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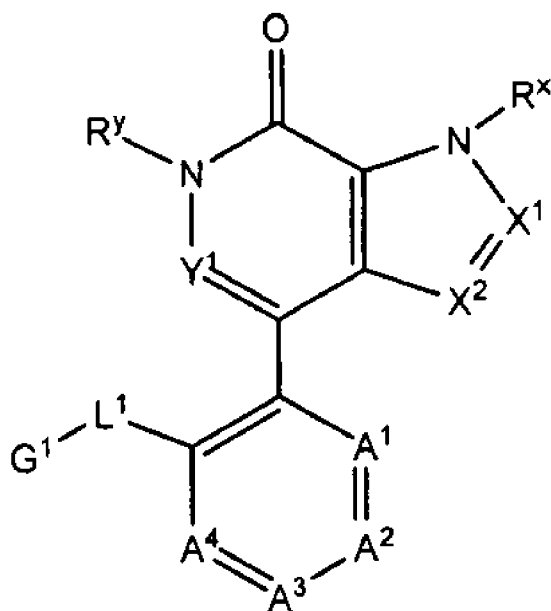
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(54) Title: BROMODOMAIN INHIBITORS



(I)

(57) Abstract: Provided are compounds of formula (I), wherein A¹, A², A³, A⁴, X¹, X², Y¹, L¹, G¹, R^x, and R^y have any of the values defined therefor in the specification, and pharmaceutically acceptable salts thereof, that are useful as agents in the treatment of diseases and conditions, including inflammatory diseases, cancer, and AIDS. Also provided are pharmaceutical compositions comprising one or more compounds of formula (I).



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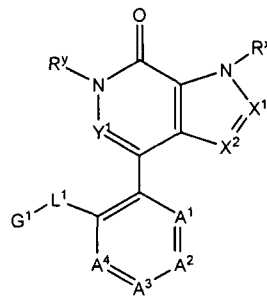
BROMODOMAIN INHIBITORS

BACKGROUND

Bromodomains refer to conserved protein structural folds which bind to N-acetylated lysine residues that are found in some proteins. The BET family of bromodomain containing proteins is comprised of four members (BRD2, BRD3, BRD4 and BRDt). Each member of the BET family employs two bromodomains to recognize N-acetylated lysine residues found primarily, but not exclusively, on the amino-terminal tails of histone proteins. These interactions modulate gene expression by recruiting transcription factors to specific genome locations within chromatin. For example, histone-bound BRD4 recruits the transcription factor P-TEFb to promoters, resulting in the expression of a subset of genes involved in cell cycle progression (Yang et al., Mol. Cell. Biol. 28: 967-976 (2008)). BRD2 and BRD3 also function as transcriptional regulators of growth promoting genes (LeRoy et al., Mol. Cell 30: 51-60 (2008)). BET family members were recently established as being important for the maintenance of several cancer types (Zuber et al., Nature 478: 524-528 (2011); Mertz et al.; Proc. Nat'l. Acad. Sci. 108: 16669-16674 (2011); Delmore et al., Cell 146: 1-14, (2011); Dawson et al., Nature 478: 529-533 (2011)). BET family members have also been implicated in mediating acute inflammatory responses through the canonical NF-KB pathway (Huang et al., Mol. Cell. Biol. 29: 1375-1387 (2009)) resulting in the upregulation of genes associated with the production of cytokines (Nicodeme et al., Nature 468: 1119-1123, (2010)). The human immunodeficiency virus utilizes BRD4 to initiate transcription of viral RNA from stably integrated viral DNA (Jang et al., Mol. Cell, 19: 523-534 (2005)). Thus, compounds that inhibit the binding of BET family bromodomains to their cognate acetylated lysine proteins are being pursued for the treatment of cancer, inflammatory diseases and some viral infections. Accordingly, there is an ongoing medical need to develop new drugs to treat these indications.

SUMMARY

In one aspect the present invention provides for compounds of formula (I) or pharmaceutically acceptable thereof,



(I)

wherein

R^x is hydrogen or C1-C3 alkyl;

5 R^y is C1-C3 alkyl, $-(C_2-C_3 \text{ alkylene})-OH$, or C-C₃ haloalkyl;

X^1 is N or CR^{x1} wherein

R^{x1} is hydrogen, C₂-C₆ alkenyl, C₂-C₆

alkynyl, $-C(0)OR^{ax1}$, $-C(0)NR^{bx1}R^{cx1}$, $-C(0)R^{dx1}$,

$S(0)_2R^{dx1}$, $-S(0)_2NR^{bx}$, R^{cx1} , G^{x1} , C₁-C₆ haloalkyl, or C-C₆ alkyl;

10 wherein the C1-C0 alkyl is optionally substituted with one substituent selected from the group consisting of OR^{ax1} , SR^{ax1} , $S(0)R^{dx1}$,

$S(0)_2R^{dx1}$,

$NR^{bx1}R^{cx1}$, $-C(0)R^{ax1}$, $-C(0)OR^{ax1}$, $-C(0)NR^{bx1}R^{cx1}$, $-S(0)_2NR^{bx1}R^{cx1}$, and G^{x1} ;

15 R^{ax1} , R^{bx1} , and R^{cx1} , at each occurrence, are each independently hydrogen, C_i-C₆ alkyl, C₁-C₆ haloalkyl, G^a , or $-(C_1-C_6 \text{ alkylene})-G^a$;

R^{dx1} , at each occurrence, are each independently C₁-C₆ alkyl, C₁-C₆ haloalkyl, G^a , or $-(C_1-C_6 \text{ alkylene})-G^a$;

X^2 is N or CR^{x2} ; wherein

20 R^{x2} is hydrogen, C₂-C₆ alkenyl, C₂-C₆

alkynyl, $-C(0)OR^{ax2}$, $-C(0)NR^{bx2}R^{cx2}$, $-C(0)R^{dx2}$,

$S(0)_2R^{dx2}$, $-S(0)_2NR^{bx2}R^{cx2}$, G^{x2} , C₁-C₆ haloalkyl, or C-C₆ alkyl;

wherein the C_i-C₆ alkyl is optionally substituted with one substituent selected from the group consisting of OR^{ax2} , SR^{ax2} , $S(0)R^{dx2}$,

25 $S(0)_2R^{dx2}$,

$NR^{bx2}R^{cx2}$, $-C(0)R^{ax2}$, $-C(0)OR^{ax2}$, $-C(0)NR^{bx2}R^{cx2}$, $-S(0)_2NR^{bx2}R^{cx2}$, and G^{x2} ;

R^{ax2} , R^{bx2} , and R^{cx2} , at each occurrence, are each independently hydrogen, C₁-C₆ alkyl, C-C₆ haloalkyl, G^b , or $-(C_1-C_6 \text{ alkylene})-G^b$;

R^{dx2} , at each occurrence, is independently Ci-C₆ alkyl, Ci-C₆ haloalkyl, G^b,
or -(Ci-C₆ alkylenyl)-G^b;

Y¹ is N or CR^U; wherein R^u is hydrogen, Ci-C₆ alkyl, halogen, or Ci-C₆ haloalkyl;
A¹ is N or CR¹, A² is N or CR², A³ is N or CR³; and A⁴ is N or CR⁴; with the proviso
5 that zero, one, two, or three of A¹, A², A³, and A⁴ are N;

R¹, R³, and R⁴ are each independently hydrogen, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆
alkynyl, halogen, Cl-C₆ haloalkyl, CN, or N₂;

R² is hydrogen, Ci-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, halogen, C₁-C₆
haloalkyl, -CN, N₂,

10 G^{2a}, -OR^{2a}, -OC(O)R^{2d}, -OC(O)NR^{2b}R^{2c}, -SR^{2a}, -S(O)₂R^{2d}, -S(O)₂NR^{2b}R^{2c}, -C(O)R^{2d},
-C(O)OR^{2a}, -C(O)NR^{2b}R^{2c}, -NR^{2b}R^{2c}, -N(R^{2e})C(O)R^{2d}, -N(R^{2e})S(O)₂R^{2d},
-N(R^{2e})C(O)R^{2d}, -N(R^{2e})C(O)NR^{2b}R^{2c}, -N(R^{2e})S(O)₂NR^{2b}R^{2c}, -(Ci-C₆
alkylenyl)-G^{2a}, -(C₁-C₆ alkylenyl)-OR^{2a}, -(C₁-C₆ alkylenyl)-OC(O)R^{2d}, -(C₁-
C₆ alkylenyl)-OC(O)NR^{2b}R^{2c}, -(C₁-C₆ alkylenyl)-S(O)₂R^{2d}, -(C₁-C₆
15 alkylenyl)-S(O)₂NR^{2b}R^{2c}, -(Ci-C₆ alkylenyl)-C(O)R^{2d}, -(Ci-C₆
alkylenyl)-C(O)OR^{2a}, -(C₁-C₆ alkylenyl)-C(O)NR^{2b}R^{2c}, -(C₁-C₆
alkylenyl)-NR^{2b}R^{2c}, -(C₁-C₆ alkylenyl)-N(R^{2e})C(O)R^{2d}, -(C₁-C₆
alkylenyl)-N(R^{2e})S(O)₂R^{2d}, -(C₁-C₆ alkylenyl)-N(R^{2e})C(O)R^{2a}, -(C₁-C₆
alkylenyl)-N(R^{2e})C(O)NR^{2b}R^{2c}, -(C₁-C₆ alkylenyl)-N(R^{2e})S(O)₂NR^{2b}R^{2c}, and
20 -(C₁-C₆ alkylenyl)-CN;

R^{2a}, R^{2b}, R^{2c}, and R^{2e}, at each occurrence, are each independently hydrogen, C₂-C₆
alkenyl, C₂-C₆ alkynyl, C₁-C₆ haloalkyl, G^{2b}, or C₁-C₆ alkyl wherein the C₁-C₆
alkyl is optionally substituted with one substituent selected from the group
consisting of-OR^{z1},

25 NR^{z1}R^{z2}, -C(O)OR^{z1}, -C(O)NR^{z1}R^{z2}, -S(O)₂R^{z1}, -S(O)₂NR^{z1}R^{z2}, and G^{2b};

R^{2d}, at each occurrence, is independently C₂-C₆ alkenyl, C₂-C₆ alkynyl, Ci-C₆
haloalkyl, G^{2b}, or Ci-C₆ alkyl wherein the C₁-C₆ alkyl is optionally substituted
with one substituent selected from the group consisting of -OR^{z1},

NR^{z1}R^{z2}, -C(O)OR^{z1}, -C(O)NR^{z1}R^{z2}, -S(O)₂R^{z1}, -S(O)₂NR^{z1}R^{z2}, and G^{2b};

30 R^{z1} and R^{z2}, at each occurrence, are each independently hydrogen, Ci-C₆ alkyl, or Cl-
C₆ haloalkyl;

G^{x1}, G^{x2}, G^a, G^b, G^{2a}, and G^{2b}, at each occurrence, are each independently aryl,
heteroaryl, heterocycle, cycloalkyl, or cycloalkenyl, and each of which is
independently unsubstituted or substituted with 1, 2, 3, 4, or 5 of R^v;

L^1 is absent, CH_2 , $C(O)$, $(CH_2)_mO$, $(CH_2)_mS(O)$, wherein n is 0, 1, or 2; or
 $(CH_2)_mN(R^z)$ wherein R^z is hydrogen, C_1 - C_3 alkyl, C - C_3 haloalkyl, $(C_2$ - C_3
 alkylene)-OH, or unsubstituted cyclopropyl;

m is 0 or 1;

5 G^1 is G^{1a} or $-(C_1$ - C_6 alkylene)- G^{1a} ; wherein each G^{1a} is independently aryl, heteroaryl, heterocycle, cycloalkyl, or cycloalkenyl, and each G^{1a} is independently unsubstituted or substituted with 1, 2, 3, 4, or 5 of R^w ;

R^v and R^w , at each occurrence, are each independently C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, halogen, C_1 - C_6 haloalkyl, -CN,

10 oxo, $-OR^h$, $-OC^iR^i$, $-OC(O)NR^jR^k$, $-SR^h$, $-S(O)_2R^h$, $-S(O)_2NR^jR^k$, $-C(O)R^h$, $-C(O)OR^h$, $-C(O)NR^jR^k$, $-NR^jR^k$, $-N(R^h)C(O)R^i$, $-N(R^h)S(O)_2R^i$, $-N(R^h)C(O)O(R^i)$, $-N(R^h)C(O)NR^jR^k$, $-(C_1$ - C_6 alkylene)- OR^h , $-(C_1$ - C_6 alkylene)- $OCCO^i$, $-(C_1$ - C_6 alkylene)- $OC(O)NR^jR^k$, $-(C_1$ - C_6 alkylene)- $S(O)_2R^h$, $-(C_1$ - C_6 alkylene)- $S(O)_2NR^jR^k$, $-(C_1$ - C_6 alkylene)- $C(O)R^h$, $-(C_1$ - C_6 alkylene)- $C(O)OR^h$, $-(C_1$ - C_6 alkylene)- $C(O)NR^jR^k$, $-(C_1$ - C_6 alkylene)- NR^jR^k , $-(C_1$ - C_6 alkylene)- $N(R^h)C(O)R^i$, $-(C_1$ - C_6 alkylene)- $N(R^h)S(O)_2R^i$, $-(C_1$ - C_6 alkylene)- $N(R^h)C(O)O(R^i)$, $-(C_1$ - C_6 alkylene)- $N(R^h)C(O)NR^jR^k$, or $-(C_1$ - C_6 alkylene)-CN;

20 R^h , R^j , R^k , at each occurrence, are each independently hydrogen, C_1 - C_6 alkyl, or C_1 - C_6 haloalkyl; and

R^i , at each occurrence, is independently C_1 - C_6 alkyl or C_1 - C_6 haloalkyl.

In another aspect, the present invention provides for methods for treating or preventing disorders that are ameliorated by inhibition of BET. Such methods comprise of administering to the subject a therapeutically effective amount of a compound of formula (I), alone, or in combination with a pharmaceutically acceptable carrier.

Some of the methods are directed to treating or preventing an inflammatory disease or cancer or AIDS.

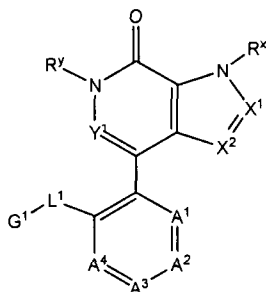
A further aspect of the invention provides the use of a compound of formula (I), alone or in combination with a second active pharmaceutical agent, in the manufacture of a medicament for treating or preventing conditions and disorders disclosed herein, with or without a pharmaceutically acceptable carrier.

Pharmaceutical compositions comprising a compound of formula (I), or a pharmaceutically acceptable salt, alone or in combination with a second active

pharmaceutical agent, are also provided.

DETAILED DESCRIPTION

Disclosed herein are compounds of formula (I)



(I)

wherein A¹, A², A³, A⁴, X¹, X², Y¹, L¹, G¹, R^x, and R^y are defined above in the Summary of the Invention and below in the Detailed Description. Further, compositions comprising such compounds and methods for treating conditions and disorders using such compounds and compositions are also disclosed.

Compounds disclosed herein may contain one or more variable(s) that occur more than one time in any substituent or in the formulae herein. Definition of a variable on each occurrence is independent of its definition at another occurrence. Further, combinations of substituents are permissible only if such combinations result in stable compounds. Stable compounds are compounds, which can be isolated from a reaction mixture.

a). Definitions

It is noted that, as used in this specification and the intended claims, the singular form "a," "an," and "the" include plural referents unless the context clearly dictates otherwise. Thus, for example, reference to "a compound" includes a single compound as well as one or more of the same or different compounds, reference to "optionally a pharmaceutically acceptable carrier" refers to a single optional pharmaceutically acceptable carrier as well as one or more pharmaceutically acceptable carriers, and the like.

As used in the specification and the appended claims, unless specified to the contrary, the following terms have the meaning indicated:

The term "alkenyl" as used herein, means a straight or branched hydrocarbon chain containing from 2 to 10 carbons and containing at least one carbon-carbon double bond, optionally substituted with 1, 2, or 3 halogen atoms. The term "C₂-C₆ alkenyl" means an alkenyl group containing 2-6 carbon atoms. Non-limiting examples of alkenyl include buta-

1,3-dienyl, ethenyl, 2-propenyl, 2-methyl-2-propenyl, 3-butenyl, 4-pentenyl, 5-hexenyl, 2-heptenyl, 2-methyl-1-heptenyl, and 3-decenyl.

The term "alkenylene" means a divalent group derived from a straight or branched chain hydrocarbon of 2 to 4 carbon atoms and contains at least one carbon-carbon double bond. Representative examples of alkenylene include, but are not limited to, **-CH=CH-** and **-CH₂CH=CH-**.

The term "alkyl" as used herein, means a saturated, straight or branched hydrocarbon chain radical. In some instances, the number of carbon atoms in an alkyl moiety is indicated by the prefix "C_x-C_y", wherein x is the minimum and y is the maximum number of carbon atoms in the substituent. Thus, for example, "C₁-C₆ alkyl" refers to an alkyl substituent containing from 1 to 6 carbon atoms and "C₁-C₃ alkyl" refers to an alkyl substituent containing from 1 to 3 carbon atoms. Representative examples of alkyl include, but are not limited to, methyl, ethyl, n-propyl, iso-propyl, n-butyl, sec-butyl, iso-butyl, tert-butyl, n-pentyl, isopentyl, neopentyl, n-hexyl, 1-methylbutyl, 2-methylbutyl, 3-methylbutyl, 1,1-dimethylpropyl, 1,2-dimethylpropyl, 2,2-dimethylpropyl, 1-methylpropyl, 1-ethylpropyl, 1,2,2-trimethylpropyl, 3-methylhexyl, 2,2-dimethylpentyl, 2,3-dimethylpentyl, *rc*-heptyl, *n*-octyl, *n*-nonyl, and *w*-decyl.

The term "alkylene" or "alkylenyl" means a divalent radical derived from a straight or branched, saturated hydrocarbon chain, for example, of 1 to 10 carbon atoms or of 1 to 6 carbon atoms (C₁-C₆ alkylenyl) or of 1 to 4 carbon atoms or of 2 to 3 carbon atoms (C₂-C₃ alkylenyl). Examples of alkylene and alkylenyl include, but are not limited to, **-CH₂-**, **-CH₂CH₂-**, **-CH₂CH₂CH₂-**, **-CH₂CH₂CH₂CH₂-**, and **-CH₂CH(CH₃)CH₂-**.

The term "alkynyl" as used herein, means a straight or branched chain hydrocarbon radical containing from 2 to 10 carbon atoms and containing at least one carbon-carbon triple bond, optionally substituted with 1, 2, or 3 halogen atoms. The term "C₂-C₆ alkynyl" means an alkynyl group of 2 to 6 carbon atoms. Representative examples of alkynyl include, but are not limited, to acetylenyl, 1-propynyl, 2-propynyl, 3-butyne, 2-pentyne, and 1-butyne.

The term "aryl" as used herein, means phenyl or a bicyclic aryl. The bicyclic aryl is naphthyl, or a phenyl fused to a monocyclic cycloalkyl, or a phenyl fused to a monocyclic cycloalkenyl. Non-limiting examples of the aryl groups include dihydroindenyl, indenyl, naphthyl, dihydronaphthalenyl, and tetrahydronaphthalenyl. The bicyclic aryls are attached to the parent molecular moiety through any carbon atom contained within the bicyclic ring systems and can be unsubstituted or substituted.

The term "cycloalkyl" as used herein, refers to a radical that is a monocyclic cyclic alkyl, a bicyclic cycloalkyl, or a spiro cycloalkyl. The monocyclic cycloalkyl is a carbocyclic ring system containing three to eight carbon atoms, zero heteroatoms and zero double bonds. Examples of monocyclic ring systems include cyclopropyl, cyclobutyl, cyclopentyl, 5 cyclohexyl, cycloheptyl, and cyclooctyl. The bicyclic cycloalkyl is a monocyclic cycloalkyl fused to a monocyclic cycloalkyl ring. The monocyclic and the bicyclic cycloalkyl groups may contain one or two alkylene bridges, each consisting of one, two, three, or four carbon atoms in length, and each bridge links two non-adjacent carbon atoms of the ring system. Non-limiting examples of bicyclic ring systems include bicyclo[3.1.1]heptane, 10 bicyclo[2.2.1]heptane, bicyclo[2.2.2]octane, bicyclo[3.2.2]nonane, bicyclo[3.3.1]nonane, and bicyclo[4.2.1]nonane, tricyclo[3.3.1.0^{3,7}]nonane (octahydro-2,5-methanopentalene or noradamantane), and tricyclo[3.3.1.1^{3,7}]decane (adamantane). A spiro cycloalkyl is a monocyclic cycloalkyl wherein two substituents on the same carbon atom of the monocyclic cycloalkyl ring together with said carbon atom form a second monocyclic cycloalkyl ring. 15 The monocyclic, the bicyclic, and the spiro cycloalkyl groups can be unsubstituted or substituted, and are attached to the parent molecular moiety through any substitutable atom contained within the ring system.

The term "cycloalkenyl" as used herein, refers to a monocyclic or a bicyclic hydrocarbon ring radical. The monocyclic cycloalkenyl has four-, five-, six-, seven- or eight 20 carbon atoms and zero heteroatoms. The four-membered ring systems have one double bond, the five- or six-membered ring systems have one or two double bonds, and the seven- or eight-membered ring systems have one, two, or three double bonds. Representative examples of monocyclic cycloalkenyl groups include, but are not limited to, cyclobutenyl, cyclopentenyl, cyclohexenyl, cycloheptenyl, and cyclooctenyl. The bicyclic cycloalkenyl is a 25 monocyclic cycloalkenyl fused to a monocyclic cycloalkyl group, or a monocyclic cycloalkenyl fused to a monocyclic cycloalkenyl group. The monocyclic or bicyclic cycloalkenyl ring may contain one or two alkylene bridges, each consisting of one, two, or three carbon atoms, and each linking two non-adjacent carbon atoms of the ring system. Representative examples of the bicyclic cycloalkenyl groups include, but are not limited to, 30 4,5,6,7-tetrahydro-3aH-indene, octahydronaphthalenyl, and 1,6-dihydro-pentalene. The monocyclic and bicyclic cycloalkenyls can be attached to the parent molecular moiety through any substitutable atom contained within the ring systems, and can be unsubstituted or substituted.

The term "halo" or "halogen" as used herein, means Cl, Br, I, and F.

The term "haloalkyl" as used herein, means an alkyl group, as defined herein, in which one, two, three, four, five or six hydrogen atoms are replaced by halogen. The term "C1-C6 haloalkyl" means a C₁-C₆ alkyl group, as defined herein, in which one, two, three, four, five or six hydrogen atoms are replaced by halogen. The term "C₁-C₃ haloalkyl" means
5 a C₁-C₃ alkyl group, as defined herein, in which one, two, or three hydrogen atoms are replaced by halogen. Representative examples of haloalkyl include, but are not limited to, chloromethyl, 2-fluoroethyl, 2,2-difluoroethyl, 2,2,2-trifluoroethyl, trifluoromethyl, difluoromethyl, pentafluoroethyl, 2-chloro-3-fluoropentyl, trifluorobutyl, and trifluoropropyl.

The term "heterocycle" or "heterocyclic" as used herein, means a radical of a
10 monocyclic heterocycle, a bicyclic heterocycle, and a spiro heterocycle. A monocyclic heterocycle is a three-, four-, five-, six-, seven-, or eight-membered carbocyclic ring also containing at least one heteroatom independently selected from the group consisting of O, N, and S. A three- or four-membered ring contains zero or one double bond, and one heteroatom selected from the group consisting of O, N, and S. When two O atoms or one O
15 atom and one S atom are present in a heterocyclic ring, then the two O atoms or one O atom and one S atom are not bonded directly to each other. A five-membered ring contains zero or one double bond and one, two, or three heteroatoms selected from the group consisting of O, N, and S. Examples of five-membered heterocyclic rings include those containing in the ring:
20 1 O; 1 S; 1 N; 2 N; 3 N; 1 S and 1 N; 1 S, and 2 N; 1 O and 1 N; or 1 O and 2 N. Examples of 5-membered heterocyclic groups include tetrahydrofuranyl, dihydrofuranyl, tetrahydrothienyl, dihydrothienyl, imidazolidinyl, oxazolidinyl, imidazolyl, isoxazolidinyl, pyrrolidinyl, 2-pyrrolinyl, and 3-pyrrolinyl. A six-membered ring contains zero, one, or two double bonds and one, two, or three heteroatoms selected from the group consisting of O, N, and S. Examples of six-membered heterocyclic rings include those containing in the ring:
25 O; 2 O; 1 S; 2 S; 1 N; 2 N; 3 N; 1 S, 1 O, and 1 N; 1 S and 1 N; 1 S and 2 N; 1 S and 1 O; 1 S and 2 O; 1 Q and 1 N; and 1 O and 2 N. Examples of 6-membered heterocyclic groups include tetrahydropyranyl, dihydropyranyl, dioxanyl, 1,3-dioxolanyl, 1,4-dithianyl, hexahydropyrimidine, morpholinyl, piperazinyl, piperidinyl, 2H-pyranyl, 4H-pyranyl, pyrazolidinyl, pyrazolyl, 1,2,3,6-tetrahydropyridinyl, tetrahydrothiopyranyl, 1,1-dioxo-
30 hexahydro-1-thiopyranyl, 1,1-dioxo-R⁶-thiomorpholinyl, thiomorpholinyl, thioxanyl, and trithianyl. Seven- and eight-membered rings contains zero, one, two, or three double bonds and one, two, or three heteroatoms selected from the group consisting of O, N, and S. Representative examples of monocyclic heterocycles include, but are not limited to, azetidyl, azepanyl, aziridinyl, diazepanyl, 1,3-dioxanyl, 1,3-dioxolanyl, 1,3-dithiolanyl,

1,3-dithianyl, imidazolynyl, imidazolidynyl, isothiazolynyl, isothiazolidynyl, isoxazolynyl, isoxazolidynyl, morpholynyl, oxadiazolynyl, oxadiazolidynyl, oxazolynyl, oxazolidynyl, oxetanyl, piperazynyl, piperidynyl, pyranyl, pyrazolynyl, pyrazolidynyl, pyrrolynyl, pyrrolidynyl, tetrahydrofuranyl, tetrahydropyridynyl, tetrahydropyranyl, tetrahydrothienyl, thiadiazolynyl, thiadiazolidynyl, thiazolynyl, thiazolidynyl, thiomorpholynyl, thiopyranyl, and trithianyl. The bicyclic heterocycle is a monocyclic heterocycle fused to a phenyl group, or a monocyclic heterocycle fused to a monocyclic cycloalkyl, or a monocyclic heterocycle fused to a monocyclic cycloalkenyl, or a monocyclic heterocycle fused to a monocyclic heterocycle. Representative examples of bicyclic heterocycles include, but are not limited to, benzopyranyl, benzothiopyranyl, 2,3-dihydrobenzofuranyl, 2,3-dihydrobenzothienyl, 2,3-dihydro-1H-indolyl, 3,4-dihydroisoquinolin-2(1H)-yl, 2,3,4,6-tetrahydro-1H-pyrido[1,2-a]pyrazin-2-yl, hexahydropyrano[3,4-b][1,4]oxazin-1(5H)-yl. The monocyclic heterocycle and the bicyclic heterocycle may contain one or two alkylene bridges or an alkenylene bridge, or mixture thereof, each consisting of no more than four carbon atoms and each linking two non adjacent atoms of the ring system. Examples of such bridged heterocycle include, but are not limited to, azabicyclo[2.2.1]heptyl (including 2-azabicyclo[2.2.1]hept-2-yl), 8-azabicyclo[3.2.1]oct-8-yl, octahydro-2,5-epoxypentalene, hexahydro-2*H*-2,5-methanocyclopenta[6]furan, hexahydro-1*H*-1,4-methanocyclopenta[*c*]furan, aza-admantane (1-azatricyclo[3.3.1.1^{3,7}]decane), and oxa-adamantane (2-oxatricyclo[3.3.1.1^{3,7}]decane). A spiro heterocycle is a monocyclic heterocycle wherein two substituents on the same carbon atom of the monocyclic heterocycle ring together with said carbon atom form a second ring system selected from a monocyclic cycloalkyl, a bicyclic cycloalkyl, a monocyclic heterocycle, or a bicyclic heterocycle. Examples of spiro heterocycle include, but not limited to, 6-azaspiro[2.5]oct-6-yl, 1'*H*, 4*H*-spiro[1,3-benzodioxine-2,4'-piperidin]-1'-yl, 1'*H*, 3*H*-spiro[2-benzofuran-1,4'-piperidin]-1'-yl, and 1,4-dioxa-8-azaspiro[4.5]dec-8-yl. The monocyclic, the bicyclic, and the spiro heterocycles can be unsubstituted or substituted. The monocyclic, the bicyclic and the spiro heterocycles are connected to the parent molecular moiety through any carbon atom or any nitrogen atom contained within the ring systems. The nitrogen and sulfur heteroatoms in the heterocycle rings may optionally be oxidized (e.g. 1,1-dioxidotetrahydrothienyl, 1,2-dioxido-1,2-thiazolidynyl, 1,1-dioxidothiomorpholynyl) and the nitrogen atoms may optionally be quarternized.

The term "heteroaryl" as used herein, means a monocyclic heteroaryl and a bicyclic heteroaryl. The monocyclic heteroaryl is a five- or six-membered ring. The five-membered ring contains two double bonds. The five membered ring may contain one heteroatom

selected from O or S; or one, two, three, or four nitrogen atoms and optionally one oxygen or one sulfur atom. The six-membered ring contains three double bonds and one, two, three or four nitrogen atoms. Representative examples of monocyclic heteroaryl include, but are not limited to, furanyl, imidazolyl, isoxazolyl, isothiazolyl, oxadiazolyl, 1,3-oxazolyl, pyridinyl, 5 pyridazinyl, pyrimidinyl, pyrazinyl, pyrazolyl, pyrrolyl, tetrazolyl, thiadiazolyl, 1,3-thiazolyl, thienyl, triazolyl, and triazinyl. The bicyclic heteroaryl consists of a monocyclic heteroaryl fused to a phenyl, or a monocyclic heteroaryl fused to a monocyclic cycloalkyl, or a monocyclic heteroaryl fused to a monocyclic cycloalkenyl, or a monocyclic heteroaryl fused to a monocyclic heteroaryl, or a monocyclic heteroaryl fused to a monocyclic heterocycle.

10 Representative examples of bicyclic heteroaryl groups include, but are not limited to, benzofuranyl, benzothienyl, benzoxazolyl, benzimidazolyl, benzoxadiazolyl, phthalazinyl, 2,6-dihydropyrrolo[3,4-c]pyrazol-5(4H)-yl, 6,7-dihydro-pyrazolo[1,5-a]pyrazin-5(4H)-yl, 6,7-dihydro-1,3-benzothiazolyl, imidazo[1,2-a]pyridinyl, indazolyl, indolyl, isoindolyl, isoquinolinyl, naphthyridinyl, pyridoimidazolyl, quinolinyl, 2,4,6,7-tetrahydro-5H-

15 pyrazolo[4,3-c]pyridin-5-yl, thiazolo[5,4-b]pyridin-2-yl, thiazolo[5,4-d]pyrimidin-2-yl, and 5,6,7,8-tetrahydroquinolin-5-yl. The monocyclic and bicyclic heteroaryl groups can be substituted or unsubstituted and are connected to the parent molecular moiety through any substitutable carbon atom or any substitutable nitrogen atom contained within the ring systems. The nitrogen atom in the heteroaryl rings may optionally be oxidized and may

20 optionally be quarternized.

The term "heteroatom" as used herein, means a nitrogen, oxygen, and sulfur.

The term "oxo" as used herein, means a =O group.

If a moiety is described as "substituted", a non-hydrogen radical is in the place of hydrogen radical of any substitutable atom of the moiety. Thus, for example, a substituted 25 heterocycle moiety is a heterocycle moiety in which at least one non-hydrogen radical is in the place of a hydrogen radical on the heterocycle. It should be recognized that if there are more than one substitution on a moiety, each non-hydrogen radical may be identical or different (unless otherwise stated).

If a moiety is described as being "optionally substituted," the moiety may be either (1) 30 not substituted or (2) substituted. If a moiety is described as being optionally substituted with up to a particular number of non-hydrogen radicals, that moiety may be either (1) not substituted; or (2) substituted by up to that particular number of non-hydrogen radicals or by up to the maximum number of substitutable positions on the moiety, whichever is less. Thus, for example, if a moiety is described as a heteroaryl optionally substituted with up to 3 non-

hydrogen radicals, then any heteroaryl with less than 3 substitutable positions would be optionally substituted by up to only as many non-hydrogen radicals as the heteroaryl has substitutable positions. To illustrate, tetrazolyl (which has only one substitutable position) would be optionally substituted with up to one non-hydrogen radical. To illustrate further, if
5 an amino nitrogen is described as being optionally substituted with up to 2 non-hydrogen radicals, then a primary amino nitrogen will be optionally substituted with up to 2 non-hydrogen radicals, whereas a secondary amino nitrogen will be optionally substituted with up to only 1 non-hydrogen radical.

The terms "treat", "treating", and "treatment" refer to a method of alleviating or
10 abrogating a disease and/or its attendant symptoms.

The terms "prevent", "preventing", and "prevention" refer to a method of preventing the onset of a disease and/or its attendant symptoms or barring a subject from acquiring a disease. As used herein, "prevent", "preventing" and "prevention" also include delaying the onset of a disease and/or its attendant symptoms and reducing a subject's risk of acquiring a
15 disease.

The phrase "therapeutically effective amount" means an amount of a compound, or a pharmaceutically acceptable salt thereof, sufficient to prevent the development of or to alleviate to some extent one or more of the symptoms of the condition or disorder being treated when administered alone or in conjunction with another pharmaceutical agent or
20 treatment in a particular subject or subject population. For example in a human or other mammal, a therapeutically effective amount can be determined experimentally in a laboratory or clinical setting, or may be the amount required by the guidelines of the United States Food and Drug Administration, or equivalent foreign agency, for the particular disease and subject being treated.

The term "subject" is defined herein to refer to animals such as mammals, including, but not limited to, primates (e.g., humans), cows, sheep, goats, horses, dogs, cats, rabbits, rats, mice and the like. In preferred embodiments, the subject is a human.

b. Compounds

Compounds of the invention have the general formula (I) as described above.

Particular values of variable groups in compounds of formula (I) are as follows. Such
30 values may be used where appropriate with any of the other values, definitions, claims or embodiments defined hereinbefore or hereinafter.

In compounds of formula (I), R^x is as defined in the Summary. For example, in certain embodiments, R^x is hydrogen or methyl. In certain embodiments, R^x is hydrogen.

R^y , in compounds of formula (I), is as disclosed in the Summary. For example, in certain embodiments, R^y is C1-C3 alkyl (e.g. methyl, ethyl). In certain embodiments, R^y is methyl.

X^1 is as disclosed in the Summary. For example, in certain embodiments, X^1 is N. In certain embodiments, X^1 is CR^{x1} . R^{x1} is as defined in the Summary or embodiments herein. In certain embodiments, R^{x1} is hydrogen, $-C(0)OR^{ax1}$, $-C(0)NR^{bx1}R^{cx1}$, G^{x1} , or C₁-C₆ alkyl wherein the C₁-C₆ alkyl is optionally substituted with OR^{ax1} . In certain embodiments, R^{x1} is hydrogen, $-C(0)OR^{ax1}$, $-C(0)NR^{bx1}R^{cx1}$, optionally substituted phenyl, or C₁-C₆ alkyl wherein the C₁-C₆ alkyl is optionally substituted with OR^{ax1} . In certain embodiments, R^{x1} is hydrogen, $-C(0)OR^{ax1}$, or $-C(0)NR^{bx1}R^{cx1}$. In certain embodiments, R^{x1} is hydrogen or unsubstituted C₁-C₆ alkyl. In certain embodiments, R^{x1} is $-C(0)OR^{ax1}$, $-C(0)NR^{bx1}R^{cx1}$, or C₁-C₆ alkyl substituted with OR^{ax1} . R^{ax1} , R^{bx1} , and R^{cx1} , are as disclosed in the Summary. For example, R^{ax1} and R^{bx1} , are each independently hydrogen, C₁-C₆ alkyl (e.g. methyl, ethyl, isopropyl), or C₁-C₆ haloalkyl (e.g. trifluoromethyl). In certain embodiments, R^{ax1} and R^{bx1} , are each independently hydrogen or C₁-C₆ alkyl (e.g. methyl, ethyl, isopropyl). In certain embodiments, R^{ax1} and R^{bx1} , are each independently hydrogen, methyl, or ethyl. R^{cx1} , for example, is hydrogen, C₁-C₆ alkyl (e.g. methyl, ethyl, isopropyl), or C₁-C₆ haloalkyl (e.g. trifluoromethyl), wherein the C₁-C₆ alkyl is optionally substituted with G^{x1} . In certain embodiments, R^{cx1} , for example, is hydrogen or C₁-C₆ alkyl (e.g. methyl, ethyl, isopropyl).

X^2 is as disclosed in the Summary. For example, in certain embodiments, X^2 is N. In certain embodiments, X^2 is CR^{x2} . R^{x2} is as defined in the Summary or embodiments herein. In certain embodiments, R^{x2} is hydrogen or C₁-C₆ alkyl (e.g. methyl). In certain embodiments, R^{x2} is hydrogen.

Y^1 is N or CR^u . For example, in certain embodiments, Y^1 is N. In certain embodiments, Y^1 is CR^u . R^u is as defined in the Summary and embodiments herein. For example, in certain embodiments, R^u is hydrogen or C₁-C₆ alkyl (e.g. methyl). In certain embodiments, R^u is hydrogen or C1-C3 alkyl (e.g. methyl). In certain embodiments, R^u is hydrogen or methyl. In certain embodiments, R^u is hydrogen.

A^1 , A^2 , A^3 , and A^4 are as defined in the Summary. In certain embodiments, A^1 is CR^1 , A^2 is CR^2 , A^3 is CR^3 , and A^4 is CR^4 ; or one of A^1 , A^2 , A^3 , and A^4 is N. In certain embodiments, A^1 is CR^1 , A^2 is CR^2 , A^3 is CR^3 , and A^4 is CR^4 . In certain embodiments, one of A^1 , A^2 , A^3 , and A^4 is N. In the embodiments that one of A^1 , A^2 , A^3 , and A^4 is N, example of a group of compound includes, but is not limited to, those wherein A^1 is CR^1 , A^2 is CR^2 , A^3 is CR^3 , and A^4 is N. In certain embodiments, two of A^1 , A^2 , A^3 , and A^4 are N, for

example, A^1 is N, A^2 is CR^2 , A^3 is N, and A^4 is CR^4 ; or for example, A^1 is N, A^2 is CR^2 , A^3 is CR^3 , and A^4 is N. In certain embodiments, three of A^1 , A^2 , A^3 , and A^4 are N, for example, A^1 is N, A^2 is CR^2 , A^3 is N, and A^4 is N.

R^1 , R^3 , and R^4 , are as defined in the Summary. For example, in certain embodiments,
 5 R^1 , R^3 , and R^4 , are each independently hydrogen, Ci- C_6 alkyl (e.g. methyl, ethyl), or Ci- C_6 haloalkyl (e.g. trifluoromethyl). In certain embodiments, R^1 , R^3 , and R^4 , are each independently hydrogen or methyl. In certain embodiments, R^1 , R^3 , and R^4 are hydrogen.

R^2 is as disclosed in the Summary. In certain embodiments, R^2 , for example, is hydrogen, Ci- C_6 alkyl, NO_2 ,
 10 G^{2a} , $-S(O)_2R^{2d}$, $-S(O)_2NR^{2b}R^{2c}$, $-C(O)R^{2d}$, $-C(O)OR^{2a}$, $-C(O)NR^{2b}R^{2c}$, $-NR^{2b}R^{2c}$, $-N(R^{2e})C(O)R^{2d}$, $-N(R^{2e})S(O)_2R^{2d}$, $-N(R^{2e})S(O)_2NR^{2b}R^{2c}$, $-(C-C_6 \text{ alkylenyl})-G^{2a}$, $-(C-C_6 \text{ alkylenyl})-OR^{2a}$, $-(C-C_6 \text{ alkylenyl})-S(O)_2R^{2d}$, $-(C-C_6 \text{ alkylenyl})-S(O)_2NR^{2b}R^{2c}$, $-(C-C_6 \text{ alkylenyl})-C(O)R^{2d}$, $-(C-C_6 \text{ alkylenyl})-C(O)OR^{2a}$, $-(C-C_6 \text{ alkylenyl})-C(O)NR^{2b}R^{2c}$, $-(C-C_6 \text{ alkylenyl})-NR^{2b}R^{2c}$, $-(C-C_6 \text{ alkylenyl})-N(R^{2e})C(O)R^{2d}$, $-(C-C_6 \text{ alkylenyl})-N(R^{2e})S(O)_2R^{2d}$,
 15 or $-(C-C_6 \text{ alkylenyl})-N(R^{2e})S(O)_2NR^{2b}R^{2c}$. In certain embodiments, R^2 , for example, is hydrogen, or NO_2 . In certain embodiments, R^2 , for example, is G^{2a} , $-S(O)_2R^{2d}$, $-S(O)_2NR^{2b}R^{2c}$, $-C(O)R^{2d}$, $-C(O)OR^{2a}$, $-C(O)NR^{2b}R^{2c}$, $-NR^{2b}R^{2c}$, $-N(R^{2e})C(O)R^{2d}$, $-N(R^{2e})S(O)_2R^{2d}$, $-N(R^{2e})S(O)_2NR^{2b}R^{2c}$, $-(C-C_6 \text{ alkylenyl})-G^{2a}$, $-(C-C_6 \text{ alkylenyl})-OR^{2a}$, $-(C-C_6 \text{ alkylenyl})-S(O)_2R^{2d}$, $-(C-C_6 \text{ alkylenyl})-S(O)_2NR^{2b}R^{2c}$, $-(C-C_6 \text{ alkylenyl})-C(O)R^{2d}$, $-(C-C_6 \text{ alkylenyl})-C(O)OR^{2a}$, $-(C-C_6 \text{ alkylenyl})-C(O)NR^{2b}R^{2c}$, $-(C-C_6 \text{ alkylenyl})-NR^{2b}R^{2c}$, $-(C-C_6 \text{ alkylenyl})-N(R^{2e})C(O)R^{2d}$, $-(C-C_6 \text{ alkylenyl})-N(R^{2e})S(O)_2R^{2d}$,
 20 or $-(C-C_6 \text{ alkylenyl})-N(R^{2e})S(O)_2NR^{2b}R^{2c}$. In certain embodiments, R^2 , for example, is $-S(O)_2R^{2d}$, $-S(O)_2NR^{2b}R^{2c}$, $-C(O)R^{2d}$, $-C(O)NR^{2b}R^{2c}$, $-N(R^{2e})C(O)R^{2d}$, $-N(R^{2e})S(O)_2R^{2d}$, $-N(R^{2e})S(O)_2NR^{2b}R^{2c}$, $-(C-C_6 \text{ alkylenyl})-S(O)_2R^{2d}$, $-(C-C_6 \text{ alkylenyl})-S(O)_2NR^{2b}R^{2c}$, $-(C-C_6 \text{ alkylenyl})-C(O)R^{2d}$, $-(C-C_6 \text{ alkylenyl})-C(O)NR^{2b}R^{2c}$, $-(C-C_6 \text{ alkylenyl})-N(R^{2e})C(O)R^{2d}$, $-(C-C_6 \text{ alkylenyl})-N(R^{2e})S(O)_2R^{2d}$, or $-(C-C_6 \text{ alkylenyl})-N(R^{2e})S(O)_2NR^{2b}R^{2c}$. In certain embodiments, R^2 , for example, is $-S(O)_2R^{2d}$, $-S(O)_2NR^{2b}R^{2c}$, $-N(R^{2e})S(O)_2R^{2d}$, or $-N(R^{2e})S(O)_2NR^{2b}R^{2c}$.

G^{2a} , R^{2a} , R^{2b} , R^{2c} , R^{2d} , and R^{2e} are as disclosed in the Summary and embodiments
 30 herein below.

In the embodiments wherein R^2 is G^{2a} , G^{2a} is as disclosed in the Summary and embodiments herein. For example, in certain embodiments, G^{2a} is an optionally substituted heterocycle. In certain embodiments, G^{2a} is an optionally substituted monocyclic heterocycle.

In certain embodiments, G^{2a} is optionally substituted 1,2-dioxido-1,2-thiazolidin-2-yl. In certain embodiments, G^{2a} is unsubstituted.

In the embodiments wherein R^2 is $-(C_1-C_6 \text{ alkylenyl})-G^{2a}$, G^{2a} is as disclosed in the Summary and embodiments herein. For example, in certain embodiments, G^{2a} is a
 5 heterocycle or a heteroaryl, each of which is optionally substituted. In certain embodiments, G^{2a} is a monocyclic heterocycle or a monocyclic heteroaryl, each of which is optionally substituted. In certain embodiments, G^{2a} is 1,2-dioxido-1,2-thiazolidin-2-yl or pyrazolyl, each of which is optionally substituted. In certain embodiments, G^{2a} is unsubstituted.

Where G^{2a} group is optionally substituted, it is, for example, optionally substituted
 10 with 1, 2, 3, 4, or 5 R^v . R^v is as described in the Summary and herein, for example, R^v is C_1-C_6 alkyl (e.g. methyl), halogen (e.g. F, Cl), or C_1-C_6 haloalkyl.

In the embodiments wherein R^2 is $-S(O)_2R^{2d}$, R^{2d} is as disclosed in the Summary and embodiments herein. In certain embodiments, R^{2d} is C_1-C_6 haloalkyl or unsubstituted C_1-C_6 alkyl. In certain embodiments, R^{2d} is methyl or ethyl.

In the embodiments wherein R^2 is $-S(O)_2NR^{2b}R^{2c}$, R^{2b} and R^{2c} are as disclosed in the Summary and embodiments herein. For example, in certain embodiments, R^{2b} is hydrogen or
 15 C_1-C_6 alkyl (e.g. methyl, ethyl), and R^{2c} is hydrogen, C_1-C_6 alkyl (e.g. methyl, ethyl), or C_1-C_6 haloalkyl (e.g. 2,2,2-trifluoroethyl, 2-fluoroethyl).

