18**,


Compound I-**20**,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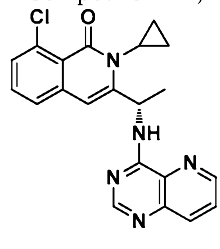
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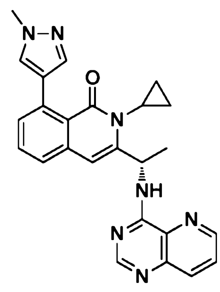
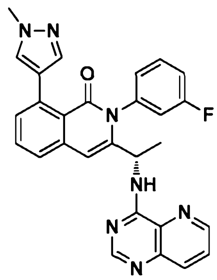

Compound I-**24**,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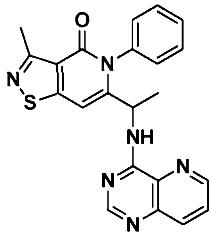
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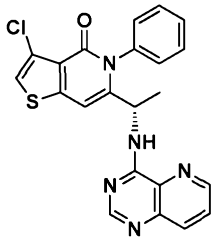
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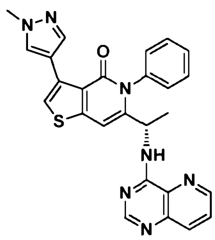
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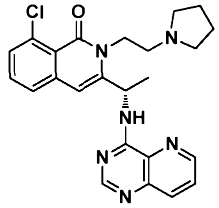
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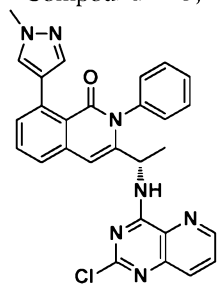
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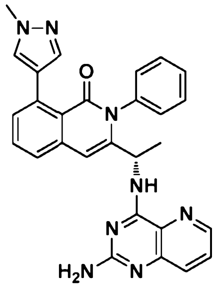
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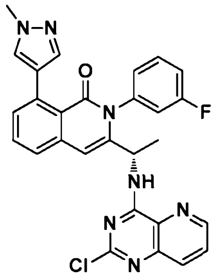
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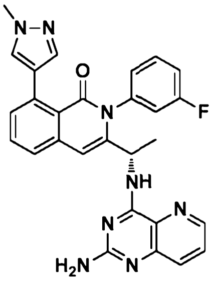
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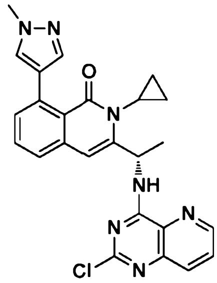
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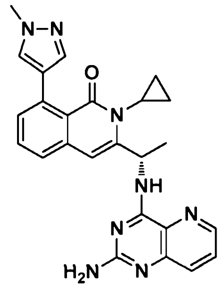
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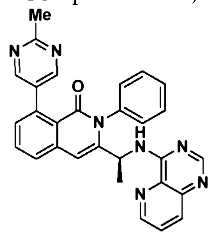
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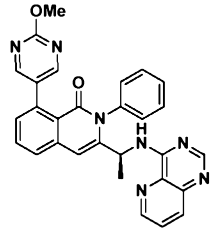
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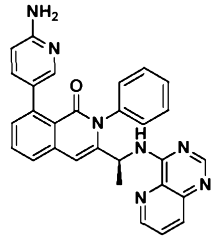
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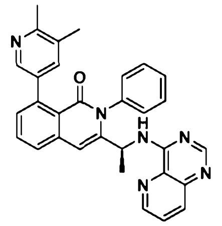
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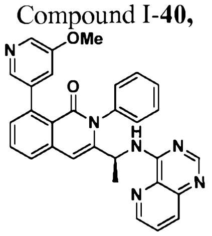
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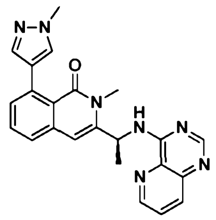
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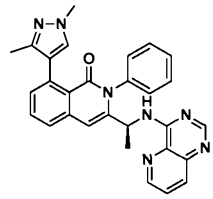
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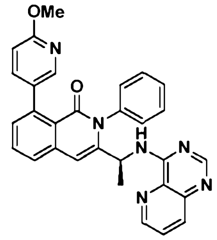
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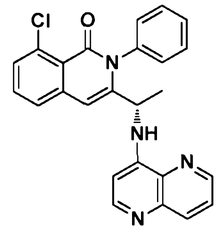
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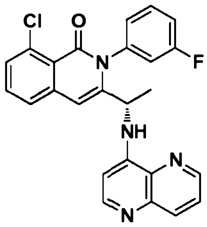
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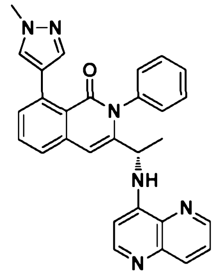
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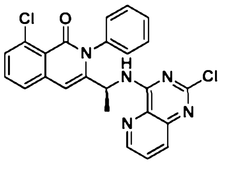
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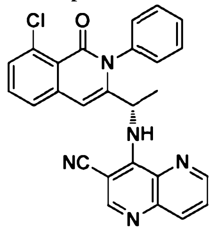
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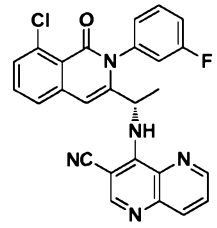
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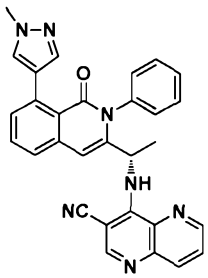
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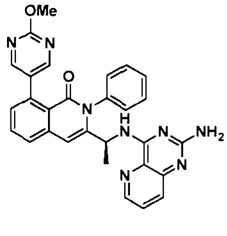
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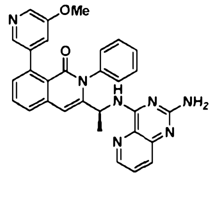
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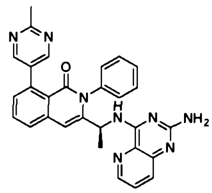
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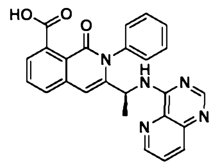
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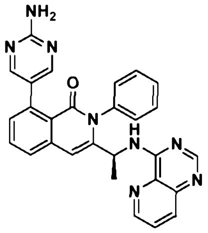
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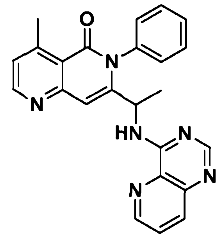
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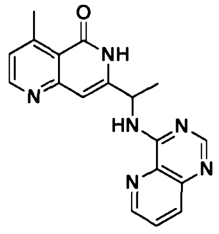
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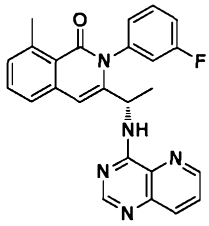
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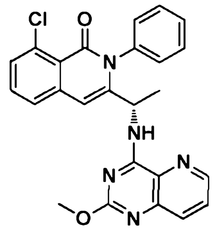
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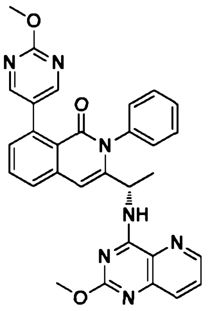
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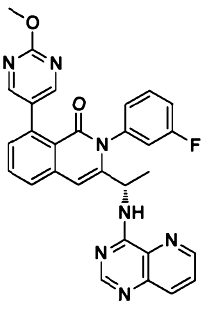
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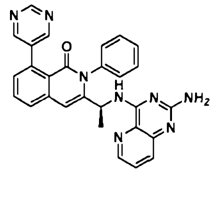
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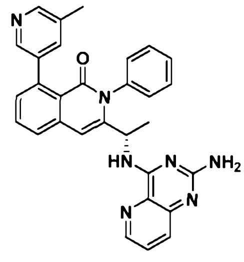
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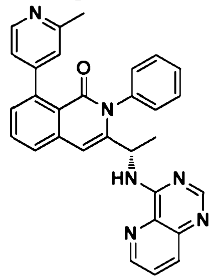
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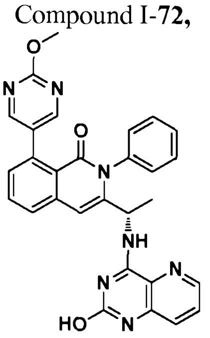
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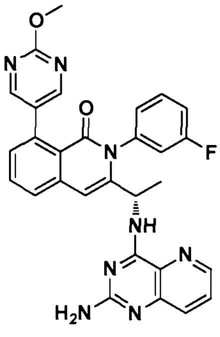
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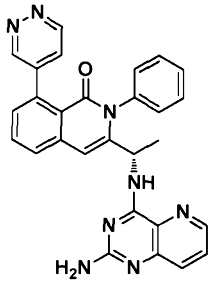
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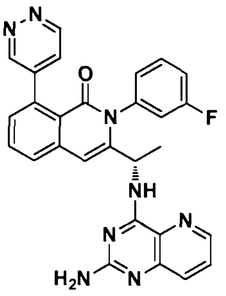
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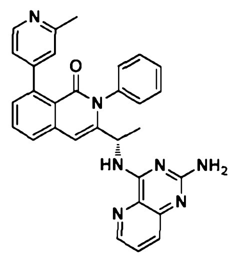
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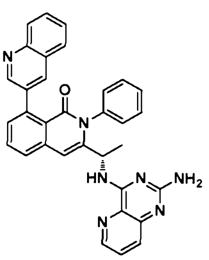
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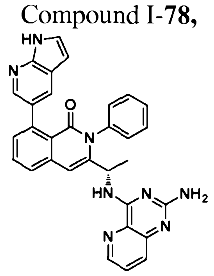
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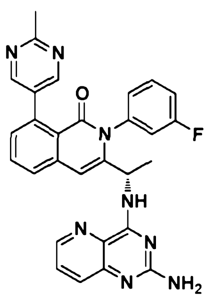
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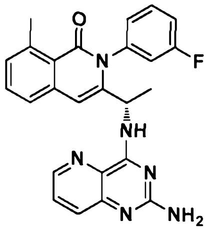
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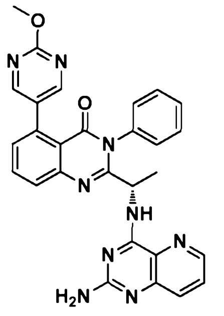
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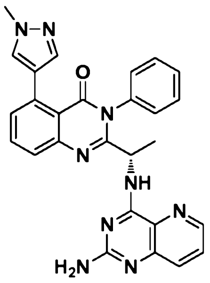

