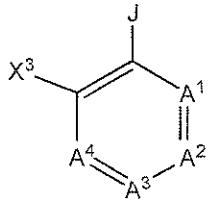
PYRIDINONE AND PYRIDAZINONE DERIVATIVES

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.

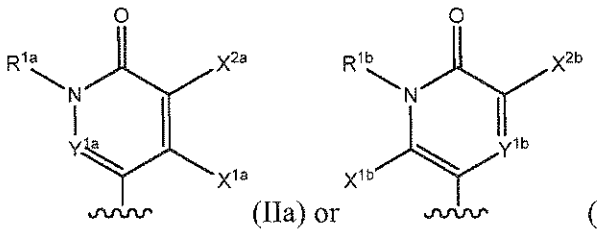
SUMMARY

In one aspect, the present disclosure relates to compounds of Formula (I) or a pharmaceutically acceptable salt thereof,



I

Wherein J is a group of formula IIa or IIb:



(IIa) or (IIb);

wherein

R^{1a} is C_1-C_3 alkyl, C_2-C_3 alkylene-OH, or C_1-C_3 haloalkyl;

Y^{1a} is N or CR^{xa}, wherein R^{xa} is H, halo, C_1-C_3 alkyl, -O-C_1-C_3 alkyl, C_1-C_3 haloalkyl, -O-C_1-C_3 haloalkyl, aryl, aryl-C_1-C_3alkylene-OH, aryl-C_1-C_3alkylene-heterocycloalkyl, $C(O)NR^{10}R^{12}$, wherein heterocycloalkyl of aryl-C_1-C_3alkylene-heterocycloalkyl may be substituted with one to three C_1-C_3alkyl,

R^{1b} is H, C_1-C_3 alkyl, C_2-C_3 alkylene-OH, or C_1-C_3 haloalkyl;

Y^{1b} is N or CR^{xb}, wherein R^{xb} is heteroaryl, H, halo, C_1-C_3 alkyl, -O-C_1-C_3 alkyl, C_1-C_3 haloalkyl, -O-C_1-C_3 haloalkyl, aryl, aryl-C_1-C_3alkylene-OH, aryl-C_1-C_3alkylene-heterocycloalkyl, $C(O)NR^{10}R^{12}$, wherein heterocycloalkyl of aryl-C_1-C_3alkylene-heterocycloalkyl may be substituted with one to three C_1-C_3alkyl; wherein said heteroaryl may be substituted with one to three groups selected from the group consisting of: C_1-C_6 alkyl, C_1-C_3alkylene-aryl, C_1-C_3alkylene-heteroaryl, C_1-C_3alkylene-heterocycloalkyl, COOH, and COO-C_1-C_4alkyl,

X^{2a} is selected from the group consisting of: H, $-NR^{10}R^{12}$, halo, OH, -O-C_1-C_4 alkyl, aryl, heteroaryl, and $-NR^{10}C(O)$-C_1-C_4 alkyl;

X^{2b} is C_1-C_3 alkyl, C_2-C_3 alkylene-OH, or C_1-C_3 haloalkyl;

X^{1a} and X^{1b} are each selected from the group consisting of: hydrogen, halo, C_1-C_6 alkyl, C_1-C_4 haloalkyl, -O-C_1-C_4 alkyl, -O-C_1-C_6 cycloalkyl, -O-C_1-C_3 alkylene-C_3-C_7 cycloalkyl, -O-C_1-C_4 haloalkyl, -O-C_1-C_3 alkylene-heterocycloalkyl, -O-C_1-C_6 alkylene-OH , -O-C_1-C_6 alkylene-$N(R^{10})_2$ -O-C_1-C_3 alkylene-C(O)O-C_1-C_4 alkyl, $-NR^{10}$-C_1-C_6 alkyl, $-NR^{10}$-C_1-C_6 haloalkyl, $-NR^{10}$-C(O)OC_1-C_6 alkyl, $-NR^{10}$-C(O)OC_1-C_6 haloalkyl, $-NR^{10}$-$C(O)NR^{10}R^{12}$, $-NR^{10}$-SO_2R^{12}, $-NR^{10}$-C_3-C_7 cycloalkyl, -O-C_1-C_3 alkylene-C(O)O-C_1-C_4 alkyl, $-NR^{10}$-C_1-C_6 alkyl, $-NR^{10}$-C_1-C_6 haloalkyl, $-NR^{10}$-C_1-C_3 alkylene-C_3-C_7 cycloalkyl, C_1-C_4 alkylene-OH, -C_1-C_3 alkylene-C(O)O C_1-C_4 alkyl, C_1-C_3 alkylene-$NR^{10}C(O)$-C_1-C_4 alkyl, -C_1-C_3 alkylene-$C(O)NR^{10}R^{12}$, -C_2-C_4

alkenylene-C(O)-O-C_1-C_4 alkyl, -C(O)-C_1-C_4 alkyl, C(O)O-C_1-C_4 alkyl, C(O)$NR^{10}R^{12}$, -NR^{10}C(O)-C_1-C_4 alkyl, -$NR^{10}SO_2$-C_1-C_4 alkyl, -NR^{10}-C_1-C_3 alkylene-C(O)-C_1-C_4 alkyl, -NR^{10}-C_1-C_3 alkylene-C(O)O-C_1-C_4 alkyl, -$SO_2NR^{10}R^{12}$, and any of groups i-v:

i) C_3-C_{14} cycloalkyl, which may be substituted with 1 to 3 of R^2, where R^2 is selected from the group consisting of: halo, oxo, CN, -O-C_1-C_4 alkyl, -O-C_1-C_4 haloalkyl, -$NR^{10}R^{12}$, C(O)$NR^{10}R^{12}$, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C(O)-C_1-C_4 alkyl, -C(O)O-C_1-C_4 alkyl, $SO_2NR^{10}R^{12}$, SO_2-C_1-C_4 alkyl, and aryl, wherein said aryl may be substituted with 1 to 3 substituents independently selected from group consisting of: halo, C_1-C_3 alkyl, C(O)-C_1-C_3alkyl, C(O)OH, C(O)$NR^{10}R^{12}$, and heteroaryl;

ii) heterocycloalkenyl, which may be substituted with 1 to 3 of R^2, where R^2 is selected from the group consisting of: halo, oxo, CN, -O-C_1-C_4 alkyl, -O-C_1-C_4 haloalkyl, -$NR^{10}R^{12}$, C(O)$NR^{10}R^{12}$, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C(O)-C_1-C_4 alkyl, -C(O)O-C_1-C_4 alkyl, $SO_2NR^{10}R^{12}$, SO_2-C_1-C_4 alkyl, and aryl, wherein said aryl may be substituted with 1 to 3 substituents independently selected from group consisting of: halo, C_1-C_3 alkyl, C(O)-C_1-C_3alkyl, C(O)OH, C(O)$NR^{10}R^{12}$, and heteroaryl;

iii) heterocycloalkyl, which may be substituted with 1 to 3 of R^3, where R^3 is selected from the group consisting of: halo, oxo, CN, -O-C_1-C_4 alkyl, -O-C_1-C_4 haloalkyl, -$NR^{10}R^{12}$, C(O)$NR^{10}R^{12}$, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C(O)-C_1-C_4 alkyl, -C(O)O-C_1-C_4 alkyl, $SO_2NR^{10}R^{12}$, SO_2-C_1-C_4 alkyl, and aryl, wherein said aryl may be substituted with 1 to 3 substituents independently selected from group consisting of: halo, C_1-C_3 alkyl, C(O)-C_1-C_3alkyl, C(O)OH, C(O)$NR^{10}R^{12}$, and heteroaryl;

iv) heteroaryl, which may be substituted with 1 to 3 of R^4, where R^4 is selected from the group consisting of: , halo, oxo, CN, -O-C_1-C_4 alkyl, -O-C_1-C_4 haloalkyl, -$NR^{10}R^{12}$, C(O)$NR^{10}R^{12}$, C_1-C_6 alkyl, C_1-C_4 haloalkyl, C_1-C_6 alkylene-heterocycloalkyl, C_1-C_6alkylene-aryl, C_1-C_6alkylene-heteroaryl, C(O)-C_1-C_4 alkyl, -C(O)O-C_1-C_4 alkyl, $SO_2NR^{10}R^{12}$, SO_2-C_1-C_4 alkyl, -NR^{14}C(O)C_1-C_4-alkyl, NH-C_1-C_4 alkylene-aryl, heterocycloalkyl, and aryl, wherein said aryl may be substituted with 1 to 3 substituents independently selected from group consisting of: halo, C_1-C_3 alkyl, C(O)-C_1-C_3alkyl, C(O)OH, C(O)$NR^{10}R^{12}$, and heteroaryl,

wherein said heterocycloalkyl or heterocycloalkyl group of C_1-C_6 alkylene-heterocycloalkyl may be substituted with 1 to 3 independently selected C_1-C_3 alkyl groups, and wherein said heteroaryl group of C_1-C_6 alkylene-heteroaryl and said aryl groups of C_1-C_6 alkylene-aryl and NH-C_1-C_4 alkylene-aryl may be substituted with substituents 1 to 3 groups independently selected from C_1-C_3 alkyl and $NR^{14}R^{16}$;

v) aryl, which may be substituted with 1 to 3 of R^6, where R^6 is selected from the group consisting of: halo, CN, -$NR^{14}R^{16}$, -$NR^{14}SO_2$-C_1-C_4 alkyl, C(O)H, -C_1-C_4 alkylene-$NR^{14}R^{16}$, $SO_2NR^{14}R^{16}$, $C(O)OC_1$-C_4 alkyl, -SO_2-heterocycloalkyl, -SO_2-C_1-C_6 alkyl, -C_1-C_6 alkyl, -O-C_1-C_6 alkyl, -C_1-C_6 haloalkyl, -O-C_1-C_6 haloalkyl, -C_1-C_6 alkylene-heterocycloalkyl, C_1-C_6alkylene-aryl, and C_1-C_6alkylene-heteroaryl,

wherein said heterocycloalkyl of said C_1-C_6 alkylene-heterocycloalkyl may be substituted with 1 to 3 groups independently selected from the group consisting of C_1-C_6 alkyl and -CH_2-phenyl, and C_1-C_4 alkylene-aryl,

wherein the heteroaryl of said C_1-C_6 alkylene-heteroaryl and the aryl of said C_1-C_6 alkylene-aryl may be substituted with 1 to 3 groups independently selected from the group consisting of C_1-C_4 alkyl, C_1-C_4 haloalkyl, and halo-C_1-C_3 alkylene-CN, -C_1-C_3 alkylene-OH, -C_1-C_3 alkylene-C(O)O-C_1-C_3 alkyl, -C_1-C_3 alkylene-O-C_1-C_3 alkyl, -C_1-C_3 alkylene-OC(O)-C_1-C_3 alkyl, -C_1-C_3 alkylene-NR^{14}-aryl, C_1-C_3 alkylene-NR^{14}-C(O)-C_1-C_4alkyl, -C_1-C_3 alkylene-$NR^{14}SO_2$-C_1-C_4 alkyl, -C(O)-C_1-C_3 alkylene, and -C(O)-heterocycloalkyl,

wherein said heterocycloalkyl of C(O)-heterocycloalkyl may be substituted with 1 to 3 groups independently selected from the group consisting of: C_1-C_6 alkyl, -C(O)-$NHCH_2$-aryl, -CH-(OH)-C_1-C_6 alkyl, -CH(OH)-C_2-C_6 alkenyl, -CH(OH)-C_3-C_7 cycloalkyl, -CH(OH)-phenyl, -C(O)$NR^{14}R^{16}$-C_3-C_{14}cycloalkyl, -C(O)NR^{14}-C_1-C_3 alkylene-$NR^{14}R^{16}$, -C(O)NR^{14}-C_1-C_3 alkylene-CN, -C(O)NR^{14}-C_1-C_3 alkylene-$NR^{14}R^{16}$, -C(O)$NR^{14}R^{16}$, -C(O)NH-C_3-C_{14} cycloalkyl, -C(O)NH-C_1-C_3 alkylene-O-C_1-C_3 alkyl, C(O)NH-C_1-C_3 alkylene-OH, -NR^{14}-C_3-C_{14} cycloalkyl, -NR^{14}-C_1-C_3 alkylene-heterocycloalkyl, -NR^{14}C(O)-C_1-C_4 alkyl, heterocycloalkyl, and heteroaryl, wherein said heterocycloalkyl or heteroaryl may be

substituted with 1-3 substituents independently selected from the group consisting of: halo, C_1-C_4 alkyl, C_1-C_4 haloalkyl and aryl;

where R^{14} and R^{16} are independently selected from the group consisting of: C_1-C_4 alkyl, C_3-C_7-cycloalkyl, -C_1-C_3-alkylene-$NR^{10}R^{12}$, aryl, and H,

where $R^{10}$and R^{12} are at each occurrence independently selected from the group consisting of H, C_1-C_4 alkyl, C_1-C_3-alkylene-aryl, C_1-C_3-alkylene-heteroarylaryl, C_1-C_3-alkylene-C_3-C_7-cycloalkyl, and cyclopropyl;

where X^3 is absent or is L-G, where L is absent or is selected from the group consisting of:

-O-, -O-C_1-C_3 alkylene-, -NR^{30}-, -C(O)-, -C_1-C_3 alkylene-, wherein said C_1-C_3 alkylene may be substituted with one to two substituents independently selected from the group consisting of: OH, -$NR^{20}R^{22}$, -NH-heterocycloalkyl, and -O-C_1-C_3 alkyl, and wherein R^{30} is H or C_1-C_4 alkyl, or C_1-C_4 haloalkyl; and

G is selected from the group consisting of:

aryl, heteroaryl, C_1-C_6 alkyl, C_3-C_7 cycloalkyl, heterocycloalkyl, wherein G may be substituted with 1 to 3 groups independently selected from the group consisting of halo, CN, OH, -C_1-C_4 alkyl, -C_1-C_4 haloalkyl, -SO_2-R^{32}, -O-R^{32}, -C(O)-R^{32}, -C(O)O-R^{32}, -$NR^{20}R^{22}$, -NR^{20}C(O)OR^{32}, -NR^{20}C(O)R^{32}, -$NR^{20}SO_2OR^{34}$, -NR^{20}C(O)$NR^{36}R^{38}$, aryl, and aryl substituted with one to three groups independently selected from the group consisting of halo, CN, OH, -C_1-C_4 alkyl, and -C_1-C_4 haloalkyl,

wherein R^{32} is selected from -C_1-C_4 alkyl and -C_1-C_4 haloalkyl,

wherein R^{34} is selected from -C_1-C_4 alkyl and -C_1-C_4 haloalkyl,

wherein R^{36} and R^{38} are independently selected from the group consisting of hydrogen, -C_1-C_4 alkyl, and -C_1-C_3 haloalkyl;

where one of A^1, A^2, A^3, and A^4 is CR^{18}, one of A^1, A^2, A^3, and A^4 is N or CR^{19}, and two of A^1, A^2, A^3, and A^4 are CR^{19}, where R^{19} is independently selected from the group consisting of: H, -OR^{20}, CN, -$NR^{20}R^{22}$, halo, C_1-C_4 alkyl, C_1-C_4 haloalkyl, and SO_2R^{20},

wherein R^{18} is selected from the group consisting of: H, NO_2, C_1-C_3 alkyene-SO_2-C_1-C_6 alkyl, C_1-C_3 alkyene-SO_2-C_1-C_6 haloalkyl, C_1-C_3 alkyene-SO_2-$NR^{20}R^{22}$, -$NR^{20}R^{22}$, -$NHSO_2$-NH_2, -$NR^{40}SO_2$-C_1-C_4 alkyl, -

$NR^{40}SO_2$-C_1-C_4 haloalkyl, -$NR^{40}SO_2$-CH_2-C(O)OH, -$NR^{40}SO_2$-CH_2-C(O)OC_1-C_4, -$NR^{40}SO_2$-C_1-C_4 alkyl, -$NR^{40}SO_2$-C_1-C_4 haloalkyl, -$NR^{40}SO_2$-C_3-C_7 cycloalkyl, -$NR^{40}SO_2$-aryl, -$NR^{40}SO_2$-heteroaryl, -$NR^{40}SO_2$-C_1-C_4 alkyl, -$NR^{40}SO_2$-C_1-C_4 haloalkyl, -$NR^{40}SO_2$-C_1-C_3 alkylene-C_3-C_{14} cycloalkyl, -$NR^{40}SO_2$-C_1-C_3 alkylene-heterocycloalkyl, -$NR^{40}SO_2$-C_1-C_3 alkylene-heteroaryl, -$NR^{40}SO_2$-C_1-C_3 alkylene-aryl, -SO_2-$NR^{40}R^{42}$, -SO_2-NR^{40}-C_1-C_4 alkyl, -SO_2-NR^{40}-C_1-C_4 haloalkyl, -SO_2-NR^{40}-C_3-C_{14} cycloalkyl, -SO_2-NR^{40}-C(O)$NR^{20}R^{22}$, -SO_2-NR^{40}-heterocycloalkyl, -SO_2-NR^{40}-heteroaryl, -SO_2-NR^{40}-aryl, -SO_2-C_1-C_6 alkyl, -SO_2-C_1-C_6 haloalkyl, -SO_2-C_3-C_{14} cycloalkyl, -SO_2-heterocycloalkyl, -SO_2-heteroaryl, -SO_2-aryl, -$NR^{40}SO_2$-$NR^{20}R^{22}$, -NR^{40}C(O)-C_1-C_4 alkyl, -NR^{40}C(O)NH-C_1-C_4 alkyl, -NR^{40}C(O)-heteroaryl, -NR^{40}C(O)-aryl, -NR^{40}C(O)O-C_1-C_4 alkyl, -NR^{40}C(O)O-heteroaryl, -NR^{40}C(O)-aryl, -NR^{40}C(O)-CH_2NH-C(O)O-C_1-C_4 alkyl, -C(O)CH_2-$NR^{20}R^{22}$, -C(O)$NR^{20}R^{22}$, C(O)OH, C_1-C_3 alkylene-NR^{40}-C(O)-C_1-C_4 alkyl, C_1-C_3 alkylene-NR^{40}-C(O)-C_1-C_3 haloalkyl, -NR^{40}-heteroaryl, C_3-C_{14} cycloalkyl, heterocycloalkyl, heterocycloalkyl-aryl, heteroaryl, aryl, C_1-C_3 alkylene-cycloalkyl, C_1-C_3 alkylene-heterocycloalkyl, C_1-C_3 alkylene-heteroaryl, and C_1-C_3 alkylene-aryl,

wherein any of the cycloalkyl, heterocycloalkyl, heteroaryl, or aryl groups of R^{18} may be substituted with 1 to 3 of C_1-C_4 alkyl, C_1-C_4 haloalkyl or halo,

wherein R^{40} and R^{42} are independently selected from the group consisting of: H and C_1-C_4 alkyl, and

wherein R^{20} and R^{22} are at each occurrence independently selected from the group consisting of: H and C_1-C_4 alkyl.

In certain embodiments, A^1 is CR^{19}, A^2 is CR^{18}, A^3 is CR^{19}, and A^4 is CR^{19}.

In certain embodiments, A^1 is CH, A^2 is CR^{18}, A^3 is CH, and A^4 is CH. In certain embodiments, R^{18} is selected from the group consisting of:

NO_2, $NR^{20}R^{22}$, $NHSO_2$-NH_2, $NR^{40}SO_2$-C_1-C_4 alkyl, $NR^{40}SO_2$-C_1-C_4 haloalkyl, $NR^{40}SO_2$-CH_2-C(O)OH, $NR^{40}SO_2$-CH_2-C(O)OC_1-C_4, -$NR^{40}SO_2$-C_1-C_4 alkyl, -$NR^{40}SO_2$-C_1-C_4 haloalkyl, $NR^{40}SO_2$-C_3-C_7 cycloalkyl, -$NR^{40}SO_2$-aryl, -$NR^{40}SO_2$-heteroaryl, -$NR^{40}SO_2$-C_1-C_4 alkyl, -$NR^{40}SO_2$-C_1-C_4 haloalkyl, -

$NR^{40}SO_2$-C_1-C_3 alkylene-C_3-C_{14} cycloalkyl, -$NR^{40}SO_2$-C_1-C_3 alkylene-heterocycloalkyl, -$NR^{40}SO_2$-C_1-C_3 alkylene-heteroaryl, -$NR^{40}SO_2$-C_1-C_3 alkylene-aryl, -SO_2-$NR^{40}R^{42}$, -SO_2-NR^{40}-C_1-C_4 alkyl, -SO_2-NR^{40}-C_1-C_4 haloalkyl, -SO_2-NR^{40}-C_3-C_{14} cycloalkyl, -SO_2-NR^{40}-heterocycloalkyl, -SO_2-NR^{40}-heteroaryl, -SO_2-NR^{40}-aryl, -SO_2-C_1-C_6 alkyl, -SO_2-C_1-C_6 haloalkyl, -SO_2-C_3-C_{14} cycloalkyl, -SO_2-heterocycloalkyl, -SO_2-heteroaryl, -SO_2-aryl, -$NR^{40}SO_2$-$NR^{20}R^{22}$, -NR^{40}C(O)-C_1-C_4 alkyl, -NR^{40}C(O)NH-C_1-C_4 alkyl, -NR^{40}C(O)-heteroaryl, NR^{40}C(O)-aryl, NR^{40}C(O)O-C_1-C_4 alkyl, -NR^{40}C(O)O-heteroaryl, NR^{40}C(O)-aryl, -NR^{40}C(O)-CH_2NH-C(O)O-C_1-C_4 alkyl, -C(O)CH_2-$NR^{20}R^{22}$, -C(O)$NR^{20}R^{22}$, C(O)OH, C_1-C_3 alkylene-NR^{40}-C(O)-C_1-C_4 alkyl, C_1-C_3 alkylene-NR^{40}-C(O)-C_1-C_3 haloalkyl, NR^{40}-heteroaryl, C_3-C_{14} cycloalkyl, heterocycloalkyl, heteroaryl, aryl, C_1-C_3 alkylene-C_3-C_{14}cycloalkyl, C_1-C_3 alkylene-heterocycloalkyl, C_1-C_3 alkylene-heteroaryl, and C_1-C_3 alkylene-aryl.

In certain embodiments, R^{18} is selected from the group consisting of:

$NR^{40}SO_2$-C_1-C_4 alkyl, $NR^{40}SO_2$-C_1-C_4 haloalkyl, -SO_2-NR^{40}-C_1-C_4 alkyl, -SO_2-NR^{40}-C_1-C_4 haloalkyl, -SO_2-C_1-C_6 alkyl, and -SO_2-C_1-C_6 haloalkyl.

In certain embodiments, R^{40} is H. In certain embodiments, X^3 is L-G and L is -O-, or -O-C_1-C_3 alkylene-. In certain embodiments, G is aryl or C_3-C_7 cycloalkyl, wherein G may be substituted with 1 to 3 groups independently selected from the group consisting of CN, OH, $NR^{20}R^{22}$, -C_1-C_4 haloalkyl, -SO_2-C_1-C_4 alkyl, halo, C(O)-C_1-C_4-alkyl, -C(O)-C_1-C_4-alkyl, -O-C_1-C_4 alkyl, -O-C_1-C_4 haloalkyl, -C_1-C_4 alkyl, -NR^{20}C(O)R^{32}, -$NR^{20}SO_2OR^{34}$, -NR^{20}C(O)$NR^{36}R^{38}$,

wherein R^{32} is selected from -C_1-C_4 alkyl and -C_1-C_4 haloalkyl,

wherein R^{34} is selected from -C_1-C_4 alkyl and -C_1-C_4 haloalkyl,

wherein R^{36} and R^{38} are independently selected from the group consisting of hydrogen, -C_1-C_4 alkyl, and -C_1-C_3 haloalkyl.

In certain embodiments, L is –O-, and –G is phenyl substituted with 1 to 3 halo. In certain embodiments, L is –O- and –G is phenyl substituted with 1 to 3 fluoro. In certain embodiments, G is 2,4-difluoro-phenyl. In certain embodiments, L is –O-C_1-C_3 alkyene, and –G is C_3-C_7 cycloalkyl. In certain embodiments, J is IIa, Y^{1a} is N, R^{1a} is methyl, and X^{2a} is hydrogen. In certain embodiments, J is IIa, Y^{1a} is CR^{xa}, wherein R^{xa} is H, R^{1a} is methyl, and

X^{2a} is hydrogen. In certain embodiments, X^{1a} is hydrogen. In certain embodiments, X^{1a} is selected from the group consisting of:

halo, -O-C_1-C_4 alkyl, and aryl, wherein said aryl may be substituted with 1 to 3 of R^6, where R^6 is selected from the group consisting of: $NR^{14}SO_2$-C_1-C_4 alkyl, -C_1-C_3 alkylene-$NR^{14}R^{16}$, -C_1-C_6 alkylene-heterocycloalkyl, wherein said heterocycloalkyl of said C_1-C_6 alkylene-heterocycloalkyl may be substituted with 1 to 3 groups independently selected from the group consisting of C_1-C_6 alkyl and -CH_2-phenyl, wherein said aryl of said C_1-C_6 alkylene-aryl may be substituted with 1 to 3 groups independently selected from the group consisting of: -C_1-C_3 alkylene-OH, and heterocycloalkyl, wherein said heterocycloalkyl may be substituted with 1-3 substituents independently selected from the group consisting of: C_1-C_4 alkyl, C_1-C_4 haloalkyl and aryl.