In the embodiments wherein R^2 is $-C(O)R^{2d}$, R^{2d} is as disclosed in the Summary and
 20 embodiments herein. For example, in certain embodiments, R^{2d} is G^{2b} wherein G^{2b} is as disclosed in the Summary and embodiments herein. For example, in certain embodiments, G^{2b} is an optionally substituted heterocycle. In certain embodiments, G^{2b} is an optionally substituted monocyclic heterocycle. In certain embodiments, G^{2b} is 1,1-
 25 dioxidothiomorpholin-4-yl, pyrrolidin-1-yl, or morpholin-4-yl, each of which is optionally substituted. Each G^{2b} is optionally substituted as described in the Summary and embodiments herein. For example, each G^{2b} is independently unsubstituted or substituted with 1, 2, or 3 R^v . R^v is as described in the Summary and embodiments herein. For example, each R^v is independently C_1-C_6 alkyl (e.g. methyl), oxo, or $N(H)C(O)O(C_1-C_6 \text{ alkyl})$.

In the embodiments wherein R^2 is $-C(O)OR^{2a}$, R^{2a} is as disclosed in the Summary and
 30 embodiments herein. For example, in certain embodiments, R^{2a} is hydrogen or C_1-C_6 alkyl (e.g. methyl, ethyl).

In the embodiments wherein R^2 is $-C(O)NR^{2b}R^{2c}$, R^{2b} and R^{2c} are as disclosed in the Summary and embodiments herein. For example, in certain embodiments, R^{2b} is hydrogen or
 C_1-C_6 alkyl (e.g. methyl), and R^{2c} is hydrogen, G^{2b} , C_1-C_6 haloalkyl (e.g. 2,2-difluoroethyl),

Ci-C₆ alkyl (e.g. methyl, ethyl) wherein the **Ci-C₆** alkyl is optionally substituted with one **G^{2b}**. **G^{2b}** is as defined in the Summary and embodiments herein. For example, **G^{2b}** is a cycloalkyl, a heterocycle, or a heterocycle, each of which is optionally substituted. In certain embodiments, **G^{2b}** is a monocyclic cycloalkyl, a monocyclic heterocycle, or a monocyclic heterocycle, each of which is optionally substituted. In certain embodiments, **G^{2b}** is cyclopentyl, thiazolyl, 1,1-dioxidotetrahydrothienyl, tetrahydrofuranyl, or pyrrolidinyl, each of which is optionally substituted. Each **G^{2b}** is optionally substituted as described in the Summary and embodiments herein. For example, each **G^{2b}** is independently unsubstituted or substituted with 1, 2, or 3 **R^v**. **R^v** is as described in the Summary and embodiments herein.

10 For example, each **R^v** is independently **Ci-C₆** alkyl (e.g. methyl) or oxo.

In the embodiments wherein **R²** is **-NR^{2b}R^{2c}**, **R^{2b}** and **R^{2c}** are as disclosed in the Summary and embodiments herein. For example, in certain embodiments, **R^{2b}** and **R^{2c}** are each independently hydrogen or **Ci-C₆** alkyl (e.g. methyl, ethyl).

In the embodiments wherein **R²** is **-N(R^{2e})C(O)R^{2d}**, **R^{2d}** and **R^{2e}** are as disclosed in the Summary and embodiments herein. For example, in certain embodiments, **R^{2e}** hydrogen or **C₁-C₆** alkyl (e.g. methyl, ethyl), and **R^{2d}** is **C₁-C₆** alkyl (e.g. methyl, ethyl, tert-butyl), **Ci-C₆** haloalkyl (e.g. 2,2,2-trifluoroethyl).

15

In the embodiments wherein **R²** is **-N(R^{2e})S(O)₂R^{2d}**, **R^{2d}** and **R^{2e}** are as disclosed in the Summary and embodiments herein. For example, in certain embodiments, **R^{2e}** is hydrogen or **C₁-C₆** alkyl (e.g. methyl, ethyl), and **R^{2d}** is **C₁-C₆** alkyl (e.g. methyl, ethyl), **Ci-C₆** haloalkyl (e.g. 2,2,2-trifluoroethyl, 2-fluoroethyl, 2,2-difluoroethyl).

20

In the embodiments wherein **R²** is **-N(R^{2e})S(O)₂NR^{2b}R^{2c}**, **R^{2b}**, **R^{2c}**, and **R^{2e}** are as disclosed in the Summary and embodiments herein. For example, in certain embodiments, **R^{2b}**, **R^{2c}**, and **R^{2e}** are each independently hydrogen or **Ci-C₆** alkyl (e.g. methyl, ethyl).

25

In the embodiments wherein **R²** is **-(C₁-C₆ alkylenyl)-OR^{2a}**, **R^{2a}** is as described in the Summary and embodiments herein. In certain embodiments **R^{2a}** is hydrogen. In certain embodiments, **R²** is **-CH₂-OH** or **-CH₂CH₂-OH**.

In the embodiments wherein **R²** is **-(Ci-C₆ alkylenyl)-C(O)OR^{2a}**, **R^{2a}** is as described in the Summary and embodiments herein. For example, **R^{2a}** is hydrogen or **Ci-C₆** alkyl (e.g. methyl, ethyl).

30

In the embodiments wherein **R²** is **-(C₁-C₆ alkylenyl)-C(O)NR^{2b}R^{2c}**, **R^{2b}** and **R^{2c}** are as disclosed in the Summary and embodiments herein. For example, in certain embodiments, **R^{2b}** and **R^{2c}** are each independently hydrogen or **C₁-C₆** alkyl (e.g. methyl, ethyl).

In the embodiments wherein R^2 is $-(C_1-C_6 \text{ alkylene})-N(R^{2e})C(O)R^{2d}$, R^{2d} and R^{2e} are as disclosed in the Summary and embodiments herein. For example, in certain embodiments, R^{2e} is hydrogen or C_1-C_6 alkyl (e.g. methyl, ethyl), and R^{2d} is C_1-C_6 alkyl (e.g. methyl) optionally substituted with $C(O)OR^{21}$.

5 L^1 is as set forth in the Summary and embodiments herein. For example, in certain embodiments, L^1 is CH_2 , $C(O)$, $(CH_2)_mO$, or $(CH_2)_mN(R^z)$. In certain embodiments, L^1 is $(CH_2)_mO$ or $(CH_2)_mN(R^z)$. In certain embodiments, L^1 is $(CH_2)_mO$. In certain embodiments, L^1 is $(CH_2)_mN(R^z)$.

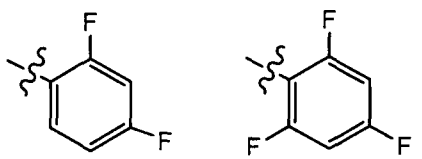
The variable, m , is 0 or 1. In certain embodiments, m is 0. In certain embodiments, 10 m is 1.

R^z is as set forth in the Summary and embodiments herein. For example, R^z is hydrogen or C_1-C_6 alkyl. In certain embodiments, R^z is hydrogen.

G^1 is as set forth in the Summary and embodiments herein. For example, G^1 is G^{1a} . In certain embodiments, G^1 is $-(C_1-C_6 \text{ alkylene})-G^{1a}$.

15 G^{1a} is as defined in the Summary and embodiments herein. For example, in certain embodiments G^{1a} is aryl, heterocycle, or cycloalkyl, each of which is optionally substituted. In certain embodiments G^{1a} is aryl, heterocycle, heteroaryl, or cycloalkyl, each of which is optionally substituted. In certain embodiments G^{1a} is optionally substituted aryl. In certain 20 embodiments G^{1a} is optionally substituted heterocycle. In certain embodiments G^{1a} is optionally substituted heteroaryl. In certain embodiments G^{1a} is optionally substituted cycloalkyl.

In the embodiments wherein G^{1a} is optionally substituted aryl, G^{1a} , for example, is optionally substituted phenyl. Examples of substituted phenyl of G^{1a} include, but are not limited to,



In the embodiments wherein G^{1a} is optionally substituted heterocycle, examples of the heterocycle include, but are not limited to, tetrahydrofuran-2-yl, tetrahydrofuran-3-yl, morpholinyl, and tetrahydropyran-4-yl, tetrahydropyran-3-yl, each of which (including the exemplary rings) is optionally substituted.

30 In the embodiments wherein G^{1a} is optionally substituted heteroaryl, G^{1a} , for example, is optionally substituted pyridinyl.

In the embodiments wherein G^{1a} is optionally substituted cycloalkyl (e.g. optionally substituted monocyclic cycloalkyl), examples of the cycloalkyl include, but are not limited to, cyclopentyl and cyclohexyl, each of which is optionally substituted. In certain embodiments, G^{1a} is a substituted cycloalkyl. In certain embodiments, G^{1a} is 4,4-difluorocyclohexyl.

5 The optional substituents of G^{1a} are as set forth in the Summary and embodiments herein. For example, each G^{1a} is independently unsubstituted or substituted with 1, 2, 3, 4, or 5 R^w . In certain embodiments, R^w is, for example, C1-C6 alkyl -CN, halogen (e.g. F, Cl), or Ci-C₆ haloalkyl (e.g. trifluoromethyl). In certain embodiments, R^w is halogen. In certain embodiments, R^w is F.

10 It is appreciated that compounds of formula (I) with combinations of the above embodiments, including particular, more particular and preferred embodiments are contemplated.

Accordingly, one aspect of the invention is directed to a group of compounds of formula (I) wherein L^1 is $(CH_2)_mO$ and G^1 is G^{1a} and G^{1a} is as disclosed in the Summary and
15 embodiments herein above.

Other examples of a group of compounds of formula (I) is directed to those wherein Y^1 is N; X^1 is CR^{x1} ; and X^2 is CR^{x2} .

Yet other examples of a group of compounds of formula (I) is directed to those wherein Y^1 is N; X^1 is CR^{x1} ; X^2 is CR^{x2} , and R^y is methyl.

20 Other examples of a group of compounds of formula (I) is directed to those wherein Y^1 is N; X^1 is CR^{x1} ; X^2 is CR^{x2} , R^y is methyl, and L^1 is CH_2 , C(O), $(CH_2)_mO$, or $(CH_2)_mN(R^z)$. In certain embodiments, L^1 is $(CH_2)_mO$. In yet othe embodiments, L^1 is $(CH_2)_mO$ and m is 0. In yet othe embodiments, L^1 is $(CH_2)_mO$ and m is 1. In certain embodiments, L^1 is $(CH_2)_mN(R^z)$. In certain embodiments, L^1 is $(CH_2)_mN(R^z)$ and m is 0. In yet othe
25 embodiments, L^1 is $(CH_2)_mN(R^z)$ and m is 1. R^z has values as described in the Summary and embodiments herein above.

Other examples of a group of compounds of formula (I) is directed to those wherein Y^1 is N; X^1 is CR^{x1} ; X^2 is CR^{x2} , R^y is methyl, L^1 is $(CH_2)_mO$, and G^1 is $-(C_{1-C_6} \text{alkylenyl})-G^{1a}$ wherein G^{1a} is optionally substituted phenyl.

30 Other examples of a group of compounds of formula (I) is directed to those wherein Y^1 is N; X^1 is CR^{x1} ; X^2 is CR^{x2} , R^y is methyl, L^1 is $(CH_2)_mO$, and G^1 is G^{1a} .

Other examples of a group of compounds of formula (I) is directed to those wherein Y^1 is N; X^1 is CR^{x1} ; X^2 is CR^{x2} , R^y is methyl, L^1 is $(CH_2)_mO$, G^1 is G^{1a} , and G^{1a} is optionally substituted aryl.

Other examples of a group of compounds of formula (I) is directed to those wherein Y^1 is N; X^1 is CR^{x1} ; X^2 is CR^{x2} , R^y is methyl, L^1 is $(CH_2)_mO$, G^1 is G^{1a} , and G^{1a} is optionally substituted phenyl.

5 Other examples of a group of compounds of formula (I) is directed to those wherein Y^1 is N; X^1 is CR^{x1} ; X^2 is CR^{x2} , R^y is methyl, L^1 is $(CH_2)_mO$, G^1 is G^{1a} , and G^{1a} is optionally substituted cycloalkyl (e.g. optionally substituted monocyclic cycloalkyl).

Other examples of a group of compounds of formula (I) is directed to those wherein Y^1 is N; X^1 is CR^{x1} ; X^2 is CR^{x2} , R^y is methyl, L^1 is $(CH_2)_mO$, G^1 is G^{1a} , and G^{1a} is optionally substituted heterocycle (e.g. optionally substituted monocyclic heterocycle).

10 Other examples of a group of compounds of formula (I) is directed to those wherein Y^1 is CR^u ; X^1 is CR^{x1} ; and X^2 is CR^{x2} .

Yet other examples of a group of compounds of formula (I) is directed to those wherein Y^1 is CR^u ; X^1 is CR^{x1} ; X^2 is CR^{x2} , and R^y is methyl.

15 Other examples of a group of compounds of formula (I) is directed to those wherein Y^1 is CR^u ; X^1 is CR^{x1} ; X^2 is CR^{x2} , R^y is methyl, and L^1 is CH_2 , $C(O)$, $(CH_2)_mO$, or $(CH_2)_mN(R^z)$. In certain embodiments, L^1 is $(CH_2)_mO$. In yet other embodiments, L^1 is $(CH_2)_mO$ and m is 0. In yet other embodiments, L^1 is $(CH_2)_mO$ and m is 1. In certain embodiments, L^1 is $(CH_2)_mN(R^z)$. In certain embodiments, L^1 is $(CH_2)_mN(R^z)$ and m is 0. In yet other embodiments, L^1 is $(CH_2)_mN(R^z)$ and m is 1. R^z has meaning as described in the
20 Summary and embodiments herein above.

Other examples of a group of compounds of formula (I) is directed to those wherein Y^1 is CR^u ; X^1 is CR^{x1} ; X^2 is CR^{x2} , R^y is methyl, L^1 is $(CH_2)_mO$, and G^1 is $-(C-C_6$ alkylenyl)- G^{1a} wherein G^{1a} is optionally substituted phenyl.

25 Other examples of a group of compounds of formula (I) is directed to those wherein Y^1 is CR^u ; X^1 is CR^{x1} ; X^2 is CR^{x2} , R^y is methyl, L^1 is $(CH_2)_mO$, and G^1 is G^{1a} .

Other examples of a group of compounds of formula (I) is directed to those wherein Y^1 is CR^u ; X^1 is CR^{x1} ; X^2 is CR^{x2} , R^y is methyl, L^1 is $(CH_2)_mO$, G^1 is G^{1a} , and G^{1a} is optionally substituted aryl.

30 Other examples of a group of compounds of formula (I) is directed to those wherein Y^1 is CR^u ; X^1 is CR^{x1} ; X^2 is CR^{x2} , R^y is methyl, L^1 is $(CH_2)_mO$, G^1 is G^{1a} , and G^{1a} is optionally substituted phenyl.

Other examples of a group of compounds of formula (I) is directed to those wherein Y^1 is CR^u ; X^1 is CR^{x1} ; X^2 is CR^{x2} , R^y is methyl, L^1 is $(CH_2)_mO$, G^1 is G^a , and G^{1a} is optionally substituted cycloalkyl (e.g. optionally substituted monocyclic cycloalkyl).

Other examples of a group of compounds of formula (1) is directed to those wherein Y^1 is CR^u ; X^1 is CR^{x1} ; X^2 is CR^{*2} , R^y is methyl, L^1 is $(CH_2)_mO$, G^1 is G^a , and G^{1a} is optionally substituted heterocycle (e.g. optionally substituted monocyclic heterocycle).

5 Within each group of compounds of formula (I) described herein above, A^1 , A^2 , A^3 , and A^4 have meanings as disclosed in the Summary and embodiments herein above.

For example, within each group of compounds of formula (I) described herein above, examples of a subgroup include those wherein A^1 is CR^1 , A^2 is CR^2 , A^3 is CR^3 , and A^4 is CR^4 ; or one of A^1 , A^2 , A^3 , and A^4 is N.

10 Other examples of a subgroup include, but are not limited to, those wherein A^1 is CR^1 , A^2 is CR^2 , A^3 is CR^3 , and A^4 is CR^4 .

Other examples of a subgroup include, but are not limited to, those wherein one of A^1 , A^2 , A^3 , and A^4 is N.

Yet other examples of a subgroup include, but are not limited to, those wherein A^1 is CR^1 , A^2 is CR^2 , A^3 is CR^3 , and A^4 is N.

15 Yet other examples of a subgroup include, but are not limited to, those wherein two of A^1 , A^2 , A^3 , and A^4 are N.

Yet other examples of a subgroup include, but are not limited to, those wherein A^1 is N, A^2 is CR^2 , A^3 is N, and A^4 is CR^4 .

20 Yet other examples of a subgroup include, but are not limited to, those wherein A^1 is N, A^2 is CR^2 , A^3 is CR^3 , and A^4 is N.

Yet other examples of a subgroup include, but are not limited to, those wherein three of A^1 , A^2 , A^3 , and A^4 are N.

Yet other examples of a subgroup include, but are not limited to, those wherein A^1 is N, A^2 is CR^2 , A^3 is N, and A^4 is N.

25 Of all the groups and subgroups of compounds of formula (I) disclosed in the preceding paragraphs, R^1 , R^2 , R^3 , R^4 , R^x , R^u ; R^{x1} , R^{x2} , m, and the optional substituents of G^1 are as described in the Summary and embodiments herein above.

For example, of all the groups and subgroups of compounds of formula (I) disclosed in the preceding paragraphs, R^2 is hydrogen, Ci- C_6 alkyl, NO_2 ,
 30 G^{2a} , $-S(O)_2R^{2d}$, $-S(O)_2NR^{2b}R^{2c}$, $-C(O)R^{2d}$, $-C(O)OR^{2a}$, $-C(O)NR^{2b}R^{2c}$, $-NR^{2b}R^{2c}$, $-N(R^{2e})C(O)R^{2d}$, $-N(R^{2e})S(O)_2R^{2d}$, $-N(R^{2e})S(O)_2NR^{2b}R^{2c}$, $-(C)C_6$ alkylenyl)- G^{2a} , $-(C)C_6$ alkylenyl)- OR^{2a} , $-(C)C_6$ alkylenyl)- $S(O)_2R^{2d}$, $-(C)C_6$ alkylenyl)- $S(O)_2NR^{2b}R^{2c}$, $-(C)C_6$ alkylenyl)- $C(O)R^{2d}$, $-(C)C_6$ alkylenyl)- $C(O)OR^{2a}$, $-(C)C_6$ alkylenyl)- $C(O)NR^{2b}R^{2c}$, $-(C)C_6$ alkylenyl)- $NR^{2b}R^{2c}$, $-(C)C_6$ alkylenyl)- $N(R^{2e})C(O)R^{2d}$, $-(C)C_6$ alkylenyl)- $N(R^{2e})S(O)_2R^{2d}$,

or-(Ci-C₆ alkylene)-N(R^{2e})S(0)₂NR^{2b}R^{2c}. In certain embodiments, R² is -S(0)₂R^{2d}, -S(0)₂NR^{2b}R^{2c}, -N(R^{2e})S(0)₂R^{2d}, or -N(R^{2e})S(0)₂NR^{2b}R^{2c}.

For example, of all the groups and subgroups of compounds of formula (I) disclosed in the preceding paragraphs, R² is -S(0)₂R^{2d}, -S(0)₂NR^{2b}R^{2c}, -N(R^{2e})S(0)₂R^{2d},
 5 or -N(R^{2e})S(0)₂NR^{2b}R^{2c}, and R^x is hydrogen or methyl. In certain embodiments, R^x is hydrogen.

For example, of all the groups and subgroups of compounds of formula (I) disclosed in the preceding paragraphs, R² is -S(0)₂R^{2d}, -S(0)₂NR^{2b}R^{2c}, -N(R^{2e})S(0)₂R^{2d},
 or -N(R^{2e})S(0)₂NR^{2b}R^{2c}, R^x is hydrogen, and R^{x1} is hydrogen, -C(0)OR^{ax1}, -C(0)NR^{bx1}R^{cx1},
 10 G^{x1}, or Ci-C₆ alkyl wherein the Ci-C₆ alkyl is optionally substituted with OR^{ax1}. In certain embodiments, R^{x1} is hydrogen, -C(0)OR^{ax1}, or -C(0)NR^{bx1}R^{cx1}.

For example, of all the groups and subgroups of compounds of formula (I) disclosed in the preceding paragraphs, R² is -S(0)₂R^{2d}, -S(0)₂NR^{2b}R^{2c}, -N(R^{2e})S(0)₂R^{2d},
 or -N(R^{2e})S(0)₂NR^{2b}R^{2c}, R^x is hydrogen, R^{x1} is hydrogen, -C(0)OR^{ax1}, or -C(0)NR^{bx1}R^{cx1},
 15 and R^{x2} is hydrogen.

Compounds of formula (I) may contain one or more asymmetrically substituted atoms. Compounds of formula I may also exist as individual stereoisomers (including enantiomers and diastereomers) and mixtures thereof. Individual stereoisomers of compounds of formula I may be prepared synthetically from commercially available starting materials that contain
 20 asymmetric or chiral centers or by preparation of racemic mixtures followed by resolution of the individual stereoisomer using methods that are known to those of ordinary skill in the art. Examples of resolution are, for example, (i) attachment of a mixture of enantiomers to a chiral auxiliary, separation of the resulting mixture of diastereomers by recrystallization or chromatography, followed by liberation of the optically pure product; or (ii) separation of the
 25 mixture of enantiomers or diastereomers on chiral chromatographic columns.

Compounds of formula I may also include the various geometric isomers and mixtures thereof resulting from the disposition of substituents around a carbon-carbon double bond, a carbon-nitrogen double bond, a cycloalkyl group, or a heterocycle group. Substituents around a carbon-carbon double bond or a carbon-nitrogen double bond are
 30 designated as being of Z or E configuration and substituents around a cycloalkyl or heterocycle are designated as being of cis or trans configuration.

Within the present invention it is to be understood that compounds disclosed herein may exhibit the phenomenon of tautomerism and all tautomeric isomers are included in the scope of the invention.

Thus, the formula drawings within this specification can represent only one of the possible tautomeric, geometric, or stereoisomeric forms. It is to be understood that the invention encompasses any tautomeric, geometric, or stereoisomeric form, and mixtures thereof, and is not to be limited merely to any one tautomeric, geometric, or stereoisomeric form utilized within the formula drawings.

Exemplary compounds of formula (I) include, but are not limited to:

6-methyl-4-(2-phenoxyphenyl)-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one;

6-methyl-4-(5-nitro-2-phenoxyphenyl)-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one;

4-(5-amino-2-phenoxyphenyl)-6-methyl-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one;

N-[3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)-4-phenoxyphenyl]methanesulfonamide;

2,2,2-trifluoro-N-[3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)-4-phenoxyphenyl]ethanesulfonamide;

N-[3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)-4-phenoxyphenyl]acetamide;

N-methyl-N-[3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)-4-phenoxyphenyl]methanesulfonamide;

ethyl 3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)-4-phenoxybenzoate;

3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)-4-phenoxybenzoic acid;

N-[3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)-4-(pyridin-3-yloxy)phenyl]methanesulfonamide;

6-methyl-4-[2-(morpholin-4-ylmethyl)phenyl]-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one;

N-ethyl-3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)-4-phenoxybenzamide;

3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)-4-phenoxy-N-(tetrahydrofuran-2-ylmethyl)benzamide;

N-cyclopentyl-3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)-4-phenoxybenzamide;

N-(2,2-difluoroethyl)-3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)-4-phenoxybenzamide;

- 3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)-4-phenoxy-N-(1,3-thiazol-2-yl)benzamide;
- N-(1,1-dioxidotetrahydrothiophen-3-yl)-3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)-4-phenoxybenzamide;
- 5 3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)-4-phenoxybenzamide;
- 4-[5-(hydroxymethyl)-2-phenoxyphenyl]-6-methyl-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one;
- N-[3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)-4-phenoxyphenyl]ethanesulfonamide;
- 10 N,N-dimethyl-N'-[3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)-4-phenoxyphenyl]sulfuric diamide;
- N-[5-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)-6-phenoxyphenyl]methanesulfonamide;
- N-[3-fluoro-5-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)-4-phenoxyphenyl]methanesulfonamide;
- 15 N-[4-(2-cyanophenoxy)-3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)phenyl]methanesulfonamide;
- N-[4-(4-fluorophenoxy)-3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)phenyl]methanesulfonamide;
- 20 N-[4-(2,4-difluorophenoxy)-3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)phenyl]methanesulfonamide;
- N-[3-chloro-5-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)-4-phenoxyphenyl]methanesulfonamide;
- N-[3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)-4-(tetrahydro-2H-pyran-4-yloxy)phenyl]methanesulfonamide;
- 25 6-methyl-4-[2-phenoxy-5-(1H-pyrazol-1-ylmethyl)phenyl]-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one;
- N-[3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)-4-(tetrahydrofuran-3-yloxy)phenyl]methanesulfonamide;
- 30 N-{3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)-4-[2-(trifluoromethyl)phenoxy]phenyl}methanesulfonamide;
- N-[4-(4-cyanophenoxy)-3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)phenyl]methanesulfonamide;

- N-[4-(2-chloro-4-fluorophenoxy)-3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)phenyl]methanesulfonamide;
- [4-(benzyloxy)-3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)phenyl]acetic acid;
- 5 N-[4-(2,4-difluorophenoxy)-3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)phenyl]ethanesulfonamide;
- N-[4-(2,4-difluorophenoxy)-3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)phenyl]acetamide;
- 10 N-[4-(2,4-difluorophenoxy)-3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)phenyl]-3,3,3-trifluoropropanamide;
- N-[4-(2,4-difluorophenoxy)-3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)phenyl]-2,2-dimethylpropanamide;
- ethyl 4-(cyclopentylamino)-3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)benzoate;
- 15 4-{5-[(1,1-dioxido-1,2-thiazolidin-2-yl)methyl]-2-phenoxyphenyl}-6-methyl-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one;
- 4-{[3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)-4-phenoxybenzyl]amino}-4-oxobutanoic acid;
- 4-[2-(2,4-difluorophenoxy)-5-(1,1-dioxido-1,2-thiazolidin-2-yl)phenyl]-6-methyl-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one;
- 20 4-[2-(benzyloxy)-5-(2-hydroxyethyl)phenyl]-6-methyl-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one;
- methyl [4-(benzyloxy)-3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)phenyl]acetate;
- 25 2-[4-(benzyloxy)-3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)phenyl]-N-ethylacetamide;
- 2-[4-(benzyloxy)-3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)phenyl]-N,N-dimethylacetamide;
- N-[4-(3,4-difluorophenoxy)-3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)phenyl]methanesulfonamide;
- 30 N-[3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)-4-(2,4,6-trifluorophenoxy)phenyl]methanesulfonamide;
- 4-(2,4-difluorophenoxy)-3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)benzamide;

4-(2,4-difluorophenoxy)-3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)-N-(tetrahydrofuran-3-yl)benzamide;

4-{2-(2,4-difluorophenoxy)-5-[(1,1-dioxidothiomorpholin-4-yl)carbonyl]phenyl}-6-methyl-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one;

5 4-(2,4-difluorophenoxy)-3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)-N-(1-methyl-2-oxopyrrolidin-3-yl)benzamide;

tert-butyl {1-[4-(2,4-difluorophenoxy)-3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)benzoyl]pyrrolidin-3-yl} carbamate;

10 4-[2-(2,4-difluorophenoxy)-5-(pyrrolidin-1-ylcarbonyl)phenyl]-6-methyl-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one;

4-[2-(2,4-difluorophenoxy)-5-(morpholin-4-ylcarbonyl)phenyl]-6-methyl-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one;

N-[4-(cyclohexyloxy)-3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)phenyl]methanesulfonamide;

15 N-[4-(cyclopentyloxy)-3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)phenyl]methanesulfonamide;

N-{4-[(4,4-difluorocyclohexyl)oxy]-3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)phenyl}methanesulfonamide;

20 N-[3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)-4-(tetrahydro-2H-pyran-3-yloxy)phenyl]methanesulfonamide;

6-methyl-4-[2-(morpholin-4-ylcarbonyl)phenyl]-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one;

N-[3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)-4-(2,4,6-trifluorophenoxy)phenyl]ethanesulfonamide;

25 N-[4-(benzyloxy)-3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)phenyl]methanesulfonamide;

N-[4-(2,4-difluorophenoxy)-3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)phenyl]-2-fluoroethanesulfonamide;

30 N-[4-(2,4-difluorophenoxy)-3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)phenyl]-N'-methylsulfuric diamide;

N-[3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)-4-(tetrahydrofuran-3-yloxy)phenyl]ethanesulfonamide;

methyl 6-methyl-7-oxo-4-(2-phenoxyphenyl)-6,7-dihydro-1H-pyrrolo[2,3-c]pyridine-2-carboxylate;

methyl 1,6-dimethyl-7-oxo-4-(2-phenoxyphenyl)-6,7-dihydro-1H-pyrrolo[2,3-c]pyridine-2-carboxylate;

ethyl 4-(5-amino-2-phenoxyphenyl)-6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridine-2-carboxylate;

5 6-methyl-4-(5-(methylsulfonamido)-2-phenoxyphenyl)-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridine-2-carboxylic acid;

ethyl 6-methyl-4-{5-[(methylsulfonyl)amino]-2-phenoxyphenyl}-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridine-2-carboxylate;

10 N-ethyl-6-methyl-4-{5-[(methylsulfonyl)amino]-2-phenoxyphenyl}-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridine-2-carboxamide;

6-methyl-4-{5-[(methylsulfonyl)amino]-2-phenoxyphenyl}-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridine-2-carboxamide;

ethyl 4-(5-amino-2-phenoxyphenyl)-6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-d]pyridazine-2-carboxylate;

15 ethyl 4-[5-(ethylamino)-2-phenoxyphenyl]-6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-d]pyridazine-2-carboxylate;

ethyl 4-{5-[ethyl(methylsulfonyl)amino]-2-phenoxyphenyl}-6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-d]pyridazine-2-carboxylate;

20 6-methyl-4-{5-[(methylsulfonyl)amino]-2-phenoxyphenyl}-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-d]pyridazine-2-carboxylic acid;

6-methyl-4-{5-[(methylsulfonyl)amino]-2-phenoxyphenyl}-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-d]pyridazine-2-carboxamide;

6-methyl-N-[2-(4-methylpiperazin-1-yl)ethyl]-4-{5-[(methylsulfonyl)amino]-2-phenoxyphenyl}-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-d]pyridazine-2-carboxamide;

25 N-[3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-d]pyridazin-4-yl)-4-phenoxyphenyl]methanesulfonamide;

N-ethyl-6-methyl-4-{5-[(methylsulfonyl)amino]-2-phenoxyphenyl}-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-d]pyridazine-2-carboxamide;

6-methyl-4-(2-phenoxyphenyl)-1,6-dihydro-7H-pyrrolo[2,3-d]pyridazin-7-one;

30 N-ethyl-N,6-dimethyl-4-{5-[(methylsulfonyl)amino]-2-phenoxyphenyl}-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-d]pyridazine-2-carboxamide;

N-[4-(4-cyanophenoxy)-3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)phenyl]ethanesulfonamide;

6-methyl-4-[5-(methylsulfonyl)-2-phenoxyphenyl]-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one;

5-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)-6-(tetrahydrofuran-3-yloxy)pyridine-3-sulfonamide;

5 N-methyl-5-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)-6-(tetrahydrofuran-3-yloxy)pyridine-3-sulfonamide;

6-methyl-4-(2-phenoxyphenyl)-2-phenyl-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one; and

10 N-{3-[2-(hydroxymethyl)-6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl]-4-phenoxyphenyl}methanesulfonamide.

In certain embodiments, a compound of formula I is selected from the group consisting of:

N-[4-(2,4-difluorophenoxy)-3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)phenyl]ethanesulfonamide;

15 N-[4-(2,4-difluorophenoxy)-3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)phenyl]methanesulfonamide;

6-methyl-4-[5-(methylsulfonyl)-2-phenoxyphenyl]-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one;

20 N-methyl-5-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)-6-(tetrahydrofuran-3-yloxy)pyridine-3-sulfonamide;

N-[4-(2-chloro-4-fluorophenoxy)-3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)phenyl]methanesulfonamide;

6-methyl-4-{5-[(methylsulfonyl)amino]-2-phenoxyphenyl}-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridine-2-carboxamide;

25 N-[3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)-4-phenoxyphenyl]methanesulfonamide;

N-[3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)-4-(2,4,6-trifluorophenoxy)phenyl]ethanesulfonamide;

30 N-{4-[(4,4-difluorocyclohexyl)oxy]-3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)phenyl}methanesulfonamide; and

N-[4-(4-fluorophenoxy)-3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)phenyl]methanesulfonamide; or a pharmaceutically acceptable salt thereof.

Compounds of formula I can be used in the form of pharmaceutically acceptable salts. The phrase "pharmaceutically acceptable salt" means those salts which are, within the scope of sound medical judgement, suitable for use in contact with the tissues of humans and lower animals without undue toxicity, irritation, allergic response and the like and are

5 commensurate with a reasonable benefit/risk ratio.

Pharmaceutically acceptable salts have been described in S. M. Berge et al. J. Pharmaceutical Sciences, 1977, 66: 1-19.

Compounds of formula (I) may contain either a basic or an acidic functionality, or both, and can be converted to a pharmaceutically acceptable salt, when desired, by using a
10 suitable acid or base. The salts may be prepared in situ during the final isolation and purification of the compounds of the invention.

Examples of acid addition salts include, but are not limited to acetate, adipate, alginate, citrate, aspartate, benzoate, benzenesulfonate, bisulfate, butyrate, camphorate, camphorsulfonate, digluconate, glycerophosphate, hemisulfate, heptanoate, hexanoate,
15 fumarate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxyethansulfonate (isothionate), lactate, malate, maleate, methanesulfonate, nicotinate, 2-naphthalenesulfonate, oxalate, palmitoate, pectinate, persulfate, 3-phenylpropionate, picrate, pivalate, propionate, succinate, tartrate, thiocyanate, phosphate, glutamate, bicarbonate, p-toluenesulfonate and undecanoate. Also, the basic nitrogen-containing groups can be quaternized with such agents as lower alkyl
20 halides such as, but not limited to, methyl, ethyl, propyl, and butyl chlorides, bromides and iodides; dialkyl sulfates like dimethyl, diethyl, dibutyl and diamyl sulfates; long chain halides such as, but not limited to, decyl, lauryl, myristyl and stearyl chlorides, bromides and iodides; arylalkyl halides like benzyl and phenethyl bromides and others. Water or oil-soluble or dispersible products are thereby obtained. Examples of acids which may be employed to
25 form pharmaceutically acceptable acid addition salts include such inorganic acids as hydrochloric acid, hydrobromic acid, sulfuric acid, and phosphoric acid and such organic acids as acetic acid, fumaric acid, maleic acid, 4-methylbenzenesulfonic acid, succinic acid and citric acid.

Basic addition salts may be prepared in situ during the final isolation and purification
30 of compounds of this invention by reacting a carboxylic acid-containing moiety with a suitable base such as, but not limited to, the hydroxide, carbonate or bicarbonate of a pharmaceutically acceptable metal cation or with ammonia or an organic primary, secondary or tertiary amine. Pharmaceutically acceptable salts include, but are not limited to, cations based on alkali metals or alkaline earth metals such as, but not limited to, lithium, sodium,

potassium, calcium, magnesium and aluminum salts and the like and nontoxic quaternary ammonia and amine cations including ammonium, tetramethylammonium, tetraethylammonium, methylamine, dimethylamine, trimethylamine, triethylamine, diethylamine, ethylamine and the like. Other examples of organic amines useful for the formation of base addition salts include ethylenediamine, ethanolamine, diethanolamine, piperidine, piperazine and the like.

The term "pharmaceutically acceptable prodrug" or "prodrug" as used herein, represents those prodrugs of the compounds of the present invention which are, within the scope of sound medical judgement, suitable for use in contact with the tissues of humans and lower animals without undue toxicity, irritation, allergic response, and the like, commensurate with a reasonable benefit/risk ratio, and effective for their intended use.

The present invention contemplates compounds of formula (1) formed by synthetic means or formed by in vivo biotransformation of a prodrug.

Compounds described herein can exist in unsolvated as well as solvated forms, including hydrated forms, such as hemi-hydrates. In general, the solvated forms, with pharmaceutically acceptable solvents such as water and ethanol among others are equivalent to the unsolvated forms for the purposes of the invention.

General Synthesis

The compounds described herein, including compounds of general formula (I) and specific examples, may be prepared, for example, through the reaction routes depicted in schemes 1-5. The variables A^1 , A^2 , A^3 , A^4 , X^1 , X^2 , Y^1 , L^1 , G^1 , R^x , and R^y used in the following schemes have the meanings as set forth in the summary and detailed description sections unless otherwise noted.

Abbreviations used in the descriptions of the schemes and the specific examples have the following meanings: BuLi for n-butyl lithium, DBU for 1,8-diazabicyclo[5.4.0]undec-7-ene, DME for 1,2-dimethoxyethane, DMF for dimethylformamide, DMSO for dimethyl sulfoxide, EtOAc for ethyl acetate; $Pd(PPh_3)_4$ for tetrakis(triphenylphosphine)palladium(0), THF for tetrahydrofuran, TFA for trifluoroacetic acid, and HPLC for high performance liquid chromatography.

Compounds of general formula (1) may be prepared (a) by treating an aryl halide, an aryl mesylate, or an aryl triflate with an aryl boronic acid or derivatives thereof (e.g. boronic esters) under Suzuki coupling condition (N. Miyama and A. Suzuki, Chem. Rev. 1995, 95:2457-2483, J. Organomet. Chem. 1999, 576:147-148), and (b) removal of the protecting group (PG), as illustrated in Scheme 1. Thus coupling of compounds of formula (1) wherein

R¹⁰¹ is Br, Cl, mesylate, or triflate with compounds of formula (2) wherein R¹⁰² is boronic acid or derivatives thereof (e.g. boronic esters), or coupling of (1) wherein R¹⁰¹ is boronic acid or derivatives thereof (e.g. boronic esters) with compounds (2) wherein R¹⁰² is Br, Cl, mesylate, or triflate, provides intermediates of formula (3). Generally, the coupling reaction is effected in the presence of a palladium catalyst and a base, and optionally in the presence of a ligand, and in a suitable solvent at elevated temperature (for example, at about 80 °C to about 150 °C). The reaction may be facilitated by microwave irradiation. Examples of the palladium catalyst include, but are not limited to, tetrakis(triphenylphosphine)palladium(0), tris(dibenzylideneacetone)dipalladium(0), and palladium(II)acetate. Examples of suitable bases that may be employed include, but are not limited to, carbonates or phosphates of sodium, potassium, and cesium; and cesium fluoride. Examples of suitable ligands include, but are not limited to, 1,3,5,7-tetramethyl-6-phenyl-2,4,8-trioxo-6-phosphaadamante, 2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl (X-phos), and 1,1'-bis(diphenylphosphanyl) ferrocene. Non-limiting examples of suitable solvent include methanol, dimethoxyethane, N,N-dimethylformamide, dimethylsulfoxide, dioxane, tetrahydropyran, and water, or a mixture thereof.

Alternatively, treatment of formula (1) wherein R¹⁰¹ is Br, Cl, or triflate with boronic acid of formula (4), followed by displacement of the fluoride atom in (4) with an appropriate alcohol or amine of formula G'-L'-H wherein L¹ is O or NH, provides compounds of formula (3) or formula (I) wherein R^x is hydrogen.

Displacement of the fluorine with an alcohol or amine may be achieved in a solvent such as, but not limited to, dimethylsulfoxide, dimethylformamide, dioxane, or tetrahydrofuran, and in the presence of a base such as, but not limited to, cesium carbonate, potassium carbonate, or sodium hydride and at a temperature from about 40°C to about 120 °C.

The protecting group (PG) may be removed in situ during the displacement reaction or the coupling conditions described above.

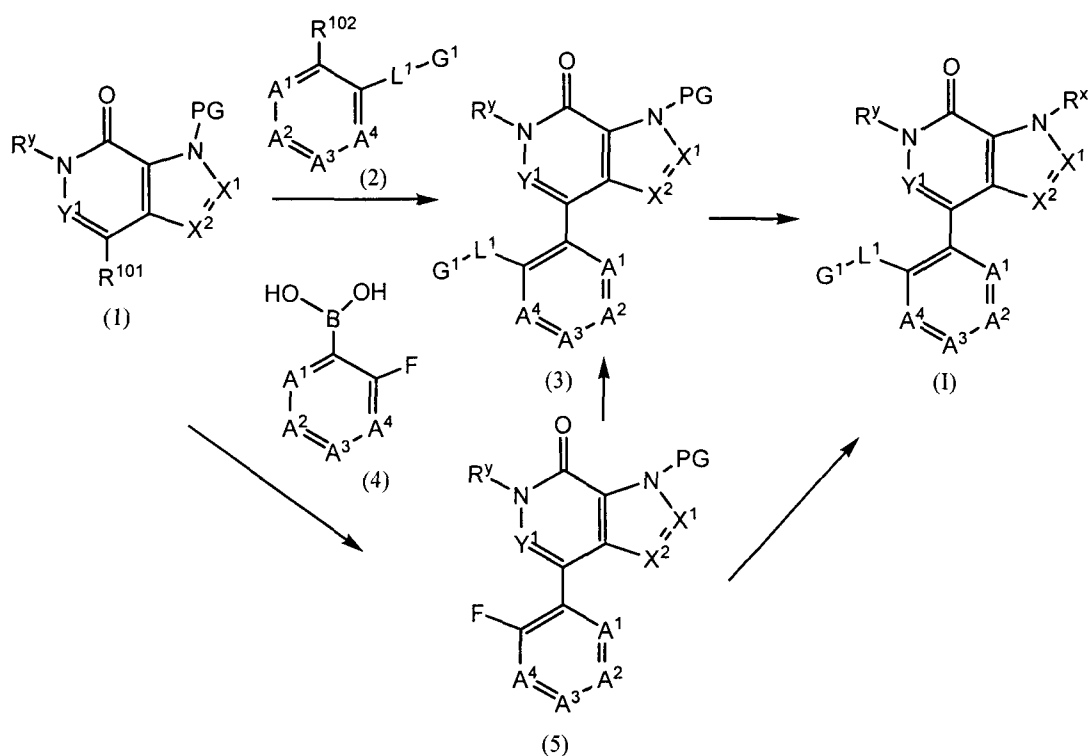
Alternatively, removal of the protecting group (PG) to afford compounds of general formula (I) wherein R^x is hydrogen can be accomplished using reaction conditions known generally to one skilled in the art, or modifications thereof. For example, the tosyl protecting group can be removed in the presence of a base such as, but not limited to, cesium carbonate, sodium hydroxide, or sodium hydride. The reaction is generally performed in the presence of a suitable solvent such as, but not limited to, dimethylsulfoxide, methanol, or tetrahydrofuran,

and at a temperature of about 40 °C to about 120 °C. The benzyl protecting group may be removed by hydrogenation in the presence of a catalyst such as, but not limited to, palladium on carbon and under hydrogen atmosphere. The reaction is typically performed in the presence of a solvent such as, but not limited to, methanol or ethyl acetate, and at about room temperature.

Removal of the (trimethylsilyl)ethoxy)methyl protecting group can be achieved by treatment with a base such as, but not limited to, cesium carbonate or sodium hydride, or with a fluoride reagent such as, but not limited to, TBAF (tetrabutylammonium fluoride). The reaction is generally performed in the presence of a suitable solvent such as, but not limited to, dimethylsulfoxide, ethanol, or tetrahydrofuran, and at a temperature of about 40 °C to about 120 °C. Removal of the (trimethylsilyl)ethoxy)methyl protecting group can also be achieved by treatment with an mild acid such as but not limited to, aqueous hydrochloric acid. The reaction is generally performed in the presence of a suitable solvent such as, but not limited to, ethanol, or methanol, and at a temperature of about 25 °C to about 80 °C.

Conversion of compounds of formula (I) wherein R^x is hydrogen to (1) wherein R^x is C₁-C₃ alkyl can be achieved with an alkylating agent of formula R^xR¹⁰³ wherein R¹⁰³ is halogen, triflate, or mesylate. Generally, the reaction may be conducted in the presence of a base such as, but not limited to, sodium hydride or potassium carbonate, and in a solvent such as, but not limited to, tetrahydrofuran or dimethylformamide, and at a temperature of about 40 °C to about 120 °C.

Scheme 1



Compounds of formula (1) wherein Y^1 is CR^u , X^1 and X^2 are CH, and R^u is hydrogen, Ci-C₆ alkyl, or C₁-C₆ haloalkyl may be prepared by general synthetic methods as shown in Scheme 2.

- 5 Treatment of compounds of formula (6) wherein halo is Br, Cl, or I, with 1,1-dimethoxy-N,N-dimethylmethanamine at elevated temperature (e.g. about 60 °C to about 100 °C), in the absence or presence of a base, and in a solvent such as, but not limited to, DMF, provide compounds of formula (7). Examples of suitable bases include, but not limited to, lithium or sodium methanolate. Catalytic hydrogenation of (7) in the presence of a catalyst
- 10 such as, but not limited to, Raney-Nickel and under hydrogen atmosphere (about 30 psi) and in a solvent such as, but not limited to, ethyl acetate, at about room temperature generally affords compounds of formula (8). Protection of the nitrogen atom with protecting group such as, but not limited to, benzyl, tosyl, and (trimethylsilyl)ethoxy)methyl group can be derived from reaction with an appropriate halide in the presence of a strong base such as, but
- 15 not limited to, sodium hydride, to provide compounds of formula (9).