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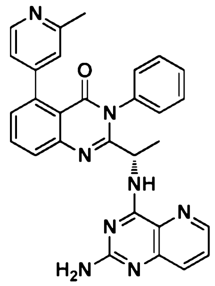

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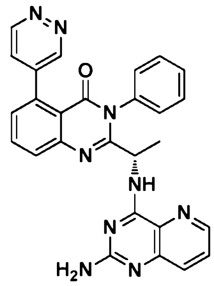

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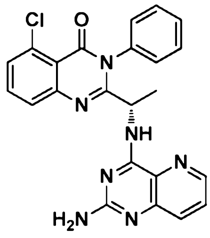

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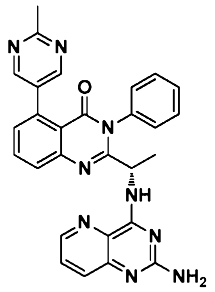

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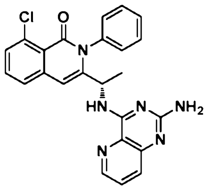

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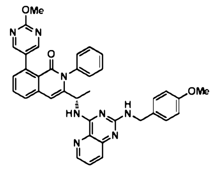

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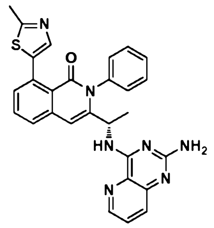

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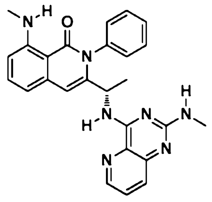

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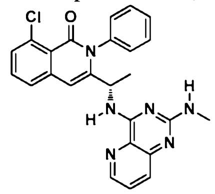

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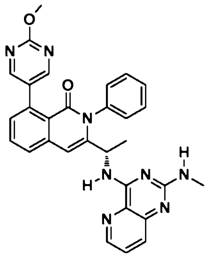

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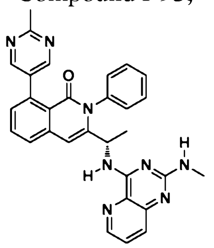
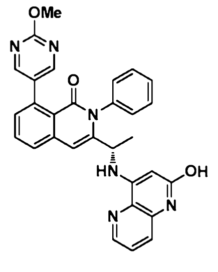


Compound I-**98**,



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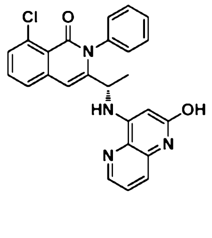
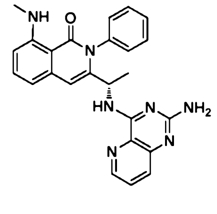
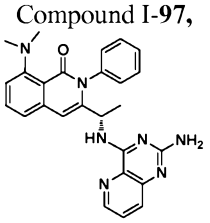


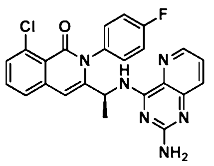
Compound I-**100**,



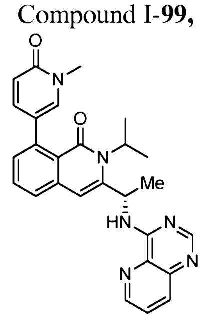
Compound I-**101**,



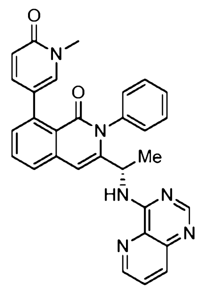
Compound I-**102**,



Compound I-**103**,



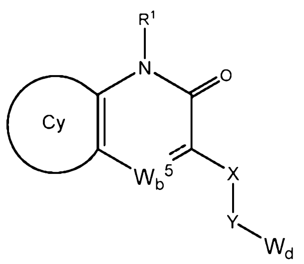
Compound **I-106**, or



Compound **I-107**,

or a pharmaceutically acceptable form thereof.

40. A compound of Formula (XI):



Formula (XI),

or an enantiomer, a mixture of enantiomers, or a mixture of two or more diastereomers thereof, or its pharmaceutically acceptable forms thereof, wherein:

W_b^5 is N, CHR^8, or CR^8;

R^8 is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heteroalkyl, alkoxy, amido, amino, acyl, acyloxy, sulfonamido, halo, cyano, hydroxyl, or nitro;

Cy is aryl or heteroaryl substituted by 0-1 occurrences of R^3 and 0-3 occurrences of R^5;

R^1 is –(L)-$R^{1'}$;

L is a bond, -S-, -N(R^{15})-, -C(R^{15})$_2$-, -C(=O)-, or –O-;

$R^{1'}$ is hydrogen, alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, alkoxy, heterocyclyloxy, amido, amino, acyl, acyloxy, alkoxycarbonyl, sulfonamido, halo, cyano, hydroxyl, nitro, phosphate, urea, carbonate, substituted nitrogen,or NR′R″ wherein R′ and R″ are taken together with nitrogen to form a cyclic moiety;

each R^{15} is independently hydrogen, alkyl, cycloalkyl, or heteroalkyl;

R^3 is alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, fluoroalkyl, heteroalkyl, alkoxy, amido, amino, acyl, acyloxy, sulfonamido, halo, cyano, heteroaryl, aryl, hydroxyl, or nitro; wherein each of the above substituents can be substituted with 0, 1, 2, or 3 R^{17};

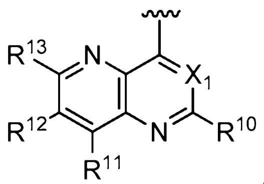
each R^5 is independently alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, alkoxy, heterocyclyloxy, amido, amino, acyl, acyloxy, alkoxycarbonyl, sulfonamido, halo, cyano, hydroxyl, nitro, phosphate, urea, carbonate, or NR′R″ wherein R′ and R″ are taken together with nitrogen to form a cyclic moiety;

X is absent or is –(CH(R^{16}))$_z$–;

Y is absent, -O-, -S-, -S(=O)-, -S(=O)$_2$-, -N(R^{16})-, -C(=O)-(CHR^{16})$_z$-, -C(=O)-, -N(R^{16})-C(=O)-, or -N(R^{16})-C(=O)NH-,-N(R^{16})C(R^{16})$_2$-, or -C(=O)-N(R^{16})-(CHR^{16})$_z$-;

each z is an integer of 1, 2, 3, or 4;

each R^{16} is independently hydrogen, alkyl, cycloalkyl, heterocyclyl, heteroalkyl, aryl, halo or heteroaryl; and

W_d is 

,

wherein X_1 is N or CR^{14};

wherein R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, and R^{17} are independently hydrogen, alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, alkoxy, heterocyclyloxy, amido, amino, acyl, acyloxy, alkoxycarbonyl, sulfonamido, halo, cyano, hydroxyl, nitro, phosphate, urea, carbonate, oxo, or NR′R″ wherein R′ and R″ are taken together with nitrogen to form a cyclic moiety.

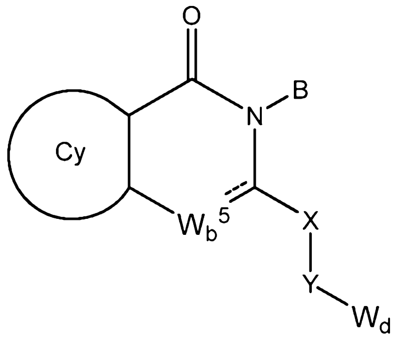
41. The compound of claim 40, wherein Cy is a 6-membered ring.