In certain embodiments, J is IIb, R^{1b} is hydrogen, X^{2b} is methyl, Y^{1b} is CR^{xb}, and R^{xb} is H. In certain embodiments, X^{1b} is hydrogen. In certain embodiments, L is –O-, and –G is phenyl substituted with 1 to 3 halo. In certain embodiments, –G is phenyl substituted with 1 to 3 halo. In certain embodiments, G is 2,4-difluoro-phenyl.

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

1-methyl-5-(2-phenoxyphenyl)pyridin-2(1H)-one;

N-[3-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-4-phenoxyphenyl]methanesulfonamide;

methyl {[3-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-4-phenoxyphenyl]sulfamoyl}acetate;

{[3-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-4-phenoxyphenyl]sulfamoyl}acetic acid;

1-methyl-N-[3-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-4-phenoxyphenyl]-1H-imidazole-4-sulfonamide;

N-[3-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-4-phenoxyphenyl]-1H-imidazole-4-sulfonamide;

2,2,2-trifluoro-N-[3-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-4-phenoxyphenyl]ethanesulfonamide;

N-methyl-N'-[3-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-4-phenoxyphenyl]sulfuric diamide;

N-{3-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-4-[4-(trifluoromethyl)phenoxy]phenyl}methanesulfonamide;

N-[4-(4-fluorophenoxy)-3-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)phenyl]methanesulfonamide;

N-[4-(4-chlorophenoxy)-3-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)phenyl]methanesulfonamide;

N-[3-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-4-(pyridin-3-yloxy)phenyl]methanesulfonamide;

N-[4-(2-chlorophenoxy)-3-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)phenyl]methanesulfonamide;

N-{3-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-4-[2-(trifluoromethyl)phenoxy]phenyl}methanesulfonamide;

N-[4-(2-cyanophenoxy)-3-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)phenyl]methanesulfonamide;

N-[4-(2-methoxyphenoxy)-3-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)phenyl]methanesulfonamide;

N-[4-(2-fluorophenoxy)-3-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)phenyl]methanesulfonamide;

N-[4-(2,4-difluorophenoxy)-3-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)phenyl]methanesulfonamide;

N-[4-(2,4-difluorophenoxy)-3-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)phenyl]ethanesulfonamide;

N-[4-(3,5-difluorophenoxy)-3-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)phenyl]methanesulfonamide;

N-[4-(3-chlorophenoxy)-3-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)phenyl]methanesulfonamide;

N-{3-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-4-[3-(trifluoromethyl)phenoxy]phenyl}methanesulfonamide;

N-[4-(3-cyanophenoxy)-3-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)phenyl]methanesulfonamide;

N-[4-(3-fluorophenoxy)-3-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)phenyl]methanesulfonamide;

N-[4-(cyclohexyloxy)-3-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)phenyl]methanesulfonamide;

N-[4-(cyclopentyloxy)-3-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)phenyl]methanesulfonamide;

N-[3-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-4-(tetrahydrofuran-3-yloxy)phenyl]methanesulfonamide;

N-[3-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-4-(tetrahydro-2H-pyran-4-ylmethoxy)phenyl]methanesulfonamide;

N-[3-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-4-phenoxyphenyl]-1H-pyrrole-2-carboxamide;

tert-butyl (2-{[3-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-4-phenoxyphenyl]amino}-2-oxoethyl)carbamate;

N-[3-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-4-phenoxyphenyl]glycinamide;

1-methyl-5-[2-phenoxy-5-(pyridin-2-ylamino)phenyl]pyridin-2(1H)-one;

N-ethyl-3-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-4-phenoxybenzenesulfonamide;

3-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-4-phenoxybenzenesulfonamide;

N-[2-methyl-5-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-4-phenoxyphenyl]methanesulfonamide;

4-methoxy-1-methyl-5-(2-phenoxyphenyl)pyridin-2(1H)-one;

N-[3-(4-methoxy-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-4-phenoxyphenyl]methanesulfonamide;

N-{4-(2,4-difluorophenoxy)-3-[1-methyl-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-3-yl]phenyl}ethanesulfonamide;

N-[3-(4-chloro-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-4-(2,4-difluorophenoxy)phenyl]methanesulfonamide;

N-[4-(2,4-difluorophenoxy)-3-(4-methoxy-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)phenyl]methanesulfonamide;

N-[4-(2,4-difluorophenoxy)-3-(4-methoxy-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)phenyl]ethanesulfonamide;

N-[4-(2,4-difluorophenoxy)-3-{4-[4-(hydroxymethyl)phenyl]-1-methyl-6-oxo-1,6-dihydropyridin-3-yl}phenyl]methanesulfonamide;

N-[4-(2,4-difluorophenoxy)-3-(1-methyl-4-{4-[(4-methylpiperazin-1-yl)methyl]phenyl}-6-oxo-1,6-dihydropyridin-3-yl)phenyl]methanesulfonamide;

N-[4-(2,4-difluorophenoxy)-3-{1-methyl-4-[4-(morpholin-4-yl)phenyl]-6-oxo-1,6-dihydropyridin-3-yl}phenyl]methanesulfonamide;

5-[2-(cyclopropylmethoxy)-5-(ethylsulfonyl)phenyl]-4-methoxy-1-methylpyridin-2(1H)-one;

5-{2-(2,4-difluorophenoxy)-5-[(methylsulfonyl)amino]phenyl}-N,1-dimethyl-2-oxo-1,2-dihydropyridine-4-carboxamide;

N-[4-(2,4-difluorophenoxy)-3-(4-ethoxy-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)phenyl]methanesulfonamide;

N-[4-(2,4-difluorophenoxy)-3-{4-[4-(hydroxymethyl)phenyl]-1-methyl-6-oxo-1,6-dihydropyridin-3-yl}phenyl]ethanesulfonamide;

N-[4-(2,4-difluorophenoxy)-3-(1-methyl-4-{4-[(4-methylpiperazin-1-yl)methyl]phenyl}-6-oxo-1,6-dihydropyridin-3-yl)phenyl]ethanesulfonamide;

N-[4-(2,4-difluorophenoxy)-3-(4-{4-[(dimethylamino)methyl]phenyl}-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)phenyl]ethanesulfonamide;

3-chloro-1-methyl-5-(2-phenoxyphenyl)pyridin-2(1H)-one;

N-[3-(5-chloro-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-4-(2,4-difluorophenoxy)phenyl]methanesulfonamide;

N-[3-(5-chloro-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-4-(2,4-difluorophenoxy)phenyl]ethanesulfonamide; and

N-[4-(2,4-difluorophenoxy)-3-{1-methyl-4-[4-(morpholin-4-yl)phenyl]-6-oxo-1,6-dihydropyridin-3-yl}phenyl]ethanesulfonamide.

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

2-methyl-6-(2-phenoxyphenyl)pyridazin-3(2H)-one;

6-[2-(benzyloxy)phenyl]-2-methylpyridazin-3(2H)-one;

-[2-(1-methyl-6-oxo-1,6-dihydropyridazin-3-yl)phenoxy]benzonitrile;

6-[2-(cyclopentyloxy)phenyl]-2-methylpyridazin-3(2H)-one;

6-[2-(4-hydroxybutoxy)phenyl]-2-methylpyridazin-3(2H)-one;

2-methyl-6-[2-(pyridin-2-yloxy)phenyl]pyridazin-3(2H)-one;

2-methyl-6-{2-[4-(trifluoromethyl)phenoxy]phenyl}pyridazin-3(2H)-one;

2-methyl-6-{2-[4-(methylsulfonyl)phenoxy]phenyl}pyridazin-3(2H)-one;

2-methyl-6-(5-nitro-2-phenoxyphenyl)pyridazin-3(2H)-one;

6-(5-amino-2-phenoxyphenyl)-2-methylpyridazin-3(2H)-one;

4-methyl-N-[3-(1-methyl-6-oxo-1,6-dihydropyridazin-3-yl)-4-phenoxyphenyl]benzenesulfonamide;

N-[3-(1-methyl-6-oxo-1,6-dihydropyridazin-3-yl)-4-phenoxyphenyl]acetamide;

3-(1-methyl-6-oxo-1,6-dihydropyridazin-3-yl)-4-phenoxybenzonitrile;

3-(1-methyl-6-oxo-1,6-dihydropyridazin-3-yl)-4-phenoxybenzamide;

3-(1-methyl-6-oxo-1,6-dihydropyridazin-3-yl)-4-phenoxybenzoic acid;

N-[3-(1-methyl-6-oxo-1,6-dihydropyridazin-3-yl)-4-phenoxybenzyl]acetamide;

2,2,2-trifluoro-N-[3-(1-methyl-6-oxo-1,6-dihydropyridazin-3-yl)-4-phenoxybenzyl]acetamide;

5-methoxy-2-methyl-6-(2-phenoxyphenyl)pyridazin-3(2H)-one;

N-[3-(4-methoxy-1-methyl-6-oxo-1,6-dihydropyridazin-3-yl)phenyl]methanesulfonamide;

6-(5-amino-2-phenoxyphenyl)-5-methoxy-2-methylpyridazin-3(2H)-one;

N-[3-(4-methoxy-1-methyl-6-oxo-1,6-dihydropyridazin-3-yl)-4-phenoxyphenyl]acetamide;

N-[3-(4-methoxy-1-methyl-6-oxo-1,6-dihydropyridazin-3-yl)-4-phenoxyphenyl]methanesulfonamide;

N-[3-(4-methoxy-1-methyl-6-oxo-1,6-dihydropyridazin-3-yl)-4-phenoxyphenyl]-N-methylmethanesulfonamide;

N-[3-(4-methoxy-1-methyl-6-oxo-1,6-dihydropyridazin-3-yl)-4-phenoxyphenyl]propane-1-sulfonamide;

2,2,2-trifluoro-N-[3-(4-methoxy-1-methyl-6-oxo-1,6-dihydropyridazin-3-yl)-4-phenoxyphenyl]ethanesulfonamide;

N-[3-(4-methoxy-1-methyl-6-oxo-1,6-dihydropyridazin-3-yl)-4-phenoxyphenyl]cyclopentanesulfonamide;

N-[3-(4-methoxy-1-methyl-6-oxo-1,6-dihydropyridazin-3-yl)-4-phenoxyphenyl]-1-phenylmethanesulfonamide;

3,3,3-trifluoro-N-[3-(4-methoxy-1-methyl-6-oxo-1,6-dihydropyridazin-3-yl)-4-phenoxyphenyl]propane-1-sulfonamide;

Ethyl [3-(4-methoxy-1-methyl-6-oxo-1,6-dihydropyridazin-3-yl)-4-phenoxyphenyl]carbamate;

1-ethyl-3-[3-(4-methoxy-1-methyl-6-oxo-1,6-dihydropyridazin-3-yl)-4-phenoxyphenyl]urea;

N'-[3-(4-methoxy-1-methyl-6-oxo-1,6-dihydropyridazin-3-yl)-4-phenoxyphenyl]-N,N-dimethylsulfuric diamide;

4-[2-(4-methoxy-1-methyl-6-oxo-1,6-dihydropyridazin-3-yl)phenoxy]benzonitrile;

6-[2-(4-fluorophenoxy)phenyl]-5-methoxy-2-methylpyridazin-3(2H)-one;

6-[2-(3-chloro-4-fluorophenoxy)phenyl]-5-methoxy-2-methylpyridazin-3(2H)-one;

5-methoxy-6-[2-(4-methoxyphenoxy)phenyl]-2-methylpyridazin-3(2H)-one;