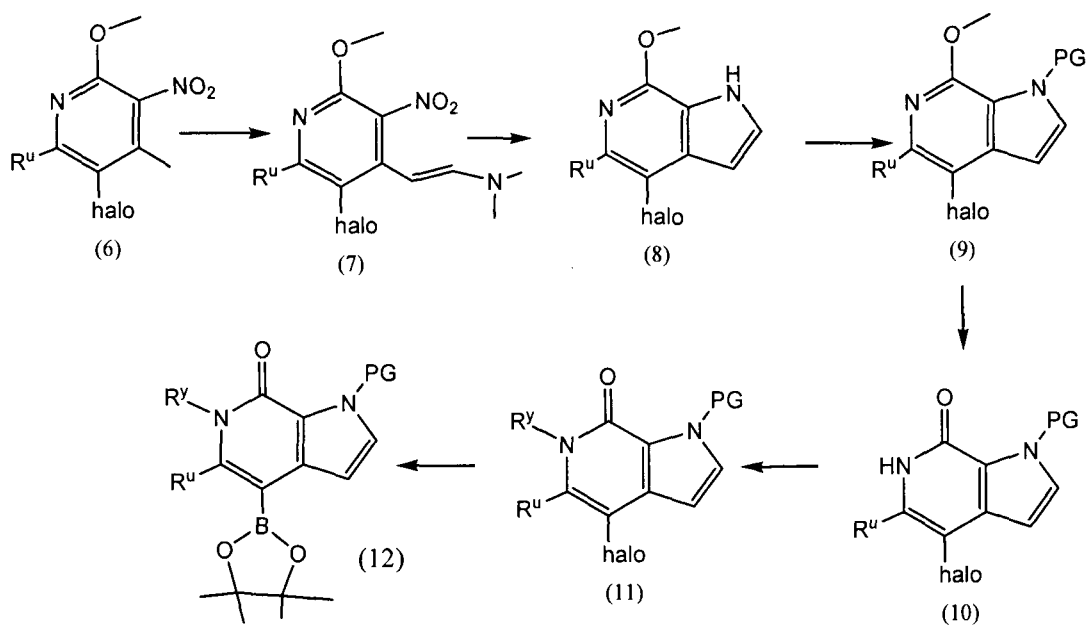
Treatment of (9) with an acid such as, but not limited to, hydrochloric acid or hydrobromic acid and in a solvent such as, but not limited to, dioxane or water, at about 40 °C to about 100 °C, typically provides compounds of formula (10).

- 20 Alkylation of (10) with a halide or mesylate, in the presence of a base such as, but not limited to, sodium hydride, cesium carbonate, or potassium carbonate, and in a solvent such

as, but not limited to, dimethylformamide or dimethylsulfoxide at a temperature of about 0 °C to about 50 °C typically provides compounds of formula (11).

Treatment of the compounds of formula (11) with 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) generally affords compounds of formula (12). In general, the conversion may be facilitated by a palladium catalyst such as, but not limited to, tetrakis(triphenylphosphine)palladium(0), tris(dibenzylideneacetone)dipalladium(0), or palladium(II)acetate, an optional ligand such as, but not limited to, 2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl, 2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl (X-phos), or 1,1'-bis(diphenylphosphanyl)ferrocene, and a base such as, but not limited to, carbonates, acetates, or phosphates of sodium, potassium, and cesium; and cesium fluoride. Non-limiting examples of suitable solvents include methanol, dimethoxyethane, N,N-dimethylformamide, dimethylsulfoxide, dioxane, tetrahydropyran, and water, or a mixture thereof.

Scheme 2



An approach to prepare compounds of formula (1) wherein Y¹ is N, R¹⁰¹ is Cl, and X¹ and X² are CH, is outlined in Scheme 3.

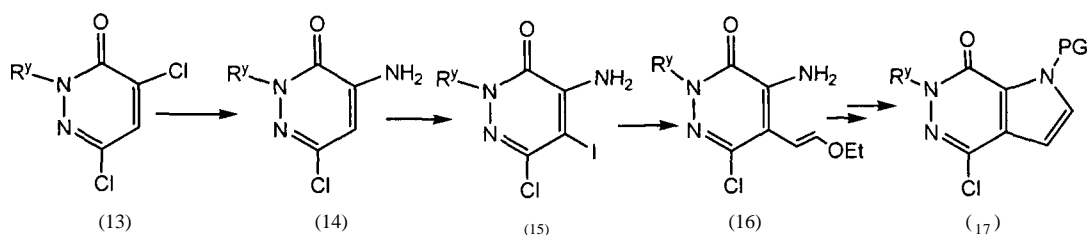
Treatment of (13) with ammonium hydroxide at about 100 °C to about 150 °C can afford amines of formula (14).

Iodination of (14) with N-iodosuccinimide in a solvent such as, but not limited to, acetonitrile or acetone, at a temperature of about 40 °C to about 85 °C, typically yields compounds of formula (15). Subsequent coupling with (E)-2-(2-ethoxyvinyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane utilizing Suzuki coupling reaction conditions as described in

Scheme 1 provides compounds of formula (16). Cyclization of (16) followed by protection of the nitrogen atom typically affords compounds of formula (17).

Cyclization of (16) may be accomplished in the presence of an acid such as, but not limited to, acetic acid or hydrochloric acid and at an elevated temperature (e.g. about 50 °C to
5 about 100 °C).

Scheme 3



Compounds of formula (1) wherein Y^1 is N, R^{101} is Cl, X^1 is $-COOR^{ax1}$ or $-C(O)NR^{bx1}R^{cx1}$, R^{ax1} , R^{bx1} , and R^{cx1} are hydrogen or C- C_6 alkyl, and X^2 is CH may be prepared using the synthetic route exemplified in Scheme 4.
10

Treatment of (15) with pyruvic acid in the presence of a palladium catalyst such as, but not limited to, palladium(II)acetate, and a base such as, but not limited to, DBU, and in a solvent such as, but not limited to, DMF and at elevated temperature (e.g. at about 80 °C to about 150 °C) generally results in acids of formula (18). Esterification of (18) to (19) may be accomplished by reaction conditions known to one skilled in the art, for example, by
15 treatment with an alcohol under acidic condition. Subsequent protection of (19) using reaction conditions described in Scheme 2 for the conversion of (8) to (9) can provide for compounds of formula (20). Transformation of (20) to (21) may be accomplished by step-wise reaction of (a) hydrolysis of the ester to the corresponding acid and (b) conversion of the
20 acid to the corresponding amides.

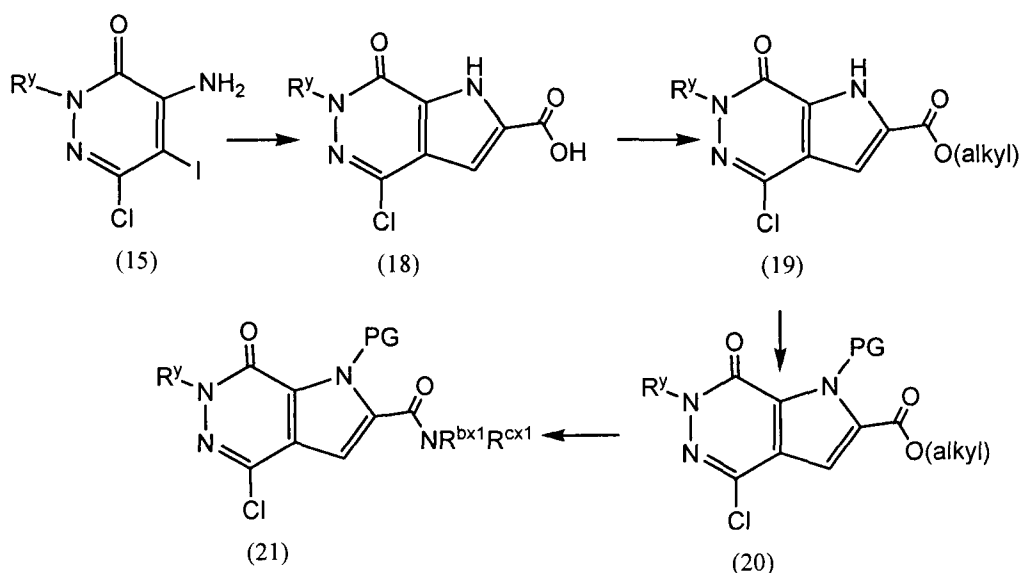
The acid can be transformed to the appropriate acid chloride by treatment with oxalyl chloride in the presence of catalytic amount of DMF at about room temperature, and in a suitable solvent such as, but not limited to, tetrahydrofuran or dichloromethane.

The resulting acid chloride may be converted to amides of formula (21) by treatment
25 with an amine of formula $HNR^{bx1}R^{cx1}$ in a solvent such as, but not limited to, tetrahydrofuran, dimethylformamide, or dichloromethane at a temperature from about room temperature to about 50 °C, optionally in the presence of a base such as, but not limited to, triethylamine, diisopropylethylamine, or potassium carbonate, and optionally in the presence of a catalyst such as 4-dimethylaminopyridine. Alternatively, the acid can be reacted with the amine of
30 formula $HNR^{bx1}R^{cx1}$ in a solvent such as, but not limited to, tetrahydrofuran or

dimethylformamide in the presence of a coupling reagent such as 1,1'-carbonyldiimidazole (CDI), bis(2-oxo-3-oxazolidinyl)phosphinic chloride (BOPCI), 1,3-dicyclohexylcarbodiimide (DCC), polymer supported 1,3-dicyclohexylcarbodiimide (PS-DCC), 0-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (HATU), or O-benzotriazol-1-yl-N,N,N',N'-tetramethyluronium tetrafluoroborate (TBTU), in the presence or absence of a coupling auxiliary such as, but not limited to, 1-hydroxy-7-azabenzotriazole (HOAT) or 1-hydroxybenzotriazole hydrate (HOBT). The reaction may be generally conducted in the presence or absence of a base such as, but not limited to, N-methyl morpholine, triethylamine, or diisopropylethylamine.

10

Scheme 4



Scheme 5 demonstrates a general approach to the preparation of compounds of formula (1) wherein Y^1 is CR^u , R^{101} is halogen, X^1 is $-COOR^{ax1}$ or $-C(O)NR^{bx1}R^{cx1}$, R^{ax1} , R^{bx1} , and R^{cx1} are hydrogen or Ci- C_6 alkyl, and X^2 is CH.

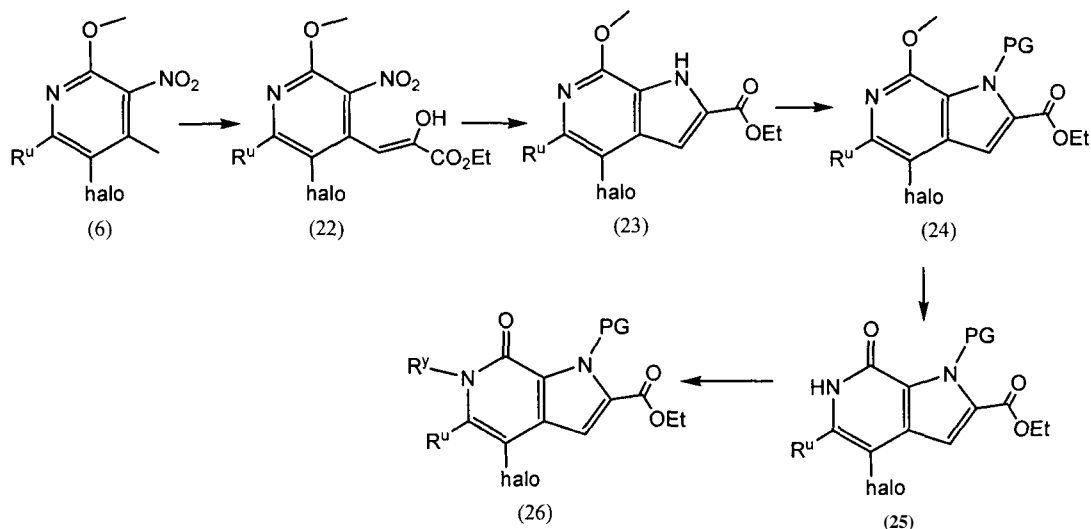
15

An ester of formula (23) may be obtained from (a) treatment of (6) with diethyl oxalate in the presence of a base such as, but not limited to, potassium ethoxide or sodium ethoxide, in a solvent such as, but not limited to, potassium ethoxide or sodium ethoxide, in a solvent such as, but not limited to, ethanol, dioxane, or diethyl ether, and at a temperature of about 40 °C to about 80 °C; and (b) cyclization of the resulting (22) in the presence of iron and in ethanol and acetic acid, at a temperature of about 80 °C to about 100 °C. Conversion of (23) to (26) can be achieved by employing reaction conditions discussed above.

20

An ethyl ester of formula (26) may subsequently be hydrolysed to the corresponding acids. The resulting acids may be transformed to an appropriate ester or amide as described in Scheme 4.

Scheme 5



5

Optimum reaction conditions and reaction times for each individual step may vary depending on the particular reactants employed and substituents present in the reactants used. Unless otherwise specified, solvents, temperatures and other reaction conditions may be readily selected by one of ordinary skill in the art. Specific procedures are provided in the Synthetic Examples section. Reactions may be further processed in the conventional manner, e.g. by eliminating the solvent from the residue and further purified according to methodologies generally known in the art such as, but not limited to, crystallization, distillation, extraction, trituration and chromatography. Unless otherwise described, the starting materials and reagents are either commercially available or may be prepared by one skilled in the art from commercially available materials using methods described in the chemical literature.

Routine experimentations, including appropriate manipulation of the reaction conditions, reagents and sequence of the synthetic route, protection of any chemical functionality that may not be compatible with the reaction conditions, and deprotection at a suitable point in the reaction sequence of the method are included in the scope of the invention. Suitable protecting groups and the methods for protecting and deprotecting different substituents using such suitable protecting groups are well known to those skilled in the art; examples of which may be found in T. Greene and P. Wuts, *Protecting Groups in Chemical Synthesis* (3rd ed.), John Wiley & Sons, NY (1999), which is incorporated herein

by reference in its entirety. Synthesis of the compounds of the invention may be accomplished by methods analogous to those described in the synthetic schemes described hereinabove and in specific examples.

Starting materials, if not commercially available, may be prepared by procedures
5 selected from standard organic chemical techniques, techniques that are analogous to the synthesis of known, structurally similar compounds, or techniques that are analogous to the above described schemes or the procedures described in the synthetic examples section.

When an optically active form of a compound of the invention is required, it may be obtained by carrying out one of the procedures described herein using an optically active
10 starting material (prepared, for example, by asymmetric induction of a suitable reaction step), or by resolution of a mixture of the stereoisomers of the compound or intermediates using a standard procedure (such as chromatographic separation, recrystallization or enzymatic resolution).

Similarly, when a pure geometric isomer of a compound of the invention is required,
15 it may be obtained by carrying out one of the above procedures using a pure geometric isomer as a starting material, or by resolution of a mixture of the geometric isomers of the compound or intermediates using a standard procedure such as chromatographic separation.

Pharmaceutical Compositions

This invention also provides for pharmaceutical compositions comprising a
20 therapeutically effective amount of a compound of Formula I, or a pharmaceutically acceptable salt thereof together with a pharmaceutically acceptable carrier, diluent, or excipient therefor. The phrase "pharmaceutical composition" refers to a composition suitable for administration in medical or veterinary use.

The pharmaceutical compositions that comprise a compound of formula (I), alone or
25 or in combination with a second active pharmaceutical agent, may be administered to the subjects orally, rectally, parenterally, intracisternally, intravaginally, intraperitoneally, topically (as by powders, ointments or drops), buccally or as an oral or nasal spray. The term "parenterally" as used herein, refers to modes of administration which include intravenous, intramuscular, intraperitoneal, intrasternal, subcutaneous and intraarticular injection and
30 infusion.

The term "pharmaceutically acceptable carrier" as used herein, means a non-toxic, inert solid, semi-solid or liquid filler, diluent, encapsulating material or formulation auxiliary of any type. Some examples of materials which can serve as pharmaceutically acceptable carriers are sugars such as, but not limited to, lactose, glucose and sucrose; starches such as,

but not limited to, corn starch and potato starch; cellulose and its derivatives such as, but not limited to, sodium carboxymethyl cellulose, ethyl cellulose and cellulose acetate; powdered tragacanth; malt; gelatin; talc; excipients such as, but not limited to, cocoa butter and suppository waxes; oils such as, but not limited to, peanut oil, cottonseed oil, safflower oil, 5 sesame oil, olive oil, corn oil and soybean oil; glycols; such a propylene glycol; esters such as, but not limited to, ethyl oleate and ethyl laurate; agar; buffering agents such as, but not limited to, magnesium hydroxide and aluminum hydroxide; alginic acid; pyrogen-free water; isotonic saline; Ringer's solution; ethyl alcohol, and phosphate buffer solutions, as well as other non-toxic compatible lubricants such as, but not limited to, sodium lauryl sulfate and 10 magnesium stearate, as well as coloring agents, releasing agents, coating agents, sweetening, flavoring and perfuming agents, preservatives and antioxidants can also be present in the composition, according to the judgment of the formulator.

Pharmaceutical compositions for parenteral injection comprise pharmaceutically acceptable sterile aqueous or nonaqueous solutions, dispersions, suspensions or emulsions as 15 well as sterile powders for reconstitution into sterile injectable solutions or dispersions just prior to use. Examples of suitable aqueous and nonaqueous carriers, diluents, solvents or vehicles include water, ethanol, polyols (such as glycerol, propylene glycol, polyethylene glycol and the like), vegetable oils (such as olive oil), injectable organic esters (such as ethyl oleate) and suitable mixtures thereof. Proper fluidity can be maintained, for example, by the 20 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.

These compositions may also contain adjuvants such as preservatives, wetting agents, emulsifying agents and dispersing agents. Prevention of the action of microorganisms can be ensured by the inclusion of various antibacterial and antifungal agents, for example, paraben, 25 chlorobutanol, phenol sorbic acid and the like. It may also be desirable to include isotonic agents such as sugars, sodium chloride and the like. 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.

In some cases, in order to prolong the effect of the drug, it is desirable to slow the 30 absorption of the drug from subcutaneous or intramuscular injection. This may be accomplished by the use of a liquid suspension of crystalline or amorphous material with poor water solubility. The rate of absorption of the drug then depends upon its rate of dissolution which, in turn, may depend upon crystal size and crystalline form. Alternatively,

delayed absorption of a parenterally-administered drug form may be accomplished by dissolving or suspending the drug in an oil vehicle.

Injectable depot forms are made by forming microencapsule matrices of the drug in biodegradable polymers such as polylactide-polyglycolide. Depending upon the ratio of drug
5 to polymer and the nature of the particular polymer employed, the rate of drug release can be controlled. Examples of other biodegradable polymers include poly(orthoesters) and poly(anhydrides). Depot injectable formulations are also prepared by entrapping the drug in liposomes or microemulsions which are compatible with body tissues.

The injectable formulations can be sterilized, for example, by filtration through a
10 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 just prior to use.

Solid dosage forms for oral administration include capsules, tablets, pills, powders and granules. In certain embodiments, solid dosage forms may contain from 1% to 95%
15 (w/w) of a compound of formula I. In certain embodiments, the compound of formula I may be present in the solid dosage form in a range of from 5% to 70% (w/w). In such solid dosage forms, the active compound may be mixed with at least one inert, pharmaceutically acceptable excipient or carrier, such as sodium citrate or dicalcium phosphate and/or a) fillers or extenders such as starches, lactose, sucrose, glucose, mannitol and silicic acid; b) binders
20 such as carboxymethylcellulose, alginates, gelatin, polyvinylpyrrolidone, sucrose and acacia; c) humectants such as glycerol; d) disintegrating agents such as agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates and sodium carbonate; e) solution retarding agents such as paraffin; i) absorption accelerators such as quaternary ammonium compounds; g) wetting agents such as cetyl alcohol and glycerol monostearate; h) absorbents
25 such as kaolin and bentonite clay and i) lubricants such as talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate and mixtures thereof. In the case of capsules, tablets and pills, the dosage form may also comprise buffering agents.

The pharmaceutical composition may be a unit dosage form. In such form the preparation is subdivided into unit doses containing appropriate quantities of the active
30 component. The unit dosage form can be a packaged preparation, the package containing discrete quantities of preparation, such as packeted tablets, capsules, and powders in vials or ampules. Also, the unit dosage form can be a capsule, tablet, cachet, or lozenge itself, or it can be the appropriate number of any of these in packaged form. The quantity of active component in a unit dose preparation may be varied or adjusted from 0.1 mg to 1000 mg,

from 1 mg to 100 mg, or from 1% to 95% (w/w) of a unit dose, according to the particular application and the potency of the active component. The composition can, if desired, also contain other compatible therapeutic agents.

The dose to be administered to a subject may be determined by the efficacy of the particular compound employed and the condition of the subject, as well as the body weight or surface area of the subject to be treated. The size of the dose also will be determined by the existence, nature, and extent of any adverse side-effects that accompany the administration of a particular compound in a particular subject. In determining the effective amount of the compound to be administered in the treatment or prophylaxis of the disorder being treated, the physician can evaluate factors such as the circulating plasma levels of the compound, compound toxicities, and/or the progression of the disease, etc. In general, the dose equivalent of a compound is from about 1 $\mu\text{g}/\text{kg}$ to 100 mg/kg for a typical subject.

For administration, compounds of the formula I can be administered at a rate determined by factors that can include, but are not limited to, the LD50 of the compound, the pharmacokinetic profile of the compound, contraindicated drugs, and the side-effects of the compound at various concentrations, as applied to the mass and overall health of the subject. Administration can be accomplished via single or divided doses.

The compounds utilized in the pharmaceutical method of the invention can be administered at the initial dosage of about 0.001 mg/kg to about 100 mg/kg daily. In certain embodiments, the daily dose range is from about 0.1 mg/kg to about 10 mg/kg . The dosages, however, may be varied depending upon the requirements of the subject, the severity of the condition being treated, and the compound being employed. Determination of the proper dosage for a particular situation is within the skill of the practitioner. Treatment may be initiated with smaller dosages, which are less than the optimum dose of the compound. Thereafter, the dosage is increased by small increments until the optimum effect under circumstances is reached. For convenience, the total daily dosage may be divided and administered in portions during the day, if desired.

Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such carriers as lactose or milk sugar as well as high molecular weight polyethylene glycols and the like.

The solid dosage forms of tablets, dragees, capsules, pills and granules can be prepared with coatings and shells such as enteric coatings and other coatings well-known in the pharmaceutical formulating art. They may optionally contain opacifying agents and may also be of a composition such that they release the active ingredient(s) only, or preferentially,

in a certain part of the intestinal tract, optionally, in a delayed manner. Examples of embedding compositions which can be used include polymeric substances and waxes.

The active compounds can also be in micro-encapsulated form, if appropriate, with one or more of the above-mentioned carriers.

5 Liquid dosage forms for oral administration include pharmaceutically acceptable emulsions, solutions, suspensions, syrups and elixirs. In addition to the active compounds, the liquid dosage forms may contain inert diluents commonly used in the art such as, for example, water or other solvents, solubilizing agents and emulsifiers such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene
10 glycol, 1,3-butylene glycol, dimethyl formamide, oils (in particular, cottonseed, groundnut, corn, germ, olive, castor and sesame oils), glycerol, tetrahydrofurfuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan and mixtures thereof.

Besides inert diluents, the oral compositions may also include adjuvants such as wetting agents, emulsifying and suspending agents, sweetening, flavoring and perfuming
15 agents.

Suspensions, in addition to the active compounds, may contain suspending agents as, for example, ethoxylated isostearyl alcohols, polyoxyethylene sorbitol and sorbitan esters, microcrystalline cellulose, aluminum metahydroxide, bentonite, agar-agar, tragacanth and mixtures thereof.

20 Compositions for rectal or vaginal administration are preferably suppositories which can be prepared by mixing the compounds of this invention with suitable non-irritating carriers or carriers such as cocoa butter, polyethylene glycol or a suppository wax which are solid at room temperature but liquid at body temperature and therefore melt in the rectum or vaginal cavity and release the active compound.

25 Compounds of formula I may also be administered in the form of liposomes. Liposomes generally may be derived from phospholipids or other lipid substances. Liposomes are formed by mono- or multi-lamellar hydrated liquid crystals which are dispersed in an aqueous medium. Any non-toxic, physiologically acceptable and metabolizable lipid capable of forming liposomes can be used. The present compositions in
30 liposome form may contain, in addition to a compound of formula (I), stabilizers, preservatives, excipients and the like. Examples of lipids include, but are not limited to, natural and synthetic phospholipids and phosphatidyl cholines (lecithins), used separately or together.

Methods to form liposomes have been described, see example, Prescott, Ed., Methods in Cell Biology, Volume XIV, Academic Press, New York, N.Y. (1976), p. 33 et seq.

Dosage forms for topical administration of a compound described herein include powders, sprays, ointments and inhalants. The active compound may be mixed under sterile
5 conditions with a pharmaceutically acceptable carrier and any needed preservatives, buffers or propellants which may be required. Ophthalmic formulations, eye ointments, powders and solutions are also contemplated as being within the scope of this invention.

Methods of Use

The compounds of formula I, or pharmaceutically acceptable salts thereof, and
10 pharmaceutical compositions comprising a compound of formula I, or a pharmaceutically acceptable salt thereof, can be administered to a subject suffering from a bromodomain-mediated disorder or condition. The term "administering" refers to the method of contacting a compound with a subject. Thus, the compounds of formula I can be administered by injection, that is, intravenously, intramuscularly, intracutaneously, subcutaneously,
15 intraduodenally, parentally, or intraperitoneally. Also, the compounds described herein can be administered by inhalation, for example, intranasally. Additionally, the compounds of formula I can be administered transdermally, topically, via implantation, transdermally, topically, and via implantation. In certain embodiments, the compounds of the formula I may be delivered orally. The compounds can also be delivered rectally, buccally, intravaginally,
20 ocularly, andially, or by insufflation. Bromodomain-mediated disorders and conditions can be treated prophylactically, acutely, and chronically using compounds of formula I, depending on the nature of the disorder or condition. Typically, the host or subject in each of these methods is human, although other mammals can also benefit from the administration of a compound of formula I.

25 A "bromodomain-mediated disorder or condition" is characterized by the participation of one or more bromodomains (e.g., BRIM) in the inception, manifestation of one or more symptoms or disease markers, severity, or progression of a disorder or condition. Accordingly, compounds of formula I may be used to treat cancer, including, but not limited to acoustic neuroma, acute leukemia, acute lymphocytic leukemia, acute myelocytic leukemia
30 (monocytic, myeloblasts, adenocarcinoma, angiosarcoma, astrocytoma, myelomonocytic and promyelocytic), acute t-cell leukemia, basal cell carcinoma, bile duct carcinoma, bladder cancer, brain cancer, breast cancer, bronchogenic carcinoma, cervical cancer, chondrosarcoma, chordoma, choriocarcinoma, chronic leukemia, chronic lymphocytic leukemia, chronic myelocytic (granulocytic) leukemia, chronic myelogenous leukemia, colon

cancer, colorectal cancer, craniopharyngioma, cystadenocarcinoma, diffuse large B-cell lymphoma, dysproliferative changes (dysplasias and metaplasias), embryonal carcinoma, endometrial cancer, endotheliosarcoma, ependymoma, epithelial carcinoma, erythroleukemia, esophageal cancer, estrogen-receptor positive breast cancer, essential thrombocythemia,

5 Ewing's tumor, fibrosarcoma, follicular lymphoma, germ cell testicular cancer, glioma, glioblastoma, gliosarcoma, heavy chain disease, hemangioblastoma, hepatoma, hepatocellular cancer, hormone insensitive prostate cancer, leiomyosarcoma, leukemia, liposarcoma, lung cancer, lymphagioendotheliosarcoma, lymphangiosarcoma, lymphoblastic leukemia, lymphoma (Hodgkin's and non-Hodgkin's), malignancies and hyperproliferative disorders of

10 the bladder, breast, colon, lung, ovaries, pancreas, prostate, skin and uterus, lymphoid malignancies of T-cell or B-cell origin, leukemia, lymphoma, medullary carcinoma, medulloblastoma, melanoma, meningioma, mesothelioma, multiple myeloma, myelogenous leukemia, myeloma, myxosarcoma, neuroblastoma, NUT midline carcinoma (NMC), non-small cell lung cancer, oligodendroglioma, oral cancer, osteogenic sarcoma, ovarian

15 cancer, pancreatic cancer, papillary adenocarcinomas, papillary carcinoma, pinealoma, polycythemia vera, prostate cancer, rectal cancer, renal cell carcinoma, retinoblastoma, rhabdomyosarcoma, sarcoma, sebaceous gland carcinoma, seminoma, skin cancer, small cell lung carcinoma, solid tumors (carcinomas and sarcomas), small cell lung cancer, stomach cancer, squamous cell carcinoma, synovioma, sweat gland carcinoma, thyroid cancer,

20 Waldenstrom's macroglobulinemia, testicular tumors, uterine cancer and Wilms' tumor.

Further, compounds of formula I may be used to treat inflammatory diseases, inflammatory conditions, and autoimmune diseases, including, but not limited to: Addison's disease, acute gout, ankylosing spondylitis, asthma, atherosclerosis, Behcet's disease, bullous skin diseases, chronic obstructive pulmonary disease (COPD), Crohn's disease, dermatitis,

25 eczema, giant cell arteritis, glomerulonephritis, hepatitis, hypophysitis, inflammatory bowel disease, Kawasaki disease, lupus nephritis, multiple sclerosis, myocarditis, myositis, nephritis, organ transplant rejection, osteoarthritis, pancreatitis, pericarditis, Polyarteritis nodosa, pneumonitis, primary biliary cirrhosis, psoriasis, psoriatic arthritis, rheumatoid arthritis, scleritis, sclerosing cholangitis, sepsis, systemic lupus erythematosus, Takayasu's Arteritis,

30 toxic shock, thyroiditis, type I diabetes, ulcerative colitis, uveitis, vitiligo, vasculitis, and Wegener's granulomatosis.

Compounds of formula I, or pharmaceutically acceptable salts thereof, may be used to treat AIDS.

The compounds of formula I can be co-administered to a subject. The term "co-administered" means the administration of two or more different pharmaceutical agents or treatments (e.g., radiation treatment) that are administered to a subject by combination in the same pharmaceutical composition or separate pharmaceutical compositions. Thus co-

5 administration involves administration at the same time of a single pharmaceutical composition comprising two or more pharmaceutical agents or administration of two or more different compositions to the same subject at the same or different times.

The compounds of the invention can be co-administered with a therapeutically effective amount of one or more agents to treat a cancer, where examples of the agents

10 include, such as radiation, alkylating agents, angiogenesis inhibitors, antibodies, antimetabolites, antimetotics, antiproliferatives, antivirals, aurora kinase inhibitors, apoptosis promoters (for example, Bcl-xL, Bcl-w and Bfl-1) inhibitors, activators of death receptor pathway, Bcr-Abl kinase inhibitors, BiTE (Bi-Specific T cell Engager) antibodies, antibody drug conjugates, biologic response modifiers, cyclin-dependent kinase inhibitors, cell cycle

15 inhibitors, cyclooxygenase-2 inhibitors, DVDs (dual variable domain antibodies), leukemia viral oncogene homolog (ErbB2) receptor inhibitors, growth factor inhibitors, heat shock protein (HSP)-90 inhibitors, histone deacetylase (HDAC) inhibitors, hormonal therapies, immunologicals, inhibitors of inhibitors of apoptosis proteins (IAPs), intercalating antibiotics, kinase inhibitors, kinesin inhibitors, Jak2 inhibitors, mammalian target of rapamycin

20 inhibitors, microRNA's, mitogen-activated extracellular signal-regulated kinase inhibitors, multivalent binding proteins, non-steroidal anti-inflammatory drugs (NSAIDs), poly ADP (adenosine diphosphate)-ribose polymerase (PARP) inhibitors, platinum chemotherapeutics, polo-like kinase (Plk) inhibitors, phosphoinositide-3 kinase (bromodomain) inhibitors, proteasome inhibitors, purine analogs, pyrimidine analogs, receptor tyrosine kinase inhibitors,

25 etinoids/deltoids plant alkaloids, small inhibitory ribonucleic acids (siRNAs), topoisomerase inhibitors, ubiquitin ligase inhibitors, and the like, and in combination with one or more of these agents .

BiTE antibodies are bi-specific antibodies that direct T-cells to attack cancer cells by simultaneously binding the two cells. The T-cell then attacks the target cancer cell.

30 Examples of BiTE antibodies include adecatumumab (Micromet MT201), blinatumomab (Micromet MT103) and the like. Without being limited by theory, one of the mechanisms by which T-cells elicit apoptosis of the target cancer cell is by exocytosis of cytolytic granule components, which include perforin and granzyme B. In this regard, Bcl-2 has been shown to attenuate the induction of apoptosis by both perforin and granzyme B. These data suggest

that inhibition of Bcl-2 could enhance the cytotoxic effects elicited by T-cells when targeted to cancer cells (V.R. Sutton, D.L. Vaux and J.A. Trapani, *J. of Immunology* 1997, 158 (12), 5783).

5 SiRNAs are molecules having endogenous RNA bases or chemically modified nucleotides. The modifications do not abolish cellular activity, but rather impart increased stability and/or increased cellular potency. Examples of chemical modifications include phosphorothioate groups, 2'-deoxynucleotide, 2'-OCH₃-containing ribonucleotides, 2'-F-ribonucleotides, 2'-methoxyethyl ribonucleotides, combinations thereof and the like. The siRNA can have varying lengths (e.g., 10-200 bps) and structures (e.g., hairpins, 10 single/double strands, bulges, nicks/gaps, mismatches) and are processed in cells to provide active gene silencing. A double-stranded siRNA (dsRNA) can have the same number of nucleotides on each strand (blunt ends) or asymmetric ends (overhangs). The overhang of 1-2 nucleotides can be present on the sense and/or the antisense strand, as well as present on the 5'- and/ or the 3'-ends of a given strand.

15 Multivalent binding proteins are binding proteins comprising two or more antigen binding sites. Multivalent binding proteins are engineered to have the three or more antigen binding sites and are generally not naturally occurring antibodies. The term "multispecific binding protein" means a binding protein capable of binding two or more related or unrelated targets. Dual variable domain (DVD) binding proteins are tetravalent or multivalent binding 20 proteins binding proteins comprising two or more antigen binding sites. Such DVDs may be monospecific (i.e., capable of binding one antigen) or multispecific (i.e., capable of binding two or more antigens). DVD binding proteins comprising two heavy chain DVD polypeptides and two light chain DVD polypeptides are referred to as DVD Ig's. Each half of a DVD Ig comprises a heavy chain DVD polypeptide, a light chain DVD polypeptide, and 25 two antigen binding sites. Each binding site comprises a heavy chain variable domain and a light chain variable domain with a total of 6 CDRs involved in antigen binding per antigen binding site. Multispecific DVDs include DVD binding proteins that bind DLL4 and VEGF, or C-met and EGFR or ErbB3 and EGFR.

Alkylating agents include altretamine, AMD-473, AP-5280, apaziquone, 30 bendamustine, brostallicin, busulfan, carboquone, carmustine (BCNU), chlorambucil, CLORETAZINE® (laromustine, VNP 40101M), cyclophosphamide, decarbazine, estramustine, fotemustine, glufosfamide, ifosfamide, KW-2170, lomustine (CCNU), mafosfamide, melphalan, mitobronitol, mitolactol, nimustine, nitrogen mustard N-oxide,

ranimustine, temozolomide, thiotepa, TREANDA[®] (bendamustine), treosulfan, rofosfamide and the like.

Angiogenesis inhibitors include endothelial-specific receptor tyrosine kinase (Tie-2) inhibitors, epidermal growth factor receptor (EGFR) inhibitors, insulin growth factor-2
 5 receptor (IGFR-2) inhibitors, matrix metalloproteinase-2 (MMP-2) inhibitors, matrix metalloproteinase-9 (MMP-9) inhibitors, platelet-derived growth factor receptor (PDGFR) inhibitors, thrombospondin analogs, vascular endothelial growth factor receptor tyrosine kinase (VEGFR) inhibitors and the like.

Antimetabolites include ALIMTA[®] (pemetrexed disodium, LY231514, MTA),
 10 5-azacitidine, XELODA[®] (capecitabine), capecitabine, LEUSTAT[®] (cladribine), clofarabine, cytarabine, cytarabine ocfosfate, cytosine arabinoside, decitabine, deferoxamine, doxifluridine, eflornithine, EICAR (5-ethynyl-1-β-D-ribofuranosylimidazole-4-carboxamide), enocitabine, ethnylcytidine, fludarabine, 5-fluorouracil alone or in combination with leucovorin, GEMZAR[®] (gemcitabine), hydroxyurea,
 15 ALKERAN[®](melphalan), mercaptopurine, 6-mercaptopurine riboside, methotrexate, mycophenolic acid, nelarabine, nolatrexed, ocfosfate, pelitrexol, pentostatin, raltitrexed, Ribavirin, triapine, trimetrexate, S-1, tiazofurin, tegafur, TS-1, vidarabine, UFT and the like.

Antivirals include ritonavir, hydroxychloroquine and the like.

Aurora kinase inhibitors include ABT-348, AZD-1152, MLN-8054, VX-680, Aurora
 20 A-specific kinase inhibitors, Aurora B-specific kinase inhibitors and pan-Aurora kinase inhibitors and the like.

Bcl-2 protein inhibitors include AT-101 ((-)-gossypol), GENASENSE[®] (G3139 or oblimersen (Bcl-2-targeting antisense oligonucleotide)), IPI-194, IPI-565, N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(dimethylamino)-1-
 25 ((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide) (ABT-737), N-(4-(4-((2-(4-chlorophenyl)-5,5-dimethyl-1-cyclohex-1-en-1-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(morpholin-4-yl)-1-((phenylsulfanyl)methyl)propyl)amino)-3-((trifluoromethyl)sulfonyl)benzenesulfonamide) (ABT-263), GX-070 (obatociclib) and the like.

Bcr-Abl kinase inhibitors include DASATINIB[®] (BMS-354825), GLEEVEC[®]
 30 (imatinib) and the like.

CDK inhibitors include AZD-5438, BMI-1040, BMS-032, BMS-387, CVT-2584, flavopyridol, GPC-286199, MCS-5A, PD0332991, PHA-690509, seliciclib (CYC-202, R-roscovitine), ZK-304709 and the like.

COX-2 inhibitors include ABT-963, ARCOXIA[®] (etoricoxib), BEXTRA[®] (valdecoxib), BMS347070, CELEBREX[®] (celecoxib), COX-189 (lumiracoxib), CT-3, DERAMAXX[®] (deracoxib), JTE-522, 4-methyl-2-(3,4-dimethylphenyl)-1-(4-sulfamoylphenyl)-1H-pyrrole, MK-663 (etoricoxib), NS-398, parecoxib, RS-57067, 5 SC-58125, SD-8381, SVT-2016, S-2474, T-614, VIOXX[®] (rofecoxib) and the like.

EGFR inhibitors include EGFR antibodies, ABX-EGF, anti-EGFR immunoliposomes, EGF-vaccine, EMD-7200, ERBITUX[®] (cetuximab), HR3, IgA antibodies, IRESSA[®] (gefitinib), TARCEVA[®] (erlotinib or OSI-774), TP-38, EGFR fusion protein, TYKERB[®] (lapatinib) and the like.

10 ErbB2 receptor inhibitors include CP-724-714, CI-1033 (canertinib), HERCEPTIN[®] (trastuzumab), TYKERB[®] (lapatinib), OMNITARG[®] (2C4, pertuzumab), TAK-165, GW-572016 (ionafarnib), GW-282974, EKB-569, PI-166, dHER2 (HER2 vaccine), APC-8024 (HER-2 vaccine), anti-HER2/neu bispecific antibody, B7.her2IgG3, AS HER2 trifunctional bispecific antibodies, mAB AR-209, mAB 2B-1 and the like.

15 Histone deacetylase inhibitors include depsipeptide, LAQ-824, MS-275, trapoxin, suberoylanilide hydroxamic acid (SAHA), TSA, valproic acid and the like.

HSP-90 inhibitors include 17-AAG-nab, 17-AAG, CNF-101, CNF-1010, CNF-2024, 17-DMAG, geldanamycin, IPI-504, KOS-953, MYCOGRAB[®] (human recombinant antibody to HSP-90), NCS-683664, PU24FC1, PU-3, radicicol, SNX-2112, STA-9090, VER49009 and 20 the like.

Inhibitors of inhibitors of apoptosis proteins include HGS1029, GDC-0145, GDC-0152, LCL-161, LBW-242 and the like.

Antibody drug conjugates include anti-CD22-MC-MMAF, anti-CD22-MC-MMAE, anti-CD22-MCC-DMI, CR-011-vcMMAE, PSMA-ADC, MEDI-547, SGN-19A, SGN-35, 25 SGN-75 and the like.

Activators of death receptor pathway include TRAIL, antibodies or other agents that target TRAIL or death receptors (e.g., DR4 and DR5) such as Apomab, conatumumab, ETR2-ST01, GDC0145, (lexatumumab), HGS-1029, LBY-135, PRO-1762 and trastuzumab.

Kinesin inhibitors include Eg5 inhibitors such as AZD4877, ARRY-520; CENPE 30 inhibitors such as GSK923295A and the like.

JAK-2 inhibitors include CEP-701 (lesaurtinib), XL019 and INCBO18424 and the like.

MEK inhibitors include ARRY-142886, ARRY-438162, PD-325901, PD-98059 and the like.

mTOR inhibitors include AP-23573, CCI-779, everolimus, RAD-001, rapamycin, temsirolimus, ATP-competitive TORC1/TORC2 inhibitors, including PI-103, PP242, PP30, Torin 1 and the like.

5 Non-steroidal anti-inflammatory drugs include AMIGESIC[®] (salsalate), DOLOBID[®] (difiunisal), MOTRIN[®] (ibuprofen), ORUDIS[®] (ketoprofen), RELAFEN[®] (nabumetone), FELDENE[®] (piroxicam), ibuprofen cream, ALEVE[®] (naproxen) and NAPROSYN[®] (naproxen), VOLTAREN[®] (diclofenac), INDOCIN[®] (indomethacin), CLINORIL[®] (suiindac), TOLECTIN[®] (tolmetin), LODINE[®] (etodolac), TORADOL[®] (ketorolac), DAYPRO[®] (oxaprozin) and the like.

10 PDGFR inhibitors include C-451, CP-673, CP-868596 and the like.

Platinum chemotherapeutics include cisplatin, ELOXATIN[®] (oxaliplatin) eptaplatin, lobaplatin, nedaplatin, PARAPLATIN[®] (carboplatin), satraplatin, picoplatin and the like.

Polo-like kinase inhibitors include BI-2536 and the like.

15 Phosphoinositide-3 kinase (PI3K) inhibitors include wortmannin, LY294002, XL-147, CAL-120, ONC-21, AEZS-127, ETP-45658, PX-866, GDC-0941, BGT226, BEZ235, XL765 and the like.

Thrombospondin analogs include ABT-510, ABT-567, ABT-898, TSP-1 and the like.

20 VEGFR inhibitors include AVASTIN[®] (bevacizumab), ABT-869, AEE-788, ANGIOZYME[™] (a ribozyme that inhibits angiogenesis (Ribozyme Pharmaceuticals (Boulder, CO.) and Chiron, (Emeryville, CA)), axitinib (AG-13736), AZD-2171, CP-547,632, IM-862, MACUGEN (pegaptamib), NEXAVAR[®] (sorafenib, BAY43-9006), pazopanib (GW-786034), vatalanib (PTK-787, ZK-222584), SUTENT[®] (sunitinib, SU-11248), VEGF trap, ZACTIMA[™] (vandetanib, ZD-6474), GA101, ofatumumab, ABT-806 (mAb-806), ErbB3 specific antibodies, BSG2 specific antibodies, DLL4 specific antibodies and C-met specific antibodies, and the like.

25 Antibiotics include intercalating antibiotics aclarubicin, actinomycin D, amrubicin, annamycin, adriamycin, BLENOXANE[®] (bleomycin), daunorubicin, CAELYX[®] or MYOCET[®] (liposomal doxorubicin), elsamitracin, epirubicin, glarubicin, ZAVEDOS[®] (idarubicin), mitomycin C, nemorubicin, neocarzinostatin, peplomycin, pirarubicin, rebeccamycin, stimalamer, streptozocin, VALSTAR[®] (valrubicin), zinostatin and the like.

30 Topoisomerase inhibitors include aclarubicin, 9-aminocamptothecin, amonafide, amsacrine, becatecarin, belotecan, BN-80915, CAMPTOSAR[®] (irinotecan hydrochloride), camptothecin, CARDIOXANE[®] (dexrazoxine), diflomotecan, edotecarin, ELLENCE[®] or

PHARMORUBICIN[®] (epirubicin), etoposide, exatecan, 10-hydroxycamptothecin, gimatecan, lurtotecan, mitoxantrone, orathecin, pirarbucic, pixantrone, rubitecan, sobuzoxane, SN-38, tafluposide, topotecan and the like.

Antibodies include AVASTIN[®] (bevacizumab), CD40-specific antibodies, chTNT-
 5 1/B, denosumab, ERBITUX[®] (cetuximab), HUMAX-CD4[®] (zanolimumab), IGF1 R-specific antibodies, lintuzumab, PANOREX[®] (edrecolomab), RENCAREX[®] (WX G250), RITUXAN[®] (rituximab), ticilimumab, trastuziniab, CD20 antibodies types I and II and the like.

Hormonal therapies include ARIMIDEX[®] (anastrozole), AROMASIN[®] (exemestane),
 10 arzoxifene, CASODEX[®] (bicalutamide), CETROTIDE[®] (cetorelix), degarelix, deslorelin, DESOPAN[®] (trilostane), dexamethasone, DROGENIL[®] (flutamide), EVISTA[®] (raloxifene), AFEMA[™] (fadrozole), FARESTON[®] (toremifene), FASLODEX[®] (fulvestrant), FEMARA[®] (letrozole), formestane, glucocorticoids, HECTOROL[®] (doxercalciferol), RENAGEL[®] (sevelamer carbonate), lasofoxifene, leuprolide acetate, MEGACE[®] (megesterol),
 15 MIFEPREX[®] (mifepristone), NILANDRON[™] (nilutamide), NOLVADEX[®] (tamoxifen citrate), PLENAXIS[™] (abarelix), prednisone, PROPECIA[®] (finasteride), rilostane, SUPREFACT[®] (buserelin), TRELSTAR[®] (luteinizing hormone releasing hormone (LHRH)), VANTAS[®] (Histrelin implant), VETORYL[®] (trilostane or modrastane), ZOLADEX[®] (fosreltin, goserelin) and the like.

20 Deltoids and retinoids include seocalcitol (EB1089, CB1093), lexacalcitrol (KH1060), fenretinide, PANRETIN[®] (aliretinoin), ATRAGEN[®] (liposomal tretinoin), TARGRETIN[®] (bexarotene), LGD-1550 and the like.

PARP inhibitors include ABT-888 (veliparib), olaparib, KU-59436, AZD-2281, AG-014699, BSI-201, BGP-15, INO-1001, ONO-2231 and the like.