42. The compound of claim 40 or claim 41, wherein Cy is a 6-membered aryl ring.

43. The compound of any one of claims 40–42, wherein W_b^5 is CH.

44. The compound of any one of claims 40–43, wherein X-Y is -CH_2-N(CH_3).

45. A compound of Formula (XII):



Formula (XII)

or an enantiomer, a mixture of enantiomers, or a mixture of two or more diastereomers thereof, or its pharmaceutically acceptable forms thereof, wherein

Cy is aryl or heteroaryl substituted by 0-1 occurrences of R^3 and 0-3 occurrences of R^5;

W_b^5 is CR^8, CHR^8, or N,

R^8 is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heteroalkyl, alkoxy, amido, amino, acyl, acyloxy, sulfonamido, halo, cyano, hydroxyl, or nitro;

B is hydrogen, alkyl, amino, heteroalkyl, cycloalkyl, heterocyclyl, aryl or heteroaryl, each of which is substituted with 0-4 R^2;

R^2 is alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, alkoxy, amido, amino, acyl, acyloxy, alkoxycarbonyl, sulfonamido, halo, cyano, hydroxyl, nitro, phosphate, urea or carbonate;

X is absent or is $-(CH(R^9))_z-$;

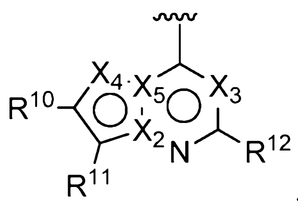
Y is absent, -O-, -S-, -S(=O)-, $-S(=O)_2-$, $-N(R^9)-$, $-C(=O)-(CHR^9)_z-$, -C(=O)-, $-N(R^9)-C(=O)-$, $-N(R^9)-C(=O)NH-$,$-N(R^9)C(R^9)_2-$, or $-C(=O)-N(R^9)-(CHR^9)_z$;

each z is independently an integer of 1, 2, 3, or 4;

R^3 is alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, haloalkyl, heteroalkyl, alkoxy, amido, amino, acyl, acyloxy, sulfinyl, sulfonyl, sulfoxide, sulfone, sulfonamido, halo, cyano, aryl, heteroaryl, hydroxyl, or nitro; wherein each of the above substituents can be substituted with 0, 1, 2, or 3 R^{17};

each R^5 is independently alkyl, alkenyl, alkynyl, cycloalkyl, heteroalkyl, alkoxy, amido, amino, acyl, acyloxy, sulfonamido, halo, cyano, hydroxyl, or nitro;

each R^9 is independently hydrogen, alkyl, cycloalkyl, or heteroalkyl; and

W_d is 

,

wherein one of X_5 and X_2 is N and one of X_5 and X_2 is C;

X_3 and X_4 are each independently CR^{13} or N;

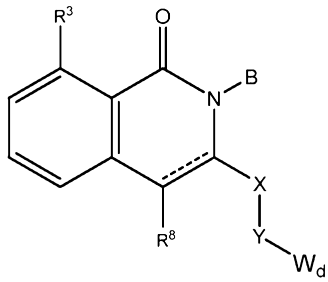
X_2 and X_3 are not both N; and

each R^{10}, R^{11}, R^{12}, R^{13}, and R^{17} is independently hydrogen, alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, alkoxy, heterocyclyloxy, amido, amino, acyl, acyloxy, alkoxycarbonyl, sulfonamido, halo, cyano, hydroxyl, nitro, phosphate, urea, carbonate, oxo, or NR′R″ wherein R′ and R″ are taken together with nitrogen to form a cyclic moiety.

46. The compound of claim 45, wherein Cy is aryl substituted with 0-1 occurrences of R^3 and 0-3 occurrences of R^5.

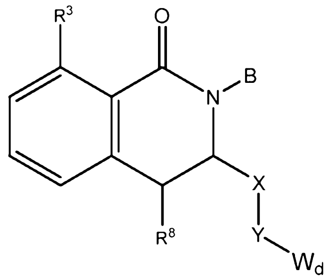
47. The compound of claim 46, wherein Cy is phenyl substituted with 1 occurrence of R^3 and 0 occurrences of R^5.

48. The compound of claim 47, wherein the compound of Formula (XII) has a structure of Formula (XIII):

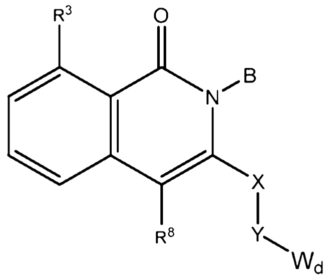


Formula (XIII) .

49. The compound of claim 48, wherein the compound of Formula (XIII) has a structure of Formula (XIIIa) or (XIIIb):

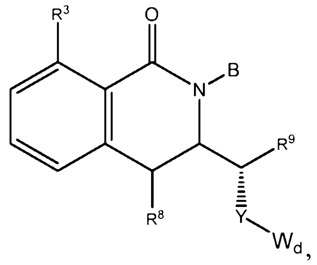


Formula (XIIIa) or

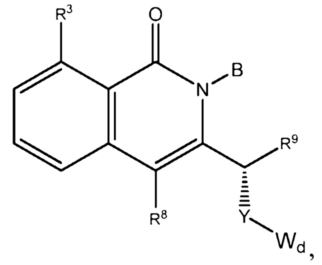


Formula (XIIIb) .

50. The compound of claim 49, wherein the compound of Formula (XIIIa) or (XIIIb) has a structure of Formula (XIVa) or (XIVb):

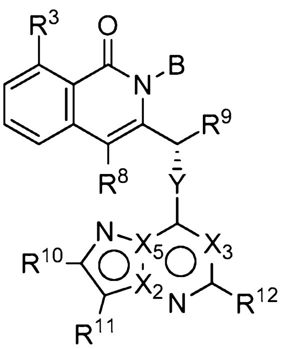


Formula (XIVa) or



Formula (XIVb).

51. The compound of claim 50, wherein the compound of Formula (XIII) has a structure of Formula (XIVb-1):



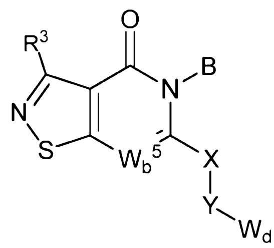
Formula (XIVb-1).

52. The compound of claim 45, wherein Cy is heteroaryl substituted with 0-1 occurrences of R^3 and 0-3 occurrences of R^5.

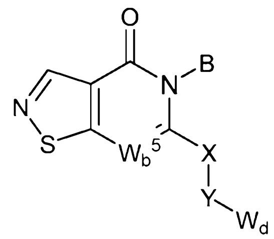
53. The compound of claim 52, wherein Cy is 5-membered heteroaryl substituted with 0-1 occurrences of R^3 and 0-3 occurrences of R^5.

54. The compound of claim 53, wherein Cy is isothiazolyl substituted with 0-1 occurrences of R^3 and 0 occurrence of R^5.

55. The compound of claim 53, wherein the compound of Formula (XII) has a structure of Formula (XVa) or (XVb):

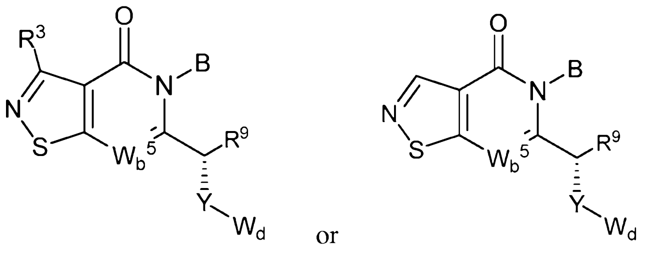


or



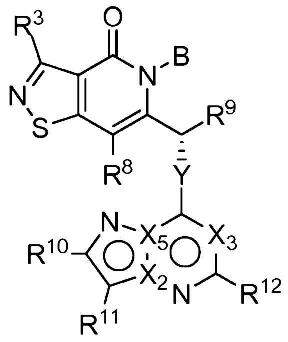
Formula (XVa) Formula (XVb).

56. The compound of claim 55, wherein the compound of Formula (XVa) or (XVb) has a structure of Formula (XVIa) or (XVIb):



Formula (XVIa) Formula (XVIb).

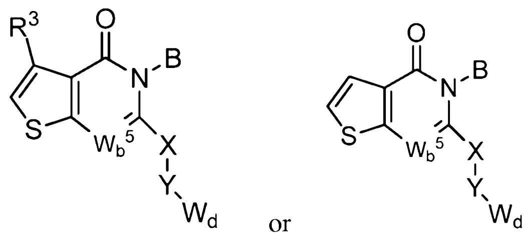
57. The compound of claim 56, wherein the compound of Formula (XII) has a structure of Formula (XVIa-1):



Formula (XVIa-1).

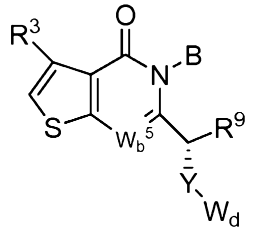
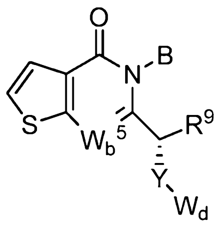
58. The compound of claim 53, wherein Cy is thiophenyl substituted with 0-1 occurrences of R^3 and 0 occurrence of R^5.

59. The compound of claim 58, wherein the compound of Formula (XII) has a structure of Formula (XVIIa) or (XVIIb):



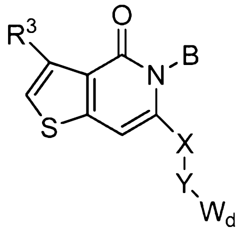
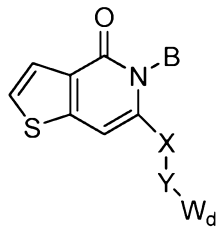
Formula (XVIIa) Formula (XVIIb).

60. The compound of claim 59, wherein the compound of Formula (XVIIa) or (XVIIb) has a structure of Formula (XVIIIa) or (XVIIIb):

 or 

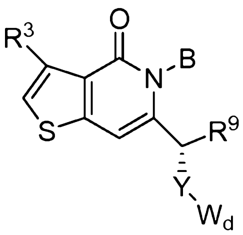
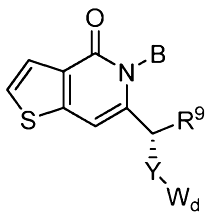
Formula (XVIIIa) Formula (XVIIIb).