6-[2-(3-fluorophenoxy)phenyl]-5-methoxy-2-methylpyridazin-3(2H)-one;
6-[2-(4-chlorophenoxy)phenyl]-5-methoxy-2-methylpyridazin-3(2H)-one;
methyl {[1-methyl-6-oxo-3-(2-phenoxyphenyl)-1,6-dihydropyridazin-4-yl]oxy}acetate;
6-[2-(cyclohexyloxy)phenyl]-5-methoxy-2-methylpyridazin-3(2H)-one;
5-methoxy-2-methyl-6-[2-(pyridin-2-ylmethoxy)phenyl]pyridazin-3(2H)-one;
6-[2-(1H-indazol-5-ylmethoxy)phenyl]-5-methoxy-2-methylpyridazin-3(2H)-one;
6-[2-(2-cyclohexylethoxy)phenyl]-5-methoxy-2-methylpyridazin-3(2H)-one;
tert-butyl 4-{[2-(4-methoxy-1-methyl-6-oxo-1,6-dihydropyridazin-3-yl)phenoxy]methyl}piperidine-1-carboxylate;
5-methoxy-2-methyl-6-[2-(piperidin-4-ylmethoxy)phenyl]pyridazin-3(2H)-one;
5-methoxy-2-methyl-6-[2-(pyridin-4-ylmethoxy)phenyl]pyridazin-3(2H)-one;
6-[2-(cyclopentylmethoxy)phenyl]-5-methoxy-2-methylpyridazin-3(2H)-one;
5-methoxy-2-methyl-6-[2-(tetrahydro-2H-pyran-4-ylmethoxy)phenyl]pyridazin-3(2H)-one;
methyl 1-[1-methyl-6-oxo-3-(2-phenoxyphenyl)-1,6-dihydropyridazin-4-yl]pyrrolidine-3-carboxylate;
Ethyl 1-[1-methyl-6-oxo-3-(2-phenoxyphenyl)-1,6-dihydropyridazin-4-yl]pyrrolidine-3-carboxylate;
methyl N-[1-methyl-6-oxo-3-(2-phenoxyphenyl)-1,6-dihydropyridazin-4-yl]glycinate;
2-methyl-5-(4-methyl-3-oxopiperazin-1-yl)-6-(2-phenoxyphenyl)pyridazin-3(2H)-one;
6-(biphenyl-2-yl)-2-methylpyridazin-3(2H)-one;
2'-(1-methyl-6-oxo-1,6-dihydropyridazin-3-yl)biphenyl-3-carbonitrile;
5-(2-fluoropyridin-4-yl)-2-methyl-6-(2-phenoxyphenyl)pyridazin-3(2H)-one;
2-methyl-5-(2-oxo-1,2-dihydropyridin-4-yl)-6-(2-phenoxyphenyl)pyridazin-3(2H)-one;
2-methyl-5-(1-methyl-2-oxo-1,2-dihydropyridin-4-yl)-6-(2-phenoxyphenyl)pyridazin-3(2H)-one;
5-(2-methoxypyridin-4-yl)-2-methyl-6-(2-phenoxyphenyl)pyridazin-3(2H)-one;
N-{3-[4-(2-methoxypyridin-4-yl)-1-methyl-6-oxo-1,6-dihydropyridazin-3-yl]-4-phenoxyphenyl}methanesulfonamide;
Ethyl 3-[1-methyl-6-oxo-3-(2-phenoxyphenyl)-1,6-dihydropyridazin-4-yl]benzoate;
2-methyl-5-{3-[(4-methylpiperazin-1-yl)methyl]phenyl}-6-(2-phenoxyphenyl)pyridazin-3(2H)-one;

2-methyl-5-{4-[(4-methylpiperazin-1-yl)methyl]phenyl}-6-(2-phenoxyphenyl)pyridazin-3(2H)-one;

N-[3-(1-methyl-4-{4-[(4-methylpiperazin-1-yl)methyl]phenyl}-6-oxo-1,6-dihydropyridazin-3-yl)-4-phenoxyphenyl]methanesulfonamide;

N-{3-[1-methyl-4-(4-methylphenyl)-6-oxo-1,6-dihydropyridazin-3-yl]-4-phenoxyphenyl}methanesulfonamide;

5-(3-amino-4-methylphenyl)-2-methyl-6-(2-phenoxyphenyl)pyridazin-3(2H)-one;

4-[1-methyl-6-oxo-3-(2-phenoxyphenyl)-1,6-dihydropyridazin-4-yl]benzaldehyde;

2-methyl-5-[4-(morpholin-4-ylmethyl)phenyl]-6-(2-phenoxyphenyl)pyridazin-3(2H)-one;

2-methyl-6-(2-phenoxyphenyl)-5-[4-(piperidin-1-ylmethyl)phenyl]pyridazin-3(2H)-one;

2-methyl-5-{4-[(4-methylpiperidin-1-yl)methyl]phenyl}-6-(2-phenoxyphenyl)pyridazin-3(2H)-one;

5-{4-[(diethylamino)methyl]phenyl}-2-methyl-6-(2-phenoxyphenyl)pyridazin-3(2H)-one;

2-methyl-6-(2-phenoxyphenyl)-5-[4-(piperazin-1-ylmethyl)phenyl]pyridazin-3(2H)-one;

2-methyl-6-(2-phenoxyphenyl)-5-[4-(pyrrolidin-1-ylmethyl)phenyl]pyridazin-3(2H)-one;

5-[4-(1-hydroxypropyl)phenyl]-2-methyl-6-(2-phenoxyphenyl)pyridazin-3(2H)-one;

5-[4-(1-hydroxy-2-methylpropyl)phenyl]-2-methyl-6-(2-phenoxyphenyl)pyridazin-3(2H)-one;

5-{4-[cyclopentyl(hydroxy)methyl]phenyl}-2-methyl-6-(2-phenoxyphenyl)pyridazin-3(2H)-one;

5-[4-(1-hydroxyethyl)phenyl]-2-methyl-6-(2-phenoxyphenyl)pyridazin-3(2H)-one;

5-{4-[hydroxy(phenyl)methyl]phenyl}-2-methyl-6-(2-phenoxyphenyl)pyridazin-3(2H)-one;

5-[4-(1-hydroxybut-3-en-1-yl)phenyl]-2-methyl-6-(2-phenoxyphenyl)pyridazin-3(2H)-one;

5-[4-(hydroxymethyl)phenyl]-2-methyl-6-(2-phenoxyphenyl)pyridazin-3(2H)-one;

5-[4-(methoxymethyl)phenyl]-2-methyl-6-(2-phenoxyphenyl)pyridazin-3(2H)-one;

4-[1-methyl-6-oxo-3-(2-phenoxyphenyl)-1,6-dihydropyridazin-4-yl]benzyl acetate;

tert-butyl 4-[1-methyl-6-oxo-3-(2-phenoxyphenyl)-1,6-dihydropyridazin-4-yl]-3,6-dihydropyridine-1(2H)-carboxylate;

2-methyl-6-(2-phenoxyphenyl)-5-(1,2,3,6-tetrahydropyridin-4-yl)pyridazin-3(2H)-one;

2-methyl-5-(1-methyl-1,2,3,6-tetrahydropyridin-4-yl)-6-(2-phenoxyphenyl)pyridazin-3(2H)-one;

5-(1-acetyl-1,2,3,6-tetrahydropyridin-4-yl)-2-methyl-6-(2-phenoxyphenyl)pyridazin-3(2H)-one;

2-methyl-5-[1-(methylsulfonyl)-1,2,3,6-tetrahydropyridin-4-yl]-6-(2-phenoxyphenyl)pyridazin-3(2H)-one;

tert-butyl 4-[1-methyl-6-oxo-3-(2-phenoxyphenyl)-1,6-dihydropyridazin-4-yl]piperidine-1-carboxylate;

2-methyl-6-(2-phenoxyphenyl)-5-(piperidin-4-yl)pyridazin-3(2H)-one;

2-methyl-5-(1-methylpiperidin-4-yl)-6-(2-phenoxyphenyl)pyridazin-3(2H)-one;

5-(1-acetylpiperidin-4-yl)-2-methyl-6-(2-phenoxyphenyl)pyridazin-3(2H)-one;

2-methyl-5-[1-(methylsulfonyl)piperidin-4-yl]-6-(2-phenoxyphenyl)pyridazin-3(2H)-one;

2-methyl-5-[4-(5-methyl-1,3,4-oxadiazol-2-yl)phenyl]-6-(2-phenoxyphenyl)pyridazin-3(2H)-one;

methyl 3-{4-[1-methyl-6-oxo-3-(2-phenoxyphenyl)-1,6-dihydropyridazin-4-yl]phenyl}propanoate;

5-(4-benzylphenyl)-2-methyl-6-(2-phenoxyphenyl)pyridazin-3(2H)-one;

{4-[1-methyl-6-oxo-3-(2-phenoxyphenyl)-1,6-dihydropyridazin-4-yl]phenyl}acetonitrile;

5-[4-(5,6-dihydro-4H-1,3-oxazin-2-yl)phenyl]-2-methyl-6-(2-phenoxyphenyl)pyridazin-3(2H)-one;

2-methyl-5-[4-(2-methylpropyl)phenyl]-6-(2-phenoxyphenyl)pyridazin-3(2H)-one;

Ethyl {4-[1-methyl-6-oxo-3-(2-phenoxyphenyl)-1,6-dihydropyridazin-4-yl]phenyl}acetate;

N-{4-[1-methyl-6-oxo-3-(2-phenoxyphenyl)-1,6-dihydropyridazin-4-yl]benzyl}methanesulfonamide;

N-{4-[1-methyl-6-oxo-3-(2-phenoxyphenyl)-1,6-dihydropyridazin-4-yl]benzyl}acetamide;

N-(2-{4-[1-methyl-6-oxo-3-(2-phenoxyphenyl)-1,6-dihydropyridazin-4-yl]phenyl}ethyl)acetamide;

5-[4-(3-hydroxypropyl)phenyl]-2-methyl-6-(2-phenoxyphenyl)pyridazin-3(2H)-one;
methyl 4-[1-methyl-6-oxo-3-(2-phenoxyphenyl)-1,6-dihydropyridazin-4-yl]benzoate;
2-methyl-5-(1-methyl-1H-pyrazol-4-yl)-6-(2-phenoxyphenyl)pyridazin-3(2H)-one;
2-methyl-6-(2-phenoxyphenyl)-5-(pyridin-4-yl)pyridazin-3(2H)-one;
N-{4-[1-methyl-6-oxo-3-(2-phenoxyphenyl)-1,6-dihydropyridazin-4-yl]phenyl}acetamide;
N-{3-[1-methyl-6-oxo-3-(2-phenoxyphenyl)-1,6-dihydropyridazin-4-yl]phenyl}acetamide;
5-(4-ethoxy-3-fluorophenyl)-2-methyl-6-(2-phenoxyphenyl)pyridazin-3(2H)-one;
N,N-dimethyl-4-[1-methyl-6-oxo-3-(2-phenoxyphenyl)-1,6-dihydropyridazin-4-yl]benzamide;
N,N-dimethyl-3-[1-methyl-6-oxo-3-(2-phenoxyphenyl)-1,6-dihydropyridazin-4-yl]benzamide;
2-methyl-5-[3-(2-methylpropoxy)phenyl]-6-(2-phenoxyphenyl)pyridazin-3(2H)-one;
5-[3-fluoro-4-(propan-2-yloxy)phenyl]-2-methyl-6-(2-phenoxyphenyl)pyridazin-3(2H)-one;
4-[1-methyl-6-oxo-3-(2-phenoxyphenyl)-1,6-dihydropyridazin-4-yl]benzenesulfonamide;
5-(1-benzyl-1H-pyrazol-4-yl)-2-methyl-6-(2-phenoxyphenyl)pyridazin-3(2H)-one;
N-cyclopropyl-4-[1-methyl-6-oxo-3-(2-phenoxyphenyl)-1,6-dihydropyridazin-4-yl]benzamide;
5-(3,5-dimethyl-1H-pyrazol-4-yl)-2-methyl-6-(2-phenoxyphenyl)pyridazin-3(2H)-one;
5-(6-methoxypyridin-3-yl)-2-methyl-6-(2-phenoxyphenyl)pyridazin-3(2H)-one;
5-(4-ethoxyphenyl)-2-methyl-6-(2-phenoxyphenyl)pyridazin-3(2H)-one;
5-(isoquinolin-4-yl)-2-methyl-6-(2-phenoxyphenyl)pyridazin-3(2H)-one;
N-{4-[1-methyl-6-oxo-3-(2-phenoxyphenyl)-1,6-dihydropyridazin-4-yl]phenyl}methanesulfonamide;
N-{3-[1-methyl-6-oxo-3-(2-phenoxyphenyl)-1,6-dihydropyridazin-4-yl]phenyl}methanesulfonamide;
N-{5-[1-methyl-6-oxo-3-(2-phenoxyphenyl)-1,6-dihydropyridazin-4-yl]pyridin-3-yl}acetamide;
N-methyl-5-[1-methyl-6-oxo-3-(2-phenoxyphenyl)-1,6-dihydropyridazin-4-yl]pyridine-3-carboxamide;

2-methyl-6-(2-phenoxyphenyl)-5-[6-(propan-2-yloxy)pyridin-3-yl]pyridazin-3(2H)-one;

5-(3-acetyl-2-fluorophenyl)-2-methyl-6-(2-phenoxyphenyl)pyridazin-3(2H)-one;