25 Plant alkaloids include, but are not limited to, vincristine, vinblastine, vindesine, vinorelbine and the like.

Proteasome inhibitors include VELCADE[®] (bortezomib), MGI32, NPI-0052, PR-171 and the like.

Examples of immunologicals include interferons and other immune-enhancing agents.
 30 Interferons include interferon alpha, interferon alpha-2a, interferon alpha-2b, interferon beta, interferon gamma-1a, ACTIMMUNE[®] (interferon gamma-1b) or interferon gamma-n1, combinations thereof and the like. Other agents include ALFAFERONE[®] (IFN- α), BAM-002 (oxidized glutathione), BEROMUN[®] (tasonermin), BEXXAR[®] (tositumomab), CAMPATH[®]

(alemtuzumab), CTLA4 (cytotoxic lymphocyte antigen 4), decarbazine, denileukin, epratuzumab, GRANOCYTE[®] (lenograstim), lentinan, leukocyte alpha interferon, imiquimod, MDX-010 (anti-CTLA-4), melanoma vaccine, mitumomab, molgramostim, MYLOTARG[™] (gemtuzumab ozogamicin), NEUPOGEN[®] (filgrastim), OncoVAC-CL, OVAREX[®] (oregovomab), pemtumomab (Y-muHMFGL), PROVENGE[®] (sipuleucel-T), sargamostim, sizofilan, teceleukin, THERACYS[®] (Bacillus Calmette-Guerin), ubenimex, VIRULIZIN[®] (immunotherapeutic, Lorus Pharmaceuticals), Z-100 (Specific Substance of Maruyama (SSM)), WF-10 (Tetrachlorodecaoxide (TCDO)), PROLEUKIN[®] (aldesleukin), ZADAXIN[®] (thymalfasin), ZENAPAX[®] (daclizumab), ZEVALIN[®] (90Y-Ibritumomab tiuxetan) and the like.

Biological response modifiers are agents that modify defense mechanisms of living organisms or biological responses, such as survival, growth or differentiation of tissue cells to direct them to have anti-tumor activity and include krestin, lentinan, sizofiran, picibanil PF-3512676 (CpG-8954), ubenimex and the like.

Pyrimidine analogs include cytarabine (ara C or Arabinoside C), cytosine arabinoside, doxifluridine, FLUDARA[®] (fludarabine), 5-FU (5-fluorouracil), floxuridine, GEMZAR[®] (gemcitabine), TOMUDEX[®] (ratitrexed), TROXATYL[™] (triacetyluridine troxacitabine) and the like.

Purine analogs include LANVIS[®] (thioguanine) and PURI-NETHOL[®] (mercaptopurine).

Antimitotic agents include batabulin, epothilone D (KOS-862), N-(2-((4-hydroxyphenyl)amino)pyridin-3-yl)-4-methoxybenzenesulfonamide, ixabepilone (BMS 247550), paclitaxel, TAXOTERE[®] (docetaxel), PNU100940 (109881), patupilone, XRP-9881 (larotaxel), vinflunine, ZK-EPO (synthetic epothilone) and the like.

Ubiquitin ligase inhibitors include MDM2 inhibitors, such as nutlins, NEDD8 inhibitors such as MLN4924 and the like.

Compounds of this invention can also be used as radiosensitizers that enhance the efficacy of radiotherapy. Examples of radiotherapy include external beam radiotherapy, teletherapy, brachytherapy and sealed, unsealed source radiotherapy and the like.

Additionally, compounds having Formula (I) may be combined with other chemotherapeutic agents such as ABRAXANE[™] (ABI-007), ABT-100 (farnesyl transferase inhibitor), ADVEXIN[®] (Ad5CMV-p53 vaccine), ALTOCOR[®] or MEVACOR[®] (lovastatin), AMPLIGEN[®] (poly Ipoly C12U, a synthetic RNA), APTOSYN[®] (exisulind), AREDIA[®] (pamidronic acid), arglabin, L-asparaginase, atamestane (1-methyl-3,17-dione-androsta-1,4-

diene), AVAGE[®] (tazarotene), AVE-8062 (combreastatin derivative) BEC2 (mitumomab), cachectin or cachexin (tumor necrosis factor), canvaxin (vaccine), CEAVAC[®] (cancer vaccine), CELEUK[®] (celmoleukin), CEPLENE[®] (histamine dihydrochloride), CERVARIX[®] (human papillomavirus vaccine), CHOP[®] (C: CYTOXAN[®] (cyclophosphamide); H: 5 ADRIAMYCIN[®] (hydroxydoxorubicin); O: Vincristine (ONCOVIN[®]); P: prednisone), CYPAT[™] (cyproterone acetate), combrestatin A4P, DAB(389)EGF (catalytic and translocation domains of diphtheria toxin fused via a His-Ala linker to human epidermal growth factor) or TransMID-107R[™] (diphtheria toxins), dacarbazine, dactinomycin, 5,6-dimethylxanthenone-4-acetic acid (DMXAA), eniluracil, EVIZON[™] (squalamine lactate), 10 DIMERICINE[®] (T4N5 liposome lotion), discodermolide, DX-8951f (exatecan mesylate), enzastaurin, EPO906 (epithilone B), GARDASIL[®] (quadrivalent human papillomavirus (Types 6, 11, 16, 18) recombinant vaccine), GASTRIMUNE[®], GENASENSE[®], GMK (ganglioside conjugate vaccine), GVAX[®] (prostate cancer vaccine), halofuginone, histerelin, hydroxycarbamide, ibandronic acid, IGN-101, IL-13-PE38, IL-13-PE38QQR (cintredekin 15 besudotox), IL-13-pseudomonas exotoxin, interferon- α , interferon- γ , JUNOVAN[™] or MEPACT[™] (mifamurtide), lonafarnib, 5,10-methylenetetrahydrofolate, miltefosine (hexadecylphosphocholine), NEOVASTAT[®](AE-941), NEUTREXIN[®] (trimetrexate glucuronate), NIPENT[®] (pentostatin), ONCONASE[®] (a ribonuclease enzyme), ONCOPHAGE[®] (melanoma vaccine treatment), ONCOVAX[®] (IL-2 Vaccine), 20 ORATHECIN[™] (rubitecan), OSIDEM[®] (antibody-based cell drug), OVAREX[®] MAb (murine monoclonal antibody), paclitaxel, PANDIMEX[™] (aglycone saponins from ginseng comprising 20(S)protopanaxadiol (aPPD) and 20(S)protopanaxatriol (aPPT)), panitumumab, PANVAC[®]-VF (investigational cancer vaccine), pegaspargase, PEG Interferon A, phenoxodiol, procarbazine, rebimastat, REMOVAB[®] (catumaxomab), REVLIMID[®] 25 (lenalidomide), RSR13 (efaproxiral), SOMATULINE[®] LA (lanreotide), SORIATANE[®] (acitretin), staurosporine (Streptomyces staurospores), talabostat (PT100), TARGRETIN[®] (bexarotene), TAXOPREXIN[®] (DHA-paclitaxel), TELCYTA[®] (canfosfamide, TLK286), temilifene, TEMODAR[®] (temozolomide), tesmilifene, thalidomide, THERATOPE[®] (STn-KLH), thymitaq (2-amino-3,4-dihydro-6-methyl-4-oxo-5-(4-pyridylthio)quinazoline 30 dihydrochloride), TNFERADE[™] (adenovector: DNA carrier containing the gene for tumor necrosis factor- α), TRACLEER[®] or ZAVESCA[®] (bosentan), tretinoin (Retin-A), tetrandrine, TRISENOX[®] (arsenic trioxide), VIRULIZIN[®], ukrain (derivative of alkaloids from the greater celandine plant), vitaxin (anti- α h β 3 antibody), XCYTRIN[®] (motexafin gadolinium), XINLAY[™] (atrasentan), XYOTAX[™] (paclitaxel poliglumex), YONDELIS[®]

(trabectedin), ZD-6126, ZINECARD[®] (dexrazoxane), ZOMETA[®] (zolendronic acid), zorubicin and the like.

The compounds of the invention can also be co-administered with a therapeutically effective amount of one or more agents to treat an inflammatory disease or condition, or
 5 autoimmune disease, where examples of the agents include, such as methotrexate, 6-mercaptapurine, azathioprine sulphasalazine, mesalazine, olsalazine chloroquinine/hydroxychloroquine, pencillamine, aurothiomalate (intramuscular and oral), azathioprine, cochicine, corticosteroids (oral, inhaled and local injection), beta-2 adrenoreceptor agonists (salbutamol, terbutaline, salmeteral), xanthines (theophylline, aminophylline), cromoglycate,
 10 nedocromil, ketotifen, ipratropium and oxitropium, cyclosporin, FK506, rapamycin, mycophenolate mofetil, leflunomide, NSAIDs, for example, ibuprofen, corticosteroids such as prednisolone, phosphodiesterase inhibitors, adenosine agonists, antithrombotic agents, complement inhibitors, adrenergic agents, agents which interfere with signalling by proinflammatory cytokines such as TNF α or IL-1 (e.g., NIK, IKK, p38 or MAP kinase
 15 inhibitors), IL-1 β converting enzyme inhibitors, T-cell signalling inhibitors such as kinase inhibitors, metalloproteinase inhibitors, sulfasalazine, 6-mercaptapurines, angiotensin converting enzyme inhibitors, soluble cytokine receptors and derivatives thereof (e.g. soluble p55 or p75 TNF receptors and the derivatives p75TNFRIgG (etanercept) and p55TNFRIgG (Lenercept), sIL-IRI, sIL-IRII, sIL-6R), antiinflammatory cytokines (e.g. IL-4, IL-10, IL-1 β ,
 20 IL-1 β and TGF β), celecoxib, folic acid, hydroxychloroquine sulfate, rofecoxib, etanercept, infliximab, naproxen, valdecoxib, sulfasalazine, methylprednisolone, meloxicam, methylprednisolone acetate, gold sodium thiomalate, aspirin, triamcinolone acetonide, propoxyphene napsylate/apap, folate, nabumetone, diclofenac, piroxicam, etodolac, diclofenac sodium, oxaprozin, oxycodone HCl, hydrocodone bitartrate/apap, diclofenac
 25 sodium/misoprostol, fentanyl, anakinra, tramadol HCl, salsalate, sulindac, cyanocobalamin/fa/pyridoxine, acetaminophen, alendronate sodium, prednisolone, morphine sulfate, lidocaine hydrochloride, indomethacin, glucosamine sulf/chondroitin, amitriptyline HCl, sulfadiazine, oxycodone HCl/acetaminophen, olopatadine HCl misoprostol, naproxen sodium, omeprazole, cyclophosphamide, rituximab, IL-1 TRAP, MRA, CTLA4-IG, IL-1 β BP,
 30 anti-IL-12, Anti-IL15, BIRB-796, SCIO-469, VX-702, AMG-548, VX-740, Roflumilast, IC-485, CDC-801, S1P1 agonists (such as FTY720), PKC family inhibitors (such as Ruboxistaurin or AEB-071) and Mesopram. In certain embodiments, combinations include

methotrexate or leflunomide and in moderate or severe rheumatoid arthritis cases, cyclosporine and anti-TNF antibodies as noted above.

Non-limiting examples of therapeutic agents for inflammatory bowel disease with which a compound of Formula (I) of the invention may be co-administered include the following: budenoside; epidermal growth factor; corticosteroids; cyclosporin, sulfasalazine; aminosalicylates; 6-mercaptopurine; azathioprine; metronidazole; lipoxygenase inhibitors; mesalamine; olsalazine; balsalazide; antioxidants; thromboxane inhibitors; IL-1 receptor antagonists; anti-IL-1 β monoclonal antibodies; anti-IL-6 monoclonal antibodies; growth factors; elastase inhibitors; pyridinyl-imidazole compounds; antibodies to or antagonists of other human cytokines or growth factors, for example, TNF, LT, IL-1, IL-2, IL-6, IL-7, IL-8, IL-12, IL-15, IL-16, IL-23, EMAP-II, GM-CSF, FGF, and PDGF; cell surface molecules such as CD2, CD3, CD4, CD8, CD25, CD28, CD30, CD40, CD45, CD69, CD90 or their ligands; methotrexate; cyclosporine; FK506; rapamycin; mycophenolate mofetil; leflunomide; NSAIDs, for example, ibuprofen; corticosteroids such as prednisolone; phosphodiesterase inhibitors; adenosine agonists; antithrombotic agents; complement inhibitors; adrenergic agents; agents which interfere with signalling by proinflammatory cytokines such as TNF α or IL-1 (e.g. NIK, IKK, or MAP kinase inhibitors); IL-1 β converting enzyme inhibitors; TNF α converting enzyme inhibitors; T-cell signalling inhibitors such as kinase inhibitors; metalloproteinase inhibitors; sulfasalazine; azathioprine; 6-mercaptopurines; angiotensin converting enzyme inhibitors; soluble cytokine receptors and derivatives thereof (e.g. soluble p55 or p75 TNF receptors, sIL-1RI, sIL-1RII, sIL-6R) and antiinflammatory cytokines (e.g. IL-4, IL-10, IL-11, IL-13 and TGFP). Preferred examples of therapeutic agents for Crohn's disease with which a compound of Formula (I) can be combined include the following: TNF antagonists, for example, anti-TNF antibodies, D2E7 (adalimumab), CA2 (infliximab), CDP 571, TNFR-Ig constructs, (p75TNFR IgG (etanercept) and p55TNFR IgG (LENERCEPTTM) inhibitors and PDE4 inhibitors. A compound of Formula (I) can be combined with corticosteroids, for example, budenoside and dexamethasone; sulfasalazine, 5-aminosalicylic acid; olsalazine; and agents which interfere with synthesis or action of proinflammatory cytokines such as IL-1, for example, IL-1 β converting enzyme inhibitors and IL-1ra; T cell signaling inhibitors, for example, tyrosine kinase inhibitors; 6-mercaptopurine; IL-11; mesalamine; prednisone; azathioprine; mercaptopurine; infliximab; methylprednisolone sodium succinate; diphenoxylate/atrop sulfate; loperamide hydrochloride; methotrexate; omeprazole; folate; ciprofloxacin/dextrose-water; hydrocodone bitartrate/apap; tetracycline

hydrochloride; fluocinonide; metronidazole; thimerosal/boric acid; cholestyramine/sucrose; ciprofloxacin hydrochloride; hyoscyamine sulfate; meperidine hydrochloride; midazolam hydrochloride; oxycodone HCl/acetaminophen; promethazine hydrochloride; sodium phosphate; sulfamethoxazole/trimethoprim; celecoxib; polycarbophil; propoxyphene napsylate; hydrocortisone; multivitamins; balsalazide disodium; codeine phosphate/apap; colesevelam HCl; cyanocobalamin; folic acid; levofloxacin; methylprednisolone; natalizumab and interferon-gamma.

Non-limiting examples of therapeutic agents for multiple sclerosis with which a compound of Formula (I) may be co-administered include the following: corticosteroids; prednisolone; methylprednisolone; azathioprine; cyclophosphamide; cyclosporine; methotrexate; 4-aminopyridine; tizanidine; interferon-piA (AVONEX[®]; Biogen); interferon-piB (BETASERON[®]; Chiron/Berlex); interferon a-n3 (Interferon Sciences/Fujimoto), interferon-a (Alfa Wassermann/J&J), interferon β 1A -IF (Serono/Inhale Therapeutics), Peginterferon α 2b (Enzon/Schering-Plough), Copolymer 1 (Cop-1; COPAXONE[®]; Teva Pharmaceutical Industries, Inc.); hyperbaric oxygen; intravenous immunoglobulin; cladribine; antibodies to or antagonists of other human cytokines or growth factors and their receptors, for example, TNF, LT, IL-1, IL-2, IL-6, IL-7, IL-8, IL-12, IL-23, IL-15, IL-16, EMAP-II, GM-CSF, FGF, and PDGF. A compound of Formula (I) can be combined with antibodies to cell surface molecules such as CD2, CD3, CD4, CD8, CD19, CD20, CD25, CD28, CD30, CD40, CD45, CD69, CD80, CD86, CD90 or their ligands. A compound of Formula (I) may also be combined with agents such as methotrexate, cyclosporine, FK506, rapamycin, mycophenolate mofetil, leflunomide, an SIPI agonist, NSAIDs, for example, ibuprofen, corticosteroids such as prednisolone, phosphodiesterase inhibitors, adenosine agonists, antithrombotic agents, complement inhibitors, adrenergic agents, agents which interfere with signalling by proinflammatory cytokines such as TNF α or IL-1 (e.g., NIK, IKK, p38 or MAP kinase inhibitors), IL-1 β converting enzyme inhibitors, TACE inhibitors, T-cell signaling inhibitors such as kinase inhibitors, metalloproteinase inhibitors, sulfasalazine, azathioprine, 6-mercaptopurines, angiotensin converting enzyme inhibitors, soluble cytokine receptors and derivatives thereof (e.g. soluble p55 or p75 TNF receptors, sIL-IRI, sIL-IRII, sIL-6R) and antiinflammatory cytokines (e.g. IL-4, IL-10, IL-13 and TGFP).

A compound of Formula (I) may also be co-administered with agents, such as alemtuzumab, dronabinol, daclizumab, mitoxantrone, xaliproden hydrochloride, fampridine, glatiramer acetate, natalizumab, sinnabidol, a-immunokine NNS03, ABR-2 15062,

AnergiX.MS, chemokine receptor antagonists, BBR-2778, calagualine, CPI-1 189, LEM (liposome encapsulated mitoxantrone), THC.CBD (cannabinoid agonist), MBP-8298, mesopram (PDE4 inhibitor), MNA-715, anti-IL-6 receptor antibody, neurovax, pirfenidone
 5 allotrap 1258 (RDP-1258), sTNF-R1, talampanel, teriflunomide, TGF-beta2, tiplimotide, VLA-4 antagonists (for example, TR- 14035, VLA4 Ultrahaler, Antegran-ELAN/Biogen), interferon gamma antagonists and IL-4 agonists.

Non-limiting examples of therapeutic agents for ankylosing spondylitis with which a compound of Formula (I) can be co-administered include the following: ibuprofen, diclofenac, misoprostol, naproxen, meloxicam, indomethacin, diclofenac, celecoxib,
 10 rofecoxib, sulfasalazine, methotrexate, azathioprine, minocyclin, prednisone, and anti-TNF antibodies, D2E7 (HUMIRA[®]), CA2 (infliximab), CDP 571, TNFR-Ig constructs, (p75TNFR1gG (ENBREL[®]) and p55TNFR1gG (LENERCEPT[®]).

Non-limiting examples of therapeutic agents for asthma with which a compound of Formula (I) may be co-administered include the following: albuterol, salmeterol/fluticasone,
 15 montelukast sodium, fluticasone propionate, budesonide, prednisone, salmeterol xinafoate, levalbuterol HCl, albuterol sulfate/ipratropium, prednisolone sodium phosphate, triamcinolone acetonide, beclomethasone dipropionate, ipratropium bromide, azithromycin, pirbuterol acetate, prednisolone, theophylline anhydrous, methylprednisolone sodium succinate, clarithromycin, zafirlukast, formoterol fumarate, influenza virus vaccine,
 20 amoxicillin trihydrate, flunisolide, allergy injection, cromolyn sodium, fexofenadine hydrochloride, flunisolide/menthol, amoxicillin/clavulanate, levofloxacin, inhaler assist device, guaifenesin, dexamethasone sodium phosphate, moxifloxacin HCl, doxycycline hyclate, guaifenesin/d-methorphan, p-ephedrine/cod/chlorphenir, gatifloxacin, cetirizine hydrochloride, mometasone furoate, salmeterol xinafoate, benzonatate, cephalixin,
 25 pe/hydrocodone/chlorphenir, cetirizine HCl/pseudoephed, phenylephrine/cod/promethazine, codeine/promethazine, cefprozil, dexamethasone, guaifenesin/pseudoephedrine, chlorpheniramine/hydrocodone, nedocromil sodium, terbutaline sulfate, epinephrine, methylprednisolone, anti-IL-13 antibody, and metaproterenol sulfate.

Non-limiting examples of therapeutic agents for COPD with which a compound of
 30 Formula (I) may be co-administered include the following: albuterol sulfate/ipratropium, ipratropium bromide, salmeterol/fluticasone, albuterol, salmeterol xinafoate, fluticasone propionate, prednisone, theophylline anhydrous, methylprednisolone sodium succinate, montelukast sodium, budesonide, formoterol fumarate, triamcinolone acetonide, levofloxacin, guaifenesin, azithromycin, beclomethasone dipropionate, levalbuterol HCl, flunisolide,

ceftriaxone sodium, amoxicillin trihydrate, gatifloxacin, zafirlukast, amoxicillin/clavulanate, flunisolide/menthol, chlorpheniramine/hydrocodone, metaproterenol sulfate, methylprednisolone, mometasone furoate, p-ephedrine/cod/chlorphenir, pirbuterol acetate, p-ephedrine/loratadine, terbutaline sulfate, tiotropium bromide, (R,R)-formoterol, TgAAT, 5 cilomilast and roflumilast.

Non-limiting examples of therapeutic agents for psoriasis with which a compound of Formula (I) may be co-administered include the following: calcipotriene, clobetasol propionate, triamcinolone acetonide, halobetasol propionate, tazarotene, methotrexate, fluocinonide, betamethasone diprop augmented, fluocinolone acetonide, acitretin, tar 10 shampoo, betamethasone valerate, mometasone furoate, ketoconazole, pramoxine/fluocinolone, hydrocortisone valerate, flurandrenolide, urea, betamethasone, clobetasol propionate/emoll, fluticasone propionate, azithromycin, hydrocortisone, moisturizing formula, folic acid, desonide, pimecrolimus, coal tar, diflorasone diacetate, etanercept folate, lactic acid, methoxsalen, hc/bismuth subgal/znox/resor, methylprednisolone acetate, prednisone, sunscreen, halcinonide, salicylic acid, anthralin, clocortolone pivalate, coal extract, coal tar/salicylic acid, coal tar/salicylic acid/sulfur, desoximetasone, diazepam, emollient, fluocinonide/emollient, mineral oil/castor oil/na lact, mineral oil/peanut oil, petroleum/isopropyl myristate, psoralen, salicylic acid, soap/tribromsalan, thimerosal/boric acid, celecoxib, infliximab, cyclosporine, alefacept, efalizumab, tacrolimus, pimecrolimus, 20 PUVA, UVB, sulfasalazine, ABT-874 and ustekinumab.

Non-limiting examples of therapeutic agents for psoriatic arthritis with which a compound of Formula (I) may be co-administered include the following: methotrexate, etanercept, rofecoxib, celecoxib, folic acid, sulfasalazine, naproxen, leflunomide, methylprednisolone acetate, indomethacin, hydroxychloroquine sulfate, prednisone, sulindac, 25 betamethasone diprop augmented, infliximab, methotrexate, folate, triamcinolone acetonide, diclofenac, dimethylsulfoxide, piroxicam, diclofenac sodium, ketoprofen, meloxicam, methylprednisolone, nabumetone, tolmetin sodium, calcipotriene, cyclosporine, diclofenac sodium/misoprostol, fluocinonide, glucosamine sulfate, gold sodium thiomalate, hydrocodone bitartrate/apap, ibuprofen, risedronate sodium, sulfadiazine, thioguanine, 30 valdecoxib, alefacept, D2E7 (adalimumab), and efalizumab.

Preferred examples of therapeutic agents for SLE (Lupus) with which a compound of Formula (I) may be co-administered include the following: NSAIDS, for example, diclofenac, naproxen, ibuprofen, piroxicam, indomethacin; COX2 inhibitors, for example, celecoxib, rofecoxib, valdecoxib; anti-malarials, for example, hydroxychloroquine; steroids, for example,

prednisone, prednisolone, budenoside, dexamethasone; cytotoxics, for example, azathioprine, cyclophosphamide, mycophenolate mofetil, methotrexate; inhibitors of PDE4 or purine synthesis inhibitor, for example Cellcept®. A compound of Formula (I) may also be combined with agents such as sulfasalazine, 5-aminosalicylic acid, olsalazine, Imuran® and agents which interfere with synthesis, production or action of proinflammatory cytokines such as IL-1, for example, caspase inhibitors like IL-1 β converting enzyme inhibitors and IL-1ra. A compound of Formula (I) may also be used with T cell signaling inhibitors, for example, tyrosine kinase inhibitors; or molecules that target T cell activation molecules, for example, CTLA-4-IgG or anti-B7 family antibodies, anti-PD-1 family antibodies. A compound of Formula (I) can be combined with IL-1 or anti-cytokine antibodies, for example, fonotolizumab (anti-IFN γ antibody), or anti-receptor antibodies, for example, anti-IL-6 receptor antibody and antibodies to B-cell surface molecules. A compound of Formula (I) may also be used with LJP 394 (abetimus), agents that deplete or inactivate B-cells, for example, Rituximab (anti-CD20 antibody), lymphostat-B (anti-BlyS antibody), TNF antagonists, for example, anti-TNF antibodies, D2E7 (adalimumab), CA2 (infliximab), CDP 571, TNFR-Ig constructs, (p75TNFR-IgG (etanercept) and p55TNFR-IgG (LENERCEPT™).

The compounds of the invention can also be co-administered with a therapeutically effective amount of one or more agents used in the prevention or treatment of AIDS, where examples of the agents include, HIV reverse transcriptase inhibitors, HIV protease inhibitors, immunomodulators, and other retroviral drugs. Examples of reverse transcriptase inhibitors include, but are not limited to, abacavir, adefovir, didanosine, dipivoxil delavirdine, efavirenz, lamivudine, nevirapine, stavudine zalcitabine, and zidovudine. Examples of protease inhibitors include, but are not limited to, amprenavir, indinavir, lopinavir, nelfinavir, ritonavir, and saquinavir.

The following Examples may be used for illustrative purposes and should not be deemed to narrow the scope of the invention.

Examples

Example 1

6-methyl-4-(2-phenoxyphenyl)-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one

Example 1a

(E)-2-(5-bromo-2-methoxy-3-nitropyridin-4-yl)-N,N-dimethylethanamine

5-Bromo-2-methoxy-4-methyl-3-nitropyridine (15.0 g, 60.7 mmol) was dissolved in dimethylformamide (300 mL), and lithium methanolate (6.07 mL, 6.07 mmol, 1 M) was added. The reaction mixture was heated to 100 °C. To this mixture was added 1,1-dimethoxy-N,N-dimethylmethanamine (64.5 mL, 486 mmol) over 10 minutes. The reaction mixture was stirred at 95 °C for 16 hours. The reaction mixture was cooled to room temperature and water was added carefully (300 mL, exothermic). The resulting precipitate was collected by vacuum filtration, washed with water, and dried to provide the title compound (13.9 g, 45.9 mmol, 76 % yield).

Example 1b

10 4-bromo-7-methoxy-1H-pyrrolo[2,3-c]pyridine

Example 1a (13.9 g, 45.8 mmol) and ethyl acetate (150 mL) were added to Ra-Ni 2800 (pre-washed with ethanol), water slurry (6.9 g, 118 mmol) in a stainless steel pressure bottle and stirred for 30 minutes at 30 psi and room temperature. The reaction mixture was filtered, and concentrated. The residue was triturated with dichloromethane, and the solid filtered to provide the title compound (5.82 g). The mother liquor was evaporated and the residue triturated again with dichloromethane and filtered to provide an additional 1.63 g of the title compound. Total yield = 7.45 g, 72% yield

Example 1c

4-bromo-7-methoxy-1-tosyl-1H-pyrrolo[2,3-c]pyridine

20 A solution of Example 1b (7.42 g, 32.7 mmol) in dimethylformamide (235 mL) was stirred at room temperature. To this solution was added sodium hydride (1.18 g, 1.96 g of 60% dispersion in oil, 49.0 mmol), and the reaction mixture was stirred for 10 min. *P*-toluenesulfonyl chloride (9.35 g, 49.0 mmol) was then added portion-wise, and the mixture was stirred at room temperature under nitrogen for 16 hours. The reaction mixture was quenched carefully with water and the resulting beige solid collected by vacuum filtration on a Buchner funnel, and washed with water. The solid was collected and dried in a vacuum oven at 50 °C to provide 12.4 g (100%) of the title compound.

Example 1d

4-bromo-1-tosyl-1H-pyrrolo[2,3-c]pyridin-7(6H)-one

30 A solution of Example 1c (12.4 g, 32.6 mmol) in dioxane (140 mL) was stirred at room temperature. To this solution was added 4M HCl in dioxane (140 mL). The reaction mixture was stirred at 40 °C for 16 hours. The reaction mixture was cooled to room temperature and concentrated. The residue was triturated with diethylether, filtered, and

rinsed with additional diethylether and dried to provide the title compound (11.23 g, 30.6 mmol, 94 % yield) as a beige solid.

Example 1e

4-bromo-6-methyl-1-tosyl-1H-pyrrolo[2,3-c]pyridin-7(6H)-one

5 Sodium hydride (0.875 g, 36.5 mmol, 1.46 g of a 60% in oil dispersion) was added to a stirring solution of Example 1d (11.2 g, 30.4 mmol) in dimethylformamide (217 mL) under nitrogen. After 30 minutes, iodomethane (2.27 mL, 36.5 mmol) was added and the solution was stirred at room temperature for 3 h. Upon addition of water (250 mL) a precipitate formed. The precipitate was collected by vacuum filtration, rinsed with water (50 mL) and
10 dried in a vacuum oven at 55 °C overnight to provide 11.2 g of the title compound (96%).

Example 1f

6-methyl-4-(2-phenoxyphenyl)-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one

A mixture of Example 1e (152 mg, 0.40 mmol), 2-phenoxyphenylboronic acid (0.111 g, 0.520 mmol, 1.3 equivalents), Pd(PPh₃)₄ (0.023 g, 5 mol%) and cesium fluoride (0.182 g, 1.2 mmol) in DME (3 mL) and methanol (1.5 mL) was heated under microwave condition
15 (120 °C, 30 minutes). To this mixture was added potassium carbonate (0.055 g, 0.40 mmol) and water (1 mL) and the reaction mixture was reheated in the microwave oven at 120 °C for another 2 hours. The organic layer was separated and purified by flash chromatography (silica gel, ethyl acetate). The resulting material was triturated with acetone and filtered to
20 provide 0.075 g of the title compound (59%). ¹H NMR (500 MHz, DMSO-*d*₆) δ 3.50 (s, 3 H), 6.21-6.23 (m, 1 H), 6.88 (d, J=7.62 Hz, 2 H), 6.99-7.04 (m, 2 H), 7.24-7.30 (m, 5 H), 7.36-7.40 (m, 1 H), 7.50 (dd, J=7.48, 1.68 Hz, 1H), 11.98 (s, 1 H). MS (ESI+) m/z 317 (M+H)⁺.

Example 2

6-methyl-4-(5-nitro-2-phenoxyphenyl)-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one

25

Example 2a

4-(2-fluoro-5-nitrophenyl)-6-methyl-1-tosyl-1H-pyrrolo[2,3-c]pyridin-7(6H)-one

Method A:

Example 1e (0.687 g, 1.802 mmol), 2-fluoro-5-nitrophenylboronic acid (0.500 g, 2.70 mmol), Pd(PPh₃)₄ (0.104 g, 0.090 mmol) and sodium carbonate (2.70 mL, 5.41 mmol) were
30 combined in DME (7 mL) and water (7 mL) in a 20 mL microwave tube, sealed, sparged with nitrogen and heated under microwave at 120 °C for 30 minutes. The mixture was partitioned between EtAOc and water. The organic layer was washed with brine, dried

(Na_2SO_4), filtered and concentrated. The crude product was purified by flash chromatography (silica gel, 0-100% ethyl acetate in hexanes) to provide 0.41 g (52%) of the title compound.

Method B:

Example 1e (6.00 g, 15.7 mmol), 2-fluoro-5-nitrophenylboronic acid (5.82 g, 31.5 mmol), $\text{Pd}(\text{PPh}_3)_4$ (0.909 g, 0.787 mmol) and sodium carbonate (3.34 g, 31.5 mmol) were combined in toluene (60 mL), ethanol (15 mL) and water (15 mL) and the mixture was degassed and left under nitrogen. The reaction mixture was heated at 90 °C overnight, and then cooled to room temperature. The mixture was partitioned between ethyl acetate and water. The organic layer was washed with brine, dried (MgSO_4), filtered and concentrated. The crude product was purified by flash chromatography (silica gel, 20-50% ethyl acetate in hexanes) to provide 6.95 g (61%) of the title compound.

Example 2b

6-methyl-4-(5-nitro-2-phenoxyphenyl)-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one

Phenol (0.094 g, 0.997 mmol), Example 2a (0.4 g, 0.906 mmol) and cesium carbonate (0.325 g, 0.997 mmol) were combined in DMSO (4.53 mL) and heated at 100 °C for 2 hours. The reaction mixture was partitioned between ethyl acetate and water and pH was adjusted to pH 7. The organic layer was washed with brine, dried (Na_2SO_4), filtered and concentrated. Purification by flash chromatography (silica gel, 0-4 % methanol in dichloromethane) afforded 0.28 g (84%) of the title compound. ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 3.57 (s, 3 H) 6.28 - 6.34 (m, 1 H) 6.98 (d, $J=9.12$ Hz, 1 H) 7.16 (d, $J=7.54$ Hz, 2 H) 7.21 - 7.32 (m, 2 H) 7.40 - 7.49 (m, 3 H) 8.22 (dd, $J=9.12, 2.78$ Hz, 1 H) 8.32 (d, $J=2.78$ Hz, 1 H) 12.07 - 12.11 (m, 1 H). MS (ESI+) m/z 362 $[\text{M}+\text{H}]^+$

Example 3

4-(5-amino-2-phenoxyphenyl)-6-methyl-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one

Example 2b (0.25 g, 0.692 mmol), iron powder (0.193 g, 3.46 mmol), and ammonium chloride (0.056 g, 1.038 mmol) were combined in tetrahydrofuran (6 mL), ethanol (6 mL) and water (2 mL). The mixture was heated at 95 °C with vigorous stirring for 1.5 hours. The reaction mixture was cooled to room temperature and filtered through a plug of Celite to remove solids. The plug was rinsed repeatedly with methanol and tetrahydrofuran. The filtrate was concentrated and the residue partitioned between ethyl acetate and water. The ethyl acetate layer was washed with brine, dried (Na_2SO_4), filtered, and concentrated. The residue was purified by flash chromatography (silica gel, 1-4 % methanol in dichloromethane) to afford 0.21 g (82 %) of the title compound. ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 3.43 (s, 3 H)

5.07 (s, 2 H) 6.22 - 6.25 (m, 1 H) 6.59 (dd, J=8.48, 2.71 Hz, 1 H) 6.68 (d, J=7.80 Hz, 2 H)
6.74 (d, J=2.71 Hz, 1 H) 6.80 - 6.88 (m, 2 H) 7.11 - 7.19 (m, 3 H) 7.24 (t, J=2.71 Hz, 1 H)
11.91 (s, 1 H). MS (ESI+) m/z 362 [M+H]⁺.

Example 4

5 N-[3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)-4-
phenoxyphenyl]methanesulfonamide

Method A:

To a solution of Example 3 (0.125 g, 0.377 mmol) and triethylamine (0.131 mL, 0.943 mmol) in dichloromethane (3.0 mL) was added dropwise methanesulfonyl chloride
10 (0.064 mL, 0.830 mmol). The reaction mixture was stirred for 2 hours and then concentrated. The residue was dissolved in a mixture of dioxane (5 mL) and 1M sodium hydroxide (2 mL) and heated for 1 hour at 90 °C. The reaction mixture was cooled and diluted with ethyl acetate, brought to pH 7 with 1 M HCl and partitioned. The organic layer was washed with brine, dried (Na₂SO₄), filtered, and concentrated. The residue was purified by flash
15 chromatography (silica gel, 0-4 % methanol in dichloromethane) to afford 0.20 g (77 %) of the title compound. ¹H NMR (300 MHz, DMSO-*d*₆) δ 3.02 (s, 3 H) 3.48 (s, 3 H) 6.23 - 6.30 (m, 1 H) 6.85 (d, J=7.46 Hz, 2 H) 6.99 (t, J=7.29 Hz, 1 H) 7.04 (d, J=8.82 Hz, 1 H) 7.20 - 7.29 (m, 5 H) 7.39 (d, J=2.71 Hz, 1 H) 9.72 (s, 1 H) 12.01 (s, 1 H). MS (ESI+) m/z 410 [M+H]⁺.

20 Method B:

The product of Example 7d (1.127 g, 2 mmol), potassium hydroxide (1.82 g, 52.5 mmol) and cetyltrimethylammonium bromide (0.036 g, 0.100 mmol) were combined in tetrahydrofuran (15.00 mL) and water (5.00 mL) and the mixture heated at 100 °C for 14
25 hours. The reaction mixture was partitioned between equal volumes of EtOAc and water and the pH was adjusted to pH 7 by careful addition of concentrated HCl. The organic layer was separated, washed three times with saturated brine, dried (Na₂SO₄) and concentrated. Purification by trituration in dichloromethane afforded the title compound (0.76 g, 93%).

Example 5

30 2,2,2-trifluoro-N-[3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)-4-
phenoxyphenyl]ethanesulfonamide

To a solution of Example 3 (0.05 g, 0.151 mmol) and triethylamine (0.053 mL, 0.377 mmol) in dichloromethane (1.0 mL) was added dropwise 2,2,2-trifluoroethanesulfonyl chloride (0.036 g, 0.196 mmol). The reaction mixture was stirred for 1 hour at room temperature and then purified by flash chromatography (silica gel, 0-5% methanol in

dichloromethane) to afford 0.050 g (68 %) of the title compound. ^1H NMR (300 MHz, DMSO- d_6) δ 3.49 (s, 3 H) 4.55 (q, J=9.91 Hz, 2 H) 6.28 (t, J=2.38 Hz, 1 H) 6.86 (d, J=7.54 Hz, 2 H) 6.95 - 7.07 (m, 2 H) 7.20 - 7.31 (m, 5 H) 7.40 (d, J=2.78 Hz, 1 H) 10.43 (s, 1 H) 12.02 (s, 1 H). MS (APCI+) m/z 478 [M+H] $^+$.

5 Example 6

N-[3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)-4-phenoxyphenyl]acetamide

Example 6a

6-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-tosyl-1H-pyrrolo[2,3-c]pyridin-7(6H)-one

10

Example 1e (6.55 g, 17.2 mmol), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bis(1,3,2-dioxaborolane) (8.73 g, 34.4 mmol), potassium acetate (3.71 g, 37.8 mmol), tris(dibenzylideneacetone)dipalladium(0) (0.393 g, 0.430 mmol) and 2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl (X-PHOS, 0.819 g, 1.72 mmol) were combined and sparged with argon for 1 hour with stirring. Dioxane (86 mL) was sparged with nitrogen for 1 hour, transferred via canula under nitrogen to the solid components, and the mixture was heated under argon at 80 °C for 5 hours. The reaction mixture was cooled to room temperature, partitioned between ethyl acetate and water, and filtered through Celite. The ethyl acetate layer was washed twice with brine, dried (Na_2SO_4), filtered and concentrated. The residue was purified by chromatography (silica gel, 25-80% ethyl acetate in hexane). The resulting material from chromatography was triturated with a minimal amount of hexanes (30 mL) and the particulate solid was collected by filtration, rinsed with a minimal amount of hexanes and dried to constant mass to afford the title compound (5.4 g, 73%).

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Example 6b

N-(3-bromo-4-phenoxyphenyl)acetamide

Example 7b (0.2 g, 0.757 mmol), and acetic anhydride (1 mL, 10.60 mmol) were combined in a 5 mL microwave tube, sealed and heated under microwave at 100 °C for 30 minutes. The mixture was concentrated and the residue was purified by chromatography (silica gel, 0-50% ethyl acetate in hexanes) to afford the title compound (0.22 g, 95%).

30

Example 6c

N-(3-(6-methyl-7-oxo-1-tosyl-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)-4-phenoxyphenyl)acetamide

Example 6a (0.07 g, 0.163 mmol), Example 6b (0.075 g, 0.245 mmol), tetrakis(triphenylphosphine)palladium(0) (9.44 mg, 8.17 μmol) and sodium carbonate (2.0 M, 0.245 mL, 0.490 mmol) were combined in DME (0.817 mL) and water (0.817 mL) in a 5 mL microwave tube, sealed, sparged with nitrogen and heated under microwave at 120 °C for 30 minutes. The mixture was partitioned between ethyl acetate and water. The organic layer was washed with brine, dried (Na_2SO_4), filtered and concentrated. Purification by chromatography (silica gel, 0-5% methanol in dichloromethane) afforded the title compound (0.048 g, 56%).

Example 6d

10 N-[3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)-4-phenoxyphenyl]acetamide

Example 6c (0.048 g, 0.091 mmol) and potassium carbonate (0.044 g, 0.318 mmol) were combined in methanol (2 mL) and water (0.200 mL) in a 2 mL microwave tube, sealed, and heated under microwave at 110 °C for 30 minutes. The reaction mixture was concentrated and the residue partitioned between ethyl acetate and water, adjusting the pH to 6 with 1M HCl. The organic layer was separated and concentrated. Purification by flash chromatography (silica gel, 0-4 % methanol in dichloromethane) afforded 0.018 g (53%) of the title compound. ^1H NMR (300 MHz, DMSO- d_6) δ 2.05 (s, 3 H) 3.48 (s, 3 H) 6.25 - 6.30 (m, 1 H) 6.80 (d, J=7.46 Hz, 2 H) 6.96 (t, J=7.29 Hz, 1 H) 7.01 (d, J=8.82 Hz, 1 H) 7.18 - 7.31 (m, 4 H) 7.56 (dd, J=8.65, 2.54 Hz, 1 H) 7.79 (d, J=2.71 Hz, 1 H) 10.04 (s, 1 H) 11.97 (s, 1 H). MS (ESI+) m/z 374 $[\text{M}+\text{H}]^+$.

Example 7

N-(3-{6-methyl-1-[(4-methylphenyl)sulfonyl]-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl}-4-phenoxyphenyl)methanesulfonamide

25 Example 7a

2-bromo-4-nitro-1-phenoxybenzene

2-Bromo-1-fluoro-4-nitrobenzene (2.5 g, 11.4 mmol), phenol (1.28 g, 13.6 mmol), and cesium carbonate (4.44 g, 13.6 mmol) were combined in dimethylsulfoxide (140 mL) and heated to 110 °C for 1 hour. The reaction mixture was partitioned between ethyl acetate and brine. The combined organics were washed with brine, dried (MgSC^{\wedge}), filtered and concentrated to afford the title compound.

Example 7b

3-bromo-4-phenoxyaniline

Example 7a (3.43 g, 11.7 mmol), iron powder (3.26 g, 58.4 mmol), and ammonium chloride (1.25 g, 23.4 mmol) were combined in ethanol (50 mL), tetrahydrofuran (50 mL), and water (16.7 mL), and heated at 100 °C for 2 hour. The reaction mixture was cooled to just below reflux, vacuum filtered through diatomaceous earth, the filter cake washed with warm methanol (3x35 mL), and the filtrate concentrated under reduced pressure. The residue was partitioned between saturated aqueous NaHCO₃ and ethyl acetate (3 x 125 mL). The combined organics were washed with brine, dried (MgSC[^]), gravity filtered then concentrated to afford the title compound.

Example 7c

10 N-(3-bromo-4-phenoxyphenyl)methanesulfonamide

Example 7b (2.86 g, 10.8 mmol) and triethylamine (6.03 mL, 43.3 mmol) were stirred in dichloromethane (48.1 mL) at ambient temperature. Methanesulfonyl chloride (2.53 mL, 32.4 mmol) was added dropwise and the solution stirred at ambient temperature for 1 hour. The reaction mixture was concentrated under reduced pressure, dioxane (24 mL) and sodium hydroxide (10 % w/v, 12 mL, 0.427 mmol) were added, and the solution was heated to 70 °C for 1 h. The solution was neutralized to a pH of 7 with saturated aqueous NH₄Cl (200 mL). The aqueous phase was extracted with ethyl acetate (3x125 mL). The combined organics were washed with brine, dried (MgSC[^]), filtered, then concentrated. The residue was purified by flash chromatography (silica gel, 0-25% ethyl acetate/hexane gradient,) to afford the title compound.

Example 7d

N-(3-{6-methyl-1-[(4-methylphenyl)sulfonyl]-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl}-4-phenoxyphenyl)methanesulfonamide

Example 6a (0.670 g, 1.564 mmol), Example 7c (0.562 g, 1.643 mmol), tris(dibenzylideneacetone)dipalladium(0) (0.036 g, 0.039 mmol), 1,3,5,7-tetramethyl-6-phenyl-2,4,8-trioxo-6-phosphaadamante (0.023 g, 0.078 mmol) and potassium phosphate tribasic (1.03 g, 4.85 mmol) were combined and sparged with argon for 30 minutes. A solution of 4:1 dioxane/water (10 mL total volume) was sparged with nitrogen for 30 minutes and transferred by syringe into the reaction vessel under argon. The reaction mixture was stirred at 60 °C for 2 hours, cooled to room temperature and partitioned between ethyl acetate and water. The organic layer was washed with brine, dried (Na₂S₀₄), treated with 3-mercaptopropyl functionalized silica gel (Aldrich, 538086-IOOG) for 45 minutes, filtered and concentrated. Purification by chromatography (silica gel, 20-100% ethyl acetate in hexanes)

afforded 0.68 g (74 %) of the title compound. $^1\text{H NMR}$ (300 MHz, $\text{DMSO-}d_6$) δ 2.38 (s, 3 H) 3.02 (s, 3 H) 3.38 (s, 3 H) 6.52 (d, $J=3.39$ Hz, 1 H) 6.82 (d, $J=7.80$ Hz, 2 H) 6.96 - 7.04 (m, 2 H) 7.19 - 7.28 (m, 4 H) 7.41 (d, $J=8.14$ Hz, 2 H) 7.48 (s, 1 H) 7.89 - 7.97 (m, 3 H) 9.73 (s, 1 H). MS (ESI+) m/z 564 $[\text{M}+\text{H}]^+$.