61. The compound of claim 59, wherein the compound of Formula (XVIIa) or (XVIIb) has a structure of Formula (XIXa) or (XIXb):

 or 

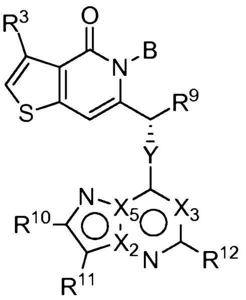
Formula (XIXa) Formula (XIXb).

62. The compound of claim 61, wherein the compound of Formula (XVIIa) or (XVIIb) has the structure of Formula (XXa) or (XXb):

 or 

Formula (XXa) Formula (XXb).

63. The compound of claim 62, wherein the compound of Formula (XII) has a structure of Formula (XXa-1):



Formula (XXa-1).

64. The compound of any one of claims 45–63, wherein each R^5 is independently selected from CH_3, OCH_3, CF_3, and halo.

65. The compound of any one of claims 45–64, wherein R^3 is selected from hydrogen, alkyl, cycloalkyl, halo, aryl, and heteroaryl.

66. The compound of any one of claims 45–65, wherein R^3 is selected from methyl, chloro, and pyrazolo.

67. The compound of any one of claims 45–66, wherein B is aryl substituted with 0-3 occurrences of R^2.

68. The compound of any one of claims 45–67, wherein B is phenyl substituted with 0-3 occurrences of R^2.

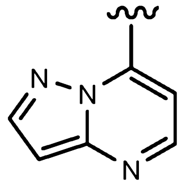
69. The compound of any one of claims 45–68, wherein B is unsubstituted phenyl.

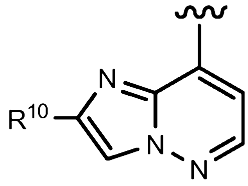
70. The compound of any one of claims 45–68, wherein B is phenyl substituted with 1 occurrence of R^2.

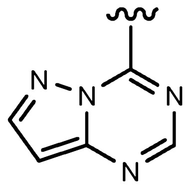
71. The compound of any one of claims 45–70, wherein R^2 is halo or alkyl.

72. The compound of any one of claims 45–66, wherein B is cycloalkyl.

73. The compound of any one of claims 45–66, wherein B is a heterocyclyl.

74. The compound of any one of claims 45–73, wherein W_d is .

75. The compound of any one of claims 45–73, wherein W_d is .

76. The compound of any one of claims 45–73, wherein W_d is .

77. The compound of any one of claims 45–76, wherein Y is absent, -O-, -NH(R^9)-, or -S(=O)$_2$-.

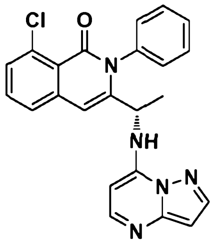
78. The compound of any one of claims 45–77, wherein X-Y is -CH_2-N(CH_3).

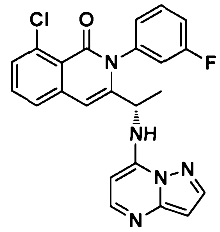
79. The compound of any one of claims 45–77, wherein X-Y is (S)-CH(CH_3)-NH-.

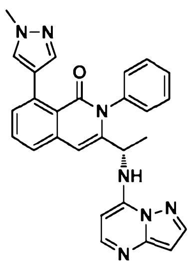
80. The compound of any one of claims 45–77, wherein X-Y is (R)-CH(CH_3)-NH-.

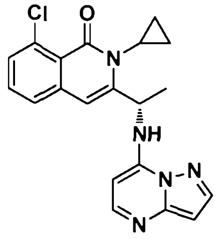
81. The compound of any one of claims 45–80, wherein R^8 is hydrogen.

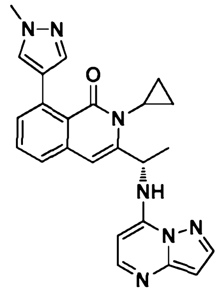
82. The compound of claim 45, wherein the compound is

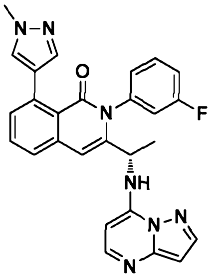

Compound II-**2**,

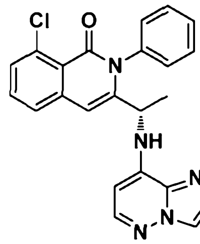

Compound II-**4**,

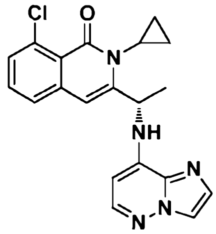

Compound II-**5**,

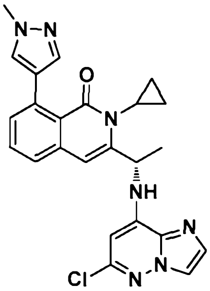

Compound II-**7**,

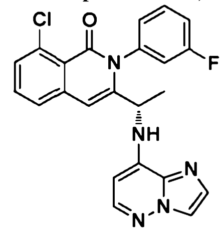

Compound II-**8**,

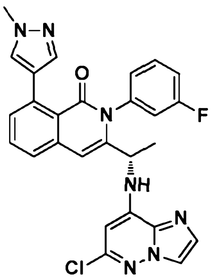

Compound II-**9**,

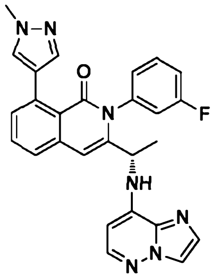

Compound II-**10**,

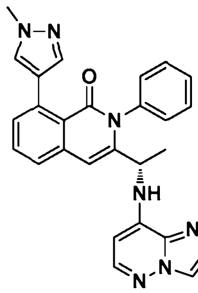

Compound II-**11**,

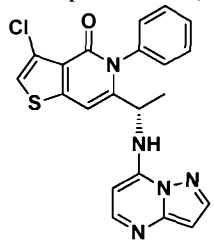

Compound II-**13**,

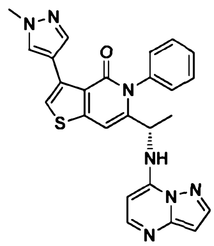

Compound II-**14**,

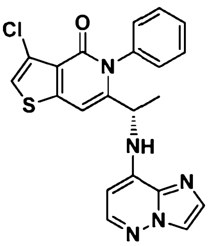

Compound II-**16**,

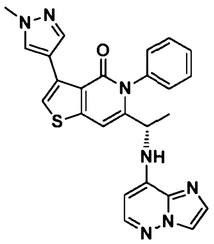

Compound II-**17**,

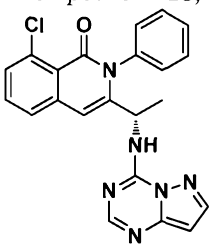

Compound II-**18**,

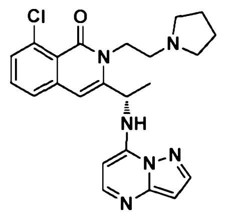

Compound II-**20**,

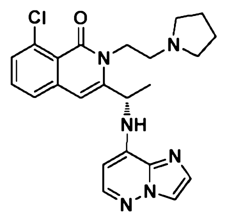

Compound II-**21**,

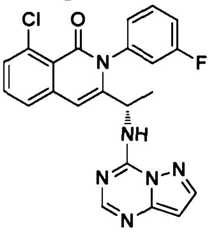

Compound II-**22**,

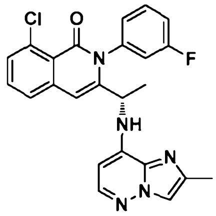

Compound II-**23**,

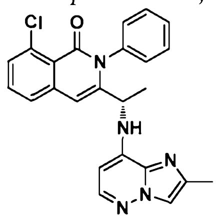

Compound II-**24**,

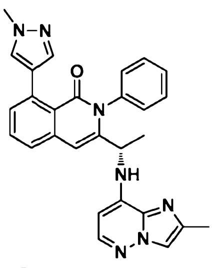

Compound II-**28**,

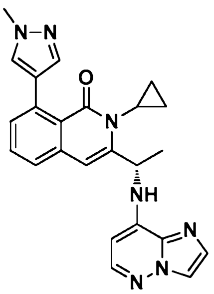

Compound II-**29**,

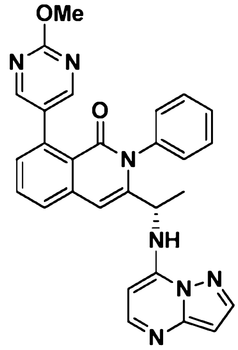

Compound II-**30**,

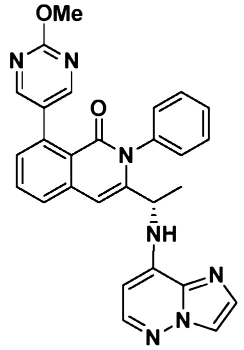

Compound II-**31**,

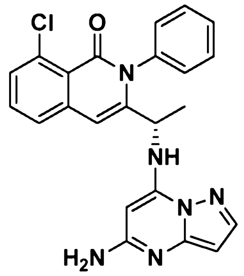

Compound II-**32**,

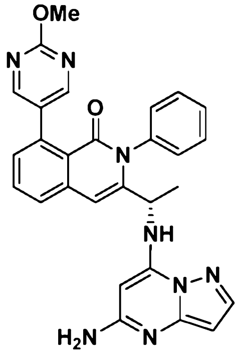

Compound II-**33**,


Compound II-**45**,


Compound **II-47**,

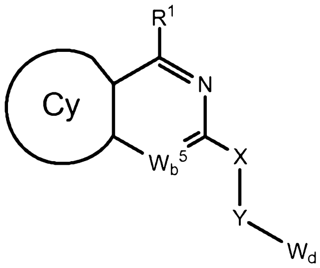

Compound **II-48**,


Compound **II-49**, or


Compound **II-50**,

or a pharmaceutically acceptable form thereof.