5-(2,6-dimethoxypyridin-3-yl)-2-methyl-6-(2-phenoxyphenyl)pyridazin-3(2H)-one;

methyl 2-[1-methyl-6-oxo-3-(2-phenoxyphenyl)-1,6-dihydropyridazin-4-yl]benzoate;

N-methyl-4-[1-methyl-6-oxo-3-(2-phenoxyphenyl)-1,6-dihydropyridazin-4-yl]benzamide;

N-methyl-3-[1-methyl-6-oxo-3-(2-phenoxyphenyl)-1,6-dihydropyridazin-4-yl]benzamide;

2-methyl-5-[1-(3-methylbutyl)-1H-pyrazol-4-yl]-6-(2-phenoxyphenyl)pyridazin-3(2H)-one;

2-methyl-6-(2-phenoxyphenyl)-5-[2-(propan-2-yloxy)pyridin-3-yl]pyridazin-3(2H)-one;

5-(1,3-benzothiazol-5-yl)-2-methyl-6-(2-phenoxyphenyl)pyridazin-3(2H)-one;

5-(5-acetyl-2-fluorophenyl)-2-methyl-6-(2-phenoxyphenyl)pyridazin-3(2H)-one;

5-(2,3-dihydro-1,4-benzodioxin-6-yl)-2-methyl-6-(2-phenoxyphenyl)pyridazin-3(2H)-one;

5-[3-(1-methoxyethyl)phenyl]-2-methyl-6-(2-phenoxyphenyl)pyridazin-3(2H)-one;

5-[4-(1-methoxyethyl)phenyl]-2-methyl-6-(2-phenoxyphenyl)pyridazin-3(2H)-one;

5-(3-ethoxy-2-fluorophenyl)-2-methyl-6-(2-phenoxyphenyl)pyridazin-3(2H)-one;

5-(2,1,3-benzothiadiazol-5-yl)-2-methyl-6-(2-phenoxyphenyl)pyridazin-3(2H)-one;

5-[5-(benzylamino)pyridin-3-yl]-2-methyl-6-(2-phenoxyphenyl)pyridazin-3(2H)-one;

2-methyl-5-[3-(morpholin-4-yl)phenyl]-6-(2-phenoxyphenyl)pyridazin-3(2H)-one;

2-methyl-6-(2-phenoxyphenyl)-5-[6-(2,2,2-trifluoroethoxy)pyridin-3-yl]pyridazin-3(2H)-one;

2-methyl-5-[3-(morpholin-4-ylmethyl)phenyl]-6-(2-phenoxyphenyl)pyridazin-3(2H)-one;

2-methyl-6-(2-phenoxyphenyl)-5-[3-(thiomorpholin-4-ylcarbonyl)phenyl]pyridazin-3(2H)-one;

5-[5-(cyclopentylamino)pyridin-3-yl]-2-methyl-6-(2-phenoxyphenyl)pyridazin-3(2H)-one;

N-cyclopropyl-5-[1-methyl-6-oxo-3-(2-phenoxyphenyl)-1,6-dihydropyridazin-4-yl]pyridine-3-carboxamide;

N-cyclopentyl-5-[1-methyl-6-oxo-3-(2-phenoxyphenyl)-1,6-dihydropyridazin-4-yl]pyridine-3-carboxamide;

N,N-diethyl-3-[1-methyl-6-oxo-3-(2-phenoxyphenyl)-1,6-dihydropyridazin-4-yl]benzenesulfonamide;

2-methyl-5-[4-(morpholin-4-ylcarbonyl)phenyl]-6-(2-phenoxyphenyl)pyridazin-3(2H)-one;

N-cyclohexyl-N-methyl-3-[1-methyl-6-oxo-3-(2-phenoxyphenyl)-1,6-dihydropyridazin-4-yl]benzamide;

2-methyl-5-[4-(morpholin-4-yl)phenyl]-6-(2-phenoxyphenyl)pyridazin-3(2H)-one;

N-[3-(dimethylamino)propyl]-4-[1-methyl-6-oxo-3-(2-phenoxyphenyl)-1,6-dihydropyridazin-4-yl]benzamide;

2-methyl-6-(2-phenoxyphenyl)-5-[6-(piperazin-1-yl)pyridin-3-yl]pyridazin-3(2H)-one;

3-fluoro-N,N-dimethyl-5-[1-methyl-6-oxo-3-(2-phenoxyphenyl)-1,6-dihydropyridazin-4-yl]benzamide;

2-methyl-5-[2-(morpholin-4-yl)pyridin-4-yl]-6-(2-phenoxyphenyl)pyridazin-3(2H)-one;

2-methyl-5-{3-[(4-methylpiperidin-1-yl)carbonyl]phenyl}-6-(2-phenoxyphenyl)pyridazin-3(2H)-one;

2-fluoro-N,N-dimethyl-5-[1-methyl-6-oxo-3-(2-phenoxyphenyl)-1,6-dihydropyridazin-4-yl]benzamide;

2-methyl-6-(2-phenoxyphenyl)-5-[3-(pyrrolidin-1-ylsulfonyl)phenyl]pyridazin-3(2H)-one;

2-methyl-6-(2-phenoxyphenyl)-5-[3-(piperidin-1-ylcarbonyl)phenyl]pyridazin-3(2H)-one;

N,N-diethyl-4-[1-methyl-6-oxo-3-(2-phenoxyphenyl)-1,6-dihydropyridazin-4-yl]benzamide;

N-methyl-4-[1-methyl-6-oxo-3-(2-phenoxyphenyl)-1,6-dihydropyridazin-4-yl]benzenesulfonamide;

N,N-diethyl-3-[1-methyl-6-oxo-3-(2-phenoxyphenyl)-1,6-dihydropyridazin-4-yl]benzamide;

2-methyl-5-[4-(4-methylpiperazin-1-yl)phenyl]-6-(2-phenoxyphenyl)pyridazin-3(2H)-one;

2-methyl-5-(6-{[2-(morpholin-4-yl)ethyl]amino}pyridin-3-yl)-6-(2-phenoxyphenyl)pyridazin-3(2H)-one;

N-[3-(dimethylamino)propyl]-3-[1-methyl-6-oxo-3-(2-phenoxyphenyl)-1,6-dihydropyridazin-4-yl]benzamide;

5-[6-(benzylamino)pyridin-3-yl]-2-methyl-6-(2-phenoxyphenyl)pyridazin-3(2H)-one;

N-(2-cyanoethyl)-4-[1-methyl-6-oxo-3-(2-phenoxyphenyl)-1,6-dihydropyridazin-4-yl]benzamide;

2-methyl-5-[5-methyl-6-(morpholin-4-yl)pyridin-3-yl]-6-(2-phenoxyphenyl)pyridazin-3(2H)-one;

N,N-diethyl-3-fluoro-5-[1-methyl-6-oxo-3-(2-phenoxyphenyl)-1,6-dihydropyridazin-4-yl]benzamide;

N-tert-butyl-4-[1-methyl-6-oxo-3-(2-phenoxyphenyl)-1,6-dihydropyridazin-4-yl]benzamide;

N-cyclopentyl-4-[1-methyl-6-oxo-3-(2-phenoxyphenyl)-1,6-dihydropyridazin-4-yl]benzamide;

4-[1-methyl-6-oxo-3-(2-phenoxyphenyl)-1,6-dihydropyridazin-4-yl]-N-(2-methylpropyl)benzamide;

N-(3-methoxypropyl)-4-[1-methyl-6-oxo-3-(2-phenoxyphenyl)-1,6-dihydropyridazin-4-yl]benzamide;

2-methyl-5-{1-[2-(morpholin-4-yl)ethyl]-1H-pyrazol-4-yl}-6-(2-phenoxyphenyl)pyridazin-3(2H)-one;

N-(2-methoxyethyl)-4-[1-methyl-6-oxo-3-(2-phenoxyphenyl)-1,6-dihydropyridazin-4-yl]benzamide;

2-methyl-5-[2-(4-methylpiperazin-1-yl)pyridin-4-yl]-6-(2-phenoxyphenyl)pyridazin-3(2H)-one;

2-methyl-5-[3-(morpholin-4-ylcarbonyl)phenyl]-6-(2-phenoxyphenyl)pyridazin-3(2H)-one;

2-methyl-5-[3-(5-methyl-1,3,4-oxadiazol-2-yl)phenyl]-6-(2-phenoxyphenyl)pyridazin-3(2H)-one;

N-cyclopropyl-3-[1-methyl-6-oxo-3-(2-phenoxyphenyl)-1,6-dihydropyridazin-4-yl]benzamide;

2-methyl-6-(2-phenoxyphenyl)-5-[4-(pyrrolidin-1-ylsulfonyl)phenyl]pyridazin-3(2H)-one;

2-methyl-5-[6-(morpholin-4-yl)pyridin-3-yl]-6-(2-phenoxyphenyl)pyridazin-3(2H)-one;

2-methyl-6-(2-phenoxyphenyl)-5-{4-[4-(propan-2-yl)piperazin-1-yl]phenyl}pyridazin-3(2H)-one;

N,N-diethyl-2-fluoro-5-[1-methyl-6-oxo-3-(2-phenoxyphenyl)-1,6-dihydropyridazin-4-yl]benzamide;

N-benzyl-4-[1-methyl-6-oxo-3-(2-phenoxyphenyl)-1,6-dihydropyridazin-4-yl]benzamide;

2-methyl-6-(2-phenoxyphenyl)-5-[4-(pyrrolidin-1-ylcarbonyl)phenyl]pyridazin-3(2H)-one;

2-methyl-6-(2-phenoxyphenyl)-5-[6-(piperidin-1-yl)pyridin-3-yl]pyridazin-3(2H)-one;

N-cyclohexyl-4-[1-methyl-6-oxo-3-(2-phenoxyphenyl)-1,6-dihydropyridazin-4-yl]benzamide;

N-[2-(dimethylamino)ethyl]-3-[1-methyl-6-oxo-3-(2-phenoxyphenyl)-1,6-dihydropyridazin-4-yl]benzamide;

2-methyl-6-(2-phenoxyphenyl)-5-{4-[(phenylamino)methyl]phenyl}pyridazin-3(2H)-one;

2-methyl-5-[2-(4-methylpiperazin-1-yl)pyrimidin-5-yl]-6-(2-phenoxyphenyl)pyridazin-3(2H)-one;

methyl {4-[1-methyl-6-oxo-3-(2-phenoxyphenyl)-1,6-dihydropyridazin-4-yl]phenyl}acetate;

5-(5-ethoxypyridin-3-yl)-2-methyl-6-(2-phenoxyphenyl)pyridazin-3(2H)-one;

2-methyl-5-[4-(methylamino)phenyl]-6-(2-phenoxyphenyl)pyridazin-3(2H)-one;

5-[2-(dimethylamino)pyrimidin-5-yl]-2-methyl-6-(2-phenoxyphenyl)pyridazin-3(2H)-one;

{3-[1-methyl-6-oxo-3-(2-phenoxyphenyl)-1,6-dihydropyridazin-4-yl]phenyl}acetonitrile;

2-methyl-5-(1-methyl-1H-pyrrol-2-yl)-6-(2-phenoxyphenyl)pyridazin-3(2H)-one;

2-methyl-6-(2-phenoxyphenyl)-5-(pyridin-3-yl)pyridazin-3(2H)-one;

2-methyl-5-(6-methylpyridin-3-yl)-6-(2-phenoxyphenyl)pyridazin-3(2H)-one;

5-(3-methoxyphenyl)-2-methyl-6-(2-phenoxyphenyl)pyridazin-3(2H)-one;

2-methyl-5-(4-methyl-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazin-7-yl)-6-(2-phenoxyphenyl)pyridazin-3(2H)-one;

5-(4-fluoro-3-methoxyphenyl)-2-methyl-6-(2-phenoxyphenyl)pyridazin-3(2H)-one;

5-(2-aminopyridin-4-yl)-2-methyl-6-(2-phenoxyphenyl)pyridazin-3(2H)-one;

5-(3-acetylphenyl)-2-methyl-6-(2-phenoxyphenyl)pyridazin-3(2H)-one;

N-ethyl-4-[1-methyl-6-oxo-3-(2-phenoxyphenyl)-1,6-dihydropyridazin-4-yl]benzamide;

5-(3-fluoro-4-methoxyphenyl)-2-methyl-6-(2-phenoxyphenyl)pyridazin-3(2H)-one;

5-(1,5-dimethyl-1H-pyrazol-4-yl)-2-methyl-6-(2-phenoxyphenyl)pyridazin-3(2H)-one;

2-methyl-5-(2-methylpyridin-4-yl)-6-(2-phenoxyphenyl)pyridazin-3(2H)-one;