5

Example 8

N-methyl-N-[3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)-4-phenoxyphenyl]methanesulfonamide

A mixture of Example 7d (0.113 g, 0.2 mmol) and potassium carbonate (0.11 g, 0.800 mmol) in methanol (0.9 mL) and water (0.1 mL) was heated at 100 °C for 1 hour. The reaction was partitioned between ethyl acetate and water adjusting the pH to 7. The organic layer was separated, dried (Na_2SO_4), filtered and concentrated. The residue was purified by reverse phase HPLC (C18, 0-100 % $\text{CH}_3\text{CN}/\text{water}$ (0.1% TFA)) to afford the title compound (0.012 g, 14%). $^1\text{H NMR}$ (300 MHz, $\text{DMSO-}d_6$) δ 2.99 (s, 3 H) 3.27 (s, 3 H) 3.51 (s, 3 H) 6.27 - 6.32 (m, 1 H) 6.93 (d, $J=7.80$ Hz, 2 H) 6.99 (d, $J=8.82$ Hz, 1 H) 7.03 - 7.10 (m, 1 H) 7.25 - 7.34 (m, 4 H) 7.40 (dd, $J=8.65, 2.88$ Hz, 1 H) 7.55 (d, $J=2.71$ Hz, 1 H) 12.01 (s, 1 H). MS (ESI+) m/z 424 $[\text{M}+\text{H}]^+$.

10

15

Example 9

ethyl 3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)-4-phenoxybenzoate

Example 9a

20

ethyl 4-fluoro-3-(6-methyl-7-oxo-1-tosyl-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)benzoate

25

30

A mixture of Example 1e (1.33 g, 3.5 mmol), 5-(ethoxycarbonyl)-2-fluorophenylboronic acid (1.04 g, 4.9 mmol), $\text{Pd}(\text{PPh}_3)_4$ (0.20 g, 5 mol%), and sodium carbonate (0.742 g, 7.0 mmol) in toluene (12 mL), ethanol (3 mL) and water (3 mL) was degassed and stirred under a nitrogen atmosphere. The reaction mixture was heated at 90 °C for 24 hours. The reaction mixture was cooled to room temperature and partitioned between water and ethyl acetate. The aqueous layer was extracted with additional ethyl acetate twice. The combined organic layers were washed with brine, dried over MgSO_4 , filtered, and concentrated. The residue was purified by flash chromatography (silica gel, 20-50% ethyl acetate in hexanes) to afford 1.43 g (87%) of the title compound.

Example 9b

ethyl 3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)-4-phenoxybenzoate

A mixture of Example 9a (1.43 g, 3.05 mmol), phenol (0.344 g, 3.66 mmol) and cesium carbonate (0.995, 3.05 mmol), in DMSO (15 mL) was heated at 110 °C for 12 hours.

After cooling to room temperature, the reaction mixture was partitioned between water and ethyl acetate. The aqueous layer was extracted with additional ethyl acetate twice. The combined organic layers were washed with brine, dried over MgSO_4 , filtered, and concentrated. The residue was purified by flash chromatography (silica gel, 30-80% ethyl acetate/hexane) to afford 0.85 g (72%) of the title compound. ^1H NMR (500 MHz, $\text{DMSO-}d_6$) δ 1.31 (t, $J=7.02$ Hz, 3H), 3.55 (s, 3H), 4.32 (q, $J=7.22$ Hz, 2H), 6.23 (t, $J=2.29$ Hz, 1H), 6.97 (d, $J=8.54$ Hz, 1H), 7.06 (d, $J=8.24$ Hz, 2H), 7.17 (t, $J=7.32$ Hz, 1H), 7.28 (t, $J=2.75$ Hz, 1H), 7.36-7.51 (m, 3H), 7.94 (dd, $J=8.7, 2.29$ Hz, 1H), 8.04 (d, $J=2.14$ Hz, 1H), 12.02 (s, 1H). MS (ESI+) m/z 389.2 (M+H)⁺.

10

Example 10

3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)-4-phenoxybenzoic acid

A mixture of Example 9b (0.23 g, 0.59 mmol) and sodium hydroxide (0.89 mL of 2.0 M aqueous solution) in dioxane (10 mL) was heated at 60 °C for 2 hours. The reaction mixture was cooled to room temperature and poured into water (100 mL). After addition of concentrated HCl (5 mL), the mixture was extracted with ethyl acetate (3 x 40 mL). The combined organic layers were washed with brine, dried over MgSO_4 , filtered, and concentrated to afford 0.21 g (98 %) of the title compound. ^1H NMR (500 MHz, $\text{DMSO-}d_6$) δ 3.55 (s, 3H), 6.24-6.25 (m, 1H), 6.94 (d, $J=8.54$ Hz, 1H), 7.05 (d, $J=7.63$ Hz, 2H), 7.16 (t, $J=7.32$ Hz, 1H), 7.27 (t, $J=2.9$ Hz, 1H), 7.35-7.40 (m, 3H), 7.92 (dd, $J=8.7, 2.29$ Hz, 1H), 8.04 (d, $J=2.14$ Hz, 1H), 12.03 (s, 1H). MS (ESI+) m/z 361.2 (M+H)⁺.

20

Example 11

N-[3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)-4-(pyridin-3-yloxy)phenyl]methanesulfonamide

Example 11a

6-methyl-4-(5-nitro-2-(pyridin-3-yloxy)phenyl)-1H-pyrrolo[2,3-c]pyridin-7(6H)-one

25

Example 11a was prepared according to the procedure used for the preparation of Example 2b, substituting pyridin-3-ol for phenol, to provide the title compound.

Example 11b

4-(5-amino-2-(pyridin-3-yloxy)phenyl)-6-methyl-1H-pyrrolo[2,3-c]pyridin-7(6H)-one

30

Example 11b was prepared according to the procedure used for the preparation of Example 3, substituting Example 11a for Example 2b, to provide the title compound.

Example 11c

N-[3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)-4-(pyridin-3-yloxy)phenyl]methanesulfonamide

Example 11c was prepared according to the procedure used in method A of Example 4, substituting Example 11b for Example 3, to provide the title compound. ¹H NMR (300 MHz, DMSO) δ 3.49 (s, 3H), 3.05 (s, 3H), 6.25 (dd, J = 2.8, 1.9 Hz, 1H), 7.16 (d, J = 8.7 Hz, 1H), 7.34 - 7.21 (m, 5H), 7.40 (d, J = 2.6 Hz, 1H), 8.23 - 8.16 (m, 2H), 9.80 (s, 1H), 12.02 (bs, 1H). MS (ESI+) m/z 411.1 (M+H)⁺.

Example 12

6-methyl-4-[2-(morpholin-4-ylmethyl)phenyl]-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one

Example 12 was prepared according to the procedure used for the preparation of Example 1f, substituting 2-(morpholinomethyl)phenylboronic acid for 2-phenoxyphenylboronic acid, to provide the title compound. ¹H NMR (500 MHz, DMSO-*d*₆) δ 2.85 (br, 2H), 3.09 (br, 2H), 3.56 (s, 3H), 3.74 (br, 2H), 4.26 (br, 2H), 5.89-5.90 (m, 1H), 7.20 (s, 1H), 7.29 (t, J=2.75 Hz, 1H), 7.39-7.43 (m, 1H), 7.53-7.55 (m, 2H), 7.75-7.77 (m, 1H), 9.73 (br, 1H), 12.12 (s, 1H). MS (ESI+) m/z 324.0 (M+H)⁺.

Example 13

N-ethyl-3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)-4-phenoxybenzamide

Example 13a

3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)-4-phenoxybenzoyl chloride

A solution of Example 10 (0.24 g, 0.67 mmol) in dichloromethane (10 mL) was treated with oxalyl chloride (0.17 g, 1.33 mmol) and dimethylformamide (5 mg, 10 mol %). The reaction mixture was stirred at room temperature for 2 hours. The solvent was removed under reduced pressure to afford the title compound (0.25 g, quantitative).

Example 13b

N-ethyl-3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)-4-phenoxybenzamide

A solution of Example 13a (0.040 g, 0.11 mmol) in tetrahydrofuran (1 mL) was treated with ethylamine (0.21 mL of a 2 M solution in tetrahydrofuran, 0.42 mmol) for 2 h. The reaction mixture was concentrated and the residue purified by preparative HPLC (CI 8, 10-90% acetonitrile in 0.1% TFA in water) to afford the title compound (0.025 g, 61%). ¹H NMR (500 MHz, DMSO-*d*₆) δ 1.12 (t, J=7.32 Hz, 3H), 3.25-3.32 (m, 2H), 3.54 (s, 3H), 6.23-6.24 (m, 1H), 6.95-6.99 (m, 3H), 7.11 (t, J=7.48 Hz, 1H), 7.27 (t, J=2.75 Hz, 1H), 7.31-7.37 (m, 3H), 7.84 (dd, J=8.54, 2.44 Hz, 1H), 7.98 (d, J=2.44 Hz, 1H), 8.46 (t, J=5.49 Hz, 1H), 11.99 (s, 1H). MS (ESI+) m/z 388.2 (M+H)⁺.

Example 14

3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)-4-phenoxy-N-(tetrahydrofuran-2-ylmethyl)benzamide

Example 14 was prepared according to the procedure used for the preparation of Example 13b, substituting (tetrahydrofuran-2-yl)methanamine for ethylamine, and dichloromethane for tetrahydrofuran, respectively, to provide the title compound. ¹H NMR (500 MHz, DMSO- *d*₆) δ 1.56-1.57 (m, 1H), 1.79-1.89 (m, 3H), 3.26-3.32 (m, 3H), 3.53 (s, 3H), 3.58-3.63 (m, 1H), 3.73-3.78 (m, 1H), 3.94-3.97 (m, 1H), 6.21-6.22 (m, 1H), 6.93-6.98 (m, 3H), 7.10 (t, J=7.48 Hz, 1H), 7.25 (t, J=2.9 Hz, 1H), 7.30-7.35 (m, 3H), 7.84 (dd, J=8.54, 2.44 Hz, 1H), 7.98 (d, J=2.14 Hz, 1H), 8.52 (t, J=5.8 Hz, 1H), 12.00 (s, 1 H). MS (ESI+) m/z 444.2 (M+H) ⁺.

Example 15

N-cyclopentyl-3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)-4-phenoxybenzamide

Example 15 was prepared according to the procedure used for the preparation of Example 13b, substituting cyclopentylamine for ethylamine, and dichloromethane for tetrahydrofuran, respectively, to provide the title compound. ¹H NMR (500 MHz, DMSO- *d*₆) δ 1.49-1.66 (m, 4H), 1.65-1.69 (m, 2H), 1.85-1.91 (m, 2H), 3.54 (s, 3H), 4.20-4.26 (m, 1H), 6.20-6.22 (m, 1H), 6.95-6.98 (m, 3H), 7.01 (t, J=7.32 Hz, 1H), 7.26 (t, J=2.75 Hz, 1H), 7.30-7.36 (m, 3H), 7.85 (dd, J=8.54, 2.14 Hz, 1H), 7.99 (d, J=2.44 Hz, 1H), 8.52 (t, J=5.8 Hz, 1H), 12.01 (s, 1 H). MS (ESI+) m/z 428.3 (M+H) ⁺.

Example 16

N-(2,2-difluoroethyl)-3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)-4-phenoxybenzamide

Example 16 was prepared according to the procedure used for the preparation of Example 13b, substituting 2,2-difluoroethanamine for ethylamine, and dichloromethane for tetrahydrofuran, respectively, to provide the title compound. ¹H NMR (500 MHz, DMSO- *d*₆) δ 3.55 (s, 3H), 3.62-3.72 (m, 3H), 5.97 (t, J=3.97 Hz, 0.25H), 6.11 (t, J=4.12 Hz, 0.5H), 6.23-6.26 (m, 1.25H), 6.98 (d, J=8.54 Hz, 1H), 7.01 (d, J=7.63 Hz, 2H), 7.13 (t, J=7.48 Hz, 1H), 7.27 (t, J=2.75 Hz, 1H), 7.33-7.36 (m, 3H), 7.88 (dd, J=8.54, 2.44 Hz, 1H), 8.03 (d, J=2.14 Hz, 1H), 8.85 (t, J=5.8 Hz, 1H), 12.03 (s, 1 H). MS (ESI+) m/z 424.2 (M+H) ⁺.

Example 17

3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)-4-phenoxy-N-(1,3-thiazol-2-yl)benzamide

Example 17 was prepared according to the procedure used for the preparation of Example 13b, substituting thiazol-2-amine for ethylamine, and dichloromethane for tetrahydrofuran, respectively, to provide the title compound. $^1\text{H NMR}$ (500 MHz, DMSO- d_6) δ 3.58 (s, 3H), 6.30-6.31 (m, 1H), 6.23-6.26 (m, 1H), 6.98 (d, J=8.54 Hz, 1H), 7.07 (d, J=7.63 Hz, 2H), 7.17 (t, J=7.32 Hz, 1H), 7.27-7.29 (m, 2H), 7.38-7.42 (m, 3H), 7.56 (d, J=3.36 Hz, 1H), 8.09 (dd, J=8.55, 2.44 Hz, 1H), 8.28 (d, J=2.44 Hz, 1H), 12.04 (s, 1H), 12.61 (s, 1H). MS (ESI+) m/z 443.1 (M+H)⁺.

Example 18

N-(1,1-dioxidotetrahydrothiophen-3-yl)-3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)-4-phenoxybenzamide

Example 18 was prepared according to the procedure used for the preparation of Example 13b, substituting 1,1-dioxidotetrahydrothien-3-ylamine for ethylamine, and dichloromethane for tetrahydrofuran, respectively, to provide the title compound. $^1\text{H NMR}$ (500 MHz, DMSO- d_6) δ 2.20-2.23 (m, 1H), 2.41-2.45 (m, 1H), 3.04-3.09 (m, 1H), 3.19-3.23 (m, 1H), 3.34-3.37 (m, 1H), 3.48-3.53 (m, 1H), 3.55 (s, 3H), 4.66-4.76 (m, 1H), 6.30-6.31 (m, 1H), 6.21-6.22 (m, 1H), 6.99 (dd, J=8.09, 2.59 Hz, 2H), 7.12 (t, J=7.48 Hz, 1H), 7.27 (t, J=2.75 Hz, 1H), 7.31-7.37 (m, 3H), 7.87 (dd, J=8.54, 2.14 Hz, 1H), 8.02 (d, J=2.14 Hz, 1H), 8.72 (d, J=7.02 Hz, 1H), 12.03 (s, 1 H). MS (ESI+) m/z 478.2 (M+H)⁺.

Example 19

3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)-4-phenoxybenzamide

Example 19 was prepared according to the procedure used for the preparation of Example 13b, substituting aqueous ammonium hydroxide for ethylamine to provide the title compound. $^1\text{H NMR}$ (500 MHz, DMSO- d_6) δ 3.54 (s, 3H), 6.23-6.24 (m, 1H), 6.94 (d, J=8.54 Hz, 1H), 6.98-7.00 (m, 2H), 7.11 (t, J=7.48 Hz, 1H), 7.26 (t, J=2.75 Hz, 1H), 7.31-7.37 (m, 4H), 7.86 (dd, J=8.54, 2.44 Hz, 1H), 7.96 (s, 1H), 8.02 (d, J=2.44 Hz, 1H), 12.01 (s, 1 H). MS (ESI+) m/z 360.2 (M+H)⁺.

Example 20

4-[5-(hydroxymethyl)-2-phenoxyphenyl]-6-methyl-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one

Example 20a

ethyl 3-(6-methyl-7-oxo-1-tosyl-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)-4-phenoxybenzoate

Example 20a was prepared according to the procedure used for the preparation of Example 1c, substituting Example 9b for Example 1b to provide the title compound.

Example 20b

4-[5-(hydroxymethyl)-2-phenoxyphenyl]-6-methyl-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one

Example 20a (0.32 g, 0.59 mmol) in tetrahydrofuran (5 mL) was cooled to 0 °C. To this solution was added 1.0 N aluminum lithium hydride (0.59 mL, 0.59 mmol). The reaction mixture was stirred at room temperature for 1 hour. The reaction mixture was quenched with 2.0 N HCl (5 mL), and then partitioned between water and ethyl acetate. The aqueous layer was extracted with additional ethyl acetate twice. The combined organic layers were washed with brine, dried over MgSO₄, filtered, and concentrated. The residue was purified by flash chromatography on silica gel eluting with 50-100% ethyl acetate in hexanes to afford 0.08 g (39%) of the title compound. ¹H NMR (500 MHz, DMSO-*d*₆) δ 3.49 (s, 3H), 4.54 (d, J=5.49 Hz, 2H), 5.21 (t, J=5.8 Hz, 1H), 6.23-6.24 (m, 1H), 6.94 (d, J=7.93 Hz, 2H), 6.97-7.01 (m, 2H), 7.22-7.28 (m, 4H), 7.32 (dd, J=8.39, 2.29 Hz, 1H), 7.16 (d, J=1.83 Hz, 1H), 11.97 (s, 1H). MS (ESI+) m/z 347.3 (M+H)⁺.

15

Example 21

N-[3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)-4-phenoxyphenyl]ethanesulfonamide

Example 21 was prepared according to the procedure used in method A of Example 4, substituting ethanesulfonyl chloride for methanesulfonyl chloride, to provide the title compound. ¹H NMR (300 MHz, DMSO-*i*/₆) δ 1.24 (t, J = 7.3 Hz, 3H), 3.13 (q, J = 7.3 Hz, 2H), 3.48 (s, 3H), 6.26 (t, J = 2.3 Hz, 1H), 6.88 - 6.80 (m, 2H), 7.07 - 6.95 (m, 2H), 7.31 - 7.18 (m, 5H), 7.40 (d, J = 2.7 Hz, 1H), 9.79 (s, 1H), 12.02 (bs, 1H). MS (ESI+) m/z 424.2 (M+H)⁺.

25

Example 22

N,N-dimethyl-N'-[3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)-4-phenoxyphenyl]sulfuric diamide

Example 22 was prepared according to the procedure used in method A of Example 4, substituting dimethylsulfamoyl chloride for methanesulfonyl chloride, to provide the title compound. ¹H NMR (300 MHz, DMSO-*d*₆) δ 2.74 (s, 6H), 3.48 (s, 3H), 6.28 - 6.23 (m, 1H), 6.85 - 6.78 (m, 2H), 7.06 - 6.93 (m, 2H), 7.3 J - 7.17 (m, 5H), 7.40 (d, J = 2.7 Hz, 1H), 9.91 (s, 1H), 12.04 - 12.00 (m, 1H). MS (ESI+) m/z 439.1 (M+H)⁺.

30

Example 23

N-[5-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)-6-phenoxyphenyl]methanesulfonamide

Example 23a

3-bromo-5-nitro-2-phenoxy pyridine

Phenol (0.416 g, 4.42 mmol), 3-bromo-2-chloro-5-nitropyridine (Combi-Blocks, CAS [5470-17-7], 1 g, 4.21 mmol) and cesium carbonate (1.372 g, 4.21 mmol) were combined in
 5 DMSO (8 mL) and heated at 80 °C for 30 minutes. The reaction mixture was cooled and partitioned between ethyl acetate and water. The organic layer was washed with brine, dried (Na₂S₂O₄), filtered and concentrated. Purification of the residue by chromatography (silica gel, 0-30 % ethyl acetate in hexanes) afforded the title compound (1.13 g, 91%).

Example 23b

10 6-methyl-4-(5-nitro-2-phenoxy pyridin-3-yl)-1-tosyl-1H-pyrrolo[2,3-c]pyridin-7(6H)-one

Example 23b was prepared according to the procedure used for the preparation of Example 7d, substituting the product of Example 23a for the product of Example 7c and stirring at 60 °C for 24 hours, to provide the title compound.

Example 23c

15 4-(5-amino-2-phenoxy pyridin-3-yl)-6-methyl-1-tosyl-1H-pyrrolo[2,3-c]pyridin-7(6H)-one

Example 23c was prepared according to the procedure used for the preparation of Example 3, substituting the product of Example 23b for the product of Example 2, to provide the title compound.

Example 23d

20 N-[5-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)-6-phenoxy pyridin-3-yl]methanesulfonamide

Example 23d was prepared according to the procedure used in method A of Example 4, substituting the product of Example 23c for the product of Example 3, to provide the title compound (0.035 g, 36%). ¹H NMR (300 MHz, DMSO- *d*₆) δ 3.05 (s, 3 H) 3.57 (s, 3 H) 6.28 - 6.36 (m, 1 H) 7.10 (d, J=7.54 Hz, 2 H) 7.16 (t, J=7.54 Hz, 1 H) 7.28 - 7.41 (m, 3 H) 7.48 (s, 1 H) 7.78 (d, J=2.78 Hz, 1 H) 7.96 (d, J=2.38 Hz, 1 H) 9.79 (s, 1 H) 12.11 (s, 1 H). MS (ESI+) m/z 411.0 (M+H)⁺.

Example 24

30 N-[3-fluoro-5-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)-4-phenoxy phenyl]methanesulfonamide

Example 24a

4-(2,3-difluoro-5-nitrophenyl)-6-methyl-1-tosyl-1H-pyrrolo[2,3-c]pyridin-7(6H)-one

Example 24a was prepared according to the procedure used for the preparation of Example 7d, substituting 1-bromo-2,3-difluoro-5-nitrobenzene (Oakwood Products) for the product of Example 7c, to provide the title compound.

Example 24b

5 4-(3-fluoro-5-nitro-2-phenoxyphenyl)-6-methyl-1H-pyrrolo[2,3-c]pyridin-7(6H)-one

Phenol (0.043 g, 0.457 mmol), Example 24a (0.2 g, 0.435 mmol) and cesium carbonate (0.142 g, 0.435 mmol) were combined in DMSO (2.177 mL) and heated at 80 °C for 30 minutes. The reaction mix was cooled and partitioned between ethyl acetate and water. The organic layer was washed with brine, dried (Na₂SO₄), filtered and concentrated to afford
10 the title compound.

Example 24c

4-(5-amino-3-fluoro-2-phenoxyphenyl)-6-methyl-1H-pyrrolo[2,3-c]pyridin-7(6H)-one

Example 24c was prepared according to the procedure used for the preparation of Example 3, substituting the product of Example 24b for the product of Example 2, to provide
15 the title compound.

Example 24d

N-[3-fluoro-5-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)-4-phenoxyphenyl]methanesulfonamide

Example 24d was prepared according to the procedure used in method A of Example
20 4, substituting the product of Example 24c for the product of Example 3, to provide the title compound (0.13 g, 67%). ¹H NMR (300 MHz, DMSO-*d*₆) δ 3.05 (s, 3 H) 3.57 (s, 3 H) 6.28 - 6.36 (m, 1 H) 7.10 (d, J=7.54 Hz, 2 H) 7.16 (t, J=7.54 Hz, 1 H) 7.28 - 7.41 (m, 3 H) 7.48 (s, 1 H) 7.78 (d, J=2.78 Hz, 1 H) 7.96 (d, J=2.38 Hz, 1 H) 9.79 (s, 1 H) 12.11 (s, 1 H).

Example 25

25 N-[4-(2-cyanophenoxy)-3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)phenyl]methanesulfonamide

Example 25a

2-(2-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)-4-nitrophenoxy)benzoni-
30 trile

Example 25a was prepared according to the procedure used for the preparation of Example 2b, substituting 2-hydroxybenzoni-
30 trile for phenol, to provide the title compound.

Example 25b

2-(4-amino-2-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)phenoxy)benzoni-
30 trile

Example 25b was prepared according to the procedure used for the preparation of Example 3, substituting the product of Example 25a for the product of Example 2b, to provide the title compound.

Example 25c

5 N-[4-(2-cyanophenoxy)-3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)phenyl]methanesulfonamide

Example 25c was prepared according to the procedure used in method A of Example 4, substituting the product of Example 25b for the product of Example 3, to provide the title compound. ¹H NMR (300 MHz, DMSO-*d*₆) δ 3.07 (s, 3H), 3.50 (s, 3H), 6.26 (dd, J = 2.8, 1.9 Hz, 1H), 6.73 (dd, J = 8.6, 0.9 Hz, 1H), 7.07 (td, J = 7.6, 0.9 Hz, 1H), 7.34 - 7.23 (m, 4H), 7.53 - 7.40 (m, 2H), 7.71 (dd, J = 7.7, 1.7 Hz, 1H), 9.89 (s, 1H), 12.03 (bs, 1H). MS (ESI+) m/z 435.2 (M+H)⁺.

Example 26

15 N-[4-(4-fluorophenoxy)-3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)phenyl]methanesulfonamide

Example 26a

4-(2-(4-fluorophenoxy)-5-nitrophenyl)-6-methyl-1H-pyrrolo[2,3-c]pyridin-7(6H)-one

Example 26a was prepared according to the procedure used for the preparation of Example 2b, substituting 4-fluorophenol for phenol, to provide the title compound.

20

Example 26b

4-(5-amino-2-(4-fluorophenoxy)phenyl)-6-methyl-1H-pyrrolo[2,3-c]pyridin-7(6H)-one

Example 26b was prepared according to the procedure used for the preparation of Example 3, substituting the product of Example 26a for the product of Example 2b, to provide the title compound.

25

Example 26c

N-[4-(4-fluorophenoxy)-3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)phenyl]methanesulfonamide

Example 26c was prepared according to the procedure used in method A of Example 4, substituting the product of Example 26b for the product of Example 3, to provide the title compound. ¹H NMR (300 MHz, DMSO-*d*₆) δ 3.02 (s, 3H), 3.50 (s, 3H), 6.29 - 6.23 (m, 1H), 6.94 - 6.82 (m, 2H), 7.14 - 6.96 (m, 3H), 7.21 (dd, J = 8.7, 2.7 Hz, 1H), 7.31 - 7.24 (m, 2H), 7.38 (d, J = 2.7 Hz, 1H), 9.71 (s, 1H), 12.02 (bs, 1H). MS (ESI+) m/z 428.1 (M+H)⁺.

30

Example 27

N-[4-(2,4-difluorophenoxy)-3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)phenyl]methanesulfonamide

Example 27a

4-(2-(2,4-difluorophenoxy)-5-nitrophenyl)-6-methyl-1H-pyrrolo[2,3-c]pyridin-7(6H)-one

5 Example 27a was prepared according to the procedure used for the preparation of Example 2b, substituting 2,4-difluorophenol for phenol, to provide the title compound.

Example 27b

4-(5-amino-2-(2,4-difluorophenoxy)phenyl)-6-methyl-1H-pyrrolo[2,3-c]pyridin-7(6H)-one

10 Example 27b was prepared according to the procedure used for the preparation of Example 3, substituting the product of Example 27a for the product of Example 2b, to provide the title compound.

Example 27c

N-[4-(2,4-difluorophenoxy)-3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)phenyl]methanesulfonamide

15 Example 27b (50 mg, 0.136 mmol) and triethylamine (0.057 mL, 0.408 mmol) were combined in CH₂Cl₂ (9 mL). Methanesulfonyl chloride (0.042 mL, 0.544 mmol) was added dropwise and the solution stirred at ambient temperature for 1 hour. The solution was concentrated under reduced pressure, dioxane (5 mL) and sodium hydroxide (10% w/v, 3 mL, 0.136 mmol) were added and the solution heated at 70 °C for 1 hour. The mixture was cooled
20 to ambient temperature and then neutralized with saturated NH₄Cl (100 mL) to a pH of 8. The organic layer was separated and the aqueous phase was extracted with ethyl acetate (3x25 mL). The combined organic layers were washed with brine, dried (MgSO₄), filtered, and concentrated. Purification by reverse phase HPLC (CI 8, 0-100% acetonitrile/water, 0.1 % TFA) afforded 27.5 mg (45.4 %) of the title compound. ¹H NMR (300 MHz, DMSO- *d*₆)
25 δ 3.01 (s, 3H), 3.53 (s, 3H), 6.29-6.23 (m, 1H), 7.04-6.90 (m, 2H), 7.09 (td, J = 9.1, 5.6 Hz, 1H), 7.44-7.14 (m, 5H), 9.70 (s, 1H), 12.04 (bs, 1H). MS (ESI+) m/z 446.1 (M+H)⁺.

Example 28

N-[3-chloro-5-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)-4-phenoxyphenyl]methanesulfonamide

30 Example 28a

4-(3-chloro-2-fluoro-5-nitrophenyl)-6-methyl-1-tosyl-1H-pyrrolo[2,3-c]pyridin-7(6H)-one

Example 28a was prepared according to the procedure used for the preparation of Example 6c, substituting 1,3-dichloro-2-fluoro-5-nitrobenzene (0.176 g, 0.841 mmol) for the product of Example 6b, to provide the title compound.

Example 28b

5 N-[3-chloro-5-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)-4-phenoxyphenyl]methanesulfonamide

Example 28b was prepared according to the procedures used for the preparation of Examples 24b-24d, substituting Example 28a for the product of Example 24a, to provide the title compound. ¹H NMR (300 MHz, DMSO- *ct*) δ 3.12 (s, 3 H) 3.43 (s, 3 H) 6.25 - 6.29 (m, 10 1 H) 6.63 (d, J=7.93 Hz, 2 H) 6.87 (t, J=7.34 Hz, 1 H) 7.10 - 7.18 (m, 2 H) 7.27 - 7.31 (m, 2 H) 7.39 (s, 2 H) 10.05 (s, 1 H) 12.04 (s, 1 H). MS (ES1+) m/z 444 (M+H)⁺.

Example 29

N-[3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)-4-(tetrahydro-2H-pyran-4-15 yloxy)phenyl]methanesulfonamide

15 Example 29a

6-methyl-4-(5-nitro-2-(tetrahydro-2H-pyran-4-yloxy)phenyl)-1H-pyrrolo[2,3-c]pyridin-7(6H)-one

Tetrahydro-2H-pyran-4-ol (0.046 g, 0.453 mmol) in tetrahydrofuran (2 mL) was treated with sodium hydride (0.022g, 0.906 mmol, 0.036 g of 60% dispersion in oil) at room 20 temperature. The reaction mixture was stirred for 10 minutes. To this solution was added Example 2a (0.1 g, 0.227 mmol). The reaction mixture was heated at 50 °C for 2 hours. After cooling to room temperature, the reaction mixture was partitioned between water and ethyl acetate. The aqueous layer was extracted twice with additional ethyl acetate. The combined organic layers were washed with brine, dried over MgSO₄, filtered, and concentrated. The 25 residue was purified by flash chromatography on silica gel eluting with ethyl acetate to afford 0.055 g of the title compound.

Example 29b

4-(5-amino-2-(tetrahydro-2H-pyran-4-yloxy)phenyl)-6-methyl-1H-pyrrolo[2,3-c]pyridin-7(6H)-one

30 A mixture of Example 29b (0.055g) and 10% palladium on carbon (0.050 g) in ethyl acetate (10 mL) was treated with a balloon of hydrogen overnight. The solid was removed by filtration. The filtrate was concentrated under reduced pressure to provide 0.042 g of the title compound.

Example 29c

N-[3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)-4-(tetrahydro-2H-pyran-4-yloxy)phenyl]methanesulfonamide

Example 29c was prepared according to the procedure used in method A of Example 4, substituting the product of Example 29b for the product of Example 3, to provide the title compound. ¹H NMR (500 MHz, DMSO-*d*₆) δ 1.45-1.51 (m, 2H), 1.82-1.87 (m, 2H), 2.94 (s, 3H), 3.35-3.41 (m, 2), 3.56 (s, 3H), 3.60-3.68 (m, 2H), 4.45-4.49 (m, 1H), 6.20 (t, J=2.29 Hz, 1H), 7.14-7.16 (m, 2H), 7.28-7.29 (m, 3H), 9.45 (s, 1H), 12.01 (s, 1H). (ESI+) m/z 418.2 (M+H)⁺.

10

Example 30

6-methyl-4-[2-phenoxy-5-(1H-pyrazol-1-yl)methyl]phenyl-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one

A mixture of Example 20b (0.04 g, 0.115 mmol), 1H-pyrazole (0.016 g, 0.231 mmol), and triphenylphosphine (0.061 g, 0.231 mmol) in tetrahydrofuran (1 mL) was stirred for 2 minutes. To this solution was added di-*n*-butyl azodicarboxylate (DTBAD, 0.053 g, 0.231 mmol). The reaction mixture was stirred at room temperature for 3 hours. The solvent was removed under reduced pressure, and the residue was purified by preparative HPLC (CI 8, 10-80% acetonitrile/water with 0.1% TFA) to afford 0.006 g of the title compound. ¹H NMR (500 MHz, DMSO-*d*₆) δ 3.49 (s, 3H), 5.37 (s, 2H), 5.21 (t, J=5.8 Hz, 1H), 6.17-6.18 (m, 1H), 6.28 (t, J=1.98 Hz, 1H), 6.86 (d, J=7.63 Hz, 2H), 6.97 (d, J=8.24 Hz, 1H), 7.02 (t, J=7.32 Hz, 4H), 7.22-7.29 (m, 5H), 7.39 (d, J=2.14 Hz, 1H), 7.47 (d, J=1.83 Hz, 1H), 7.53-7.46 (m, 3H), 7.86 (d, J=2.44 Hz, 1H), 11.97 (s, 1H). (ESI+) m/z 397.2 (M+H)⁺.

20

Example 31

N-[3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)-4-(tetrahydrofuran-3-yloxy)phenyl]methanesulfonamide

25

Example 31a

6-methyl-4-(5-nitro-2-(tetrahydrofuran-3-yloxy)phenyl)-1H-pyrrolo[2,3-c]pyridin-7(6H)-one

Example 31a was prepared according to the procedure used for the preparation of Example 29a, substituting tetrahydrofuran-3-ol for tetrahydro-2H-pyran-4-ol, to provide the title compound.

30

Example 31b

4-(5-amino-2-(tetrahydrofuran-3-yloxy)phenyl)-6-methyl-1H-pyrrolo[2,3-c]pyridin-7(6H)-one

Example 31b was prepared according to the procedure used for the preparation of Example 29b, substituting the product of Example 31a for the product of Example 29a, to provide the title compound.

Example 31c

5 N-[3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)-4-(tetrahydrofuran-3-yloxy)phenyl]methanesulfonamide

Example 31 was prepared according to the procedure used in method A of Example 4, substituting the product of Example 31b for the product of Example 3, to provide the title compound. ¹H NMR (500 MHz, DMSO-*d*₆) δ 1.84-1.90 (m, 1H), 2.08-2.17 (m, 1H), 2.95 (s, 10 3H), 3.35-3.41 (m, 2), 3.56 (s, 3H), 3.62-3.69 (M, 2H), 3.80-3.84 (m, 1H), 4.96-4.98 (m, 1H), 6.17-6.18 (m, 1H), 7.06-7.08 (m, 1H), 7.16-7.18 (m, 1H), 7.25 (s, 1H), 7.27-7.29 (m, 2H), 9.45 (s, 1H), 12.00 (s, 1H). (ESI+) m/z 404.2 (M+H)⁺.

Example 32

15 N-{3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)-4-[2-(trifluoromethyl)phenoxy]phenyl}methanesulfonamide

Example 32a

6-methyl-4-(5-nitro-2-(2-(trifluoromethyl)phenoxy)phenyl)-1H-pyrrolo[2,3-c]pyridin-7(6H)-one

20 Example 32a was prepared according to the procedure used for the preparation of Example 2b, substituting 2-(trifluoromethyl)phenol for phenol, to provide the title compound.

Example 32b

4-(5-amino-2-(2-(trifluoromethyl)phenoxy)phenyl)-6-methyl-1H-pyrrolo[2,3-c]pyridin-7(6H)-one

25 Example 32b was prepared according to the procedure used for the preparation of Example 3, substituting the product of Example 32a for the product of Example 2b, to provide the title compound.

Example 32c

N-{3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)-4-[2-(trifluoromethyl)phenoxy]phenyl}methanesulfonamide

30 Example 32c was prepared according to the procedure used in method A of Example 4, substituting the product of Example 32b for the product of Example 3, to provide the title compound. ¹H NMR (300 MHz, DMSO) δ 3.05 (s, 3H), 3.44 (s, 3H), 6.32 - 6.26 (m, 1H), 6.75 (d, J = 8.4 Hz, 1H), 7.17 - 7.07 (m, 2H), 7.34 - 7.18 (m, 3H), 7.53 - 7.38 (m, 2H), 7.65 (dd, J = 7.8, 1.6 Hz, 1H), 9.84 (s, 1H), 12.09 - 11.99 (m, 1H). MS (ESI+) m/z 478.1 (M+H)⁺.

Example 33

N-[4-(4-cyanophenoxy)-3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)phenyl]methanesulfonamide

Example 33a

5 4-(2-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)-4-nitrophenoxy)benzotrile

Example 33a was prepared according to the procedure used for the preparation of Example 2b, substituting 4-hydroxybenzotrile for phenol, to provide the title compound.

Example 33b

10 4-(4-amino-2-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)phenoxy)benzotrile

Example 33b was prepared according to the procedure used for the preparation of Example 3, substituting the product of Example 33a for the product of Example 2b, to provide the title compound.

15 Example 33c

N-[4-(4-cyanophenoxy)-3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)phenyl]methanesulfonamide

Example 33c was prepared according to the procedure used in method A of Example 4, substituting the product of Example 33b for the product of Example 3, to provide the title compound. ¹H NMR (300 MHz, DMSO) δ 3.07 (s, 3H), 3.46 (s, 3H), 6.27 - 6.21 (m, 1H), 6.94 - 6.87 (m, 2H), 7.32 - 7.20 (m, 4H), 7.42 (d, J = 2.5 Hz, 1H), 7.70 - 7.63 (m, 2H), 9.87 (s, 1H), 12.03 (bs, 1H). MS (ESI+) m/z 435.2 (M+H)⁺.

Example 34

25 N-[4-(2-chloro-4-fluorophenoxy)-3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)phenyl]methanesulfonamide

Example 34a

4-(2-(2-chloro-4-fluorophenoxy)-5-nitrophenyl)-6-methyl-1H-pyrrolo[2,3-c]pyridin-7(6H)-one

Example 34a was prepared according to the procedure used for the preparation of Example 2b, substituting 2-chloro-4-fluorophenol for phenol, to provide the title compound.

Example 34b

4-(5-amino-2-(2-chloro-4-fluorophenoxy)phenyl)-6-methyl-1H-pyrrolo[2,3-c]pyridin-7(6H)-one

Example 34b was prepared according to the procedure used for the preparation of Example 3, substituting the product of Example 34a for the product of Example 2b, to provide the title compound.

Example 34c

5 N-[4-(2-chloro-4-fluorophenoxy)-3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)phenyl]methanesulfonamide

Example 34c was prepared according to the procedure used in method A of Example 4, substituting the product of Example 34b for the product of Example 3, to provide the title compound. ¹H NMR (300 MHz, DMSO) δ 3.02 (s, 3H), 3.52 (s, 3H), 6.29 (t, J = 2.3 Hz, 1H), 10 6.99 - 6.88 (m, 2H), 7.14 - 7.03 (m, 1H), 7.21 (dd, J = 8.7, 2.7 Hz, 1H), 7.28 (t, J = 2.8 Hz, 1H), 7.34 (s, 1H), 7.41 (d, J = 2.7 Hz, 1H), 7.49 (dd, J = 8.3, 3.0 Hz, 1H), 9.75 (s, 1H), 12.05 (bs, 1H). MS (ESI+) m/z 462.1 (M+H)⁺.

Example 35

15 [4-(benzyloxy)-3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)phenyl]acetic acid

Example 35a

ethyl 2-(3-bromo-4-hydroxyphenyl)acetate

To a solution of ethyl 2-(4-hydroxyphenyl)acetate (Alfa, 2.70 g, 15 mmol) in acetic acid (20 mL) was added drop wise over 15 minutes a solution of bromine (0.773 mL, 15.00 20 mmol) in acetic acid (15 mL). The mixture was stirred at ambient temperature for 30 minutes and evaporated. Purification by chromatography (silica gel, 10-20% ethyl acetate in hexane) afforded the title compound (3.66 g, 94%).

Example 35b

ethyl 2-(4-(benzyloxy)-3-bromophenyl)acetate

25 A solution of Example 35a (2.01 g, 16.90 mmol), and potassium carbonate (5.84 g, 42.3 mmol) in ethanol (100 mL) was refluxed for 2 hours, cooled, concentrated and the residue was partitioned with ethyl acetate and water. The organic layer was washed with brine, dried (Na₂SO₄), filtered and concentrated. Purification of the residue by chromatography (silica gel, 0-20% ethyl acetate in hexane) afforded the title compound (4.84 30 g, 98%).

Example 35c

ethyl 2-(4-(benzyloxy)-3-(6-methyl-7-oxo-1-tosyl-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)phenyl)acetate

Example 35c was prepared according to the procedure used for the preparation of Example 7d, substituting the product of Example 35b for the product of Example 7c to provide the title compound.

Example 35d

5 [4-(benzyloxy)-3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)phenyl]acetic acid

Example 35c (0.4 g, 0.701 mmol), potassium hydroxide (0.787 g, 14.02 mmol) and cetyltrimethylammonium bromide (0.013 g, 0.035 mmol) were combined in dioxane (10 mL) and water (5 mL) and heated at 100 °C for 3 hours, cooled and partitioned between equal
10 volumes of ethyl acetate and water (20 mL each). The pH was adjusted to pH 2 by careful addition of concentrated HCl. The organic layer was separated and washed with saturated brine, dried (Na₂SO₄), filtered and concentrated. Trituration of the residue in hexane afforded the title compound (0.27 g, 98%). ¹H NMR (300 MHz, DMSO- *d*₆) δ 3.52 (s, 3 H) 3.55 (s, 2 H) 5.09 (s, 2 H) 6.14 - 6.21 (m, 1 H) 7.10 - 7.33 (m, 10 H) 11.97 (s, 1 H) 12.25 (s, 1 H). MS
15 (ESI+) m/z 389.0 (M+H)⁺.

Example 36

N-[4-(2,4-difluorophenoxy)-3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)phenyl]ethanesulfonamide

Example 36 was prepared according to the procedure used for the preparation of
20 Example 27c, substituting ethanesulfonyl chloride for methanesulfonyl chloride, to provide the title compound. ¹H NMR (300 MHz, DMSO) δ 1.23 (t, J = 7.3 Hz, 3H), 3.11 (q, J = 7.3 Hz, 2H), 3.53 (s, 3H), 6.27 - 6.22 (m, 1H), 6.91 (d, J = 8.7 Hz, 1H), 7.13 - 6.93 (m, 2H), 7.19 (dd, J = 8.8, 2.7 Hz, 1H), 7.32 - 7.25 (m, 2H), 7.42 - 7.31 (m, 2H), 9.77 (s, 1H), 12.04 (bs, 1H). MS (ESI+) m/z 460.1 (M+H)⁺.

25 Example 37

N-[4-(2,4-difluorophenoxy)-3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)phenyl]acetamide

Example 27b (50 mg, 0.136 mmol) and triethylamine (56.9 μL, 0.408 mmol) were combined in CH₂Cl₂ (10 mL). Acetyl chloride (11.6 μL, 0.163 mmol) was added dropwise
30 and the solution stirred for 1 hour at ambient temperature. Water (25 mL) and saturated aqueous sodium bicarbonate (25 mL) were added, and the mixture was extracted with CH₂Cl₂ (3x25 mL). The combined organics were washed with brine, dried (MgSO₄), filtered, and concentrated. Purification of the residue by reverse phase HPLC (CI 8, 0-100%

acetonitrile/water, 0.1% TFA) afforded 15 mg (28 %) of the title compound. ^1H NMR (300 MHz, DMSO) δ 2.04 (s, 3H), 3.52 (s, 3H), 6.29 6.23 (m, 1H), 7.08-6.85 (m, 3H), 7.39-7.25 (m, 3H), 7.53 (dd, J = 8.8, 2.6 Hz, 1H), 7.77 (d, J = 2.6 Hz, 1H), 10.00 (s, 1H), 12.07-1 1.96 (m, 1H). MS (ESI+) m/z 410.3 (M+H)⁺.

5

Example 38

N-[4-(2,4-difluorophenoxy)-3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)phenyl]-3,3,3-trifluoropropanamide

Example 38 was prepared according to the procedure used for the preparation of Example 37, substituting 3,3,3-trifluoropropanoyl chloride for acetyl chloride, to provide the title compound. ^1H NMR (300 MHz, DMSO) δ 3.54-3.46 (m, 2H), 3.53 (s, 3H), 6.27 (t, J = 2.3 Hz, 1H), 7.14-6.87 (m, 3H), 7.28 (t, J = 2.7 Hz, 1H), 7.31 (s, 1H), 7.37 (ddd, J = 11.3, 8.7, 2.8 Hz, 1H), 7.50 (dd, J = 8.8, 2.6 Hz, 1H), 7.76 (d, J = 2.6 Hz, 1H), 10.38 (s, 1H), 12.03 (bs, 1H). MS (ESI+) m/z 478.2 (M+H)⁺.

10

Example 39

15 N-[4-(2,4-difluorophenoxy)-3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)phenyl]-2,2-dimethylpropanamide

Example 39 was prepared according to the procedure used for the preparation of Example 37, substituting pivaloyl chloride for acetyl chloride, to provide the title compound. ^1H NMR (300 MHz, DMSO) δ 1.22 (s, 9H), 3.53 (s, 3H), 6.3 1-6.25 (m, 1H), 6.88 (d, J = 8.8 Hz, 1H), 7.08-6.92 (m, 2H), 7.3 1-7.24 (m, 2H), 7.40-7.29 (m, 1H), 7.62 (dd, J = 8.8, 2.6 Hz, 1H), 7.83 (d, J = 2.6 Hz, 1H), 9.28 (s, 1H), 12.00 (bs, 1H). MS (ESI+) m/z 452.3 (M+H)⁺.

20

Example 40

ethyl 4-(cyclopentylamino)-3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)benzoate

25 A mixture of Example 9a (0.094 g, 0.2 mmol), cyclopentanamine (0.034 g, 0.4 mmol), and triethylamine (0.081 g, 0.8 mmol) in DMSO (2 mL) was heated at 120 °C overnight. The reaction mixture was purified by preparative HPLC (CI 8, 10-80% acetonitrile in 0.1% TFA/water to afford 0.019 g of the title product. ^1H NMR (500 MHz, DMSO- d_6) δ 1.27 (t, J=7.02 Hz, 3H), 1.32-1.36 (m, 2H), 1.47-1.55 (m, 3H), 1.88-1.93 (m, 2H), 3.55 (s, 3H), 3.83-3.88 (m, 1H), 4.22 (q, J=7.02 Hz, 2H), 5.94 (t, J=2.29 Hz, 1H), 6.77 (d, J=8.85 Hz, 1H), 7.22 (s, 1H), 7.28 (t, J=2.75 Hz, 1H), 7.63 (d, J=1.83 Hz, 1H), 7.82 (dd, J=8.54, 2.14, 1H), 12.01 (s, 1H). MS (ESI+) m/z 380.2 (M+H)⁺.