83. A compound of Formula (XXIII):



Formula (XXIII)

or an enantiomer, a mixture of enantiomers, or a mixture of two or more diastereomers thereof, or its pharmaceutically acceptable forms thereof, wherein

W_b^5 is N or CR^8;

R^8 is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heteroalkyl, alkoxy, amido, amino, acyl, acyloxy, sulfonamido, halo, cyano, hydroxyl, or nitro;

Cy is aryl or heteroaryl substituted by 0-1 occurrences of R^3 and 0-3 occurrences of R^5;

R^1 is –(L)-$R^{1'}$;

L is a bond, -S-, -N(R^{16})-, -C(R^{15})$_2$-, -C(=O)-, or –O-;

$R^{1'}$ is hydrogen, alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, heterocyclylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, alkoxy, heterocycloalkyloxy, amido, amino, acyl, acyloxy, alkoxycarbonyl, sulfonamido, halo, cyano, hydroxy, nitro, phosphate, urea, carbonate, substituted nitrogen,or NR′R″ wherein R′ and R″ are taken together with nitrogen to form a cyclic moiety;

R^3 is alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, haloalkyl, heteroalkyl, alkoxy, amido, amino, acyl, acyloxy, sulfinyl, sulfonyl, sulfoxide, sulfone, sulfonamido, halo, cyano, heteroaryl, aryl, hydroxyl, or nitro; wherein each of the above substituents can be substituted with 0, 1, 2, or 3 R^{17};

each R^5 is independently alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, alkoxy, heterocycloalkyloxy, amido, amino, acyl, acyloxy, alkoxycarbonyl, sulfonamido, halo, cyano, hydroxy, nitro, phosphate, urea, carbonate, or NR′R″ wherein R′ and R″ are taken together with nitrogen to form a cyclic moiety;

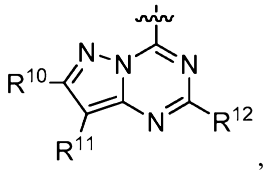
X is absent or is –(CH(R^{14}))$_z$;

Y is absent, -O-, -S-, -S(=O)-, $-S(=O)_2-$, $-N(R^9)-$, $-C(=O)-(CHR^{14})_z-$, -C(=O)-, $-N(R^9)-C(=O)-$, or $-N(R^9)-C(=O)NH-$, $-N(R^9)C(R^{14})_2-$, or $-C(=O)-(CHR^{14})_z-$;

each z is an integer of 1, 2, 3, or 4;

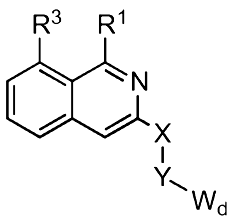
each R^9 and R^{16} is independently hydrogen, alkyl, cycloalkyl, heterocyclyl, heteroalkyl, aryl, or heteroaryl;

each R^{14} and R^{15} is independently hydrogen, alkyl, aryl, heteroaryl or halo; and

W_d is  ,

wherein R^{10}, R^{11}, R^{12}, and R^{17} are independently hydrogen, alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, alkoxy, heterocycloalkyloxy, amido, amino, acyl, acyloxy, alkoxycarbonyl, sulfonamido, halo, cyano, hydroxy, nitro, phosphate, urea, carbonate, oxo, or NR′R″ wherein R′ and R″ are taken together with nitrogen to form a cyclic moiety.

84. The compound of claim 83, wherein the compound of of Formula (XXIII) has a structure of Formula (XXIV):



Formula (XXIV) .

85. The compound of claim 83 or claim 84, wherein R^3 is halo, alkyl, heteroalkyl, haloalkyl, alkenyl, alkynyl, cycloalkyl, heteroaryl, or heterocyclyl.

86. The compound of any one of claims 83–85, wherein R^3 is alkyl or halo.

87. The compound of any one of claims 83–86, wherein L is -C(=O)- or –O-.

88. The compound of any one of claims 83–87, wherein $R^{1'}$ is substituted alkyl, substituted nitrogen, or NR′R″ wherein R′ and R″ are taken together with nitrogen to form a cyclic moiety.

89. The compound of claim 88, wherein the cyclic moiety is a morpholino group.

90. The compound of any one of claims 83–89, wherein X is $-CH_2-$ or $-CH(CH_3)-$.

91. The compound of any one of claims 83–90, wherein the CH carbon of the $-CH(CH_3)-$ moiety has a (S) stereochemical configuration.

92. The compound of any one of claims 83–90, wherein the CH carbon of the $-CH(CH_3)-$ moiety has a (R) stereochemical configuration.

93. The compound of any one of claims 83–92, wherein Y is absent, -O-, $-NH(R^9)-$, or $-S(=O)_2-$.

94. The compound of any one of claims 83–93, wherein R^9 is methyl or hydrogen.

95. The compound of any one of claims 83–94, wherein X-Y is -CH_2-N(CH_3).

96. The compound of any one of claims 83–94, wherein X-Y is (S) -CH(CH_3)-NH-.

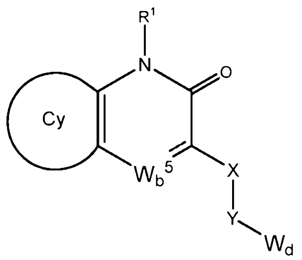
97. The compound of any one of claims 83–94, wherein X-Y is (R) -CH(CH_3)-NH-.

98. The compound of any one of claims 83–97, wherein R^{10}, R^{11}, and R^{12} are independently selected from hydrogen, alkyl, heteroalkyl, alkenyl, alkynyl, alkoxy, amido, amino, acyl, acyloxy, alkoxycarbonyl, sulfonamido, halo, cyano, and hydroxyl.

99. The compound of any one of claims 83–98, wherein R^{10}, R^{11}, and R^{12} are independently selected hydrogen, amino, and chloro.

100. The compound of any one of claims 83–99, wherein R^{10} is amino or chloro.

101. A compound of Formula (XXII):



Formula (XXII),

or an enantiomer, a mixture of enantiomers, or a mixture of two or more diastereomers thereof, or its pharmaceutically acceptable forms thereof, wherein:

W_b^5 is N, CHR^8 or CR^8;

R^8 is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heteroalkyl, alkoxy, amido, amino, acyl, acyloxy, sulfonamido, halo, cyano, hydroxyl, or nitro;

Cy is aryl or heteroaryl substituted by 0-1 occurrences of R^3 and 0-3 occurrences of R^5;

R^1 is –(L)-$R^{1'}$;

L is a bond, -S-, -N(R_{15})-, -C(R_{15})$_2$-, -C(=O)-, or –O-;

$R^{1'}$ is hydrogen, alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, alkoxy, heterocyclyloxy, amido, amino, acyl, acyloxy, alkoxycarbonyl, sulfonamido, halo, cyano, hydroxy, nitro, phosphate, urea, carbonate, substituted nitrogen,or NR′R″ wherein R′ and R″ are taken together with nitrogen to form a cyclic moiety;

each R^{15} is independently hydrogen, alkyl, cycloalkyl, or heteroalkyl;

R^3 is alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, haloalkyl, heteroalkyl, alkoxy, amido, amino, acyl, acyloxy, sulfinyl, sulfonyl, sulfoxide, sulfone, sulfonamido, halo, cyano, heteroaryl, aryl, hydroxyl, or nitro; wherein each of the above substituents can be substituted with 0, 1, 2, or 3 R^{17};

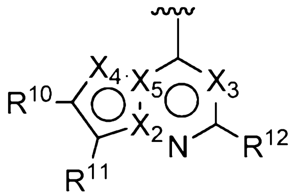
each R^5 is independently alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, alkoxy, heterocyclyloxy, amido, amino, acyl, acyloxy, alkoxycarbonyl, sulfonamido, halo, cyano, hydroxy, nitro, phosphate, urea, carbonate, or NR′R″ wherein R′ and R″ are taken together with nitrogen to form a cyclic moiety;

X is absent or is –(CH(R^9))$_z$;

Y is absent, -O-, -S-, -S(=O)-, -S(=O)$_2$-, -N(R^9)-, -C(=O)-(CHR^9)$_z$-, -C(=O)-, -N(R^9)-C(=O)-, or -N(R^9)-C(=O)NH-,-N(R^9)C(R^9)$_2$-, or -C(=O)-N(R^9)-(CHR^9)$_z$-;

each z is an integer of 1, 2, 3, or 4;

each R^9 is independently hydrogen, alkyl, cycloalkyl, heterocyclyl, heteroalkyl, aryl, halo or heteroaryl; and

W_d is 

,

wherein one of X_5 and X_2 is N and one of X_5 and X_2 is C;

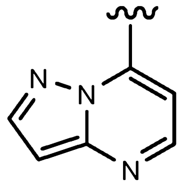
wherein X_3 and X_4 are each independently selected from CR^{13} and N; and

each R^{10}, R^{11}, R^{12}, R^{13}, and R^{17} is independently hydrogen, alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, alkoxy, heterocyclyloxy, amido, amino, acyl, acyloxy, alkoxycarbonyl, sulfonamido, halo, cyano, hydroxyl, nitro, phosphate, urea, carbonate, or NR′R″ wherein R′ and R″ are taken together with nitrogen to form a cyclic moiety.