2-methyl-5-[1-(2-methylpropyl)-1H-pyrazol-4-yl]-6-(2-phenoxyphenyl)pyridazin-3(2H)-one;

2-methyl-5-(4-methylpyridin-3-yl)-6-(2-phenoxyphenyl)pyridazin-3(2H)-one;

2-methyl-5-(1-methyl-1H-indol-5-yl)-6-(2-phenoxyphenyl)pyridazin-3(2H)-one;

5-[3-(dimethylamino)phenyl]-2-methyl-6-(2-phenoxyphenyl)pyridazin-3(2H)-one;

5-(2-fluoro-5-methoxyphenyl)-2-methyl-6-(2-phenoxyphenyl)pyridazin-3(2H)-one;

2-methyl-5-(5-methylfuran-2-yl)-6-(2-phenoxyphenyl)pyridazin-3(2H)-one;

5-(1-ethyl-1H-pyrazol-4-yl)-2-methyl-6-(2-phenoxyphenyl)pyridazin-3(2H)-one;

5-(3-methoxypyridin-4-yl)-2-methyl-6-(2-phenoxyphenyl)pyridazin-3(2H)-one;

2-methyl-5-(1-methyl-1H-indol-2-yl)-6-(2-phenoxyphenyl)pyridazin-3(2H)-one;

N,N-dimethyl-5-[1-methyl-6-oxo-3-(2-phenoxyphenyl)-1,6-dihydropyridazin-4-yl]pyridine-3-carboxamide;

5-[5-(dimethylamino)pyridin-3-yl]-2-methyl-6-(2-phenoxyphenyl)pyridazin-3(2H)-one;

5-butyl-2-methyl-6-(2-phenoxyphenyl)pyridazin-3(2H)-one;

methyl 1-methyl-6-oxo-3-(2-phenoxyphenyl)-1,6-dihydropyridazine-4-carboxylate;

methyl (2E)-3-[1-methyl-6-oxo-3-(2-phenoxyphenyl)-1,6-dihydropyridazin-4-yl]prop-2-enoate;

methyl 3-[1-methyl-6-oxo-3-(2-phenoxyphenyl)-1,6-dihydropyridazin-4-yl]propanoate;

5-acetyl-2-methyl-6-(2-phenoxyphenyl)pyridazin-3(2H)-one;

6-(2-benzylphenyl)-2-methylpyridazin-3(2H)-one;

N-[4-(2,4-difluorophenoxy)-3-(4-ethoxy-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)phenyl]ethanesulfonamide;

N-[4-(2,4-difluorophenoxy)-3-{1-methyl-4-[2-(morpholin-4-yl)ethoxy]-6-oxo-1,6-dihydropyridin-3-yl}phenyl]ethanesulfonamide;

N-(3-(4-(cyclopropylmethoxy)-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-4-(2,4-difluorophenoxy)phenyl)ethanesulfonamide;

N-(4-(2,4-difluorophenoxy)-3-(4-(2-(dimethylamino)ethoxy)-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)phenyl)ethanesulfonamide;

N-{4-(2,4-difluorophenoxy)-3-[1-methyl-6-oxo-4-(propan-2-yloxy)-1,6-dihydropyridin-3-yl]phenyl}ethanesulfonamide;

N-{4-(2,4-difluorophenoxy)-3-[1-methyl-4-(2-methylpropoxy)-6-oxo-1,6-dihydropyridin-3-yl]phenyl}ethanesulfonamide;

N-{4-(2,4-difluorophenoxy)-3-[1-methyl-6-oxo-4-(tetrahydrofuran-3-ylmethoxy)-1,6-dihydropyridin-3-yl]phenyl}ethanesulfonamide;

N-[4-(2,4-difluorophenoxy)-3-(1-methyl-6-oxo-4-propoxy-1,6-dihydropyridin-3-yl)phenyl]ethanesulfonamide; and

N-{4-(2,4-difluorophenoxy)-3-[1-methyl-6-oxo-4-(2,2,2-trifluoroethoxy)-1,6-dihydropyridin-3-yl]phenyl}ethanesulfonamide.

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

3-methyl-5-(2-phenoxyphenyl)pyridin-2(1H)-one;

N-[3-(5-methyl-6-oxo-1,6-dihydropyridin-3-yl)-4-phenoxyphenyl]methanesulfonamide;

N-[3-(5-methyl-6-oxo-1,6-dihydropyridin-3-yl)-4-phenoxyphenyl]acetamide;

N-[4-(2,4-difluorophenoxy)-3-(5-methyl-6-oxo-1,6-dihydropyridin-3-yl)phenyl]methanesulfonamide;

N-[4-(2,4-difluorophenoxy)-3-(5-methyl-6-oxo-1,6-dihydropyridin-3-yl)phenyl]ethanesulfonamide;

N-[4-(2,4-difluorophenoxy)-3-(5-methyl-6-oxo-1,6-dihydropyridin-3-yl)phenyl]acetamide;

N-{4-[(4,4-difluorocyclohexyl)oxy]-3-(5-methyl-6-oxo-1,6-dihydropyridin-3-yl)phenyl}methanesulfonamide; and

N-{4-[(4,4-difluorocyclohexyl)oxy]-3-(5-methyl-6-oxo-1,6-dihydropyridin-3-yl)phenyl}ethanesulfonamide

In another aspect, the present disclosure relates to pharmaceutical compositions comprising a pharmaceutically acceptable exicipient and a therapeutically effective amount of a compound of formula I, or a pharmaceutically acceptable salt thereof.

In another aspect, the present disclosure relates to a pharmaceutical composition comprising a therapeutically effective amount of a compound of formula (I) as disclosed herein, or a pharmaceutically acceptable acceptable salt thereof, in combination with a pharmaceutically acceptable carrier.

In another aspect, the present disclosure relates to methods of treating cancer in a subject comprising administering a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable acceptable salt thereof, to a subject in need

thereof. In certain embodiments, the cancer is selected from the group consisting of: acoustic neuroma, acute leukemia, acute lymphocytic leukemia, acute myelocytic leukemia (monocytic, myeloblastic, 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, Waldenström's macroglobulinemia, testicular tumors, uterine cancer and Wilms' tumor. In certain embodiments, the methods further comprise administering a therapeutically effective amount of at least one additional therapeutic agent.

In another aspect, the present disclosure relates to methods of treating a disease or condition in a subject comprising administering a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable 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. In certain embodiments, the methods further comprise administering a therapeutically effective amount of at least one additional therapeutic agent. In certain embodiments, the methods further comprise administering a therapeutically effective amount of at least one additional therapeutic agent.

In another aspect, the present disclosure relates to methods of treating AIDS in a subject comprising administering a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable acceptable salt thereof, to a subject in need thereof. In certain embodiments, the methods further comprise administering a therapeutically effective amount of at least one additional therapeutic agent.

In another aspect, the present disclosure relates to methods of treating obesity in a subject comprising administering a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable acceptable salt thereof, to a subject in need thereof. In certain embodiments, the methods further comprise administering a therapeutically effective amount of at least one additional therapeutic agent.

In another aspect, the present disclosure relates to methods of treating type II diabetes in a subject comprising administering a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable acceptable salt thereof, to a subject in need thereof. In certain embodiments, the methods further comprise administering a therapeutically effective amount of at least one additional therapeutic agent.

In another aspect, the present disclosure relates to a use of a compound of formula (I) as disclosed herein, or a pharmaceutically acceptable acceptable salt thereof, in the manufacture of a medicament for treating cancer, wherein the medicament is to be administered to a subject in need thereof.

In another aspect, the present disclosure relates to a use of a compound of formula (I) as disclosed herein, or a pharmaceutically acceptable acceptable salt thereof in the manufacture of a medicament treating a disease or condition, wherein the medicament is to be administered 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.

In another aspect, the present disclosure relates to a use of a compound of formula (I) as disclosed herein, or a pharmaceutically acceptable acceptable salt thereof in the manufacture of a medicament for treating AIDS, wherein the medicament is to be administered to a subject in need thereof.

In another aspect, the present disclosure relates to a use of a compound of formula (I) as disclosed herein, or a pharmaceutically acceptable acceptable salt thereof in the manufacture of a medicament for treating obesity, wherein the medicament is to be administered to a subject in need thereof.

In another aspect, the present disclosure relates to a use of a compound of formula (I) as disclosed herein, or a pharmaceutically acceptable acceptable salt thereof in the manufacture of a medicament for treating type II diabetes, wherein the medicament is to be administered to a subject in need thereof.

DETAILED DESCRIPTION

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 "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, "C_1-C_6 alkyl" refers to an alkyl substituent containing from 1 to 6 carbon atoms and "C_1-C_3 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, *n*-heptyl, *n*-octyl, *n*-nonyl, and *n*-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 (C_1-C_6 alkylene) or of 1 to 4 carbon atoms or of 1 to 3 carbon atoms (C_1-C_3 alkylene). Examples of alkylene and alkylenyl include, but are not limited to, -CH_2-, -CH_2CH_2-, -$CH_2CH_2CH_2$-, -$CH_2CH_2CH_2CH_2$-, and -$CH_2CH(CH_3)CH_2$-.

The term "C_3-C_{14} cycloalkyl" (alone or in combination with another term(s)) means a saturated cyclic hydrocarbyl substituent containing from 3 to 14 carbon ring atoms. The term cycloalkyl includes monocyclic cycloalkyl, bicyclic cycloalkyl, bridged cycloalkyl, and spiro cycloalkyl groups. Examples of monocyclic cycloalkyl groups include, but are not limited to, cyclopropyl (cyclopropanyl), cyclobutyl (cyclobutanyl), cyclopentyl (cyclopentanyl), cyclopentenyl, cyclopentadienyl, cyclohexyl (cyclohexanyl), cyclohexenyl, cycloheptyl, cyclooctyl, etc. Unless otherwise indicated, the term "C_3-C_8 monocyclic cycloalkyl" refers to monocylic cycloalkyl groups containing from 3 to 8 carbons. In certain embodiments, a "C_3-C_{14} cycloalkyl" is a "C_3-C_8 monocyclic cycloalkyl" or a "C_3-C_7 monocyclic cycloalkyl."

In a spirocyclic cycloalkyl group, one atom is common to two different rings. Examples of spirocyclic cycloalkyls include spiro[2.2]pentanyl, spiro[2.4]heptanyl, and spiro[2.5]octanyl. Unless otherwise indicated, the term "C_5-C_8 spirocyclic cycloalkyl" refers to spirocyclic cycloalkyl groups containing from 5 to 8 carbons.

In a bridged cycloalkyl, the rings share at least two common non-adjacent atoms. Examples of bridged cycloalkyls include bicyclo[2.2.1]heptanyl, and adamantanyl. Unless

otherwise indicated, the term "C_7-C_{10} bridged cycloalkyl" refers to a bridged cycloalkyl groups containing from 5 to 10 carbons.

A bicyclic ring cycloalkyl is a C_5-C_7 monocyclic cycloalkyl fused to a monocyclic C_5-C_7 cycloalkyl ring. Non-limiting examples of bicyclic cycloalkyls include decahydronaphthalenyl, octahydro-1H-indenyl, octahydropentalenyl, and decahydroazulenyl. 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 bridged groups include bicyclo[3.1.1]heptanyl, bicyclo[2.2.1]heptanyl, bicyclo[2.2.2]octanyl, bicyclo[3.2.2]nonanyl, bicyclo[3.3.1]nonanyl, and bicyclo[4.2.1]nonanyl, tricyclo[3.3.1.$0^{3,7}$]nonanyl (octahydro-2,5-methanopentalenyl or noradamantanyl), and tricyclo[3.3.1.$1^{3,7}$]decanyl (adamantanyl).

The term "cycloalkenyl" (alone or in combination with another term(s)) means a partially saturated cycloalkyl substituent containing from 3 to 14 carbon ring atoms. A cycloalkenyl may be a monocyclic carbon ring, which typically contains from 3 to 8 carbon ring atoms (i.e., a C_3-C_8 cycloalkenyl) and more typically from 4 to 6 carbon ring atoms (i.e., a C_4-C_6 cycloalkenyl). Examples of single-ring cycloalkenyls include cyclopentenyl, and cyclohexenyl. A cycloalkenyl may alternatively be bicyclic. Examples of bicyclic cycloalkenyls include bridged and spirocyclic cycloalkyls.