30

Example 41

4- {5-[(1,1-dioxido-1,2-thiazolidin-2-yl)methyl]-2-phenoxyphenyl}-6-methyl-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one

Example 41a

4-(5-(hydroxymethyl)-2-phenoxyphenyl)-6-methyl-1-tosyl-1H-pyrrolo[2,3-c]pyridin-7(6H)-one

5

Example 41a was isolated as a by-product from the preparation of Example 20b.

Example 41b

3-(6-methyl-7-oxo-1-tosyl-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)-4-phenoxybenzyl methanesulfonate

10

A mixture of Example 41a (0.15 g, 0.3 mmol), methanesulfonyl chloride (0.069 g, 0.6 mmol), and triethylamine (0.121 g, 1.2 mmol) in dichloromethane (5 mL) was stirred at room temperature for 2 hours. The solvent was removed, and the residue was purified by flash chromatography on silica gel eluting with 20-40% ethyl acetate in hexanes to afford 0.105 g of the title product.

15

Example 41c

4- {5-[(1,1-dioxido-1,2-thiazolidin-2-yl)methyl]-2-phenoxyphenyl}-6-methyl-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one

1,2-thiazolidine 1,1-dioxide (0.031 g, 0.259 mmol) in dimethylformamide (1 mL) was treated with 60% sodium hydride (0.012 g, 0.518 mmol, 0.021 g of a 60% in oil dispersion).

20

The reaction mixture was stirred for 5 min. To this solution was added Example 41b (0.05 g, 0.086 mmol). The reaction mixture was stirred at room temperature for 2 hours. 2 N NaOH (1 mL) was added and the reaction mixture was heated at 65 °C for 2 hours. After cooling to room temperature, the reaction mixture was partitioned between water and ethyl acetate. The aqueous layer was extracted with additional ethyl acetate twice. The combined organic layers

25

were washed with brine, dried over MgSO₄, filtered, and concentrated. The residue was

purified by preparative HPLC (CI 8, 10-80% acetonitrile in 0.1% TFA water) to afford 0.025 g (64%) of the title compound. ¹H NMR (500 MHz, DMSO-*d*₆) δ 2.21-2.25 (m, 2H), 3.15 (t,

J=6.97 Hz, 2H), 3.23-3.27 (m, 2H), 3.50 (s, 3H), 4.13 (s, 2H), 6.25-6.26 (m, 1H), 6.88 (d,

J=7.63 Hz, 2H), 7.00 (d, J=8.54 Hz, 1H), 7.03-7.05 (m, 1H), 7.25-7.30 (m, 4H), 7.34 (dd,

30

J=8.39, 2.29, 1H), 7.48 (d, J=2.44 Hz, 1H), 12.00 (s, 1H). MS (ESI+) m/z 450.2 (M+H)⁺.

Example 42

4-[[3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)-4-phenoxybenzyl]amino]-4-oxobutanoic acid

Example 42 was prepared according to the procedure used for the preparation of Example 41c, substituting pyrrolidine-2,5-dione for 1,2-thiazolidine 1,1-dioxide, to provide the title compound. ¹H NMR (500 MHz, DMSO- *d*₆) δ 2.37-2.40 (m, 2H), 2.44-2.48 (m, 2H), 3.50 (s, 3H), 4.31 (d, J=5.8 Hz, 2H), 6.23-6.24 (m, 1H), 6.84 (d, J=7.63 Hz, 2H), 6.96 (d, J=8.24 Hz, 1H), 7.00 (t, J=7.32 Hz, 1H), 7.22-7.29 (m, 5H), 7.40 (d, J= 2.14, 1H), 8.40 (t, J=5.95 Hz, 1H), 11.98 (s, 1H). MS (ESI+) m/z 446.1 (M+H)⁺.

Example 43

4-[2-(2,4-difluorophenoxy)-5-(1,1-dioxido-1,2-thiazolidin-2-yl)phenyl]-6-methyl-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one

10

Example 43a

3-chloro-N-(3-chloropropylsulfonyl)-N-(4-(2,4-difluorophenoxy)-3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)phenyl)propane-1-sulfonamide

A mixture of Example 27b (0.1 g, 0.272 mmol), 3-chloropropane-1-sulfonyl chloride (0.145 g, 0.817 mmol), and triethylamine (0.165 g, 1.633 mmol) in dichloromethane (3 mL) was stirred for 2 hours. The solvent was removed, and the residue was used directly for the next reaction.

15

Example 43b

4-[2-(2,4-difluorophenoxy)-5-(1,1-dioxido-1,2-thiazolidin-2-yl)phenyl]-6-methyl-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one

20

Sodium (0.064 g, 2.78 mmol) was dissolved in ethanol (15 mL). To this solution was added Example 43a (0.18 g, 0.278 mmol) in ethanol (5 mL). The reaction mixture was heated at 75 °C for 2 hours. After cooling, the solvent was removed under reduced pressure, and the residue was purified by preparative HPLC (CI 8, 10-80% acetonitrile in 0.1% TFA/water) to afford 0.055 g of the title compound. ¹H NMR (500 MHz, DMSO- *d*₆) δ 2.37-2.44 (m, 2H), 3.49-3.53 (m, 2H), 3.54 (s, 3H), 3.76 (t, J=6.56 Hz, 2H), 6.27-6.28 (m, 1H), 6.95 (d, J=8.85 Hz, 1H), 7.00-7.12 (m, 2H), 7.20 (dd, J=8.85, 2.75 Hz, 1H), 7.28 (t, J=2.75 Hz, 1H), 7.32 (s, 1H), 7.35-7.41 (m, 2H), 12.05 (s, 1H). MS (ESI+) m/z 472.2 (M+H)⁺.

25

Example 44

4-[2-(benzyloxy)-5-(2-hydroxyethyl)phenyl]-6-methyl-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one

30

Example 35d (0.039 g, 0.1 mmol) in tetrahydrofuran (2 mL) was treated dropwise with borane-tetrahydrofuran complex (1M, 0.200 mL, 0.200 mmol), and the mixture was stirred at 40 °C for 1 hour, diluted with 5 mL of methanol, heated at 50 °C for 30 minutes and concentrated. Purification by chromatography (silica gel, 0.5-4 % methanol in

dichloromethane) afforded the title compound (0.03 g, 79%). ^1H NMR (300 MHz, DMSO- d_6) δ 2.70 (t, J=6.94 Hz, 2 H) 3.52 (s, 3 H) 3.57 - 3.64 (m, 2 H) 4.59 - 4.63 (m, 1 H) 5.06 (s, 2 H) 6.14 - 6.18 (m, 1 H) 7.08 - 7.18 (m, 2 H) 7.20 - 7.32 (m, 8 H) 11.95 (s, 1 H). MS (ESI+) m/z 375.0 (M+H) $^+$.

5

Example 45

methyl [4-(benzyloxy)-3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)phenyl]acetate

Example 45a

2-(4-(benzyloxy)-3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-

10

yl)phenyl)acetyl chloride

Example 35d (0.18 g, 0.463 mmol) in tetrahydrofuran (4.63 mL) was treated with one drop of dimethylformamide followed by drop-wise addition of oxalyl chloride (0.122 mL, 1.390 mmol), stirred for twenty minutes and concentrated.

Example 45b

15

methyl [4-(benzyloxy)-3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)phenyl]acetate

Example 45a (0.058 g, 0.143 mmol) in tetrahydrofuran (4 mL) was treated with methanol (5 mL, 124 mmol), stirred for 1 hour at room temperature and concentrated.

20

Purification by chromatography (silica gel, 0.5-3 % methanol in dichloromethane) afforded the title compound (0.048 g, 79%). ^1H NMR (300 MHz, DMSO- d_6) δ 3.52 (s, 3 H) 3.62 (s, 3 H) 3.66 (s, 2 H) 5.09 (s, 2 H) 6.15 - 6.20 (m, 1 H) 7.10 - 7.37 (m, 10 H) 11.97 (s, 1 H). MS (ESI+) m/z 403.0 (M+H) $^+$.

Example 46

2-[4-(benzyloxy)-3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)phenyl]-N-ethylacetamide

25

Example 46 was prepared according to the procedure used for the preparation of Example 45b, substituting ethylamine for methanol, to provide the title compound (0.039 g, 64%). ^1H NMR (300 MHz, DMSO- d_6) δ 1.01 (t, J=7.29 Hz, 3 H) 2.99 - 3.11 (m, 2 H) 3.35 (s, 2 H) 3.52 (s, 3 H) 5.07 (s, 2 H) 6.14 - 6.21 (m, 1 H) 7.08 - 7.35 (m, 10 H) 7.98 (t, J=5.43 Hz, 1 H) 11.96 (s, 1 H). MS (ESI+) m/z 416.0 (M+H) $^+$.

30

Example 47

2-[4-(benzyloxy)-3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)phenyl]-N,N-dimethylacetamide

Example 47 was prepared according to the procedure used for the preparation of Example 45b, substituting dimethylamine for methanol, to provide the title compound (0.058 g, 98%). ¹H NMR (300 MHz, DMSO- *d*₆) δ 2.83 (s, 3 H) 3.02 (s, 3 H) 3.52 (s, 3 H) 3.66 (s, 2 H) 5.08 (s, 2 H) 6.12 - 6.24 (m, 1 H) 7.06 - 7.36 (m, 10 H) 11.96 (s, 1 H). MS (ESI+) *m/z* 416.0 (M+H)⁺.

Example 48

N-[4-(3,4-difluorophenoxy)-3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)phenyl]methanesulfonamide

Example 48a

10 4-(2-(3,4-difluorophenoxy)-5-nitrophenyl)-6-methyl-1H-pyrrolo[2,3-c]pyridin-7(6H)-one
Example 48a was prepared according to the procedure used for the preparation of Example 2b, substituting 3,4-difluorophenol for phenol, to provide the title compound.

Example 48b

4-(5-amino-2-(3,4-difluorophenoxy)phenyl)-6-methyl-1H-pyrrolo[2,3-c]pyridin-7(6H)-one

15 Example 48b was prepared according to the procedure used for the preparation of Example 3, substituting the product of Example 48a for the product of Example 2b, to provide the title compound.

Example 48c

20 N-[4-(3,4-difluorophenoxy)-3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)phenyl]methanesulfonamide

Example 48c was prepared according to the procedure used in method A of Example 4, substituting the product of Example 48b for the product of Example 3, to provide the title compound. ¹H NMR (300 MHz, DMSO) δ 3.04 (s, 3H), 3.50 (s, 3H), 6.28-6.23 (m, 1H), 6.72-6.62 (m, 1H), 6.97 (ddd, J = 11.9, 6.7, 3.0 Hz, 1H), 6.97 (ddd, J = 11.9, 6.7, 3.0 Hz, 1H), 7.11 (d, J = 8.7 Hz, 1H), 7.41-7.19 (m, 5H), 9.78 (s, 1H), 12.03 (bs, 1H). MS (ESI+) *m/z* 446.1 (M+H)⁺.

Example 49

N-[3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)-4-(2,4,6-trifluorophenoxy)phenyl]methanesulfonamide

30 Example 49a

6-methyl-4-(5-nitro-2-(2,4,6-trifluorophenoxy)phenyl)-1H-pyrrolo[2,3-c]pyridin-7(6H)-one

Example 49a was prepared according to the procedure used for the preparation of Example 2b, substituting 2,4,6-trifluorophenol for phenol, to provide the title compound.

Example 49b

4-(5-amino-2-(2,4,6-trifluorophenoxy)phenyl)-6-methyl-1H-pyrrolo[2,3-c]pyridin-7(6H)-one

Example 49b was prepared according to the procedure used for the preparation of Example 3, substituting the product of Example 49a for the product of Example 2b, to provide the title compound.

5 Example 49c

N-[3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)-4-(2,4,6-trifluorophenoxy)phenyl]methanesulfonamide

Example 49c was prepared according to the procedure used in method A of Example 4, substituting the product of Example 49b for the product of Example 3, to provide the title
10 compound. $^1\text{H NMR}$ (300 MHz, DMSO) δ 2.99 (s, 3H), 3.57 (s, 3H), 6.23 (t, J = 2.3 Hz, 1H), 6.80 (d, J = 8.8 Hz, 1H), 7.15 (dd, J = 8.8, 2.7 Hz, 1H), 7.34-7.27 (m, 3H), 7.45-7.34 (m, 2H), 9.66 (s, 1H), 12.07 (bs, 1H). MS (ESI+) m/z 464.1 (M+H)⁺.

Example 50

15 4-(2,4-difluorophenoxy)-3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)benzamide

Example 50a

ethyl 4-(2,4-difluorophenoxy)-3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)benzoate

20 Example 50a was prepared according to the procedure used for the preparation of Example 9b, substituting 2,4-difluorophenol for phenol, to provide the title compound.

Example 50b

4-(2,4-difluorophenoxy)-3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)benzoic acid

25 Example 50b was prepared according to the procedure used for the preparation of Example 10, substituting Example 50a for Example 9b, to provide the title compound.

Example 50c

4-(2,4-difluorophenoxy)-3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)benzamide

30 Example 50c was prepared according to the procedure used for the preparation of Example 13a, substituting Example 50b for Example 10, to provide the title compound.

Example 50d

4-(2,4-difluorophenoxy)-3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)benzamide

Example 50d was prepared according to the procedure used for the preparation of Example 13b, substituting Example 50c for Example 13a, and aqueous ammonium hydroxide for ethylamine, respectively, to provide the title compound. ^1H NMR (500 MHz, DMSO- d_6) δ 3.57 (s, 3H), 6.24-6.25 (m, 1H), 6.83 (d, J=8.24 Hz, 1H), 7.07-7.13 (m, 1H), 7.27-7.34 (m, 4H), 7.42-7.48 (m, 1H), 7.85 (dd, J=8.54, 2.44, 1H), 7.96 (s, 1H), 8.00 (d, J=2.44 Hz, 1H), 12.04 (s, 1H). MS (ESI+) m/z 396.3 (M+H)⁺.

Example 51

4-(2,4-difluorophenoxy)-3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)-N-(tetrahydrofuran-3-yl)benzamide

Example 51 was prepared according to the procedure used for the preparation of Example 13b, substituting Example 50c for Example 13a, and tetrahydrofuran-3-amine for ethylamine, respectively, to provide the title compound. ^1H NMR (500 MHz, DMSO- d_6) δ 1.87-1.94 (m, 1H), 2.10-2.19 (m, 1H), 3.57 (s, 3H), 3.67-3.73 (m, 2H), 3.81-3.87 (m, 2H), 4.42-4.49 (m, 1H), 6.22-6.23 (m, 1H), 6.85 (d, J=8.54 Hz, 1H), 7.07-7.13 (m, 1H), 7.25-7.34 (m, 3H), 7.42-7.47 (m, 1H), 7.85 (dd, J=8.85, 2.14, 1H), 7.96 (s, 1H), 8.00 (d, J=2.14 Hz, 1H), 8.50 (d, J=6.41 Hz, 1H), 12.03 (s, 1H). MS (ESI+) m/z 466.3 (M+H)⁺.

Example 52

4-{2-(2,4-difluorophenoxy)-5-[(1,1-dioxidothiomorpholin-4-yl)carbonyl]phenyl}-6-methyl-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one

Example 52 was prepared according to the procedure used for the preparation of Example 13b, substituting 1,1-dioxo-1-thiomorpholine for ethylamine and Example 50c for Example 13a, respectively, to provide the title compound. ^1H NMR (500 MHz, DMSO- d_6) δ 3.25-3.28 (m, 4H), 3.56 (s, 3H), 3.78 (m, 4H), 4.45-4.61 (m, 1H), 3.81-3.87 (m, 2H), 6.26-6.27 (m, 1H), 6.86 (d, J=8.24 Hz, 1H), 7.07-7.12 (m, 1H), 7.27-7.33 (m, 3H), 7.42-7.48 (m, 2H), 7.63 (d, J= 2.14, 1H), 12.04 (s, 1H). MS (ESI+) m/z 514.2 (M+H)⁺.

Example 53

4-(2,4-difluorophenoxy)-3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)-N-(1-methyl-2-oxopyrrolidin-3-yl)benzamide

Example 53 was prepared according to the procedure used for the preparation of Example 13b, substituting Example 50c for Example 13a, and 3-amino-1-methylpyrrolidin-2-one for ethylamine, respectively, to provide the title compound. ^1H NMR (500 MHz, DMSO- d_6) δ 1.87-1.97 (m, 1H), 2.29-2.38 (m, 1H), 2.76 (s, 3H), 3.30-3.34 (m, 2H), 3.57 (s, 3H), 4.45-4.61 (m, 1H), 3.81-3.87 (m, 2H), 4.42-4.49 (m, 1H), 6.23-6.24 (m, 1H), 6.87 (d, J=8.54 Hz, 1H), 7.08-7.13 (m, 1H), 7.25-7.34 (m, 3H), 7.43-7.48 (m, 1H), 7.85 (dd, J=8.54, 2.44 Hz,

IH), 7.96 (s, IH), 7.99 (d, J=2.14 Hz, IH), 8.73 (d, J=8.85 Hz, IH), 12.03 (s, IH). MS (ESI+) m/z 493.2 (M+H)⁺.

Example 54

5 tert-butyl {1-[4-(2,4-difluorophenoxy)-3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)benzoyl]pyrrolidin-3-yl} carbamate

Example 54 was prepared according to the procedure used for the preparation of Example 13b, substituting Example 50c for Example 13a, and tert-butyl pyrrolidin-3-ylcarbamate for ethylamine, respectively, to provide the title compound. ¹H NMR (500 MHz, DMSO-*d*₆) δ 1.33-1.40 (m, 9H), 1.74-1.83 (m, IH), 2.01-2.03 (m, IH), 3.27-3.31 (m, IH), 10 3.56 (s, 3H), 3.62-3.56 (m, IH), 3.93-4.07 (m, IH), 6.24 (d, J=2.29 Hz, IH), 6.83 (d, J=8.54 Hz, IH), 7.0-7.13 (m, IH), 7.20-7.33 (m, 3H), 7.41-7.52 (m, 2H), 7.60 (d, J=16.2 Hz, IH), 12.03 (s, IH). MS (ESI+) m/z 565.2 (M+H)⁺.

Example 55

15 4-[2-(2,4-difluorophenoxy)-5-(pyrrolidin-1-ylcarbonyl)phenyl]-6-methyl-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one

Example 55 was prepared according to the procedure used for the preparation of Example 13b, substituting Example 50c for Example 13a, and pyrrolidine for ethylamine, respectively, to provide the title compound. ¹H NMR (500 MHz, DMSO-*d*₆) δ 1.82-1.86 (m, 4H), 3.45-3.48 (m, 4H), 3.56 (s, 3H), 6.24-6.26 (m, IH), 6.82 (d, J=8.24 Hz, IH), 7.06-7.12 20 (m, IH), 7.26-7.33 (m, 3H), 7.41-7.46 (m, IH), 7.52 (dd, J=8.54, 2.14 Hz, IH), 7.61 (d, J=2.14 Hz, IH), 12.03 (s, IH). MS (ESI+) m/z 450.3 (M+H)⁺.

Example 56

25 4-[2-(2,4-difluorophenoxy)-5-(morpholin-4-ylcarbonyl)phenyl]-6-methyl-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one

Example 56 was prepared according to the procedure used for the preparation of Example 13b, substituting Example 50c for Example 13a, and morpholine for ethylamine, respectively, to provide the title compound. ¹H NMR (500 MHz, DMSO-*d*₆) δ 3.56 (s, 3H), 3.60-3.68 (m, 8H), 6.24-6.25 (m, IH), 6.84 (d, J=8.54 Hz, IH), 7.06-7.12 (m, IH), 7.26-7.33 (m, 3H), 7.40 dd, J=8.54, 2.14 Hz, IH), 7.44-7.46 (m, IH), 7.50 (dd, J=2.14 Hz, IH), 12.03 (s, 30 IH). MS (ESI+) m/z 466.3 (M+H)⁺.

Example 57

N-[4-(cyclohexyloxy)-3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)phenyl]methanesulfonamide

Example 57a

4-(2-(cyclohexyloxy)-5-nitrophenyl)-6-methyl-1H-pyrrolo[2,3-c]pyridin-7(6H)-one

Example 57a was prepared according to the procedure used for the preparation of Example 29a, substituting cyclohexanol for tetrahydro-2H-pyran-4-ol, to provide the title compound.

5

Example 57b

4-(5-amino-2-(cyclohexyloxy)phenyl)-6-methyl-1H-pyrrolo[2,3-c]pyridin-7(6H)-one

Example 57b was prepared according to the procedure used for the preparation of Example 3, substituting the product of Example 57a for the product of Example 2b, to provide the title compound.

10

Example 57c

N-[4-(cyclohexyloxy)-3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)phenyl]methanesulfonamide

Example 57c was prepared according to the procedure used in method A of Example 4, substituting the product of Example 57b for the product of Example 3, to provide the title compound. ¹H NMR (300 MHz, DMSO) δ 1.47-1.10 (m, 6H), 1.61-1.47 (m, 2H), 1.84-1.69 (m, 2H), 2.94 (s, 3H), 3.55 (s, 3H), 4.31-4.22 (m, 1H), 6.21 (t, J = 2.3 Hz, 1H), 7.18-7.06 (m, 2H), 7.31-7.25 (m, 3H), 9.39 (s, 1H), 11.98 (bs, 1H). MS (ESI+) m/z 416.2 (M+H)⁺.

15

Example 58

N-[4-(cyclopentyloxy)-3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)phenyl]methanesulfonamide

20

Example 58a

4-(2-(cyclopentyloxy)-5-nitrophenyl)-6-methyl-1H-pyrrolo[2,3-c]pyridin-7(6H)-one

Example 58a was prepared according to the procedure used for the preparation of Example 29a, substituting cyclopentanol for tetrahydro-2H-pyran-4-ol, to provide the title compound.

25

Example 58b

4-(5-amino-2-(cyclopentyloxy)phenyl)-6-methyl-1H-pyrrolo[2,3-c]pyridin-7(6H)-one

Example 58b was prepared according to the procedure used for the preparation of Example 3, substituting the product of Example 58a for the product of Example 2b, to provide the title compound.

30

Example 58c

N-[4-(cyclopentyloxy)-3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)phenyl]methanesulfonamide

Example 58c was prepared according to the procedure used in method A of Example 4, substituting the product of Example 58b for the product of Example 3, to provide the title compound. ¹H NMR (300 MHz, DMSO) δ 1.70-1.43 (m, 6H), 1.88-1.70 (m, 2H), 2.94 (s, 3H), 3.55 (s, 3H), 4.78-4.70 (m, 1H), 6.16 (t, J = 2.3 Hz, 1H), 7.06 (d, J = 8.8 Hz, 1H), 7.16
 5 (dd, J = 8.7, 2.7 Hz, 1H), 7.22 (s, 1H), 7.30-7.23 (m, 2H), 9.39 (s, 1H), 11.97 (bs, 1H).MS (ESI+) m/z 402.1 (M+H)⁺.

Example 59

N-{4-[(4,4-difluorocyclohexyl)oxy]-3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-
 c]pyridin-4-yl)phenyl}methanesulfonamide

10

Example 59a

4-(2-(4,4-difluorocyclohexyloxy)-5-nitrophenyl)-6-methyl-1H-pyrrolo[2,3-c]pyridin-7(6H)-
 one

Example 59a was prepared according to the procedure used for the preparation of Example 29a, substituting 4,4-difluorocyclohexanol for tetrahydro-2H-pyran-4-ol, to provide
 15 the title compound.

Example 59b

4-(5-amino-2-(4,4-difluorocyclohexyloxy)phenyl)-6-methyl-1H-pyrrolo[2,3-c]pyridin-7(6H)-
 one

Example 59b was prepared according to the procedure used for the preparation of
 20 Example 3, substituting the product of Example 59a for the product of Example 2b, to provide the title compound.

Example 59c

N-{4-[(4,4-difluorocyclohexyl)oxy]-3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-
 c]pyridin-4-yl)phenyl}methanesulfonamide

25

Example 59c was prepared according to the procedure used in method A of Example 4, substituting the product of Example 59b for the product of Example 3, to provide the title compound. ¹H NMR (300 MHz, DMSO) δ 1.95-1.61 (m, 8H), 2.95 (s, 3H), 3.55 (s, 3H), 4.55-4.46 (m, 1H), 6.22-6.17 (m, 1H), 7.20-7.15 (m, 2H), 7.31-7.25 (m, 3H), 9.47 (s, 1H), 12.01 (bs, 1H).MS (ESI+) m/z 452.2 (M+H)⁺.

30

Example 60

N-[3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)-4-(tetrahydro-2H-pyran-3-
 yloxy)phenyl]methanesulfonamide

Example 60a

6-methyl-4-(5-nitro-2-(tetrahydro-2H-pyran-3-yloxy)phenyl)-1H-pyrrolo[2,3-c]pyridin-7(6H)-one

Example 60a was prepared according to the procedure used for the preparation of Example 29a, substituting tetrahydro-2H-pyran-3-ol for tetrahydro-2H-pyran-4-ol, to provide the title compound.

Example 60b

4-(5-amino-2-(tetrahydro-2H-pyran-3-yloxy)phenyl)-6-methyl-1H-pyrrolo[2,3-c]pyridin-7(6H)-one

Example 60b was prepared according to the procedure used for the preparation of Example 29b, substituting the product of Example 60a for the product of Example 29a, to provide the title compound.

Example 60c

N-[3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)-4-(tetrahydro-2H-pyran-3-yloxy)phenyl]methanesulfonamide

Example 60c was prepared according to the procedure used in method A of Example 4, substituting the product of Example 60b for the product of Example 3, to provide the title compound. ¹H NMR (500 MHz, DMSO-*d*₆) δ 1.39-1.45 (m, 1H), 1.55-1.70 (m, 2H), 1.89-1.96 (m, 1H), 2.95 (s, 3H), 3.41-3.57 (m, 7H), 3.65-3.69 (m, 1H), 6.24-6.26 (m, 1H), 6.84 (d, J=8.54 Hz, 1H), 7.14 (m, 2H), 7.29-7.31 (m, 2H), 7.38 (s, 1H), 9.45 (s, 1H), 12.03 (s, 1H). MS (ESI+) m/z 418.2 (M+H)⁺.

Example 61

6-methyl-4-[2-(morpholin-4-ylcarbonyl)phenyl]-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one

Example 61 was prepared according to the procedure used for the preparation of Example 1f, substituting morpholino(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)methanone for 2-phenoxyphenylboronic acid, to provide the title compound. ¹H NMR (500 MHz, DMSO-*d*₆) δ 2.80-2.83 (m, 2H), 2.91-2.99 (m, 2H), 3.20-3.25 (m, 2H), 3.54-3.57 (m, 5H), 6.17-6.18 (m, 1H), 7.06 (s, 1H), 7.32 (t, J=2.9 Hz, 1H), 7.40 (d, J=7.32 Hz, 1H), 7.42-7.53 (m, 3H), 12.15 (s, 1H). MS (ESI+) m/z 338.1 (M+H)⁺.

Example 62

N-[3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)-4-(2,4,6-trifluorophenoxy)phenyl]ethanesulfonamide

Example 62 was prepared according to the procedure used in method A of Example 4, substituting Example 33b for Example 3 and substituting ethanesulfonyl chloride for methanesulfonyl chloride respectively to provide the title compound. ¹H NMR (300 MHz,

DMSO) δ 1.22 (t, J = 7.3 Hz, 3H), 3.09 (q, J = 7.3 Hz, 2H), 3.56 (s, 3H), 6.22 (t, J = 2.3 Hz, 1H), 6.79 (d, J = 8.8 Hz, 1H), 7.15 (dd, J = 8.8, 2.7 Hz, 1H), 7.44-7.27 (m, 5H), 9.72 (s, 1H), 12.06 (bs, 1H).MS (ESI+) m/z 478.1 (M+H)⁺.

Example 63

5 N-[4-(benzyloxy)-3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)phenyl]methanesulfonamide

Example 63a

4-(2-(benzyloxy)-5-nitrophenyl)-6-methyl-1H-pyrrolo[2,3-c]pyridin-7(6H)-one

Example 63a was prepared according to the procedure used for the preparation of
10 Example 29a, substituting phenylmethanol for tetrahydro-2H-pyran-4-ol, to provide the title compound.

Example 63b

4-(5-amino-2-(benzyloxy)phenyl)-6-methyl-1H-pyrrolo[2,3-c]pyridin-7(6H)-one

Example 63b was prepared according to the procedure used for the preparation of
15 Example 3, substituting the product of Example 63a for the product of Example 2b, to provide the title compound.

Example 63c

N-[4-(benzyloxy)-3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)phenyl]methanesulfonamide

20 Example 63 was prepared according to the procedure used in method A of Example 4, substituting the product of Example 63b for the product of Example 3, to provide the title compound. ¹H NMR (300 MHz, DMSO) δ 2.94 (s, 3H), 3.51 (s, 3H), 5.07 (s, 2H), 6.24-6.18 (m, 1H), 7.22-7.16 (m, 2H), 7.37-7.24 (m, 8H), 9.45 (s, 1H), 12.00 (bs, 1H).MS (ESI+) m/z 424.2 (M+H)⁺.

25

Example 64

N-[4-(2,4-difluorophenoxy)-3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)phenyl]-2-fluoroethanesulfonamide

Example 64 was prepared according to the procedure used for the preparation of
Example 27c, substituting 2-fluoroethanesulfonyl chloride for methanesulfonyl chloride, and
30 bypassing the sodium hydroxide hydrolysis step, to provide the title compound. ¹H NMR (300 MHz, DMSO) δ 3.52 (s, 3H), 3.63 (t, J = 6.0 Hz, 2H), 4.12 (q, J = 6.0 Hz, 2H), 6.25-6.19 (m, 1H), 7.08-6.62 (m, 5H), 7.27-7.20 (m, 3H), 11.99-11.92 (m, 1H).MS (ESI+) m/z 478.2 (M+H)⁺.

Example 65

N-[4-(2,4-difluorophenoxy)-3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)phenyl]-N'-methylsulfuric diamide

Example 65 was prepared according to the procedure used for the preparation of Example 27c, substituting methylsulfamoyl chloride for methanesulfonyl chloride, to provide the title compound. ¹H NMR (300 MHz, DMSO) δ 2.50 (m, 3H solvent obscured), 3.52 (s, 3H), 6.28-6.22 (m, 1H), 7.08-6.86 (m, 3H), 7.15 (dd, J = 8.8, 2.7 Hz, 1H), 7.39-7.21 (m, 5H), 9.65 (s, 1H), 12.02 (bs, 1H), MS (ESI+) m/z 461.1 (M+H)⁺.

Example 66

N-[3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)-4-(tetrahydrofuran-3-yloxy)phenyl]ethanesulfonamide

Example 66 was prepared according to the procedure used in method A of Example 4, substituting the product of Example 31b for the product of Example 3, and ethanesulfonyl chloride for methanesulfonyl chloride, respectively, to provide the title compound. ¹H NMR (300 MHz, DMSO) δ 1.22 (t, J = 7.3 Hz, 3H), 1.93-1.80 (m, 1H), 2.20-2.04 (m, 1H), 3.02 (q, J = 7.3 Hz, 2H), 3.55 (s, 3H), 3.65 (m, 3H), 3.82 (dd, J = 10.0, 4.5 Hz, 1H), 5.00-4.91 (m, 1H), 6.16 (t, J = 2.3 Hz, 1H), 7.06 (d, J = 8.8 Hz, 1H), 7.16 (dd, J = 8.7, 2.7 Hz, 1H), 7.24 (s, 1H), 7.31-7.25 (m, 3H), 9.53 (s, 1H), 12.01 (bs, 1H), MS (ESI+) m/z 418.1 (M+H)⁺.

Example 67

methyl 6-methyl-7-oxo-4-(2-phenoxyphenyl)-6,7-dihydro-1H-pyrrolo[2,3-c]pyridine-2-carboxylate

Example 67a

ethyl 4-bromo-6-methyl-7-oxo-1-tosyl-6,7-dihydro-1H-pyrrolo[2,3-c]pyridine-2-carboxylate

Diisopropylamine (0.111 g, 1.102 mmol) in tetrahydrofuran (3 mL) was treated with BuLi (2.5 M, 0.44 mL, 1.102 mmol) at -78 °C. The solution was stirred for 20 minutes at -78 °C, and warmed up to room temperature for 5 minutes, and cooled down to -78 °C again. To this solution was added N1,N1,N2,N2-tetramethylethane-1,2-diamine (0.128 g, 1.102 mmol). Then Example 1e (0.30 g, 0.787 mmol) in tetrahydrofuran (3 mL) was added to the reaction mixture via cannula under nitrogen. The reaction mixture was stirred at -78 °C for 1 hour, warmed to 0 °C briefly, and cooled down to -78 °C. To this suspension was added ethyl carbonochloridate (0.205 g, 1.889 mmol) via a syringe. The reaction mixture was allowed to warm to room temperature gradually overnight. The mixture was then partitioned between water and ethyl acetate. The aqueous layer was extracted with additional ethyl acetate three times. The combined organic layers were washed with brine, dried over MgSO₄, filtered, and

concentrated. The residue was purified by flash chromatography on silica gel eluting with 30-50% ethyl acetate in hexanes to afford 0.074 g of the title compound.

Example 67b

5 methyl 6-methyl-7-oxo-4-(2-phenoxyphenyl)-6,7-dihydro-1H-pyrrolo[2,3-c]pyridine-2-carboxylate

Example 67b was prepared according to the procedure used for the preparation of Example 1f, substituting Example 67a for Example 1e, and bypassing the use of 2.0 N NaOH, to provide the title compound. ¹H NMR (500 MHz, DMSO-*d*₆) δ 3.50 (s, 3H), 3.80 (s, 3H), 6.80-6.82 (m, 3H), 7.00 (t, J=7.32 Hz, 1H), 7.06 (d, J=7.02 Hz, 1H), 7.23-7.32 (m, 4H), 7.40-10 7.42 (m, 1H), 7.52 (dd, J=7.48, 1.68 Hz, 1H), 12.85 (s, 1 H). MS (ESI+) m/z 375 (M+H)⁺.

Example 68

methyl 1,6-dimethyl-7-oxo-4-(2-phenoxyphenyl)-6,7-dihydro-1H-pyrrolo[2,3-c]pyridine-2-carboxylate

The title compound was obtained as a by-product from the preparation of Example 15 67b. ¹H NMR (500 MHz, DMSO-*d*₆) δ 3.48 (s, 3H), 3.81 (s, 3H), 4.38 (s, 3H), 6.81-6.84 (m, 3H), 6.98-7.07 (m, 2H), 7.25-7.31 (m, 3H), 7.34 (s, 1H), 7.41-7.47 (m, 1H), 7.48 (dd, J=7.48, 1.68 Hz, 1H). MS (ESI+) m/z 389 (M+H)⁺.

Example 69

20 ethyl 4-(5-amino-2-phenoxyphenyl)-6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridine-2-carboxylate

Example 69a

ethyl 1-benzyl-4-bromo-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridine-2-carboxylate

Example 69a was prepared according to the procedure used for the preparation of Example 2a (Method B), substituting Example 67a for Example 1e, to provide the title 25 compound.

Example 69b

ethyl 6-methyl-4-(5-nitro-2-phenoxyphenyl)-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridine-2-carboxylate

Example 69b was prepared according to the procedure used for the preparation of 30 Example 2b, substituting Example 69a for Example 2a, to provide the title compound.

Example 69c

ethyl 4-(5-amino-2-phenoxyphenyl)-6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridine-2-carboxylate

Example 69c was prepared according to the procedure used for the preparation of Example 29b, substituting Example 69b for Example 29a, to provide the title compound. ¹H NMR (500 MHz, DMSO- *d*₆) δ 1.30 (t, J = 7.02 Hz, 3H), 3.49 (s, 3H), 4.27 (q, J=7.12 Hz, 2H), 6.77 (d, J = 7.93 Hz, 2H), 6.86 (d, J = 2.14 Hz, 1H), 6.93-7.03 (m, 3H), 7.11 (s, 1H), 7.20-7.24 (m, 2H), 7.31 (s, 1H), 12.86 (s, 1H). MS (ES1+) m/z 404.1 (M+H)⁺.

Example 70

6-methyl-4-{5-[(methylsulfonyl)amino]-2-phenoxyphenyl}-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridine-2-carboxylic acid

Example 70a

10 (Z)-ethyl 3-(5-bromo-2-methoxy-3-nitropyridin-4-yl)-2-hydroxyacrylate

To a solution of ethanol (15 mL) and ether (150 mL) were added 5-bromo-2-methoxy-4-methyl-3-nitropyridine (14.82 g, 60 mmol), diethyl oxalate (13.15 g, 90 mmol), and potassium ethoxide (6.06 g, 72 mmol). The reaction mixture was heated at 45 °C for 24 hours. During the reaction, the flask was shaken by hand several times. After cooling, the reaction mixture was partitioned between water and ethyl acetate. The aqueous layer was extracted with additional ethyl acetate three times. The combined organic layers were washed with brine, dried over MgSO₄, filtered, and concentrated. The residue was purified by flash chromatography on silica gel eluting with 10-20% ethyl acetate in hexanes to 9.5 g of the title compound (yield 46%).

20 Example 70b

ethyl 4-bromo-7-methoxy-1H-pyrrolo[2,3-c]pyridine-2-carboxylate

A mixture Example 70a (9.5 g, 27.4 mmol) and iron (7.64 g, 137 mmol) in ethanol (60 mL) and acetic acid (60 mL) was heated at 100 °C for 1 hour. The solution turned from red to gray. The solid was filtered off, and then washed with additional ethyl acetate. The solvents were removed under reduced pressure to 20% of original volume, and it was partitioned between water and ethyl acetate. The aqueous layer was extracted with additional ethyl acetate several times. The combined organic layers were washed with brine, dried over MgSO₄, filtered, and concentrated. The residue was purified by flash chromatography on silica gel eluting with 20-40% ethyl acetate in hexanes to afford 6.05g of the title compound.

30 Example 70c

ethyl 1-benzyl-4-bromo-7-methoxy-1H-pyrrolo[2,3-c]pyridine-2-carboxylate

Example 70b (0.88 g, 2.94 mmol) in dimethylformamide (15 mL) was treated with 60% sodium hydride (0.106 g, 4.41 mmol, 0.117 g of a 60% in oil dispersion). The solution was stirred at room temperature for 10 minutes. To this solution was added benzyl bromide

(0.59 g, 3.45 mmol). The reaction mixture was stirred for another 2 hours. It was partitioned between water and ethyl acetate. The aqueous layer was extracted with additional ethyl acetate twice. The combined organic layers were washed with brine, dried over MgSO₄, filtered, and concentrated. The residue was purified by flash chromatography on silica gel eluting with 20-40% ethyl acetate in hexanes to afford 1.07 g of the title compound.

Example 70d

ethyl 1-benzyl-4-bromo-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridine-2-carboxylate

Example 70d was prepared according to the procedure used for the preparation of Example 1d, substituting Example 70c for Example 1c, to provide the title compound.

Example 70e

ethyl 1-benzyl-4-bromo-6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridine-2-carboxylate

Example 70e was prepared according to the procedure used for the preparation of Example 1e, substituting Example 70d for Example 1d, to provide the title compound.

Example 70f

ethyl 1-benzyl-4-(2-fluoro-5-nitrophenyl)-6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridine-2-carboxylate

Example 70f was prepared according to the procedure used for the preparation of Example 2a (Method B), substituting Example 70e for Example 1e, to provide the title compound.

Example 70g

ethyl 1-benzyl-6-methyl-4-(5-nitro-2-phenoxyphenyl)-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridine-2-carboxylate

Example 70g was prepared according to the procedure used for the preparation of Example 2b, substituting Example 70f for Example 2a, to provide the title compound.

Example 70h

ethyl 4-(5-amino-2-phenoxyphenyl)-1-benzyl-6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridine-2-carboxylate

Example 70h was prepared according to the procedure used for the preparation of Example 29b, substituting Example 70g for Example 29a, to provide the title compound.

Example 70i

ethyl 1-benzyl-6-methyl-4-(5-(N-(methylsulfonyl)methylsulfonamido)-2-phenoxyphenyl)-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridine-2-carboxylate

Example 70i was prepared according to the procedure used in method A of Example 4, substituting Example 70h for Example 3, except the use of 1 M NaOH, to provide the title compound.

Example 70j

5 ethyl 6-methyl-4-(5-(N-(methylsulfonyl)methylsulfonamido)-2-phenoxyphenyl)-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridine-2-carboxylate

A mixture of Example 70i (0.53 g, 0.816 mmol), anisole (0.176 g, 1.631 mmol), and concentrated H₂SO₄ (0.5 mL) in TFA (10 mL) was heated at 90 °C for 4 hours. Excess TFA was removed under reduced pressure, and the residue was partitioned between water and
10 ethyl acetate. The organic layer was separated, and the aqueous layer was extracted with additional ethyl acetate several times. The combined organic layers were washed with saturated aqueous sodium bicarbonate, followed by brine, dried over MgSO₄, filtered, and concentrated to afford 0.48 g of the title compound. The crude material was used directly for the next reaction.

15

Example 70k

6-methyl-4-{5-[(methylsulfonyl)amino]-2-phenoxyphenyl}-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridine-2-carboxylic acid

Example 70j (0.4 g, 0.858 mmol) in dioxane (5 mL) was treated with 2.0 N NaOH (1.72 mL, 3.43 mmol). The reaction mixture was heated at 65 °C for 2 hours. The reaction
20 mixture was cooled to room temperature and poured into water (100 mL). After addition of concentrated HCl (1 mL), the mixture was extracted with ethyl acetate three times (3 x 30 mL). The combined organic layers were washed with brine, dried over MgSO₄, filtered, and concentrated to afford 0.36 g (93%) of the title compound. A small amount of sample was purified by preparative HPLC (CI 8, 10-70% acetonitrile in 0.1% TFA/water). ¹H NMR (500
25 MHz, DMSO-*d*₆) δ 3.03 (s, 3H), 3.49 (s, 3H), 6.81 (d, J = 7.63 Hz, 2H), 6.84 (d, J = 2.14 Hz, 1H), 6.96-7.00 (m, 1H), 7.08 (d, J = 8.85 Hz, 1H), 7.22-7.27 (m, 3H), 7.34 (s, 1H), 7.37 (d, J = 2.75 Hz, 1H), 9.77 (s, 1H), 12.62 (d, J = 1.53 Hz, 1H), 13.00 (s, br, 1H). MS (ESI+) m/z 454.1 (M+H)⁺.

Example 71

30 ethyl 6-methyl-4-{5-[(methylsulfonyl)amino]-2-phenoxyphenyl}-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridine-2-carboxylate

Example 70k (0.2 g, 0.441 mmol) in ethanol (10 mL) was treated with concentrated H₂SO₄ (0.5 mL). The reaction mixture was heated under reflux overnight. The solvent was

removed, and the remaining was partitioned between water and ethyl acetate. The organic layer was separated, and the aqueous layer was extracted with additional ethyl acetate several times. The combined organic layers were washed with sat. NaHCO₃, brine, dried over MgSO₄, filtered, and concentrated to afford 0.19 g of the title compound. A small amount of crude product was purified by preparative HPLC to provide clean product for biological testing. ¹H NMR (500 MHz, DMSO- *d*₆) δ 1.30 (t, J = 7.17 Hz, 3H), 3.04 (s, 3H), 3.50 (s, 3H), 4.26 (q, J=7.22 Hz, 2H), 6.80 (d, J = 7.63 Hz, 2H), 6.86 (d, J = 2.14 Hz, 1H), 6.96-7.00 (m, 1H), 7.09 (d, J = 8.85 Hz, 1H), 7.21-7.28 (m, 3H), 7.35 (s, 1H), 7.36 (d, J = 2.75 Hz, 1H), 9.78 (s, 1H), 12.86 (s, 1H). (ESI+) m/z 482.1 (M+H)⁺.

10

Example 72

N-ethyl-6-methyl-4-{5-[(methylsulfonyl)amino]-2-phenoxyphenyl} -7-oxo-6,7-dihydro-1H-pyrrolo [2,3-c]pyridine-2-carboxamide

Example 72a

6-methyl-4-(5-(methylsulfonamido)-2-phenoxyphenyl)-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridine-2-carbonyl chloride

15

Example 72a was prepared according to the procedure used for the preparation of Example 13a, substituting Example 70k for Example 10, to provide the title compound.

Example 72b

N-ethyl-6-methyl-4-{5-[(methylsulfonyl)amino]-2-phenoxyphenyl}-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridine-2-carboxamide

20

Example 72b was prepared according to the procedure used for the preparation of Example 13b, substituting Example 72a for Example 13a, to provide the title compound. ¹H NMR (500 MHz, DMSO- *d*₆) δ 1.12 (t, J = 7.17 Hz, 3H), 3.03 (s, 3H), 3.23-3.30 (m, 2H), 3.49 (s, 3H), 6.81 (d, J = 7.63 Hz, 2H), 6.86 (d, J = 2.44 Hz, 1H), 6.96-7.00 (m, 1H), 7.07 (d, J = 8.54 Hz, 1H), 7.22-7.28 (m, 3H), 7.30 (s, 1H), 7.34 (d, J = 2.75 Hz, 1H), 8.34 (t, J = 5.34 Hz, 1H), 9.79 (s, 1H), 12.22 (s, 1H). (ESI+) m/z 481.1 (M+H)⁺.

25

Example 73

6-methyl-4-{5-[(methylsulfonyl)amino]-2-phenoxyphenyl} -7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridine-2-carboxamide

30

Example 73 was prepared according to the procedure used for the preparation of Example 13b, substituting Example 72a for Example 13a, and aqueous ammonium hydroxide for ethyl amine, respectively, to provide the title compound. ¹H NMR (500 MHz, DMSO- *d*₆) δ 3.03 (s, 3H), 3.50 (s, 3H), 6.82 (d, J = 7.63 Hz, 2H), 6.88 (d, J = 2.44 Hz, 1H), 6.97-7.01 (m,

1H), 7.06 (d, J = 8.54 Hz, 1H), 7.22-7.28 (m, 3H), 7.31 (s, 1H), 7.35 (d, J = 2.75 Hz, 1H), 7.46 (s, 1H), 7.81 (s, 1H), 9.78 (s, 1H), 12.22 (s, 1H). MS (ESI+) m/z 453.1 (M+H)⁺.