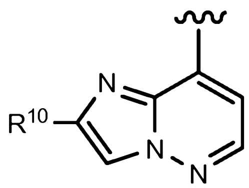
102. The compound of claim 101, wherein Cy is a 6-membered ring.

103. The compound of claim101 or claim 102, wherein Cy is a 6-membered aryl ring.

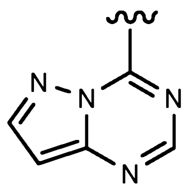
104. The compound of any one of claims 101–103, wherein W_b^5 is CH.

105. The compound of any one of claims 101–104, wherein W_d is 

.

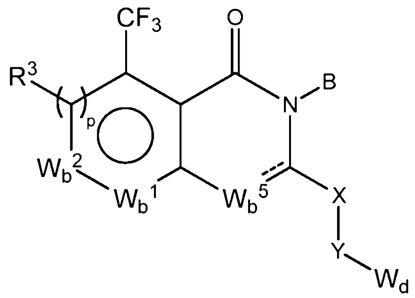
106. The compound of any one of claims 101–104, wherein W_d is 

.

107. The compound of any one of claims 101–104, wherein W_d is 

.

108. A compound of Formula (XXV):



Formula (XXV)

or an enantiomer, a mixture of enantiomers, or a mixture of two or more diastereomers thereof, or its pharmaceutically acceptable forms thereof, wherein

W_b^1 and W_b^2 are each independently CR^3, S, O, N or NR^{13}, wherein at least one of W_b^1 and W_b^2 is CR^3, N or NR^{13};

p is 0, 1, 2 or 3;

W_b^5 is CR^8, CHR^8, or N;

R^8 is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heteroalkyl, alkoxy, amido, amino, acyl, acyloxy, sulfonamido, halo, cyano, hydroxyl, or nitro;

B is hydrogen**,** alkyl, amino, heteroalkyl, cycloalkyl, heterocyclyl, heterocyclylalkyl, aryl or heteroaryl, each of which is substituted with 0-4 occurrences of R^2;

X is absent or is $–(CH(R^9))_z$-;

Y is absent, -O-, -S-, -S(=O)-, $-S(=O)_2$-, $-N(R^9)$-, $-C(=O)-(CHR^9)_z$-, -C(=O)-, $-N(R^9)-C(=O)$-, or -$N(R^9)-C(=O)NH$-,$-N(R^9)C(R^9)_2$-, or $-C(=O)-N(R^9)-(CHR^9)_z$;

each z is independently an integer of 1, 2, 3, or 4;

wherein when W_b^5 is N, no more than one of X or Y is absent;

each R^2 is independently alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, alkoxy, amido, amino, acyl, acyloxy, alkoxycarbonyl, sulfonamido, halo, cyano, hydroxyl, nitro, phosphate, urea or carbonate;

each R^3 is independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, fluoroalkyl, heteroalkyl, alkoxy, amido, amino, acyl, acyloxy, sulfinyl, sulfonyl, sulfoxide, sulfone, sulfonamido, halo, cyano, heteroaryl, aryl, hydroxyl, or nitro;

each R^9 is independently hydrogen, alkyl, cycloalkyl, heterocyclyl or heteroalkyl;

W_d is heterocyclyl, aryl, cycloalkyl, or heteroaryl which is optionally substituted with one or more R^b, R^{11} or R^{12};

wherein each R^b is independently hydrogen, halo, phosphate, urea, carbonate, alkyl, alkenyl, alkynyl, cycloalkyl, amino, heteroalkyl, or heterocyclyl; and

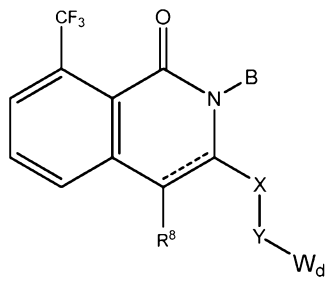
each R^{11} and R^{12} is independently hydrogen, alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, alkoxy, heterocyclyloxy, amido, amino, acyl, acyloxy, alkoxycarbonyl, sulfonamido, halo, haloalkyl, cyano, hydroxyl, nitro, phosphate, urea, carboxylic acid, carbonate, oxo, or NR′R″, wherein R′ and R″ are taken together with nitrogen to form a cyclic moiety.

109. The compound of claim 0, wherein W_b^1 and W_b^2 are CR^3.

110. The compound of claim 0, wherein W_b^1 is S and W_b^2 is CR^3.

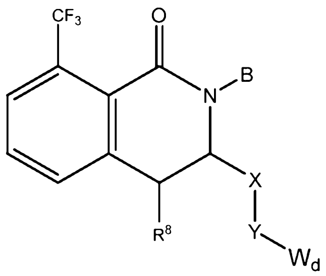
111. The compound of claim 0, wherein W_b^1 is S and W_b^2 is N.

112. The compound of claim 0, wherein the compound of Formula (XXV) has a structure of Formula (XXVI):

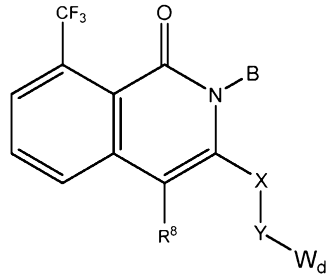


Formula (XXVI).

113. The compound of claim 112, wherein the compound of Formula (XXVI) has a structure of Formula (XXVIa) or (XXVIb):

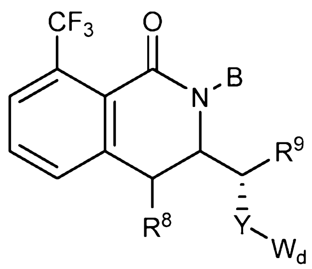


or

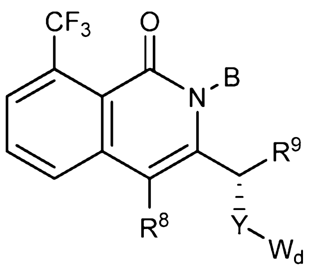


Formula (XXVIa) Formula (XXVIb).

114. The compound of claim 113, wherein the compound of Formula (XXVI) has a structure of Formula (XXVIIa) or (XXVIIb):

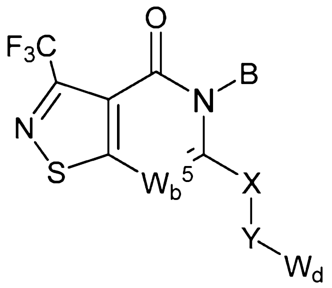


or



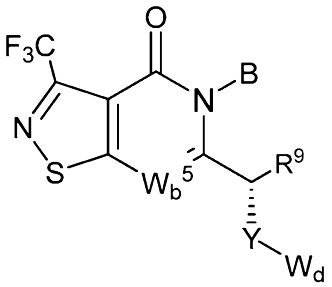
Formula (XXVIIa) Formula (XXVIIb).

115. The compound of claim 0, wherein the compound of Formula (XXV) has a structure of Formula (XXVIII):



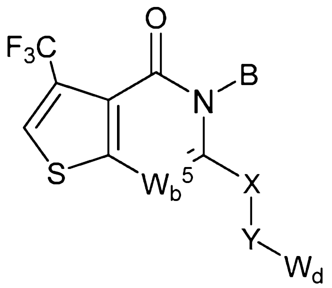
Formula (XXVIII).

116. The compound of claim 115, wherein the compound of Formula (XXVIII) has a structure of Formula (XXIX):



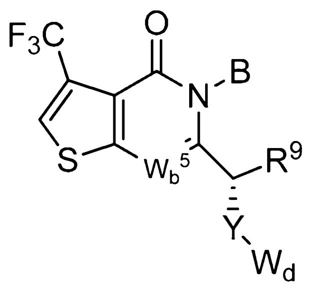
Formula (XXIX).

117. The compound of claim 0, wherein the compound of Formula (XXV) has a structure of Formula (XXX):



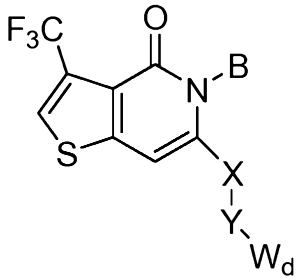
Formula (XXX).

118. The compound of claim 117, wherein the compound Formula (XXX) has a structure of Formula (XXXI):



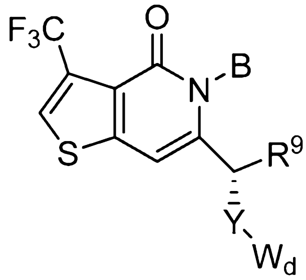
Formula (XXXI).

119. The compound of claim 118, wherein the compound of Formula (XXX) has a structure of Formula (XXXII):



Formula (XXXII).

120. The compound of claim 119, wherein the compound of Formula (XXXII) has a structure of Formula (XXXIII):



Formula (XXXIII).

121. The compound of any one of claims 0–120, wherein each R^3 is independently hydrogen, alkyl, cycloalkyl, heterocyclyl, fluoroalkyl, alkoxy, halo, cyano, heteroaryl or aryl.