The term "heterocycloalkyl" as used herein, means a 3 to 15 membered non-aromatic monocylic or bicyclic ring radical containing carbon atoms and one to three heteroatoms independently selected from O, N, or S. The nitrogen and sulfur heteroatoms in the heterocycloalkyl rings may optionally be oxidized (e.g. 1,1-dioxidotetrahydrothienyl, 1,2-dioxido-1,2-thiazolidinyl, 1,1-dioxidothiomorpholinyl)) and the nitrogen atoms may optionally be quarternized. Unless otherwise indicated, the foregoing heterocycloalkyls can be C-attached or N-attached where such is possible and which results in the creation of a stable structure. For example, piperidinyl can be piperidin-1-yl (N-attached) or piperidin-4-yl (C-attached).

Examples of heterocycloalkyls include 3- to 8-membered monocyclic heterocycloalkyls, 8-12 membered bicyclic heterocycloalkyls, and 7-15 membered bridged bicyclic heterocycloalkyls.

The phrase "3- to 8-membered monocyclic heterocycloalkyl" means a non-aromatic cyclic group having carbon atoms and 1 to 3 heteroatoms independently selected from S, N or O, wherein when two O atoms or one O atom and one S atom are present, the two O atoms or one O atom and one S atom are not bonded to each other, respectively. Illustrative examples of 3- to 8-membered monocyclic heterocycloalkyl include aziridin-1-yl, 1-oxa-

cyclobutan-2-yl, tetrahydrofuran-3-yl, morpholin-4-yl, 2-thiacyclohex-1-yl, 2-oxo-2-thiacyclohex-1-yl, 2,2-dioxo-2-thiacyclohex-1-yl, and 4-methyl-piperazin-2-yl.

A "3-membered monocyclic heterocycloalkyl" is a 3-membered, monocyclic cycloalkyl ring having 2 carbon atoms and 1 heteroatom selected from the group consisting of: 1 O; 1 S; and 1 N. Illustrative examples of 3-membered monocyclic heterocycloalkyls include oxiranyl, aziridinyl, and thiiranyl.

A "4-membered monocyclic heterocycloalkyl" is a 4-membered, monocyclic cycloalkyl ring having 3 carbon atoms and 1 heteroatom selected from the group consisting of: 1 O; 1 S; and 1 N. Illustrative examples of 4-membered monocyclic heterocycloalkyls include oxetanyl, azetidinyl, and thietanyl.

A "5-membered monocyclic heterocycloalkyl" is a 5-membered, monocyclic cycloalkyl ring having from 1 to 4 carbon atoms and from 1 to 3 heteroatoms selected from the group consisting of: 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; and 1 O and 2 N. Illustrative examples of 5-membered monocyclic heterocycloalkyls include tetrahydrofuranyl, dihydrofuranyl, tetrahydrothienyl, dihydrothienyl, imidazolidinyl, oxazolidinyl, imidazolinyl, isoxazolidinyl, pyrrolidinyl, 2-pyrrolinyl, and 3-pyrrolinyl.

A "6-membered monocyclic heterocycloalkyl" is a 6-membered, monocyclic cycloalkyl ring having from 3 to 5 carbon atoms and from 1 to 3 heteroatoms selected from the group consisting of: 1 O; 2 O; 3 O; 1 S; 2 S; 3 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 O and 1 N; and 1 O and 2 N. Illustrative examples of 6-membered monocyclic heterocycloalkyls include tetrahydropyranyl, dihydropyranyl, dioxanyl, 1,3-dioxolanyl, 1,4-dithianyl, hexahydropyrimidine, morpholinyl, piperazinyl, piperidinyl, 2H-pyranyl, 4H-pyranyl, pyrazolidinyl, pyrazolinyl, 1,2,3,6-tetrahydropyridinyl, tetrahydrothiopyranyl, thiomorpholinyl, thioxanyl, and trithianyl.

A "7-membered monocyclic heterocycloalkyl" is a 7-membered, monocyclic cycloalkyl ring having from 5 or 6 carbon atoms and from 1 to 3 heteroatoms selected from the group consisting of: 1 O; 2 O; 1 S; 2 S; 1 N; 2 N; 1 S, 1 O, and 1 N; 1 S and 1 N; 1 S and 2 N; 1 S and 10; 1 S and 2 O; 1 O and 1 N; and 1 O and 2 N. Illustrative examples of 7-membered monocyclic heterocycloalkyls include azepanyl, 2,3,4,5-tetrahydro-1H-azepinyl, oxepanyl, 2,3,4,5-tetrahydro-1H-oxepinyl, thiepanyl, and 2,3,4,5-tetrahydro-1H-thiepinyl.

An "8-membered monocyclic heterocycloalkyl" is a 8-membered, monocyclic cycloalkyl ring having from 5 to 7 carbon atoms and from 1 to 3 heteroatoms selected from the group consisting of: 1 O; 2 O; 3 O; 1 S; 2 S; 3 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 1O; 1 S and 2 O; 1 O and 1 N; and 1 O and 2 N. Illustrative

examples of 8-membered monocyclic heterocycloalkyls include azocanyl, thiocanyl, oxocanyl, 3,4,5,6-tetrahydro-2H-oxocinyl, etc.

A bicyclic 8-12 membered heterocycloalkyl is a monocyclic 5 to 7 membered heterocycloalkyl fused to a phenyl group, or a monocyclic 5 to 7 membered heterocycloalkyl fused to a monocyclic C_5-C_7 cycloalkyl, or a monocyclic 5 to 7 membered heterocycloalkyl fused to a monocyclic 5 to 7 membered heterocycloalkyl. Representative examples of bicyclic heterocycloalkyls 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 heterocycloalkyl and the bicyclic heterocycloalkyl 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 heterocycloalkyls 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[*b*]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). The term "6- to 9-membered bridged bicyclic heterocycloalkyl" refers to a ring radical which is either saturated or unsaturated, and which is the result of the fusion of 5-, 6-, or 7-membered monocyclic heterocycloalkyl to a 3-, 4-, or 5-membered monocyclic heterocycloalkyl; or a 5-, 6-, or 7-membered monocyclic heterocycloalkyl to a C_5-C_7-cycloalkyl, wherein the fusion junctions have 1 to 3 intervening ring atoms. The term "6- to 9-membered bridged bicyclic heterocycloalkyl" includes saturated and unsaturated "6- to 9-membered bridged bicyclic heterocycloalkyls." "6- to 9-membered bridged bicyclic heterocycloalkyls" may be substituted as set out above for alkyl. Examples of "6- to 9-membered bridged bicyclic heterocycloalkyls" include 3-azabicyclo[4.2.1]nonanyl and 7-azabicyclo[2.2.1]heptanyl.

A spiro heterocycloalkyl is a 7 to 15 membered heterocycloalkyl wherein two substituents on the same carbon atom of a monocyclic 5 to 7 membered heterocycloalkyl ring together with said carbon atom form a second ring system selected from a monocyclic cycloalkyl, a bicyclic cycloalkyl, a monocyclic heterocycloalkyl, or a bicyclic heterocycloalkyl. Examples of spiro heterocycloalkyls include, but not limited to, 6-azaspiro[2.5]oct-6-yl, 1'H, 4H-spiro[1,3-benzodioxine-2,4'-piperidin]-1'-yl, 1'H, 3H-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 heterocycloalkyls can be unsubstituted or substituted. The monocyclic, the bicyclic and the spiro heterocycloalkyls 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 heterocycloalkyl rings may optionally be oxidized (e.g. 1,1-dioxidotetrahydrothienyl, 1,2-dioxido-1,2-thiazolidinyl, 1,1-dioxidothiomorpholinyl)) and the nitrogen atoms may optionally be quarternized.

An aryl group is an aromatic hydrocarbon radical. Furthermore, the term "aryl" includes multicyclic aryl groups, bicyclic, e.g., naphthyl. Typical aryl groups include phenyl, and naphthyl. The term "9- to 12-membered bicyclic aryl" is a ring structure formed by the fusion of a benzene ring to: (1) a C_5-C_8 monocyclic cycloalkyl (e.g., indanyl; 1,2,3,4-tetrahydro-naphthalenyl; 6,7,8,9-tetrahydro-5H-benzocycloheptenyl, etc.); or (2) another benzene ring (e.g., naphthalenyl); wherein the fusion junctions are at adjacent carbons on the benzene ring.

The term "heteroaryl" as used herein, means a monocyclic 5 or 6 membered heteroaryl and a bicyclic 8 to 12 membered heteroaryl.

A "5-membered heteroaryl" is a 5-membered, monocyclic, aromatic ring radical having from 1 to 4 carbon atoms and from 1 to 4 heteroatoms selected from the group consisting of: 1 O; 1 S; 1 N; 2 N; 3 N; 4 N; 1 S and 1 N; 1 S and 2 N; 1 O and 1 N; and 1 O and 2 N. Illustrative examples of 5-membered heteroaryls include, but are not limited to, furanyl, 2-furanyl, 3-furanyl, imidazolyl, isoxazolyl, isothiazolyl, oxadiazolyl, oxazolyl, pyrazolyl, pyrrolyl, 2- or 3-pyrrolyl, thienyl, 2-thienyl, 3-thienyl, tetrazolyl, thiazolyl, thiadiazolyl, and triazolyl.

A "6-membered heteroaryl" is a 6-membered, monocyclic, aromatic ring radical having from 3 to 5 carbon atoms and from 1 to 3 heteroatoms selected from the group consisting of: 1 N; 2 N; and 3 N. Illustrative examples of 6-membered heteroaryls include, but are not limited to, pyridinyl, 2-, 3-, or 4-pyridinyl, pyrimidinyl, 2-, 4-, or 5-pyrimidinyl, pyrazinyl, pyridazinyl, 3- or 4-pyridazinyl, 2-pyrazinyl, and triazinyl.

An "8- to 12-membered bicyclic heteroaryl" is a ring structure formed by the fusion of 5- or 6-membered heteroaryl to: (1) an independently selected 5-membered heteroaryl; (2) an independently selected 6-membered heteroaryl (e.g., naphthyridinyl, pteridinyl, phthalazinyl, purinyl, etc.); (3) a C_5-C_8 monocyclic cycloalkyl; (4) a 5- to 7-membered heterocycloalkyl; or (5) a benzene ring (e.g., benzimidazolyl, benzofuranyl, benzofurazanyl, 2H-1-benzopyranyl, benzothiadiazine, benzothiazinyl, benzothiazolyl, benzothiophenyl, benzoxazolyl, cinnolinyl, furopyridinyl, indolinyl, indolizinyl, indolyl, or 2-, 3-, 4-, 5-, 6-, or

7-indolyl, 3H-indolyl, quinazolinyl, quinoxalinyl, isoindolyl, and isoquinolinyl), wherein the fusion junctions are at adjacent ring atoms. The fusion junctions may be at nitrogen (e.g., indolizine) or carbon atoms in the 5- or 6-membered heteroaryl.

The term "hydrogen" (alone or in combination with another term(s)) means a hydrogen radical, and may be depicted as -H.

The term "hydroxy" (alone or in combination with another term(s)) means -OH.

The term "carboxy" (alone or in combination with another term(s)) means -C(O)-OH.

The term "amino" (alone or in combination with another term(s)) means $-NH_2$.

The term "halogen" or "halo" (alone or in combination with another term(s)) means a fluorine radical (which may be depicted as -F), chlorine radical (which may be depicted as -Cl), bromine radical (which may be depicted as -Br), or iodine radical (which may be depicted as -I). The prefix "halo" indicates that the substituent to which the prefix is attached is substituted with one or more independently selected halogen radicals. For example, haloalkyl means an alkyl substituent in which at least one hydrogen radical is replaced with a halogen radical. Examples of haloalkyls include chloromethyl, 1-bromoethyl, fluoromethyl, difluoromethyl, trifluoromethyl, and 1,1,1-trifluoroethyl. It should be recognized that if a substituent is substituted by more than one halogen radical, those halogen radicals may be identical or different (unless otherwise stated). Examples of haloalkyl include C_1-C_3 haloalkyls, which is a halogenated alkyl containing from 1 to 3 carbons.

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 heteroaryl moiety is a heteroaryl moiety in which at least one non-hydrogen radical is in the place of a hydrogen radical on the heterocyclic ring. 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) 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 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 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 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 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.

Compounds

Geometric isomers may exist in the present compounds. Compounds of this invention may contain carbon-carbon double bonds or carbon-nitrogen double bonds in the E or Z configuration, wherein the term "E" represents higher order substituents on opposite sides of the carbon-carbon or carbon-nitrogen double bond and the term "Z" represents higher order substituents on the same side of the carbon-carbon or carbon-nitrogen double bond as determined by the Cahn-Ingold-Prelog Priority Rules. The compounds of this invention may also exist as a mixture of "E" and "Z" isomers. Substituents around a cycloalkyl or heterocycloalkyl may also be designated as being of cis or trans configuration.