Example 74

ethyl 4-(5-amino-2-phenoxyphenyl)-6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-
d]pyridazine-2-carboxylate

Example 74a

4-amino-6-chloro-2-methylpyridazin-3(2H)-one

A mixture of 4,6-dichloro-2-methylpyridazin-3(2H)-one (5.0 g, 27.9 mmol) and ammonium hydroxide (55 mL, 1412 mmol) was heated at 150 °C for 2 hours and then cooled to room temperature. The solvent was removed, and the residue was dissolved in ethyl acetate and washed with water. The aqueous layer was extracted with additional ethyl acetate three times. The combined organic layers were washed with brine, dried and concentrated. The residue was purified by flash chromatography (silica gel, eluted with 40% ethyl acetate in hexanes to afford 3.85 g (87%) of the title compound.

Example 74b

4-amino-6-chloro-5-iodo-2-methylpyridazin-3(2H)-one

A mixture of Example 74a (2.12 g, 13.3 mmol) and N-iodosuccinimide (5.38 g, 23.9 mmol) in acetonitrile (30 mL) was heated under reflux for 6 hours. The reaction mixture was cooled to room temperature and partitioned between ethyl acetate and water. The aqueous layer was extracted with additional ethyl acetate twice. The combined organic layers were washed with brine, dried over anhydrous magnesium sulfate, filtered, and concentrated. The residue was purified by flash chromatography on silica gel eluting with 20-40% ethyl acetate in hexanes to afford 3.27 g (86%) of the title compound.

Example 74c

4-chloro-6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[3,2-d]pyridazine-2-carboxylic acid

A mixture of Example 74b (0.59 g, 2.1 mmol), pyruvic acid (0.546 g, 6.2 mmol), 1,4-diazabicyclo[2.2.2]octane (0.695 g, 6.2 mmol), and palladium(II)acetate (0.046 g, 10 mol%) in dimethylformamide (8 mL) was degassed and back-filled with nitrogen three times. The reaction mixture was then heated at 105 °C overnight. The reaction mixture was cooled to room temperature and partitioned between ethyl acetate and water. The aqueous layer was extracted with additional ethyl acetate twice. The combined organic layers were washed with brine, dried over anhydrous magnesium sulfate, filtered, and concentrated. The residue was triturated in 30% ethyl acetate in hexanes to afford 0.25 g (53%) of the title compound.

Example 74d

ethyl 4-chloro-6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[3,2-d]pyridazine-2-carboxylate

Example 74c (0.45 g, 2.0 mmol) in ethanol (15 mL) was treated concentrated sulfuric acid (1 mL). The reaction mixture was heated under reflux for 16 hours. The reaction mixture
5 was cooled to room temperature and partitioned between ethyl acetate and water. The aqueous layer was extracted with additional ethyl acetate twice. The combined organic layers were washed with brine, dried over anhydrous magnesium sulfate, filtered, and concentrated to afford 0.45 g (89%) of the title compound.

Example 74e

10 ethyl 4-chloro-6-methyl-7-oxo-1-((2-(trimethylsilyl)ethoxy)methyl)-6,7-dihydro-1H-pyrrolo[3,2-d]pyridazine-2-carboxylate

A solution of Example 74d (0.41 g, 1.6 mmol) in dimethylformamide (15 mL) was treated with 60% sodium hydride (0.096 g, 2.4 mmol) at room temperature. The reaction mixture was stirred for 30 min, and then was treated with (2-
15 (chloromethoxy)ethyl)trimethylsilane (0.40 g, 2.4 mmol). The reaction mixture was then stirred for 2 hours. It was partitioned between ethyl acetate and water. The aqueous layer was extracted with additional ethyl acetate twice. The combined organic layers were washed with brine, dried over anhydrous magnesium sulfate, filtered, and concentrated. The residue was purified by flash chromatography on silica gel, eluting with 20% ethyl acetate to afford 0.50
20 g (81%) of the title compound.

Example 74f

ethyl 4-(2-fluoro-5-nitrophenyl)-6-methyl-7-oxo-1-((2-(trimethylsilyl)ethoxy)methyl)-6,7-dihydro-1H-pyrrolo[3,2-d]pyridazine-2-carboxylate

Example 74f was prepared according to the procedure used for the preparation of
25 Example 2a (Method B), substituting Example 74e for Example 1e, to provide the title compound

Example 74g

ethyl 6-methyl-4-(5-nitro-2-phenoxyphenyl)-7-oxo-6,7-dihydro-1H-pyrrolo[3,2-d]pyridazine-2-carboxylate

30 A mixture of Example 74f (0.26 g, 0.53 mmol), phenol (0.060 g, 0.64 mmol) and cesium carbonate (0.21 g, 0.63 mmol) in dimethylsulfoxide (5 mL) was heated at 110 °C for 6 hours. After cooling to room temperature, the reaction mixture was partitioned between water and ethyl acetate. The aqueous layer was extracted with additional ethyl acetate three

times. The combined organic layers were washed with brine, dried over anhydrous magnesium sulfate, filtered, and concentrated. The residue was then treated with 15 mL of ethanol and 1 mL of concentrated H₂SO₄. The mixture was heated under reflux overnight. The reaction mixture was cooled to room temperature and partitioned between ethyl acetate and water. The organic layer was washed with brine, dried over anhydrous magnesium sulfate, filtered, and concentrated. The residue was purified by flash chromatography on silica gel eluting with 40-80% ethyl acetate to afford 0.14 g (61 %) of the title compound.

Example 74h

ethyl 4-(5-amino-2-phenoxyphenyl)-6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-d]pyridazine-2-carboxylate

Example 74h was prepared according to the procedure used for the preparation of Example 29b, substituting Example 74g for Example 29a, and ethanol for ethyl acetate, respectively, to provide the title compound. ¹H NMR (500 MHz, DMSO- *d*₆) δ 1.29 (t, J=7.02 Hz, 3H), 3.61 (s, 3H), 4.28 (q, J=7.22 Hz, 2H), 5.22 (s, 2H), 6.65 (d, J=7.33 Hz, 2H), 6.74 (dd, J=8.85, 2.75 Hz, 1H), 6.79 (t, J=2.75 Hz, 1H), 6.87 (d, J=7.32 Hz, 1H), 6.91-6.93 (m, 2H), 7.13-7.17 (m, 2H), 13.37 (br s, 1H). MS (ESI+) m/z 405.1 (M+H)⁺.

Example 75

ethyl 4-[5-(ethylamino)-2-phenoxyphenyl]-6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-d]pyridazine-2-carboxylate

Example 75 was obtained as a by-product from the preparation of Example 74h ¹H NMR (500 MHz, DMSO- *d*₆) δ 1.19 (t, J=7.17 Hz, 3H), 1.30 (t, J=7.02 Hz, 3H), 3.03-3.08 (m, 2H), 3.62 (s, 3H), 4.29 (q, J=7.02 Hz, 2H), 5.71 (t, J=5.19 Hz, 1H), 6.65 (d, J=7.63 Hz, 2H), 6.72-6.74 (m, 2H), 6.87 (t, J=7.32 Hz, 1H), 6.91 (s, 1H), 6.99 (d, J=9.16 Hz, 1H), 7.13-7.17 (m, 2H), 13.47 (br s, 1H). MS (ESI+) m/z 433.1 (M+H)⁺.

Example 76

ethyl 4-{5-[ethyl(methylsulfonyl)amino]-2-phenoxyphenyl}-6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-d]pyridazine-2-carboxylate

Example 76 was prepared according to the procedure used in method A of Example 4, substituting Example 75 for Example 3, except the use of NaOH, to provide the title compound. ¹H NMR (500 MHz, DMSO- *d*₆) δ 1.07 (t, J=7.02 Hz, 3H), 1.30 (t, J=7.17 Hz, 3H), 3.02 (s, 3H), 3.67-3.72 (m, 5H), 4.23 (q, J=7.22 Hz, 2H), 6.93 (d, J=7.93 Hz, 2H), 6.99 (d, J=2.14 Hz, 1H), 7.07-7.12 (m, 2H), 7.30-7.34 (m, 2H), 7.52-7.55 (m, 1H), 7.85 (d, J=2.75 Hz, 1H). MS (ESI+) m/z 511.1 (M+H)⁺.

Example 77

6-methyl-4- {5-[(methylsulfonyl)amino]-2-phenoxyphenyl }-7-oxo-6,7-dihydro- 1H-
pyrrolo[2,3-d]pyridazine-2-carboxylic acid

Example 77 was prepared according to the procedure used in method A of Example 4,
5 substituting Example 74h for Example 3, to provide the title compound. ¹H NMR (500 MHz,
DMSO- *d*₆) δ 3.04 (s, 3H), 3.66 (s, 3H), 6.39-6.40 (m, 1H), 6.81-6.83 (m, 2H), 6.93 (d, J =
1.53 Hz, 1H), 6.98-7.01 (m, 1H), 7.14 (d, J= 8.85 Hz, 1H), 7.23-7.27 (m, 2H), 7.37-7.42 (m,
1H), 7.43 (d, J=2.75 Hz, 1H), 9.82 (s, 1H), 13.35 (s, 1H). MS (ESI+) m/z 455.1 (M+H)⁺.

Example 78

10 6-methyl-4- {5-[(methylsulfonyl)amino]-2-phenoxyphenyl } -7-oxo-6,7-dihydro-1H-
pyrrolo[2,3-d]pyridazine-2-carboxamide

Example 78a

6-methyl-4-(5-(methylsulfonamido)-2-phenoxyphenyl)-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-
d]pyridazine-2-carbonyl chloride

15 Example 78a was prepared according to the procedure used for the preparation of
Example 13a, substituting Example 77 for Example 10, to provide the title compound.

Example 78b

6-methyl-4- {5-[(methylsulfonyl)amino]-2-phenoxyphenyl }-7-oxo-6,7-dihydro- 1H-
pyrrolo[2,3-d]pyridazine-2-carboxamide

20 Example 78b was prepared according to the procedure used for the preparation of
Example 13b, substituting Example 78a for Example 13a, and aqueous ammonium hydroxide
for ethylamine, respectively, to provide the title compound. ¹H NMR (500 MHz, DMSO- *d*₆)
δ 3.03 (s, 3H), 3.67 (s, 3H), 6.85 (d, J=7.63 Hz, 2H), 6.99-7.04 (m, 2H), 7.10 (d, J = 8.54 Hz,
1H), 7.23-7.28 (m, 2H), 7.37-7.40 (m, 2H), 7.57 (s, 1H), 7.91 (s, 1H), 9.82 (s, 1H), 12.95 (s,
25 1H). MS (ESI+) m/z 454.1 (M+H)⁺.

Example 79

6-methyl-N-[2-(4-methylpiperazin-1-yl)ethyl]-4- {5-[(methylsulfonyl)amino]-2-
phenoxyphenyl}-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-d]pyridazine-2-carboxamide

30 Example 79 was prepared according to the procedure used for the preparation of
Example 13b, substituting Example 78a for Example 13a, and 2-(4-methylpiperazin-1-
yl)ethanamine for ethylamine, respectively, to provide the title compound. ¹H NMR (500
MHz, DMSO- *d*₆) δ 2.67-2.80 (m, 6H), 3.04 (s, 3H), 3.49 (br, 8 H), 3.67 (s, 3H), 6.82 (d,
J=7.63 Hz, 2H), 6.99-7.03 (m, 2H), 7.13 (d, J = 8.85 Hz, 1H), 7.24-7.28 (m, 2H), 7.37-7.40
(m, 2H), 8.50-8.52 (m, 1H), 9.85 (s, 1H), 13.03 (s, 1H). MS (ESI+) m/z 580.2 (M+H)⁺.

Example 80

N-[3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-d]pyridazin-4-yl)-4-phenoxyphenyl]methanesulfonamide

Example 80a

5 (E)-4-amino-6-chloro-5-(2-ethoxyvinyl)-2-methylpyridazin-3(2H)-one

Example 80a was prepared according to the procedure used for the preparation of Example 2a (Method B), substituting Example 74b for Example 1e, and (E)-2-(2-ethoxyvinyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane for 2-fluoro-5-nitrophenylboronic acid, respectively, to provide the title compound.

10 Example 80b

4-chloro-6-methyl-1H-pyrrolo[3,2-d]pyridazin-7(6H)-one

Example 80a (0.1 g, 0.435 mmol) in acetic acid (5 mL) was heated at 90 °C overnight. The solvent was evaporated under reduced pressure to afford 0.071 g of the title compound.

Example 80c

15 4-chloro-6-methyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[3,2-d]pyridazin-7(6H)-one

Example 80c was prepared according to the procedure used for the preparation of Example 74e, substituting Example 80b for Example 74c, to provide the title compound.

Example 80d

20 4-(2-fluoro-5-nitrophenyl)-6-methyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[3,2-d]pyridazin-7(6H)-one

Example 80c was prepared according to the procedure used for the preparation of Example 2a (Method B), substituting Example 80c for Example 1e, to provide the title compound.

25 Example 80e

6-methyl-4-(5-nitro-2-phenoxyphenyl)-1H-pyrrolo[3,2-d]pyridazin-7(6H)-one

Example 80e was prepared according to the procedure used for the preparation of Example 2b, substituting Example 80d for Example 2a, to provide the title compound.

Example 80f

30 4-(5-amino-2-phenoxyphenyl)-6-methyl-1H-pyrrolo[3,2-d]pyridazin-7(6H)-one

Example 80f was prepared according to the procedure used for the preparation of Example 29b, substituting Example 80e for Example 29a, to provide the title compound.

Example 80g

N-[3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-d]pyridazin-4-yl)-4-phenoxyphenyl]methanesulfonamide

Example 80g was prepared according to the procedure used in method A of Example 4, substituting Example 80f for Example 3, to provide the title compound. ¹H NMR (500 MHz, DMSO- *ck*) δ 3.03 (s, 3H), 3.67 (s, 3H), 6.39-6.40 (m, 1H), 6.87 (d, J=7.63 Hz, 2H), 7.01 (t, J = 7.48 Hz, 1H), 7.08 (d, J=8.54 Hz, 1H), 7.24-7.28 (m, 2H), 7.35 (dd, J=8.85, 2.75 Hz, 1H), 7.42-7.43 (m, 2H), 9.80 (s, 1H), 12.67 (s, 1H). MS (ESI+) m/z 411.1 (M+H)⁺.

Example 81

N-ethyl-6-methyl-4-{5-[(methylsulfonyl)amino]-2-phenoxyphenyl}-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-d]pyridazine-2-carboxamide

Example 81 was prepared according to the procedure used for the preparation of Example 13b, substituting Example 78a for Example 13a, to provide the title compound. ¹H NMR (500 MHz, DMSO- *d₆*) δ 1.12 (t, J=7.17 Hz, 3H), 3.03 (s, 3H), 3.27-3.30 (m, 2H), 3.66 (s, 3H), 6.82-6.84 (m, 2H), 6.98-7.02 (m, 2H), 6.97-7.01 (m, 1H), 7.12 (d, J = 9.16 Hz, 1H), 7.23-7.28 (m, 2H), 7.37-7.40 (m, 2H), 8.44 (t, J=5.34 Hz, 1H), 9.83 (s, 1H), 12.97 (s, 1H). MS (ESI+) m/z 482.1 (M+H)⁺.

Example 82

6-methyl-4-(2-phenoxyphenyl)-1,6-dihydro-7H-pyrrolo[2,3-d]pyridazin-7-one

Example 82 was prepared according to the procedure used for the preparation of Example 1f, substituting Example 80b for Example 1e, except the use of 2.0 N NaOH, to provide the title compound. ¹H NMR (500 MHz, DMSO- *d₆*) δ 3.70 (s, 3H), 6.36-6.37 (m, 1H), 6.91-6.93 (m, 2H), 7.02-7.07 (m, 2H), 7.27-7.31 (m, 3H), 7.41 (t, J=2.75 Hz, 1H), 7.47-7.52 (m, 1H), 7.56 (dd, J=7.63, 1.83 Hz, 1H), 12.65 (s, 1H). MS (ESI+) m/z 318.1 (M+H)⁺.

Example 83

N-ethyl-N,6-dimethyl-4-{5-[(methylsulfonyl)amino]-2-phenoxyphenyl}-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-d]pyridazine-2-carboxamide

Example 83 was prepared according to the procedure used for the preparation of Example 13b, substituting Example 78a for Example 13a, and N-methylethanamine for ethylamine, respectively, to provide the title compound. ¹H NMR (500 MHz, DMSO- *d₆*) δ 1.07 (br, 3H), 2.94 (s, 3H), 3.03 (s, 3H), 3.45 (br, 2H), 3.68 (s, 3H), 6.88 (d, J=7.93 Hz, 2H), 7.01 (t, J = 7.32 Hz, 1H), 7.12 (d, J=8.85 Hz, 1H), 7.24-7.28 (m, 2H), 7.36 (dd, J=8.85, 2.75 Hz, 1H), 7.43 (d, J=2.75 Hz, 1H), 9.81 (s, 1H), 13.01 (s, 1H). MS (ESI+) m/z 496.1 (M+H)⁺.

Example 84

N-[4-(4-cyanophenoxy)-3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)phenyl]ethanesulfonamide

Example 84 was prepared according to the procedure used in method A of Example 4, substituting the product of Example 33b for the product of Example 3, and substituting
5 ethanesulfonyl chloride for methanesulfonyl chloride, to provide the title compound. ¹H NMR (300 MHz, DMSO-*d*₆) δ ppm 1.25 (t, J = 7.3 Hz, 3H), 3.36 (q, J = 7.3 Hz, 2H), 3.47 (s, 3H), 6.28 - 6.22 (m, 1H), 6.86 - 6.79 (m, 2H), 7.21 - 7.10 (m, 1H) 7.30 - 7.21 (m, 3H), 7.42 (d, J = 2.6 Hz, 1H), 7.81 - 7.71 (m, 2H), 9.86 (s, 1H), 12.01 (bs, 1H). MS (ESI+) m/z 450.1 (M+H)⁺.

10

Example 85

6-methyl-4-[5-(methylsulfonyl)-2-phenoxyphenyl]-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one

Example 85a

4-(methylsulfonyl)-2-nitro-1-phenoxybenzene

15

Example 85a was prepared according to the procedure used for the preparation of Example 2b, substituting 1-fluoro-4-(methylsulfonyl)-2-nitrobenzene for Example 2a, to provide the title compound.

Example 85b

5-(methylsulfonyl)-2-phenoxyaniline

20

Example 85a was prepared according to the procedure used for the preparation of Example 29b, substituting 85a for Example 29a, to provide the title compound.

Example 85c

2-iodo-4-(methylsulfonyl)-1-phenoxybenzene

25

Example 85b (0.27 g, 1.025 mmol) in dioxane (1 mL) was treated with concentrated HCl (6 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 10 minutes. To this solution was added sodium nitrite (0.085 g, 1.23 mmol) in water (1 mL). The reaction was stirred at 0 °C for another 1 hour. To this solution was added potassium iodide (0.34 g, 1.051 mmol) in water (2 mL). The reaction was stirred for 1 hour at room temperature. The reaction mixture was partitioned between water and ethyl acetate. The organic layer was extracted with
30 additional ethyl acetate twice. The combined organic layer were washed with brine, dried over MgSO₄, filtered and concentrated. The residue was purified by flash chromatography on silica gel eluting with 10-30% ethyl acetate in hexanes to afford 0.28 g of the title product.

Example 85d

6-methyl-4-[5-(methylsulfonyl)-2-phenoxyphenyl]-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one

Example 85d was prepared according to the procedure used for the preparation of Example If, substituting 85c for Example le, and Example 6a for 2-phenoxyphenylboronic acid, to provide the title compound. ¹H NMR (500 MHz, DMSO-*d*₆) δ 3.26 (s, 3H), 3.57 (s, 3H), 6.29-6.30 (m, 1H), 7.03 (d, J=8.54 Hz, 1H), 7.11 (d, J=7.63 Hz, 2H), 7.20 (t, J=7.32 Hz, 1H), 7.30 (t, J=2.75 Hz, 1H), 7.40-7.44 (m, 3H), 7.88 (dd, J=8.54, 2.44 Hz, 1H), 8.00 (d, J=2.44 Hz, 1H), 12.07 (s, 1H). MS (ESI+) m/z 395.2 (M+H)⁺.

Example 86

10 5-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)-6-(tetrahydrofuran-3-yloxy)pyridine-3-sulfonamide

Example 86a

5-bromo-6-chloropyridine-3-sulfonamide

15 5-Bromo-6-chloropyridine-3-sulfonyl chloride (8.2 g) in methanol (20 mL) was cooled to 0 °C. To this solution was added 7N NH₃ in methanol (80 mL). The reaction mixture was stirred over night at room temperature. The solvent was removed at low temperature, and the residue was partitioned between ethyl acetate and water. The aqueous layer was extracted with ethyl acetate three times. The combined organic layers were washed with brine, dried (MgSO₄), filtered, and concentrated. The solid was purified by flash column chromatography on silica gel to afford 4.2 g of the clean product.

Example 86b

5-bromo-6-(tetrahydrofuran-3-yloxy)pyridine-3-sulfonamide

25 Example 86b was prepared according to the procedure used for the preparation of Example 29a, substituting 86a for Example 2a, and tetrahydrofuran-3-ol for tetrahydro-2H-pyran-4-ol, to provide the title compound.

Example 86c

5-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)-6-(tetrahydrofuran-3-yloxy)pyridine-3-sulfonamide

30 Example 86c was prepared according to the procedure used for the preparation of Example If, substituting 86b for Example le, and Example 6a for 2-phenoxyphenylboronic acid, to provide the title compound. ¹H NMR (500 MHz, DMSO-*d*₆) δ 1.91-1.97 (m, 1H), 2.18-2.25 (m, 1H), 3.59 (s, 3H), 3.66-3.76 (m, 3H), 3.92-3.95 (m, 1H), 5.63-5.66 (m, 1H), 6.19-6.21 (m, 1H), 7.34 (t, J=2.75 Hz, 1H), 7.41 (s, 1H), 7.47 (s, 2H), 8.14 (d, J=2.44 Hz, 1H), 8.54 (d, J=2.44 Hz, 1H), 12.11 (s, 1H). MS (ESI+) m/z 391.1 (M+H)⁺.

Example 87

N-methyl-5-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)-6-(tetrahydrofuran-3-yloxy)pyridine-3-sulfonamide

Example 87 was obtained as a by-product from the preparation of Example 86c. ¹H
5 NMR (500 MHz, DMSO- *d*₆) δ 1.93-1.98 (m, 1H), 2.17-2.24 (m, 1H), 2.48 (d, J= 5.19 Hz, 3H), 3.57 (s, 3H), 3.67-3.78 (m, 3H), 3.91-3.94 (m, 1H), 5.65-5.67 (m, 1H), 6.19 (t, J=2.29 Hz, 1H), 7.33 (t, J=2.75 Hz, 1H), 7.43 (s, 1H), 7.55 (q, J=4.88 Hz, 1H), 8.06 (d, J=2.44 Hz, 1H), 8.51 (d, J=2.44 Hz, 1H), 12.13 (s, 1H). MS (ESI+) m/z 405.1 (M+H)⁺.

Example 88

10 6-methyl-4-(2-phenoxyphenyl)-2-phenyl-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one
4-bromo-2-iodo-6-methyl-1-tosyl-1H-pyrrolo[2,3-c]pyridin-7(6H)-one

Example 88a

To a cold (-78 °C, dry ice/acetone bath) solution of Example 1e (0.2 g, 0.525 mmol) in tetrahydrofuran (6 mL) was added a freshly prepared solution of lithium di-isopropyl
15 amide (1.2 equivalents). The reaction mixture was stirred at -78 °C for 45 minutes. A solution of iodine (0.054 ml, 1.049 mmol) in tetrahydrofuran (0.5 mL) was added at -78 °C. The cooling bath was removed, and the reaction mixture was allowed to warm to room temperature and stirred for 1 hour. The reaction was quenched by the addition of saturated aqueous sodium thiosulfate (20 mL). The reaction mixture was partitioned between water
20 and ethyl acetate. The layers were separated, and the aqueous layer was extracted with additional ethyl acetate. The combined organics were washed with brine, dried with anhydrous MgSO₄, filtered and concentrated to dryness. The residue was purified by flash chromatography (silica gel, 1-100% ethyl acetate/hexane). The recovered material was further purified by reverse phase HPLC (CI 8, 0-100% acetonitrile in 0.1% TFA/water) to
25 afford the title compound (55 mg, 21%).

Example 88b

4-bromo-6-methyl-2-phenyl- 1-tosyl 1H-pyrrolo[2,3-c]pyridin-7(6H)-one

A mixture of Example 88a (0.1g, 0.197 mmol), phenylboronic acid (0.024 g, 0.197 mmol), Pd(PPh₃)₄ (0.011g, 0.0096 mmol), and sodium hydrogencarbonate (0.041 g, 0.493
30 mmol) in dimethylformamide (2 mL) and water (0.6 mL) was heated at 85 °C for 4 hours. After cooling, the reaction mixture was partitioned between water and ethyl acetate. The aqueous layer was extracted with additional ethyl acetate twice. The combined organic layers were washed with brine, dried over MgSO₄, filtered, and concentrated. The residue was

purified by flash chromatography on silica gel eluting with 30% ethyl acetate to afford 0.084 g of the title compound.

Example 88c

6-methyl-4-(2-phenoxyphenyl)-2-phenyl-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one

5 Example 88c was prepared according to the procedure used for the preparation of Example 1f, substituting 88b for Example 1e, to provide the title compound. ¹H NMR (500 MHz, DMSO-*d*₆) δ 3.53 (s, 3H), 6.67 (d, J=1.22 Hz, 1H), 6.93 (d, J=7.63 Hz, 2H), 7.01-7.04 (m, 2H), 7.26-7.31 (m, 5H), 7.36-7.43 (m, 3H), 7.56 (dd, J=7.48, 1.68 Hz, 1H), 7.89 (d, J=7.32 Hz, 1H), 12.31 (s, 1H). MS (ESI+) m/z 393.3 (M+H)⁺.

10

Example 89

N-{3-[2-(hydroxymethyl)-6-methyl-7-oxo-6,7-dihydro-1*H*-pyrrolo[2,3-c]pyridin-4-yl]-4-phenoxyphenyl}methanesulfonamide

Example 89 was prepared according to the procedure used for the preparation of Example 20b, substituting 71 for Example 20a, to provide the title compound. ¹H NMR (500 MHz, 15 DMSO-*d*₆) δ 3.02 (s, 3H), 3.47 (s, 3H), 4.50 (s, 2H), 6.19 (d, J=1.83 Hz, 1H), 6.82 (d, J=7.63 Hz, 2H), 6.99 (t, J=7.32 Hz, 1H), 7.05 (d, J=8.85 Hz, 1H), 7.21-7.27 (m, 4H), 7.38 (d, J=2.75 Hz, 1H), 9.75 (s, 1H), 11.60 (s, 1H). MS (ESI+) m/z 440.1 (M+H)⁺.

Biological Examples

20

Biological Examples for 11389 Bromodomain inhibitor application

Bromodomain domain binding assay

25 A time-resolved fluorescence resonance energy transfer (TR-FRET) assay was used to determine the affinities of compounds of the Examples listed in Table 1 for each bromodomain of BRD4. His-tagged first (BD1: amino acids K57-E168) and second (BD2: amino acids E352- E168) bromodomains of BRD4 were expressed and purified. An Alexa647-labeled BET-inhibitor was used as the fluorescent probe in the assay.

30

Synthesis of Alexa647-labeled bromodomain inhibitor compound

2-((6*S*,*Z*)-4-(4-chlorophenyl)-2,3,9-trimethyl-6*H*-thieno[3,2-*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepin-6-yl)acetic acid. Methyl 2-((6*S*,*Z*)-4-(4-chlorophenyl)-2,3,9-trimethyl-6*H*-

thieno[3,2-*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepin-6-yl)acetate (see e.g., WO

2006 129623)(100.95 mg, 0.243 mmol) was suspended in 1 mL methanol to which was added

35 a freshly prepared solution of lithium hydroxide monohydrate (0.973 mL, 0.5 M, 0.487 mmol)

and shaken at ambient temperature for 3 hours. The methanol was evaporated and the pH adjusted with aqueous hydrochloric acid (1 M, 0.5 mL, 0.5 mmol) and extracted four times with ethyl acetate. The combined ethyl acetate layers were dried over magnesium sulfate and evaporated to afford 2-((6S,Z)-4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetic acid (85.3 mg, 87.0%); ESI-MS m/z = 401.1 [(M+H)⁺] which was used directly in the next reaction.

N-(2-(2-(2-aminoethoxy)ethoxy)ethyl)-2-((6S,Z)-4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamide bis(2,2,2-trifluoroacetate).

2-((6S,Z)-4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetic acid (85.3 mg, 0.213 mmol) was combined with 2,2'-(ethane-1,2-diylbis(oxy))diethanamine (Sigma-Aldrich, 0.315 mg, 2.13 mmol) were combined in 5 mL anhydrous dimethylformamide. (1H-benzo[d][1,2,3]triazol-1-yloxy)tripyrrolidin-1-ylphosphonium hexafluorophosphate(V) (PyBOB, CSBio, Menlo Park CA; 332 mg, 0.638 mmol) was added and the reaction shaken at ambient temperature for 16 hours. The reaction was diluted to 6 mL with dimethylsulfoxide:water (9:1, v:v) and purified in two injections with time collection Waters Deltapak C18 200 x 25 mm column eluted with a gradient of 0.1% trifluoroacetic acid (v/v) in water and acetonitrile. The fractions containing the two purified products were lyophilized to afford N-(2-(2-(2-aminoethoxy)ethoxy)ethyl)-2-((6S,Z)-4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamide bis(2,2,2-trifluoroacetate) (134.4 mg, 82.3%); ESI-MS m/z = 531.1 [(M+H)⁺], 529.1 [(M-H)⁻] and (S,Z)-N,N'-(2,2'-(ethane-1,2-diylbis(oxy))bis(ethane-2,1-diyl))bis(2-((6S,Z)-4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamide) bis(2,2,2-trifluoroacetate) (3.0 mg, 1.5%); ESI-MS m/z = 913.2 [(M+H)⁺]; 911.0 [(M-H)⁻].

N-(2-(2-(2-amido-(Alexa647)-ethoxy)ethoxy)ethyl)-2-((6S,Z)-4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamide(2,2,2-trifluoroacetate). N-(2-(2-(2-aminoethoxy)ethoxy)ethyl)-2-((6S,Z)-4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamide bis(2,2,2-trifluoroacetate) (5.4 mg, 0.0071 mmol) was combined with Alexa Fluor® 647 carboxylic Acid, succinimidyl ester (Life Technologies, Grand Island, NY; 3 mg, 0.0024 mmol) were combined in 1 mL anhydrous dimethylsulfoxide containing diisopropylethylamine (1% v/v) and shaken at ambient temperature for 16 hours. The reaction was diluted to 3 mL with

dimethylsulfoxide:water (9:1, v:v) and purified in one injection with time collection Waters Deltapak CI8 200 x 25 mm column eluted with a gradient of 0.1% trifluoroacetic acid (v/v) in water and acetonitrile. The fractions containing the purified product were lyophilized to afford N-(2-(2-(2-amido-(Alexa647)-ethoxy)ethoxy)ethyl)-2-((6S,Z)-4-(4-chlorophenyl)-
5 2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamide(2,2,2-trifluoroacetate) (1.8 mg); MALDI-MS $m/z = 1371.1, 1373.1 [(M+H)^+]$ as a dark blue powder.

Assay

Compound dilution series were prepared in DMSO via a 3-fold serial dilution from
10 2.5 mM to 42 nM. Compounds were then diluted 6:100 in assay buffer (20 mM Sodium Phosphate, pH 6.0, 50 mM NaCl, 1 mM EDTA, 0.01% Triton X-100, 1 mM DTT) to yield 3X working solutions. Six microliters (μL) of the working solution was then transferred to white, low-volume assay plates (Costar #3673). A 1.5X assay mixture containing His-tagged bromodomain, Europium-conjugated anti-His antibody (Invitrogen PV5596) and the Alexa-
15 647-conjugated probe molecule was also prepared. Twelve μL of this solution were added to the assay plate to reach a final volume of 18 μL . The final concentration of IX assay buffer contains 2% DMSO, 50 μM - 0.85 nM compound, 8 nM bromodomain, 1 nM antibody and 100 or 30 nM probe (for BDI or BDII, respectively). After a one-hour incubation at room temperature, TR-FRET ratios were determined using an Envision multilabel plate reader (Ex
20 340, Em 495/520).

TR-FRET data were normalized to the means of 24 no-compound controls ("high") and 8 controls containing 1 μM un-labeled probe ("low"). Percent inhibition was plotted as a function of compound concentration and the data were fit with the 4 parameter logistic
25 equation to obtain $\text{IC}_{50\text{s}}$. Inhibition constants (K_j) were calculated from the $\text{IC}_{50\text{s}}$, probe K_d and probe concentration. Typical Z' values were between 0.65 and 0.75. The minimum significant ratio was determined to evaluate assay reproducibility (Eastwood et al., (2006) J Biomol Screen, 11: 253-261). The MSR was determined to be 2.03 for BDI and 1.93 for BDII, and a moving MSR (last six run MSR overtime) for both BDI and BDII was typically <
30 3. The K_j values are reported in Table 1.

MX-1 cell line proliferation assay

The impact of compounds of the Examples on cancer cell proliferation was determined using the breast cancer cell line MX-1 (ATCC) in a 3-day proliferation assay. MX-1 cells were maintained in RPMI supplemented with 10% FBS at 37 C° and an atmosphere of 5% CO₂. For compound testing, MX-1 cells were plated in 96-well black bottom plates at a density of 5000 cells/well in 5 90 µl of culture media and incubated at 37° overnight to allow cell adhesion and spreading. Compound dilution series were prepared in DMSO via a 3-fold serial dilution from 3 mM to 0.1 µM. The DMSO dilution series were then diluted 1:100 in phosphate buffered saline, and 10 µL of the resulted solution were added to the appropriate wells of the MX-1 cell plate. The final 10 compound concentrations in the wells were 3, 1, 0.3, 0.1, 0.03, 0.01, 0.003, 0.001, 0.0003 and 0.0001 µM. After the addition of compounds, the cells were incubated for 72 more hours and the amounts of viable cells were determined using the Cell Titer Glo assay kit (Promega) according to manufacturer suggested protocol.

Luminescence readings from the Cell Titer Glo assay were normalized to the DMSO treated 15 cells and analyzed using the GraphPad Prism software with sigmoidal curve fitting to obtain EC₅₀s. The minimum significant ratio (MSR) was determined to evaluate assay reproducibility (Eastwood et al., (2006) J Biomol Screen, 11: 253-261). The overall MSR was determined to be 2.1 and a moving MSR (last six run MSR overtime) has been <2.

Proliferation panel assay.

20 The compounds of Examples 4 and 78 were tested for their impact on proliferation of a panel of cancer cell lines types (with specific cell line tested) as set out in (Table 2). Cells were plated in 96-well plates at 1500 cells/well in the appropriate culture media. Series dilution of compounds were prepared and added to the wells as in the MX-1 proliferation assay. After the addition of compounds, cells were incubated for another 5 days and the amounts of viable cells were 25 determined using the Cell Titer Glo assay kit (Promega) according to manufacturer suggested protocol. Cell proliferation data were analyzed as described above in the MX-1 proliferation assay to obtain the EC₅₀ for the compounds of Examples 4 and 78 and reported in Table 2.

Table 1

Compound of Example #	TR-FRET Binding Ki: BRD4 (BDI_K57-E168) (μM)	TR-FRET Binding Ki: BRD4 (BDII_E352-M457) (μM)	Cellular proliferation: EC ₅₀ (μM)
1	0.136	0.041	0.97
2	0.529	0.178	0.86
3	0.0646	0.0736	0.185
4	0.00135	0.00195	0.0164
5	0.015	0.00639	0.031
6	0.00532	0.00581	0.046
7	0.119	0.0773	>3.0
8	0.00257	0.00394	0.0244
9	0.018	0.0101	0.113
10	0.0154	0.00858	>3.0
11	0.00184	0.00241	0.0342
12	1.84	4.33	>3.0
13	0.00369	0.0034	0.128
14	0.00551	0.0123	0.17
15	0.00421	0.00745	0.14
16	0.00431	0.00525	0.0946
17	0.0171	0.0322	0.283
18	0.0102	0.0103	0.209
19	0.0074	0.00417	0.123
20	0.0109	0.00068	0.19
21	0.000385	0.000249	0.0139
22	0.00224	0.0010	0.0652
23	0.00115	0.00075	0.0459
24	0.00253	0.00205	0.0126
25	0.00299	0.00359	0.0562
26	0.00205	0.00325	0.0171
27	0.00239	0.00173	0.0317
28	0.00169	0.00197	0.0239
29	0.00114	0.00666	0.0718
30	0.0177	0.0104	0.562
31	0.0018	0.0134	0.0398
32	0.016	0.00754	0.0833
33	0.00261	0.00482	0.0417
34	0.00348	0.00213	0.0268
35	0.661	1.14	N/A
36	0.00284	0.00143	0.0174
37	0.0113	0.0108	0.0593
38	0.148	0.257	N/A
39	0.112	0.124	N/A
40	0.0145	0.0439	0.167
41	0.00279	0.000506	0.0298
42	0.0546	0.0934	>3.0
43	0.00173	0.00123	0.0169

Compound of Example #	TR-FRET Binding Ki: BRD4 (BDI_K57-E168) (μM)	TR-FRET Binding Ki: BRD4 (BDII_E352-M457) (μM)	Cellular proliferation: EC ₅₀ (μM)
44	0.286	0.236	0.828
45	0.0128	0.019	0.233
46	0.0516	0.0169	0.588
47	0.235	0.205	1.11
48	0.00229	0.00332	0.0235
49	0.00169	0.00147	0.0196
50	0.0215	0.00808	0.206
51	0.00965	0.0161	0.101
52	0.0241	0.026	0.309
53	0.0622	0.00538	0.0765
54	0.0951	0.0375	0.266
55	0.0555	0.0336	0.20
56	0.0122	0.00239	0.251
57	0.000884	0.00196	0.0138
58	0.00213	0.00806	0.0451
59	0.000835	0.00163	0.0187
60	0.000747	0.00655	0.0142
61	13.0	22.2	N/A
62	0.00244	0.0021	0.0101
63	0.018	0.0427	0.105
64	0.0423	0.081	0.773
65	0.0115	0.00673	0.0255
66	0.000739	0.00339	0.0332
67	0.0561	0.211	0.341
68	1.65	5.74	5.85
69	0.039	0.0276	0.14
70	0.0118	0.105	>3.0
71	0.00081	0.0027	0.0175
72	0.00151	0.00258	0.0457
73	0.000981	0.00113	0.0207
74	0.0961	0.101	0.275
75	0.137	0.0594	0.478
76	0.0658	0.0297	0.29
77	0.0124	0.0157	>3.0
78	0.00253	0.00181	0.40
79	0.00623	0.00184	0.887
80	0.0091	0.00614	0.062
81	0.00945	0.000986	0.103
82	0.519	0.183	0.767
83	0.0209	0.0422	0.424
84	0.000645	0.00167	0.231
85	0.00165	0.00644	0.052
86	0.00237	0.00433	0.182
87	0.00666	0.00563	0.0534

Compound of Example #	TR-FRET Binding Ki: BRD4 (BDI_K57-E168) (μM)	TR-FRET Binding Ki: BRD4 (BDII_E352-M457) (μM)	Cellular proliferation: EC_{50} (μM)
88	0.236	0.635	>3.0
89	0.00205	0.00161	0.0252

Table 2

		Compound of Example 4	Compound of Example 78
Cell line Type	Cell Line	Cellular Proliferation EC_{50} (μM)	Cellular Proliferation EC_{50} (μM)
AML	SKM1	0.005	0.058
AML	Raji	0.006	0.084
Bladder	EJ-1	0.202	2.090
Breast	MDAMB231	0.22	1.22
Breast	MDAMB453	0.02	0.24
Colon	GEO	0.08	1.29
Colon	DLD-1	0.20	4.97
Glioblastoma	D54MG	0.038	2.299
Head & Neck	FaDu	0.02	0.39
Hepatocellular	HepG2	0.074565	0.8851
Melanoma	A-375	0.020	3.606
Multiple Myeloma	OPM2	0.001	0.039
Multiple Myeloma	RPMI-8226	0.011	1.402
Multiple Myeloma	NCI-H929	0.003	0.154
NHL	Ramos	0.02	0.32
NHL	Ly18	0.02	0.42
NSCLC	H1299	0.06	2.57
NSCLC	H1975	0.02	1.37
NSCLC	H460	3.77	>10
Pancreas	HPAC	0.05	1.19
Pancreas	BxPC3FP5	0.01	0.74
Prostate	PC3M	0.07	8.11
RCC	786-0	0.011	0.884
Sarcoma	SK-LMS-1	0.025	0.934

Human, rat, and mouse microsome stability assay

5 Microsome stability assays were carried out on compounds of the Examples listed in Table 3 ("test compounds"). Human, rat and mouse liver microsomal incubations were carried out at 37 °C with a final incubation volume of 135 μl . Human liver microsomes

(mixed gender, Catalog No. H2610) were obtained from XenoTech. Rat liver microsomes (male Sprague-Dawley, Catalog No. 42501) were obtained from BD Gentest. Mouse liver microsomes (male CD1, Catalog No. 452701) were obtained from BD Gentest. Incubations were conducted using a test compound (initially dissolved in DMSO at 5 μ M concentration) concentration of 0.5 μ M and 0.25 mg/mL microsomal protein in 50 mM phosphate buffer at pH 7.4. Time zero samples were prepared by transferring 13.5 μ L of compound-microsomal mix to the quench plates containing 45 μ L of quench solution made of 10 nM Buspirone (Sigma) as internal standard in 1:1 methanol.-acetonitrile. An aliquot of 1.5 μ L β -Nicotinamide adenine dinucleotide phosphate reduced tetrasodium salt (NADPH) was also added to the time 0 plates. The reaction was then initiated by the addition of 13.5 μ L NADPH to the compound-microsomal mix. At each of the remaining time points (5, 10, 15, 20 and 30 min) 15 μ L of incubation mixture was added to 45 μ L of quench solution. Samples from six compounds centrifuged for 30 min at 3800 rpm. An aliquot of 60 μ L of supernatant was transferred to 384-well plate, and a 5 μ L aliquot was injected and analyzed by LC-MS/MS (Applied Biosystems API 5500 QTrap). The intrinsic clearance of a compound was calculated by converting the peak area ratios (analyte peak area/IS peak area) to % parent remaining using the area ratio at time 0 as 100%. The slope (k) was determined from the plot of the % parent remaining versus incubation time, from which the half life ($t_{1/2}$; min), intrinsic clearance (CL_{int} ; μ L/ η η / η η protein for liver microsomes and μ Lv η η / η η cells for hepatocytes) and scaled intrinsic clearance (scaled CL_{int} ; L/h/kg) were then derived. The $t_{1/2}$ values are reported in Table 3. The term "N/A" means not determined.

Table 3

Compound of Example #	$t_{1/2}$ (human liver microsomes, min.)	$t_{1/2}$ (rat liver microsomes, min.)	$t_{1/2}$ (mouse liver microsomes, min.)
1	8.76	0.567	0.539
4	59.4	3.97	63.7
5	99.7	5.74	24.4
6	30.1	7.06	3.39
7	12.1	2.15	3.64
8	18.8	0.762	9.0
9	N/A	0.505	1.3
10	77.5	>120	>120
11	48.1	18.5	27.2
12	51.1	10.3	33.2
13	65.6	1.75	21.5
14	36.9	6.01	8.43
15	10.3	3.71	6.6

Compound of Example #	t _{1/2} (human liver microsomes, min.)	t _{1/2} (rat liver microsomes, min.)	t _{1/2} (mouse liver microsomes, min.)
16	>120	3.66	22.1
17	30.5	17.8	16.2
18	31.2	10.7	15.3
19	92.4	12.7	33.1
20	18.4	1.25	6.68
21	>120	2.69	21.8
22	31.7	2.9	10.7
23	64.4	10.5	>120
24	29.1	4.78	55.2
27	32.0	>120	58.8
28	21.3	9.33	N/A
29	>120	25.9	>120
31	55.6	>120	19.2
32	23.7	82.1	31.8
33	>120	>120	45.9
34	36.6	41.9	34.5
35	37.2	>120	42.3
36	>120	>120	31.6
37	88.9	53.8	2.91
38	16.8	25.1	N/A
39	9.65	8.09	N/A
40	13.1	0.753	5.8
41	13.6	1.02	10.4
42	>120	>120	>120
43	34.9	2.02	5.39
44	33.7	5.73	26.8
45	N/A	1.73	2.79
46	10.1	3.73	12.9
47	8.21	3.48	5.05
48	37.3	31.6	34.9
49	70.6	50.9	45.7
50	35.2	87.6	45.9
51	5.98	62.5	>120
54	3.21	30.4	2.4
55	24.7	9.37	13.3
56	38.9	30.3	35.6
57	12.8	5.71	5.44
58	>120	1.23	3.77
59	>120	39.6	23.4
60	68.4	64.1	34.1
61	>120	>120	>120
62	63.8	44.7	24.9
63	38.7	13.0	17.8
64	N/A	3.17	4.13
65	87.9	>120	11.0

Compound of Example #	t _{1/2} (human liver microsomes, min.)	t _{1/2} (rat liver microsomes, min.)	t _{j/2} (mouse liver microsomes, min.)
66	>120	>120	N/A
67	6.24	4.89	6.08
69	5.58	1.97	2.99
70	41.2	9.43	68.0
71	1.85	0.561	6.0
72	33.5	0.587	69.8
73	36.3	1.96	31.2
74	16.9	2.71	4.89
75	8.95	2.86	3.6
80	61.8	2.0	31.4
82	19.3	1.79	1.73
83	N/A	2.84	42.7
85	43.0	5.61	34.2
86	>120	>120	42.6
87	>120	23.0	N/A
88	23.0	11.5	N/A

LPS (Iipopolysaccharide) induced IL-6 production mouse assay

Compounds of the Examples listed in Table 4 were assayed for their ability to inhibit LPS (Iipopolysaccharide) induced IL-6 production in mice. Severe combined

5 immunodeficient female mice (8 per group) received an intraperitoneal challenge of Iipopolysaccharide (2.5 mg/kg, L2630 E.coii 01 11:B4) one hour after oral administration of compounds. Mice were euthanized 2 hours after Iipopolysaccharide injection, blood was removed by cardiac puncture, and then the serum harvested from the blood samples was frozen at -80 °C. On the day of the assay the serum samples were brought to room

10 temperature and then diluted 1:20 in phosphate-buffered saline containing 2 % bovine serum albumin. Interleukin-6 measurements were performed using a cytokine assay from Meso Scale Discovery (Gaithersburg, Maryland) for mouse serum analysis according to the manufacturer's protocol and read on a SECTOR Imager 6000 (Meso Scale Discovery, Gaithersburg, Maryland) instrument. Statistical analysis was performed using Prism software

15 (version 5.0) incorporating Dunnett's one way ANOVA. The IL-6 mean and standard deviation of the group of vehicle treated animals were compared with the IL-6 mean and standard deviation of the group treated with drug. A p value < 0.05 means that there is less than a 5% probability that the mean values in the two groups are equal. The % inhibition values in Table 4 all exhibited a p value less than 0.05.