122. The compound of any one of claims 0–121, wherein R^3 is hydrogen, alkyl, fluoroalkyl, alkoxy or aryl.

123. The compound of any one of claims 0–122, wherein p is 0 or 1.

124. The compound of any one of claims 0–123, wherein B is aryl substituted with 0-4 occurrences of R^2.

125. The compound of any one of claims 0–124, wherein B is phenyl substituted with 0-4 occurrences or R^2.

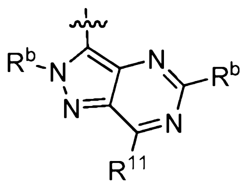
126. The compound of any one of claims 0–125, wherein X is –(CH(R^9))$_z$-.

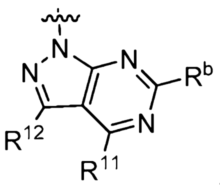
127. The compound of any one of claims 0–126, wherein z is 1.

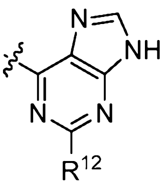
128. The compound of any one of claims 0–127, wherein Y is absent or –N(R^9)-.

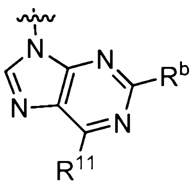
129. The compound of any one of claims 0–128, wherein W_d is heteroaryl.

130. The compound of any one of claims 0–129, wherein W_d is selected from:

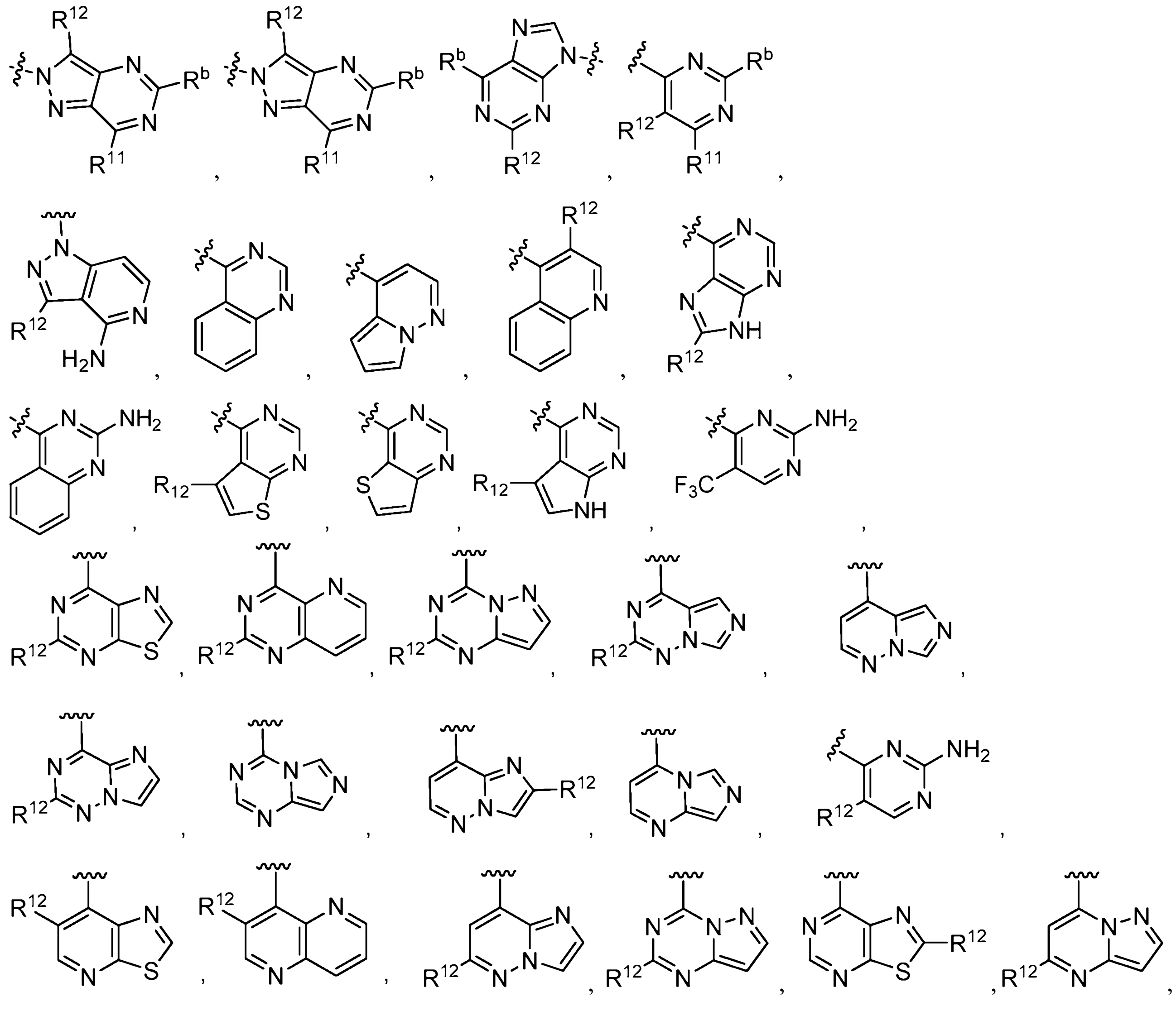


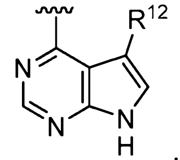
,


,


,


,



and  .

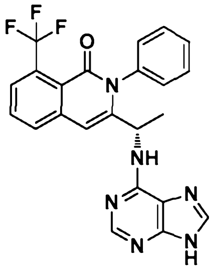
131. The compound of any one of claims 0–130, wherein R^{12} is hydrogen, alkyl,haloalkyl, halo, cyano, amino or amido.

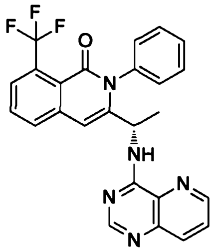
132. The compound of any one of claims 0–131, wherein R^{12} is hydrogen.

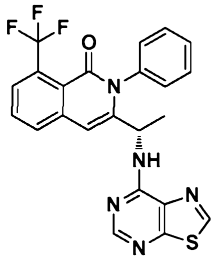
133. The compound of any one of claims 0–132, wherein R^{11} is hydrogen or amino.

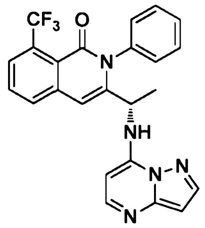
134. The compound of any one of claims 0–133, wherein R^b is hydrogen or amino.

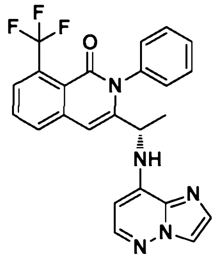
135. The compound of claim 0, wherein the compound is