Table 4

Inhibition of LPS induced IL-6 production

Example #	% inhibition
4	67 % at 3 mg/kg
5	74 % at 50 mg/kg
24	58 % at 3 mg/kg
26	60 % at 3 mg/kg
27	89 % at 3 mg/kg
28	52 % at 3 mg/kg
32	69 % at 3 mg/kg
34	78 % at 3 mg/kg
36	78 % at 3 mg/kg
48	62 % at 3 mg/kg
56	28 % at 3 mg/kg
59	54 % at 3 mg/kg
80	69 % at 30 mg/kg
84	69 % at 3 mg/kg
85	80 % at 3 mg/kg
86	53 % at 3 mg/kg
87	57 % at 3 mg/kg

Xenograft tumor growth inhibition assay

- 5 The effect of the compound of Example 36 to inhibit the growth of OPM-2 and MX-1 xenograft tumors implanted in SCID female mice (Charles Rivers Labs) was evaluated. Briefly, 5 x10⁶ human cancer cells (OPM-2) or 1:10 tumor brie (MX-1) (in S-MEM (MEM, Suspension, no Calcium, no Glutamine))(Life Technologies Corporation) was inoculated subcutaneously into the right hind flank of female SCID mice on study day 0. Administration of compound (in (2% EtOH, 5% Tween-80, 20% PEG-400, 73% HPMC))(PO, QDx14) was initiated at the time of size match on day 17 (OPM-2) or day 12 (MX-1). The tumors were measured by a pair of calipers twice a week starting at the time of size match and tumor volumes were calculated according to the formula $V = L \times W^2 / 2$ (V: volume, mm³; L: length, mm. W: width, mm). Tumor volume was measured for the duration of the experiment until the mean tumor volume in each group reached an endpoint of >1000 mm³ for OPM-2 or until day 27 post inoculation for MX-1. Results are shown in Tables 5 and 6.

Table 5. OPM-2 human multiple myeloma cancer xenograft model.

Group	Treatment	Dose route, regimen	% TGI ^a	% TGD ^b
1	Vehicle	0 mg/kg/day IP, QDx14	---	---
2	Compound of Example 36	3 mg/kg/day PO, QDx14	90***	78***

a. Tumor growth inhibition, $\%TGI = 100 - \text{mean tumor volume of treatment group} / \text{mean tumor volume of control group} \times 100$. The p values (as indicated by asterisks) are derived from Student's T test comparison of treatment group vs. control group. Based on day 31. *p<0.05, ** p<0.01, *** p<0.001.

- 5 b. Tumor growth delay, $\%TGD = (T - C) / C \times 100$, where T = median time to endpoint of treatment group and C = median time to endpoint of control group. The p values (as indicated by asterisks) derived from Kaplan Meier log-rank comparison of treatment group vs. treatment control group. Based on an endpoint of 1000 mm³. *p<0.05, ** p<0.01, *** p<0.001 .

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Table 6. Efficacy of BET inhibitor in the MX-1 human breast cancer xenograft model.

Group	Treatment	Dose route, regimen	%TGI ^a
1	Vehicle	0 mg/kg/day PO, QDx14	---
2	Compound of Example 36	0.3 mg/kg/day PO, QDx14	43**
3	Compound of Example 36	1 mg/kg/day PO, QDx14	60***
4	Compound of Example 36	3 mg/kg/day PO, QDx14	76***

a. Tumor growth inhibition, $\%TGI = 100 - \text{mean tumor volume of treatment group} / \text{tumor volume of control group} \times 100$. p values (as indicated by asterisks) are derived from Student's T test comparison of treatment group vs. control group. Based on day 27.

- 15 *p<0.05, ** p<0.01, *** p<0.001.

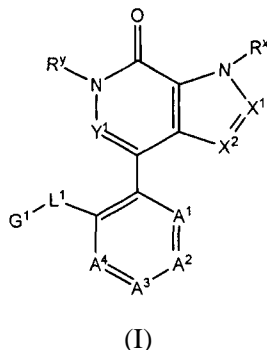
It is understood that the foregoing detailed description and accompanying examples are merely illustrative and are not to be taken as limitations upon the scope of the invention, which is defined solely by the appended claims and their equivalents. Various changes and modifications to the disclosed embodiments will be apparent to those skilled in the art. Such changes and modifications, including without limitation those relating to the chemical structures, substituents, derivatives, intermediates, syntheses, formulations and/or methods of use of the invention, may be made without departing from the spirit and scope thereof. All publications, patents, and patent applications cited herein are hereby incorporated by reference in their entirety for all purposes.

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CLAIMS:

1. A compound of formula (I) or a pharmaceutically acceptable salt thereof



wherein

R^x is hydrogen or C_1 - C_3 alkyl;

R^y is C_1 - C_3 alkyl, $-(C_2-C_3 \text{ alkylene})-OH$, or C_1 - C_3 haloalkyl;

X^1 is N or CR^{x1} wherein

R^{x1} is hydrogen, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, $-C(O)OR^{ax1}$, $-C(O)NR^{bx1}R^{cx1}$, $-C(O)R^{dx1}$, $S(O)_2R^{dx1}$, $-S(O)_2NR^{bx1}R^{cx1}$, G^{x1} , C - C_6 haloalkyl, or d - C_6 alkyl; wherein the C - C_6 alkyl is optionally substituted with one substituent selected from the group consisting of OR^{ax1} , SR^{ax1} , $S(O)R^{dx1}$, $S(O)_2R^{dx1}$, $NR^{bx1}R^{cx1}$, $-C^*R^{ax1}$, $-C(O)OR^{ax1}$, $-C(O)NR^{bx1}R^{cx1}$, $-S(O)_2NR^{bx1}R^{cx1}$, and G^{x1} ;

R^{ax1} , R^{bx1} , and R^{cx1} , at each occurrence, are each independently hydrogen, C_1 - C_6 alkyl, C - C_6 haloalkyl, G^a , or $-(C_1-C_6 \text{ alkylene})-G^a$;

R^{dx1} , at each occurrence, are each independently C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, G^a , or $-(C_1-C_6 \text{ alkylene})-G^a$;

X^2 is N or CR^{x2} ; wherein

R^{x2} is hydrogen, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, $-C(O)OR^{ax2}$, $-C(O)NR^{bx2}R^{cx2}$, $-C(O)R^{dx2}$, $S(O)_2R^{dx2}$, $-S(O)_2NR^{bx2}R^{cx2}$, G^{x2} , C - C_6 haloalkyl, or C_1 - C_6 alkyl; wherein the C - C_6 alkyl is optionally substituted with one substituent selected from the group consisting of OR^{ax2} , SR^{ax2} , $S(O)R^{dx2}$, $S(O)_2R^{dx2}$,

$\text{NR}^{\text{bx}2}\text{R}^{\text{cx}2}$, $-\text{C}(0)\text{R}^{\text{ax}2}$, $-\text{C}(0)\text{OR}^{\text{ax}2}$, $-\text{C}(0)\text{NR}^{\text{bx}2}\text{R}^{\text{cx}2}$, $-\text{S}(0)_2\text{NR}^{\text{bx}2}\text{R}^{\text{cx}2}$,
and $\text{G}^{\text{x}2}$;

$\text{R}^{\text{ax}2}$, $\text{R}^{\text{bx}2}$, and $\text{R}^{\text{cx}2}$, at each occurrence, are each independently hydrogen, C_1 - C_6 alkyl, Ci-C_6 haloalkyl, G^{b} , or $-(\text{C}_1\text{-C}_6 \text{ alkylenyl})\text{-G}^{\text{b}}$;

$\text{R}^{\text{dx}2}$, at each occurrence, is independently Ci-C_6 alkyl, Ci-C_6 haloalkyl, G^{b} ,
or $-(\text{Ci-Ce alkylenyl})\text{-G}^{\text{b}}$;

Y^1 is N or CR^{u} ; wherein R^{u} is hydrogen, $\text{C}_1\text{-C}_6$ alkyl, halogen, or $\text{C}_1\text{-C}_6$ haloalkyl;

A^1 is N or CR^1 , A^2 is N or CR^2 , A^3 is N or CR^3 ; and A^4 is N or CR^4 ; with the proviso
that zero, one, two, or three of A^1 , A^2 , A^3 , and A^4 are N ;

R^1 , R^3 , and R^4 are each independently hydrogen, $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_2\text{-C}_6$ alkenyl, $\text{C}_2\text{-C}_6$
alkynyl, halogen, $\text{C}_1\text{-C}_6$ haloalkyl, CN , or N_0 ;

R^2 is hydrogen, Ci-C_6 alkyl, $\text{C}_2\text{-C}_6$ alkenyl, $\text{C}_2\text{-C}_6$ alkynyl, halogen, Ci-C_6
haloalkyl, $-\text{CN}$, N_0 ;

$\text{G}^{2\text{a}}$, $-\text{OR}^{2\text{a}}$, $-\text{OC}(0)\text{R}^{2\text{d}}$, $-\text{OC}(0)\text{NR}^{2\text{b}}\text{R}^{2\text{c}}$, $-\text{SR}^{2\text{a}}$, $-\text{S}(0)_2\text{R}^{2\text{d}}$, $-\text{S}(0)_2\text{NR}^{2\text{b}}\text{R}^{2\text{c}}$, $-\text{C}(0)\text{R}^{2\text{d}}$, $-\text{C}(0)\text{OR}^{2\text{a}}$, $-\text{C}(0)\text{NR}^{2\text{b}}\text{R}^{2\text{c}}$, $-\text{NR}^{2\text{b}}\text{R}^{2\text{c}}$, $-\text{N}(\text{R}^{2\text{e}})\text{C}(0)\text{R}^{2\text{d}}$, $-\text{N}(\text{R}^{2\text{e}})\text{S}(0)_2\text{R}^{2\text{d}}$, $-\text{N}(\text{R}^{2\text{e}})\text{C}(0)\text{O}(\text{R}^{2\text{d}})$, $-\text{N}(\text{R}^{2\text{e}})\text{C}(0)\text{NR}^{2\text{b}}\text{R}^{2\text{c}}$, $-\text{N}(\text{R}^{2\text{e}})\text{S}(0)_2\text{NR}^{2\text{b}}\text{R}^{2\text{c}}$, $-(\text{C}_1\text{-C}_6 \text{ alkylenyl})\text{-G}^{2\text{a}}$, $-(\text{C}_1\text{-C}_6 \text{ alkylenyl})\text{-OR}^{2\text{a}}$, $-(\text{C}_1\text{-C}_6 \text{ alkylenyl})\text{-OC}(0)\text{R}^{2\text{d}}$, $-(\text{C}_1\text{-C}_6 \text{ alkylenyl})\text{-OC}(0)\text{NR}^{2\text{b}}\text{R}^{2\text{c}}$, $-(\text{C}_1\text{-C}_6 \text{ alkylenyl})\text{-S}(0)_2\text{R}^{2\text{d}}$, $-(\text{C}_1\text{-C}_6 \text{ alkylenyl})\text{-S}(0)_2\text{NR}^{2\text{b}}\text{R}^{2\text{c}}$, $-(\text{C}_1\text{-C}_6 \text{ alkylenyl})\text{-C}(0)\text{R}^{2\text{d}}$, $-(\text{C}_1\text{-C}_6 \text{ alkylenyl})\text{-C}(0)\text{OR}^{2\text{a}}$, $-(\text{C}_1\text{-C}_6 \text{ alkylenyl})\text{-C}(0)\text{NR}^{2\text{b}}\text{R}^{2\text{c}}$, $-(\text{C}_1\text{-C}_6 \text{ alkylenyl})\text{-NR}^{2\text{b}}\text{R}^{2\text{c}}$, $-(\text{C}_1\text{-C}_6 \text{ alkylenyl})\text{-N}(\text{R}^{2\text{e}})\text{C}(0)\text{R}^{2\text{d}}$, $-(\text{C}_1\text{-C}_6 \text{ alkylenyl})\text{-N}(\text{R}^{2\text{e}})\text{S}(0)_2\text{R}^{2\text{d}}$, $-(\text{Ci-C}_6 \text{ alkylenyl})\text{-N}(\text{R}^{2\text{e}})\text{C}(0)\text{O}(\text{R}^{2\text{a}})$, $-(\text{C}_1\text{-C}_6 \text{ alkylenyl})\text{-N}(\text{R}^{2\text{e}})\text{C}(0)\text{NR}^{2\text{b}}\text{R}^{2\text{c}}$, $-(\text{C}_1\text{-C}_6 \text{ alkylenyl})\text{-N}(\text{R}^{2\text{e}})\text{S}(0)_2\text{NR}^{2\text{b}}\text{R}^{2\text{c}}$, and $-(\text{Ci-C}_6 \text{ alkylenyl})\text{-CN}$;

$\text{R}^{2\text{a}}$, $\text{R}^{2\text{b}}$, $\text{R}^{2\text{c}}$, and $\text{R}^{2\text{e}}$, at each occurrence, are each independently hydrogen, $\text{C}_2\text{-C}_6$
alkenyl, $\text{C}_2\text{-C}_6$ alkynyl, Ci-C_6 haloalkyl, $\text{G}^{2\text{b}}$, or $\text{C}_1\text{-C}_6$ alkyl wherein the Ci-C_6
alkyl is optionally substituted with one substituent selected from the group
consisting of $-\text{OR}^{2\text{a}}$,

$\text{NR}^{\text{z}1}\text{R}^{\text{z}2}$, $-\text{C}(0)\text{OR}^{\text{z}1}$, $-\text{C}(0)\text{NR}^{\text{z}1}\text{R}^{\text{z}2}$, $-\text{S}(0)_2\text{R}^{\text{z}1}$, $-\text{S}(0)_2\text{NR}^{\text{z}1}\text{R}^{\text{z}2}$, and $\text{G}^{2\text{b}}$;

$\text{R}^{2\text{d}}$, at each occurrence, is independently $\text{C}_2\text{-C}_6$ alkenyl, $\text{C}_2\text{-C}_6$ alkynyl, $\text{C}_1\text{-C}_6$
haloalkyl, $\text{G}^{2\text{b}}$, or $\text{C}_1\text{-C}_6$ alkyl wherein the Ci-C_6 alkyl is optionally substituted
with one substituent selected from the group consisting of $-\text{OR}^{2\text{a}}$,

$\text{NR}^{\text{z}1}\text{R}^{\text{z}2}$, $-\text{C}(0)\text{OR}^{\text{z}1}$, $-\text{C}(0)\text{NR}^{\text{z}1}\text{R}^{\text{z}2}$, $-\text{S}(0)_2\text{R}^{\text{z}1}$, $-\text{S}(0)_2\text{NR}^{\text{z}1}\text{R}^{\text{z}2}$, and $\text{G}^{2\text{b}}$;

R^{z1} and R^{z2} , at each occurrence, are each independently hydrogen, Ci-C₆ alkyl, or C₁-C₆ haloalkyl;

G^{x1} , G^{x2} , G^a , G^b , G^{2a} , and G^{2b} , at each occurrence, are each independently aryl, heteroaryl, heterocycle, cycloalkyl, or cycloalkenyl, and each of which is independently unsubstituted or substituted with 1, 2, 3, 4, or 5 of R^v ;

L^1 is absent, CH₂, C(O), (CH₂)_mO, (CH₂)_mS(O)_n wherein n is 0, 1, or 2; or (CH₂)_mN(R^z) wherein R^z is hydrogen, C,-C₃ alkyl, C,-C₃ haloalkyl, (C₂-C₃ alkylenyl)-OH, or unsubstituted cyclopropyl;

m is 0 or 1;

G^1 is G^a or -(Ci-C₆ alkylenyl)- G^{1a} ; wherein each G^{1a} is independently aryl, heteroaryl, heterocycle, cycloalkyl, or cycloalkenyl, and each G^{1a} is independently unsubstituted or substituted with 1, 2, 3, 4, or 5 of R^w ;

R^v and R^w , at each occurrence, are each independently Ci-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, halogen, Ci-C₆ haloalkyl, -CN, oxo, -OR^h, -OC(O)[^], -OC(O)NR^jR^k, -SR^h, -S(O)₂R^h, -S(O)₂NR^jR^k, -C(O)R^h, -C(O)OR^h, -C(O)NR^jR^k, -NR^jR^k, -N(R^h)C(O)Rⁱ, -N(R^h)S(O)₂Rⁱ, -N(R^h)C(O)O(Rⁱ), -N(R^h)C(O)NR^jR^k, -(C,-C₆ alkylenyl)-OR^h, -(C,-C₆ alkylenyl)-OC(O)Rⁱ, -(Ci-C₆ alkylenyl)-OC(O)NR^jR^k, -(Ci-C₆ alkylenyl)-S(O)₂R^h, -(C,-C₆ alkylenyl)-S(O)₂NR^jR^k, -(C,-C₆ alkylenyl)-C(O)R^h, -(C,-C₆ alkylenyl)-C(O)OR^h, -(C,-C₆ alkylenyl)-C(O)NR^jR^k, -(C₁-C₆ alkylenyl)-NR^jR^k, -(Ci-C₆ alkylenyl)-N(R^h)C(O)Rⁱ, -(C,-C₆ alkylenyl)-N(R^h)S(O)₂Rⁱ, -(C,-C₆ alkylenyl)-N(R^h)C(O)O(Rⁱ), -(C,-C₆ alkylenyl)-N(R^h)C(O)NR^jR^k, or-(C,-C₆ alkylenyl)-CN;

R^h , R^j , R^k , at each occurrence, are each independently hydrogen, Ci-C₆ alkyl, or Ci-C₆ haloalkyl; and

R^i , at each occurrence, is independently CpC₆ alkyl or C₁-C₆ haloalkyl.

2. The compound of claim 1 or a pharmaceutically acceptable salt thereof, wherein R^y is C,-C₃ alkyl.
3. The compound of claim 1 or a pharmaceutically acceptable salt thereof, wherein R^y is methyl.

4. The compound of claim 1 or a pharmaceutically acceptable salt thereof, wherein X^1 is CR^{x1} ; and X^2 is CR^{x2} .
5. The compound of claim 1 or a pharmaceutically acceptable salt thereof, wherein Y^1 is N.
6. The compound of claim 1 or a pharmaceutically acceptable salt thereof, wherein Y^1 is CR^U .
7. The compound of claim 6 or a pharmaceutically acceptable salt thereof, wherein R^u is hydrogen or C1-C3 alkyl.
8. The compound of claim 1 or a pharmaceutically acceptable salt thereof, wherein L^1 is CH_2 , $C(O)$, $(CH_2)_mO$, or $(CH_2)_mN(R^z)$.
9. The compound of claim 1 or a pharmaceutically acceptable salt thereof, wherein L^1 is $(CH_2)_mO$ and G^1 is G^{1a} .
10. The compound of claim 1 or a pharmaceutically acceptable salt thereof, wherein A^1 is CR^1 ; A^2 is CR^2 ; A^3 is CR^3 ; and A^4 is CR^4 .
11. The compound of claim 1 or a pharmaceutically acceptable salt thereof, wherein one of A^1 , A^2 , A^3 , and A^4 is N.
12. The compound of claim 1 or a pharmaceutically acceptable salt thereof, wherein R^2 is hydrogen, C, -C₆ alkyl, $N0_2$, G^{2a} , $-S(O)_2R^{2d}$, $-S(O)_2NR^{2b}R^{2c}$, $-C(O)R^{2d}$, $-C(O)OR^{2a}$, $-C(O)NR^{2b}R^{2c}$, $-NR^{2b}R^{2c}$, $-N(R^{2e})C(O)R^{2d}$, $-N(R^{2e})S(O)_2R^{2d}$, $-N(R^{2e})S(O)_2NR^{2b}R^{2c}$, $-(C, -C_6 \text{ alkylenyl})-G^{2a}$, $-(Ci-Ce \text{ alkylenyl})-OR^{2a}$, $-(C, -C_6 \text{ alkylenyl})-S(O)_2R^{2d}$, $-(C, -C_6 \text{ alkylenyl})-S(O)_2NR^{2b}R^{2c}$, $-(d-C_6 \text{ alkylenyl})-C(O)R^{2d}$, $-(d-C_6 \text{ alkylenyl})-C(O)OR^{2a}$, $-(Ci-C_6$

alkylenyl)-C(0)NR^{2b}R^{2c}, -(C,-C₆ alkylenyl)-NR^{2b}R^{2c}, -(C,-C₆ alkylenyl)-N(R^{2e})C(0)R^{2d}, -(C₁-C₆ alkylenyl)-N(R^{2e})S(0)₂R^{2d}, or -(C,-C₆ alkylenyl)-N(R^{2e})S(0)₂NR^{2b}R^{2c}.

13. The compound of claim 1 or a pharmaceutically acceptable salt thereof, wherein R² is -S(0)₂R^{2d}, -S(0)₂NR^{2b}R^{2c}, -C(0)R^{2d}, -C(0)NR^{2b}R^{2c}, -N(R^{2e})C(0)R^{2d}, -N(R^{2e})S(0)₂R^{2d}, -N(R^{2e})S(0)₂NR^{2b}R^{2c}, -(C,-C₆ alkylenyl)-S(0)₂R^{2d}, -(C₁-C₆ alkylenyl)-S(0)₂NR^{2b}R^{2c}, -(C,-C₆ alkylenyl)-C(0)R^{2d}, -(C₁-C₆ alkylenyl)-C(0)NR^{2b}R^{2c}, -(e,-C₆ alkylenyl)-N(R^{2e})C(0)R^{2d}, -(C,-C₆ alkylenyl)-N(R^{2e})S(0)₂R^{2d}, or -(C,-C₆ alkylenyl)-N(R^{2e})S(0)₂NR^{2b}R^{2c}.
14. The compound of claim 1 or a pharmaceutically acceptable salt thereof, wherein R² is -S(0)₂R^{2d}, -S(0)₂NR^{2b}R^{2c}, -N(R^{2e})S(0)₂R^{2d}, or -N(R^{2e})S(0)₂NR^{2b}R^{2c}.
15. The compound of claim 1 or a pharmaceutically acceptable salt thereof, wherein Y¹ is N;
X¹ is CR^{X1}; and
X² is CR^{X2}.
16. The compound of claim 15 or a pharmaceutically acceptable salt thereof, selected from the group consisting of:
ethyl 4-(5-amino-2-phenoxyphenyl)-6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-d]pyridazine-2-carboxylate;
ethyl 4-[5-(ethylamino)-2-phenoxyphenyl]-6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-d]pyridazine-2-carboxylate;
ethyl 4-{5-[ethyl(methylsulfonyl)amino]-2-phenoxyphenyl}-6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-d]pyridazine-2-carboxylate;
6-methyl-4-{5-[(methylsulfonyl)amino]-2-phenoxyphenyl}-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-d]pyridazine-2-carboxylic acid;
6-methyl-4-{5-[(methylsulfonyl)amino]-2-phenoxyphenyl}-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-d]pyridazine-2-carboxamide;
6-methyl-N-[2-(4-methylpiperazin-1-yl)ethyl]-4-{5-[(methylsulfonyl)amino]-2-phenoxyphenyl}-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-d]pyridazine-2-carboxamide;

N-[3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-d]pyridazin-4-yl)-4-phenoxyphenyl]methanesulfonamide;

N-ethyl-6-methyl-4-{5-[(methylsulfonyl)amino]-2-phenoxyphenyl}-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-d]pyridazine-2-carboxamide;

6-methyl-4-(2-phenoxyphenyl)-1,6-dihydro-7H-pyrrolo[2,3-d]pyridazin-7-one; and

N-ethyl-N,6-dimethyl-4-{5-[(methylsulfonyl)amino]-2-phenoxyphenyl}-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-d]pyridazine-2-carboxamide; or pharmaceutically acceptable salt thereof.

17. The compound of claim 15 or a pharmaceutically acceptable salt thereof, wherein R^y is methyl.
18. The compound of claim 17 or a pharmaceutically acceptable salt thereof, wherein L^1 is CH_2 , $C(O)$, $(CH_2)_mO$, or $(CH_2)_mN(R^z)$.
19. The compound of claim 17, or a pharmaceutically acceptable salt thereof, wherein L^1 is $(CH_2)_mO$.
20. The compound of claim 19 or a pharmaceutically acceptable salt thereof, wherein G^1 is G^{1a} .
21. The compound of claim 20 or a pharmaceutically acceptable salt thereof, wherein G^{1a} is optionally substituted aryl.
22. The compound of claim 20 or a pharmaceutically acceptable salt thereof, wherein G^{1a} is optionally substituted phenyl.
23. The compound of claim 20 or a pharmaceutically acceptable salt thereof, wherein G^{1a} is optionally substituted cycloalkyl.
24. The compound of claim 20 or a pharmaceutically acceptable salt thereof, wherein G^{1a} is optionally substituted monocyclic cycloalkyl.
25. The compound of claim 20 or a pharmaceutically acceptable salt thereof, wherein

G^{1a} is optionally substituted heterocycle.

26. The compound of claim 20 or a pharmaceutically acceptable salt thereof, wherein G^{1a} is optionally substituted monocyclic heterocycle.
27. The compound of claim 1 or a pharmaceutically acceptable salt thereof, wherein Y¹ is CR^u;
X¹ is CR^{x1}; and
X² is CR^{x2}.
28. The compound of claim 27 or a pharmaceutically acceptable salt thereof, selected from the group consisting of
6-methyl-4-(2-phenoxyphenyl)-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one;
6-methyl-4-(5-nitro-2-phenoxyphenyl)-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one;
4-(5-amino-2-phenoxyphenyl)-6-methyl-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one;
N-[3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)-4-phenoxyphenyl]methanesulfonamide;
2,2,2-trifluoro-N-[3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)-4-phenoxyphenyl]ethanesulfonamide;
N-[3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)-4-phenoxyphenyl]acetamide;
N-methyl-N-[3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)-4-phenoxyphenyl]methanesulfonamide;
ethyl 3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)-4-phenoxybenzoate;
3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)-4-phenoxybenzoic acid;
N-[3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)-4-(pyridin-3-yloxy)phenyl]methanesulfonamide;
6-methyl-4-[2-(morpholin-4-ylmethyl)phenyl]-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one;
N-ethyl-3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)-4-phenoxybenzamide;

3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)-4-phenoxy-N-(tetrahydrofuran-2-ylmethyl)benzamide;

N-cyclopentyl-3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)-4-phenoxybenzamide;

N-(2,2-difluoroethyl)-3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)-4-phenoxybenzamide;

3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)-4-phenoxy-N-(1,3-thiazol-2-yl)benzamide;

N-(1,1-dioxidotetrahydrothiophen-3-yl)-3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)-4-phenoxybenzamide;

3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)-4-phenoxybenzamide;

4-[5-(hydroxymethyl)-2-phenoxyphenyl]-6-methyl-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one;

N-[3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)-4-phenoxyphenyl]ethanesulfonamide;

N,N-dimethyl-N'-[3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)-4-phenoxyphenyl]sulfuric diamide;

N-[5-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)-6-phenoxy-pyridin-3-yl]methanesulfonamide;

N-[3-fluoro-5-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)-4-phenoxyphenyl]methanesulfonamide;

N-[4-(2-cyanophenoxy)-3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)phenyl]methanesulfonamide;

N-[4-(4-fluorophenoxy)-3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)phenyl]methanesulfonamide;

N-[4-(2,4-difluorophenoxy)-3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)phenyl]methanesulfonamide;

N-[3-chloro-5-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)-4-phenoxyphenyl]methanesulfonamide;

N-[3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)-4-(tetrahydro-2H-pyran-4-yloxy)phenyl]methanesulfonamide;

6-methyl-4-[2-phenoxy-5-(1H-pyrazol-1-ylmethyl)phenyl]-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one;

N-[3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)-4-(tetrahydrofuran-3-yloxy)phenyl]methanesulfonamide;

N-{3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)-4-[2-(trifluoromethyl)phenoxy]phenyl}methanesulfonamide;

N-[4-(4-cyanophenoxy)-3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)phenyl]methanesulfonamide;

N-[4-(2-chloro-4-fluorophenoxy)-3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)phenyl]methanesulfonamide;

[4-(benzyloxy)-3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)phenyl]acetic acid;

N-[4-(2,4-difluorophenoxy)-3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)phenyl]ethanesulfonamide;

N-[4-(2,4-difluorophenoxy)-3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)phenyl]acetamide;

N-[4-(2,4-difluorophenoxy)-3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)phenyl]-3,3,3-trifluoropropanamide;

N-[4-(2,4-difluorophenoxy)-3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)phenyl]-2,2-dimethylpropanamide;

ethyl 4-(cyclopentylamino)-3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)benzoate;

4-{5-[(1,1-dioxido-1,2-thiazolidin-2-yl)methyl]-2-phenoxyphenyl}-6-methyl-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one;

4-{[3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)-4-phenoxybenzyl]amino}-4-oxobutanoic acid;

4-[2-(2,4-difluorophenoxy)-5-(1,1-dioxido-1,2-thiazolidin-2-yl)phenyl]-6-methyl-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one;

4-[2-(benzyloxy)-5-(2-hydroxyethyl)phenyl]-6-methyl-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one;

methyl [4-(benzyloxy)-3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)phenyl]acetate;

2-[4-(benzyloxy)-3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)phenyl]-N-ethylacetamide;

2-[4-(benzyloxy)-3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)phenyl]-N,N-dimethylacetamide;

N-[4-(3,4-difluorophenoxy)-3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)phenyl]methanesulfonamide;

N-[3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)-4-(2,4,6-trifluorophenoxy)phenyl]methanesulfonamide;

4-(2,4-difluorophenoxy)-3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)benzamide;

4-(2,4-difluorophenoxy)-3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)-N-(tetrahydrofuran-3-yl)benzamide;

4-{2-(2,4-difluorophenoxy)-5-[(1,1-dioxidothiomorpholin-4-yl)carbonyl]phenyl}-6-methyl-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one;

4-(2,4-difluorophenoxy)-3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)-N-(1-methyl-2-oxopyrrolidin-3-yl)benzamide;

tert-butyl {1-[4-(2,4-difluorophenoxy)-3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)benzoyl]pyrrolidin-3-yl} carbamate;

4-[2-(2,4-difluorophenoxy)-5-(pyrrolidin-1-ylcarbonyl)phenyl]-6-methyl-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one;

4-[2-(2,4-difluorophenoxy)-5-(morpholin-4-ylcarbonyl)phenyl]-6-methyl-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one;

N-[4-(cyclohexyloxy)-3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)phenyl]methanesulfonamide;

N-[4-(cyclopentyloxy)-3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)phenyl]methanesulfonamide;

N-{4-[(4,4-difluorocyclohexyl)oxy]-3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)phenyl}methanesulfonamide;

N-[3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)-4-(tetrahydro-2H-pyran-3-yloxy)phenyl]methanesulfonamide;

6-methyl-4-[2-(morpholin-4-ylcarbonyl)phenyl]-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one;

N-[3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)-4-(2,4,6-trifluorophenoxy)phenyl]methanesulfonamide;

N-[4-(benzyloxy)-3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)phenyl]methanesulfonamide;

N-[4-(2,4-difluorophenoxy)-3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)phenyl]-2-fluoroethanesulfonamide;

- N-[4-(2,4-difluorophenoxy)-3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)phenyl]-N'-methylsulfuric diamide;
- N-[3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)-4-(tetrahydrofuran-3-yloxy)phenyl]ethanesulfonamide;
- methyl 6-methyl-7-oxo-4-(2-phenoxyphenyl)-6,7-dihydro-1H-pyrrolo[2,3-c]pyridine-2-carboxylate;
- methyl 1,6-dimethyl-7-oxo-4-(2-phenoxyphenyl)-6,7-dihydro-1H-pyrrolo[2,3-c]pyridine-2-carboxylate;
- ethyl 4-(5-amino-2-phenoxyphenyl)-6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridine-2-carboxylate;
- 6-methyl-4-(5-(methylsulfonamido)-2-phenoxyphenyl)-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridine-2-carboxylic acid;
- ethyl 6-methyl-4-{5-[(methylsulfonyl)amino]-2-phenoxyphenyl}-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridine-2-carboxylate;
- N-ethyl-6-methyl-4-{5-[(methylsulfonyl)amino]-2-phenoxyphenyl}-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridine-2-carboxamide;
- 6-methyl-4-{5-[(methylsulfonyl)amino]-2-phenoxyphenyl}-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridine-2-carboxamide;
- N-[4-(4-cyanophenoxy)-3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)phenyl]ethanesulfonamide;
- 6-methyl-4-[5-(methylsulfonyl)-2-phenoxyphenyl]-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one;
- 5-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)-6-(tetrahydrofuran-3-yloxy)pyridine-3-sulfonamide;
- N-methyl-5-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)-6-(tetrahydrofuran-3-yloxy)pyridine-3-sulfonamide;
- 6-methyl-4-(2-phenoxyphenyl)-2-phenyl-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one;
- and
- N-{3-[2-(hydroxymethyl)-6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl]-4-phenoxyphenyl}methanesulfonamide.

29. The compound of claim 27 or a pharmaceutically acceptable salt thereof, wherein R^Y is methyl.

30. The compound of claim 29 or a pharmaceutically acceptable salt thereof, wherein L^1 is CH_2 , $\text{C}(\text{O})$, $(\text{CH}_2)_m\text{O}$, or $(\text{CH}_2)_m\text{N}(\text{R}^Z)$.
31. The compound of claim 29 or a pharmaceutically acceptable salt thereof, wherein L^1 is $(\text{CH}_2)_m\text{O}$.
32. The compound of claim 31 or a pharmaceutically acceptable salt thereof, wherein G^1 is G^{1a} .
33. The compound of claim 32 or a pharmaceutically acceptable salt thereof, wherein G^{1a} is optionally substituted aryl.
34. The compound of claim 32 or a pharmaceutically acceptable salt thereof, wherein G^{1a} is optionally substituted phenyl.
35. The compound of claim 32 or a pharmaceutically acceptable salt thereof, wherein G^{1a} is optionally substituted cycloalkyl.
36. The compound of claim 32 or a pharmaceutically acceptable salt thereof, wherein G^{1a} is optionally substituted monocyclic cycloalkyl.
37. The compound of claim 32 or a pharmaceutically acceptable salt thereof, wherein G^{1a} is optionally substituted heterocycle.
38. The compound of claim 32 or a pharmaceutically acceptable salt thereof, wherein G^{1a} is optionally substituted monocyclic heterocycle.
39. The compound of any one of claims 15, 17-27, and 29-38, or a pharmaceutically acceptable salt thereof, wherein A^1 is CR^1 , A^2 is CR^2 , A^3 is CR^3 , and A^4 is CR^4 ; or one of A^1 , A^2 , A^3 , and A^4 is N.
40. The compound of claim 39 or a pharmaceutically acceptable salt thereof, wherein R^2 is hydrogen, C_{1-6} alkyl, NO_2 ,

G^{2a} , $-S(O)_2R^{2d}$, $-S(O)_2NR^{2b}R^{2c}$, $-C(O)R^{2d}$, $-C(O)OR^{2a}$, $-C(O)NR^{2b}R^{2c}$, $-NR^{2b}R^{2c}$, $-N(R^{2e})C(O)R^{2d}$, $-N(R^{2e})S(O)_2R^{2d}$, $-N(R^{2e})S(O)_2NR^{2b}R^{2c}$, $-(C,-C_6 \text{ alkylenyl})-G^{2a}$, $-(C,-C_6 \text{ alkylenyl})-OR^{2a}$, $-(C,-C_6 \text{ alkylenyl})-S(O)_2R^{2d}$, $-(C,-C_6 \text{ alkylenyl})-S(O)_2NR^{2b}R^{2c}$, $-(C,-C_6 \text{ alkylenyl})-C(O)R^{2d}$, $-(C,-C_6 \text{ alkylenyl})-C(O)OR^{2a}$, $-(C,-C_6 \text{ alkylenyl})-C(O)NR^{2b}R^{2c}$, $-(C,-C_6 \text{ alkylenyl})-NR^{2b}R^{2c}$, $-(C,-C_6 \text{ alkylenyl})-N(R^{2e})C(O)R^{2d}$, $-(C,-C_6 \text{ alkylenyl})-N(R^{2e})S(O)_2R^{2d}$, or $-(C,-C_6 \text{ alkylenyl})-N(R^{2e})S(O)_2NR^{2b}R^{2c}$.

41. The compound of claim 39 or a pharmaceutically acceptable salt thereof, wherein R^2 is $-S(O)_2R^{2d}$, $-S(O)_2NR^{2b}R^{2c}$, $-N(R^{2e})S(O)_2R^{2d}$, or $-N(R^{2e})S(O)_2NR^{2b}R^{2c}$.
42. The compound of claim 41 or a pharmaceutically acceptable salt thereof, wherein R^x is hydrogen or methyl.
43. The compound of claim 41 or a pharmaceutically acceptable salt thereof, wherein R^x is hydrogen.
44. The compound of claim 43 or a pharmaceutically acceptable salt thereof, wherein R^{x1} is hydrogen, $-C(O)OR^{ax1}$, $-C(O)NR^{bx1}R^{cx1}$, G^{x1} , or $C,-C_6 \text{ alkyl}$ wherein the $C,-C_6 \text{ alkyl}$ is optionally substituted with OR^{ax1} .
45. The compound of claim 43 or a pharmaceutically acceptable salt thereof, wherein R^{x1} is hydrogen, $-C(O)OR^{ax1}$, or $-C(O)NR^{bx1}R^{cx1}$.
46. The compound of claim 45 or a pharmaceutically acceptable salt thereof, wherein R^{x2} is hydrogen.
47. A pharmaceutical composition comprising a therapeutically effective amount of a compound of formula (I) according to claim 1, or a pharmaceutically acceptable salt thereof, in combination with a pharmaceutically acceptable carrier.
48. A method for treating cancer in a subject comprising administering a therapeutically effective amount of a compound of formula (I) according to claim 1 or a pharmaceutically acceptable salt thereof, to a subject in need thereof.

49. The method of claim 48 wherein the cancer is selected from the group consisting of: acoustic neuroma, acute leukemia, acute lymphocytic leukemia, acute myelocytic leukemia (monocytic, myeloblasts, adenocarcinoma, angiosarcoma, astrocytoma, myelomonocytic and promyelocytic), acute t-cell leukemia, basal cell carcinoma, bile duct carcinoma, bladder cancer, brain cancer, breast cancer, bronchogenic carcinoma, cervical cancer, chondrosarcoma, chordoma, choriocarcinoma, chronic leukemia, chronic lymphocytic leukemia, chronic myelocytic (granulocytic) leukemia, chronic myelogenous leukemia, colon cancer, colorectal cancer, craniopharyngioma, cystadenocarcinoma, diffuse large B-cell lymphoma, dysproliferative changes (dysplasias and metaplasias), embryonal carcinoma, endometrial cancer, endotheliosarcoma, ependymoma, epithelial carcinoma, erythroleukemia, esophageal cancer, estrogen-receptor positive breast cancer, essential thrombocythemia, Ewing's tumor, fibrosarcoma, follicular lymphoma, germ cell testicular cancer, glioma, glioblastoma, gliosarcoma, heavy chain disease, hemangioblastoma, hepatoma, hepatocellular cancer, hormone insensitive prostate cancer, leiomyosarcoma, leukemia, liposarcoma, lung cancer, lymphagioendotheliosarcoma, lymphangiosarcoma, lymphoblastic leukemia, lymphoma (Hodgkin's and non-Hodgkin's), malignancies and hyperproliferative disorders of the bladder, breast, colon, lung, ovaries, pancreas, prostate, skin and uterus, lymphoid malignancies of T-cell or B-cell origin, leukemia, lymphoma, medullary carcinoma, medulloblastoma, melanoma, meningioma, mesothelioma, multiple myeloma, myelogenous leukemia, myeloma, myxosarcoma, neuroblastoma, NUT midline carcinoma (NMC), non-small cell lung cancer, oligodendroglioma, oral cancer, osteogenic sarcoma, ovarian cancer, pancreatic cancer, papillary adenocarcinomas, papillary carcinoma, pinealoma, polycythemia vera, prostate cancer, rectal cancer, renal cell carcinoma, retinoblastoma, rhabdomyosarcoma, sarcoma, sebaceous gland carcinoma, seminoma, skin cancer, small cell lung carcinoma, solid tumors (carcinomas and sarcomas), small cell lung cancer, stomach cancer, squamous cell carcinoma, synovioma, sweat gland carcinoma, thyroid cancer, Waldenstrom's macroglobulinemia, testicular tumors, uterine cancer and Wilms' tumor.

50. A method for treating a disease or condition in a subject comprising administering a therapeutically effective amount of a compound of formula (1) according to claim 1 or a pharmaceutically acceptable salt thereof, to a subject in need thereof, wherein said disease or condition is selected from the group consisting of: Addison's disease, acute gout, ankylosing spondylitis, asthma, atherosclerosis, Behcet's disease, bullous skin diseases,

chronic obstructive pulmonary disease (COPD), Crohn's disease, dermatitis, eczema, giant cell arteritis, glomerulonephritis, hepatitis, hypophysitis, inflammatory bowel disease, Kawasaki disease, lupus nephritis, multiple sclerosis, myocarditis, myositis, nephritis, organ transplant rejection, osteoarthritis, pancreatitis, pericarditis, Polyarteritis nodosa, pneumonitis, primary biliary cirrhosis, psoriasis, psoriatic arthritis, rheumatoid arthritis, scleritis, sclerosing cholangitis, sepsis systemic lupus erythematosus, Takayasu's Arteritis, toxic shock, thyroiditis, type I diabetes, ulcerative colitis, uveitis, vitiligo, vasculitis, and Wegener's granulomatosis.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/CN2011/002224

A. CLASSIFICATION OF SUBJECT MATTER

See extra sheet

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC: C07D471/-, C07D487/-, A61K31/-, A61P35/-, A61P11/-, A61P1/-, A61P13/-, A61P19/-, A61P17/-, A61P37/-, A61P3/-

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

WPI, EPODOC, CNPAT, CNKI, REGISTRY, CAPLUS: cancer, tumor, bromodomain

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 065221 8A1(TAKEDA CHEMICAL INDUSTRIES, LTD.) 10 May 1995 (10.05.1995) see claims 1-27	1-50
A	JP 08-337583 A(TAKEDA CHEMICAL INDUSTRIES, LTD.) 24 Dec. 1996 (24.12.1996) see claims 1-15	1-50
A	pAL PIAZ, Vittorio et al., Synthesis and Evaluation of Novel Pyrrolo[2,3-d] and Thieno[2,3-d]Pyridazinones as in Vitro Antiproliferative Agents, Acta Chim. Slov, 2009, vol. 56, No. 3, pages 571-579, see pages 572-574	1-50
A	YOSHITNORI, Ikeura et al., Potent NK ₁ Receptor Antagonists: Synthesis and Antagonistic Activity of Various Heterocycles with an N-[3,5-Bis(trifluoromethyl)benzyl]-N-methylcarbamoyl Substituent, Chem. Pharm. Bull., 1997, vol. 45, No. 10, pages 1642-1652, see pages 1645-1646, Tables 1,2	1-50

1-1 Further documents are listed in the continuation of Box C. See patent family annex.

<p>* Special categories of cited documents:</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier application or patent but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim (S) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p>	<p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art</p> <p>"&" document member of the same patent family</p>
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Date of the actual completion of the international search 07 Sept. 2012(07.09.2012)	Date of mailing of the international search report 25 Oct. 2012 (25.10.2012)
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INTERNATIONAL SEARCH REPORT

International application No.

PCT/CN201 1/002224

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.: 48-50
because they relate to subject matter not required to be searched by this Authority, namely:
Claims 48-50 relate to a method of treatment and shall not be granted patent rights, but the examination report has been carried out and based on the use of compounds according to claim 1 for the manufacture of medicaments for treating cancer and diseases mentioned in claim 50.
2. Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos. :
4. No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos. :

- Remark on protest**
- The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
 - The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
 - No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/CN201 1/002224

Patent Documents referred in the Report	Publication Date	Patent Family	Publication Date
EP 065221 8A1	10.05.1995	AU7773894A	18.05.1995
		N0944252A	11.05.1995
		CA2135440A	11.05.1995
		FI945281A	11.05.1995
		HUT68810A	28.07.1995
		BR9404403A	18.07.1995
		TW263498A	21.11.1995
		JP8067678A	12.03.1996
		BR9501976A	30.04.1996
		US5585385A	17.12.1996
		NZ264887A	20.12.1996
		AU678295B	22.05.1997
		CN1107476A	30.08.1995
		NO301764B1	08.12.1997
		NZ272711A	29.06.1999
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		EP0652218B1	11.07.2001
		DE69427675E	16.08.2001
		JP 08-337583A	24.12.1996

INTERNATIONAL SEARCH REPORT

International application No.

PCT/CN201 1/002224

Continuation of : CLASSIFICATION OF SUBJECT MATTER:

C07D471/04 (2006. 01) i

C07D487/04 (2006. 01) i

A61K3 1/437 (2006. 01) i

A61K3 1/495 (2006. 01) i

A61P35/00 (2006. 01) i

A61P1 1/06 (2006. 01) i

A61P17/00 (2006. 01) i

A61P1/16 (2006. 01) i

A61P13/12 (2006. 01) i

A61P1/02 (2006. 01) i

A61P17/06 (2006. 01) i

A61P1/18 (2006. 01) i

A61P37/06 (2006. 01) i

A61P3/10 (2006. 01) i