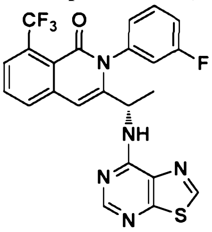

Compound III-**3**,

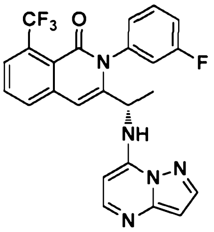

Compound III-**4**,

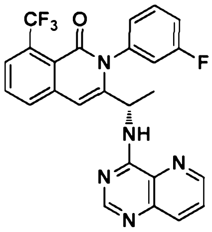

Compound III-**5**,

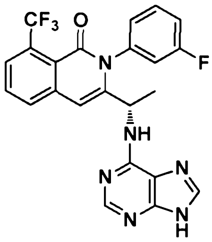

Compound III-**6**,

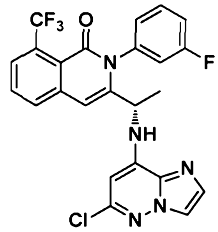

Compound III-**8**,

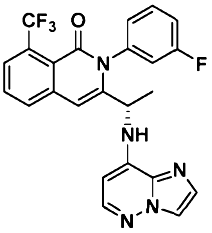

Compound III-**10**,

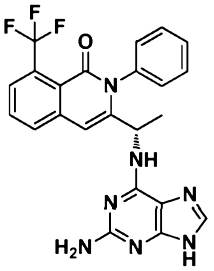

Compound III-**11**,

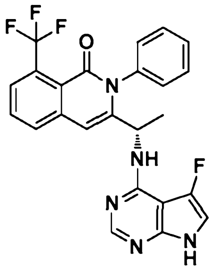

Compound III-**12**,

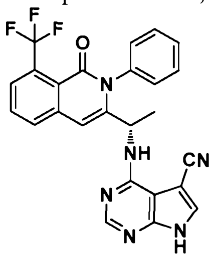

Compound III-**13**,

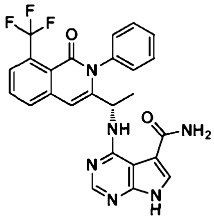

Compound III-**14**,

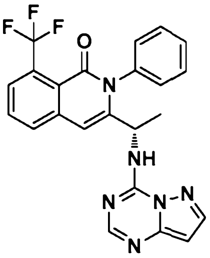

Compound III-**15**,

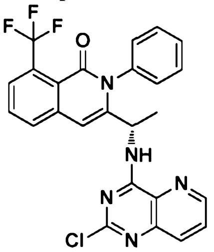

Compound III-**17**,

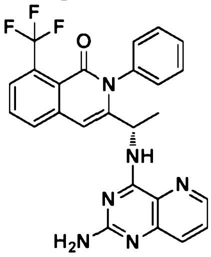

Compound III-**18**,

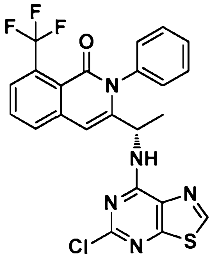

Compound III-**19**,

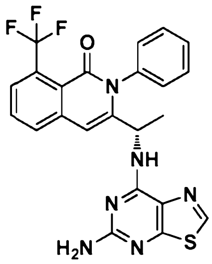

Compound III-**20**,

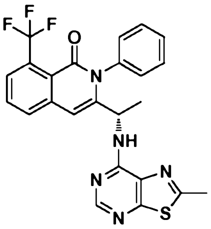

Compound III-**21**,

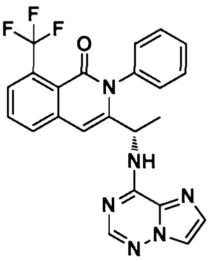

Compound III-**22**,

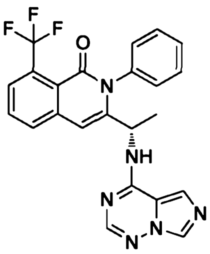

Compound III-**23**,

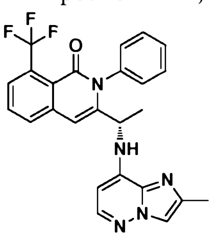

Compound III-**24**,

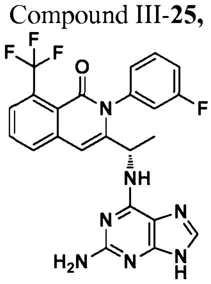

Compound III-**25**,


Compound III-**26**,


Compound III-**27**,


Compound III-**28**,


Compound III-**29**,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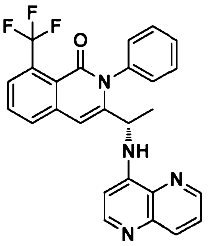
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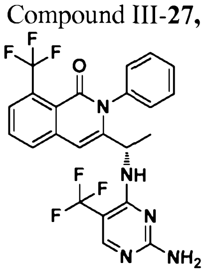
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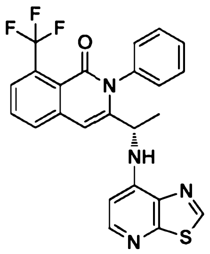
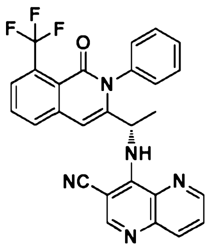
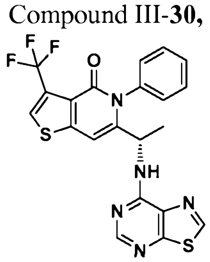

Compound III-**36**,


Compound III-**37**,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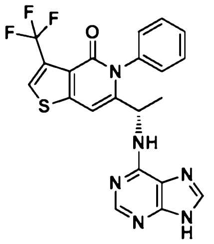

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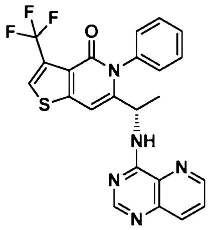
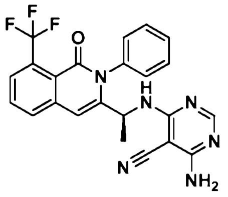
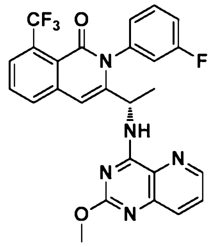


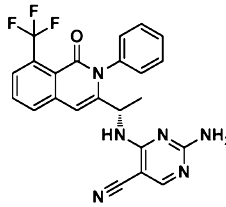
Compound III-**41**,



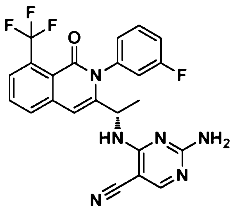
Compound III-**42**,



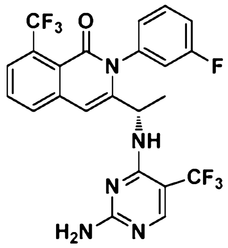
Compound III-**43**,



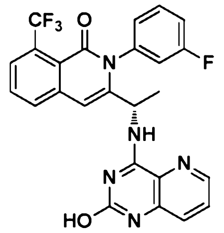
Compound III-**44**,



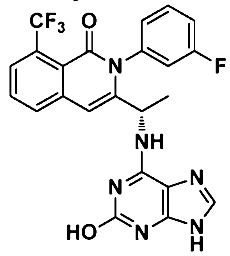
Compound III-**45**,



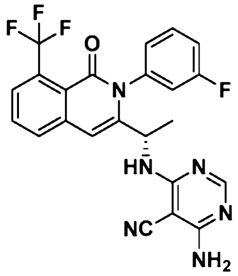
Compound III-**46**,



Compound III-**47**,



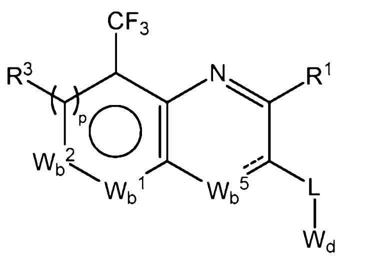
Compound III-**48**, or



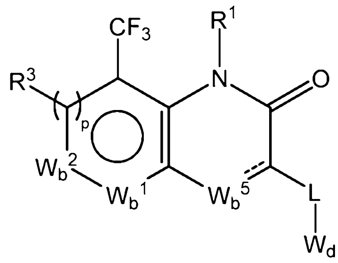
Compound **III-49**,

or a pharmaceutically acceptable form thereof.

136. A compound of Formula (XXXIV) or (XXXV):



or



Formula (XXXIV) Formula (XXXV)

or an enantiomer, a mixture of enantiomers, or a mixture of two or more diastereomers thereof, or their pharmaceutically acceptable forms thereof, wherein:

W_b^1 and W_b^2 are each independently CR^3, S, O, N or NR^{13}, wherein at least one of W_b^1 and W_b^2 is CR^3, N or NR^{13};

p is 0, 1, 2 or 3;

W_b^5 is CR^8, CHR^8, or N;

R^8 is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heteroalkyl, alkoxy, amido, amino, acyl, acyloxy, sulfonamido, halo, cyano, hydroxyl, or nitro;

R^1 is –(L)-$R^{1'}$;

L is a bond, -S-, -N(R^{15})-, -C(=O)-, or –O-;

$R^{1'}$ is hydrogen, alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, alkoxy, heterocyclyloxy, amido, amino, acyl, acyloxy, alkoxycarbonyl, sulfonamido, halo, cyano, hydroxyl, nitro, phosphate, urea, carbonate, substituted nitrogen, or NR′R″ wherein R′ and R″ are taken together with nitrogen to form a cyclic moiety;

each R^{15} is independently hydrogen, alkyl, cycloalkyl, or heteroalkyl;

X is absent or is –(CH(R^{16}))$_z$;

Y is absent, -O-, -S-, -S(=O)-, $-S(=O)_2-$, $-N(R^{16})-$, $-C(=O)-(CHR^{16})_z-$, -C(=O)-, $-N(R^{16})-C(=O)-$, or $-N(R^{16})-C(=O)NH-$, $-N(R^{16})C(R^{16})_2-$, or $-C(=O)-N(R^{16})-(CHR^{16})_z-$;

each z is an integer of 1, 2, 3, or 4;

each R^3 is independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, fluoroalkyl, heteroalkyl, alkoxy, amido, amino, acyl, acyloxy, sulfinyl, sulfonyl, sulfoxide, sulfone, sulfonamido, halo, cyano, heteroaryl, aryl, hydroxyl, or nitro;

each R^{13} is independently hydrogen, alkyl, cycloalkyl, heterocyclyl or heteroalkyl;

each R^{16} is independently hydrogen, alkyl, cycloalkyl, heterocyclyl, heteroalkyl, aryl, halo or heteroaryl;

W_d is heterocyclyl, aryl, cycloalkyl, or heteroaryl which is optionally substituted with one or more R^b, R^{11} or R^{12};

wherein each R^b is independently hydrogen, halo, phosphate, urea, carbonate, alkyl, alkenyl, alkynyl, cycloalkyl, amino, heteroalkyl, or heterocyclyl; and

each R^{11} and R^{12} is independently hydrogen, alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, alkoxy, heterocyclyloxy, amido, amino, acyl, acyloxy, alkoxycarbonyl, sulfonamido, halo, haloalkyl, cyano, hydroxyl, nitro, phosphate, urea, carboxylic acid, carbonate, oxo, or NR′R″, wherein R′ and R″ are taken together with nitrogen to form a cyclic moiety.

137. The compound of claim 136, wherein W_b^1 is CR^3 and W_b^2 is CR^3.

138. The compound of claim 136 or claim 137, wherein W_b^5 is CH.

139. The compound of any one of claims 136–138, wherein L is a bond, $-N(R^{15})-$ or -C(=O)-.

140. A pharmaceutical composition comprising a compound according to any one of claims 1–139 and one or more pharmaceutically acceptable excipients.

141. A method of treating a PI3K mediated disorder in a subject, the method comprising administering a therapeutically effective amount of a compound according to any one of claims 1–139 or a pharmaceutical composition according to claim 140 to said subject.

142. The method of claim 141, wherein the disorder is cancer, an inflammatory disease or an auto-immune disease.