Compounds of this invention may contain asymmetrically substituted carbon atoms in the R or S configuration, in which the terms "R" and "S" are as defined by the IUPAC 1974 Recommendations for Section E, Fundamental Stereochemistry, Pure Appl. Chem. (1976) 45, 13-10. Compounds having asymmetrically substituted carbon atoms with equal amounts of R and S configurations are racemic at those carbon atoms. Atoms with an excess of one configuration over the other are assigned the configuration present in the higher amount, preferably an excess of about 85%-90%, more preferably an excess of about 95%-99%, and still more preferably an excess greater than about 99%. Accordingly, this invention includes racemic mixtures, relative and absolute stereoisomers, and mixtures of relative and absolute stereoisomers.

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 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 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 heterocycloalkyl group. Substituents around a carbon-carbon double bond or a carbon-nitrogen double bond are designated as being of Z or E configuration and substituents around a cycloalkyl or heterocycloalkyl 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.

Isotope Enriched or Labeled Compounds

Compounds of the invention can exist in isotope-labeled or -enriched form containing one or more atoms having an atomic mass or mass number different from the atomic mass or mass number most abundantly found in nature. Isotopes can be radioactive or non-radioactive isotopes. Isotopes of atoms such as hydrogen, carbon, phosphorous, sulfur, fluorine, chlorine, and iodine include, but are not limited to, ^{2}H, ^{3}H, ^{13}C, ^{14}C, ^{15}N, ^{18}O, ^{32}P, ^{35}S, ^{18}F, ^{36}Cl, and ^{125}I. Compounds that contain other isotopes of these and/or other atoms are within the scope of this invention.

In another embodiment, the isotope-labeled compounds contain deuterium (^{2}H), tritium (^{3}H) or ^{14}C isotopes. Isotope-labeled compounds of this invention can be prepared by the general methods well known to persons having ordinary skill in the art. Such isotope-labeled compounds can be conveniently prepared by carrying out the procedures disclosed in the Examples disclosed herein and Schemes by substituting a readily available isotope-labeled reagent for a non-labeled reagent. In some instances, compounds may be treated with isotope-labeled reagents to exchange a normal atom with its isotope, for example, hydrogen for deuterium can be exchanged by the action of a deuteric acid such as D_2SO_4/D_2O. In addition to the above, relevant procedures and intermediates are disclosed, for instance, in Lizondo, J et al., *Drugs Fut*, 21(11), 1116 (1996); Brickner, S J *et al., J Med Chem*, 39(3), 673 (1996); Mallesham, B et al., *Org Lett*, 5(7), 963 (2003); PCT publications WO1997010223, WO2005099353, WO1995007271, WO2006008754; US Patent Nos. 7538189; 7534814; 7531685; 7528131; 7521421; 7514068; 7511013; and US Patent Application Publication Nos. 20090137457; 20090131485; 20090131363; 20090118238; 20090111840; 20090105338; 20090105307; 20090105147; 20090093422; 20090088416; and 20090082471, the methods are hereby incorporated by reference.

The isotope-labeled compounds of the invention may be used as standards to determine the effectiveness of BET bromodomain inhibitors in binding assays. Isotope containing compounds have been used in pharmaceutical research to investigate the in vivo metabolic fate of the compounds by evaluation of the mechanism of action and metabolic pathway of the nonisotope-labeled parent compound (Blake et al. *J. Pharm. Sci.* 64, 3, 367-391 (1975)). Such metabolic studies are important in the design of safe, effective therapeutic drugs, either because the *in vivo* active compound administered to the patient or because the metabolites produced from the parent compound prove to be toxic or carcinogenic (Foster et al., Advances in Drug Research Vol. 14, pp. 2-36, Academic press, London, 1985; Kato et al.,

J. *Labelled Comp. Radiopharmaceut.*, 36(10):927-932 (1995); Kushner et al., *Can. J. Physiol. Pharmacol.*, 77, 79-88 (1999).

In addition, non-radio active isotope containing drugs, such as deuterated drugs called "heavy drugs," can be used for the treatment of diseases and conditions related to BET bromodomain activity. Increasing the amount of an isotope present in a compound above its natural abundance is called enrichment. Examples of the amount of enrichment include from about 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 16, 21, 25, 29, 33, 37, 42, 46, 50, 54, 58, 63, 67, 71, 75, 79, 84, 88, 92, 96, to about 100 mol %. Replacement of up to about 15% of normal atom with a heavy isotope has been effected and maintained for a period of days to weeks in mammals, including rodents and dogs, with minimal observed adverse effects (Czajka D M and Finkel A J, Ann. N.Y. Acad. Sci. 1960 84: 770; Thomson J F, Ann. New York Acad. Sci 1960 84: 736; Czakja D M et al., Am. J. Physiol. 1961 201: 357). Acute replacement of as high as 15%-23% in human fluids with deuterium was found not to cause toxicity (Blagojevic N et al. in "Dosimetry & Treatment Planning for Neutron Capture Therapy", Zamenhof R, Solares G and Harling O Eds. 1994. Advanced Medical Publishing, Madison Wis. pp.125-134; Diabetes Metab. 23: 251 (1997)).

Stable isotope labeling of a drug can alter its physico-chemical properties such as pKa and lipid solubility. These effects and alterations can affect the pharmacodynamic response of the drug molecule if the isotopic substitution affects a region involved in a ligand-receptor interaction. While some of the physical properties of a stable isotope-labeled molecule are different from those of the unlabeled one, the chemical and biological properties are the same, with one important exception: because of the increased mass of the heavy isotope, any bond involving the heavy isotope and another atom will be stronger than the same bond between the light isotope and that atom. Accordingly, the incorporation of an isotope at a site of metabolism or enzymatic transformation will slow said reactions potentially altering the pharmacokinetic profile or efficacy relative to the non-isotopic compound.

Schemes

General Synthesis

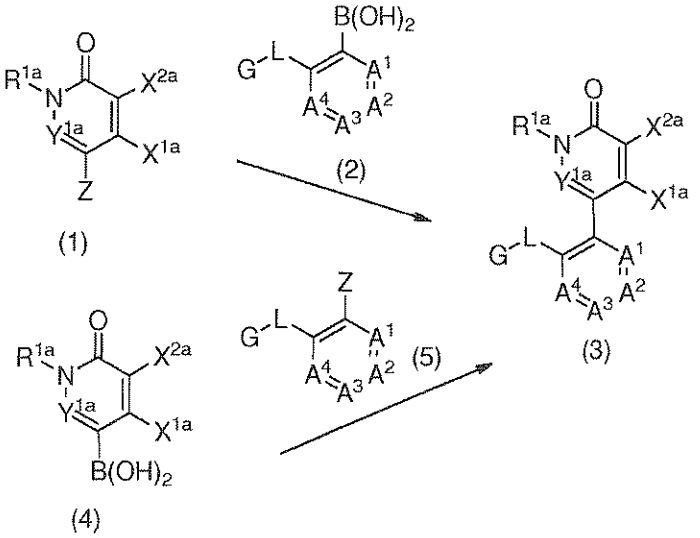
The compounds described herein, including compounds of general formula (I) and specific examples, can be prepared by methodologies in the reaction schemes depicted in schemes 1-8. The variables A^1, A^2, A^3, A^4, R^{1a}, X^{1a}, X^{2a}, R^{1b}, X^{1b}, X^{2b}, Y^{1a}, Y^{1b}, X^3, L, and G used in the 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: Boc for tert-butoxycarbonyl; DME for 1,2-dimethoxyethane, DMF for dimethylformamide, DMSO for dimethyl sulfoxide, EtOH for ethanol; EtOAc for ethyl acetate; HATU for O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate, MeOH for methanol; mCPBA for 3-chloroperbenzoic acid; NH_4OAc for ammonium acetate; $Pd(PPh_3)_4$ for tetrakis(triphenylphosphine)palladium(0); $PdCl_2(PPh_3)_2$ for bis(triphenylphosphine)palladium(II) dichloride; $PdCl_2$(dppf) for [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II); THF for tetrahydrofuran, TFA for trifluoroacetic acid, TLC for thin layer chromatography, and triflate for trifluoromethanesulfonate.

Compounds of general formula (I) wherein X^3 is L-G and J is IIa may be prepared using the general procedure as outlined in Scheme 1. Conversion of (1), wherein Z is Cl, Br, I, or triflate to compounds of general formula (3) may be achieved by reaction of (1) with a boronic acid of formula (2) or derivative thereof (e.g., pinacol ester) under Suzuki coupling conditions (N. Miyama and A. Suzuki, Chem. Rev. 1995, 95:2457-2483, J. Organomet. Chem. 1999, 576:147-148). For example, the coupling reaction may be conducted 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 (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), bis(triphenylphosphine)palladium(II) dichloride, and palladium(II)acetate. Examples of suitable bases that may be employed include, but 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-trioxa-6-phosphaadamante, 2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl (X-phos), and 1,1'- bis(diphenylphosphanyl) ferrocene. Non-limiting examples of suitable solvent include methanol, ethanol, dimethoxyethane, N,N-dimethylformamide, dimethylsulfoxide, dioxane, tetrahydropyran, and water,or a mixture thereof.

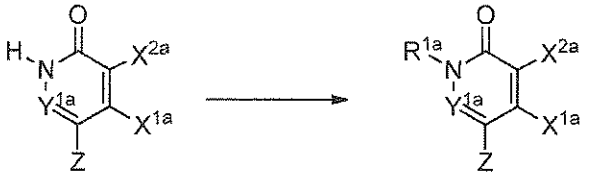
Alternatively, compounds of formula (3) may be synthesized by reaction of boronic acid (4) or a derivative thereof (e.g., pinacol ester) under Suzuki coupling conditions as described above with compounds of formula (5) wherein Z is Br, Cl, I, or triflate.

Scheme 1



Compounds of formula (1) wherein R^{1a} is C_1-C_3 alkyl may be may be prepared using synthetic routes such as, but not limited to, those illustrated in Scheme 2. Reaction of compounds of formula (6), wherein Z is Br, Cl, I, with a C_1-C_3 alkyl halide, in the presence of a base such as carbonate of cesium, sodium, or potassium and in a solvent such as, but not limited to, dimethylformamide, tetrahydrofuran, or dimethylsulfoxide, provides intermediates of formula (1) wherein R^{1a} is C_1-C_3 alkyl. The reaction may be conducted at temperature such as, but not limited to, about 25 °C to about 60 °C.

Scheme 2



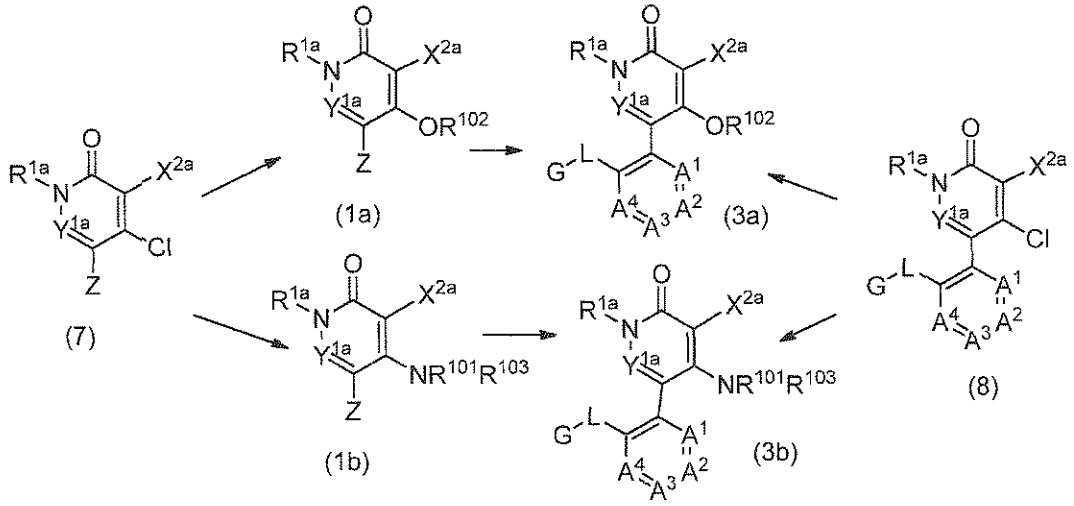
Compounds of formula (1) wherein X^{1a} is -C_2-C_4 alkenylene-C(O)-O-C_1-C_3 alkyl, -O-C_1-C_4alkyl, an optionally substituted heterocycloalkyl or optionally substituted heterocycloalkenyl, wherein said heterocycloalkyl or heterocycloalkenyl is attached to the parent moiety through a nitrogen atom, or X^{1a} is NHR^{101} wherein R^{101} is C(O)-C_1-C_3 alkyl, -SO_2-C_1-C_3 alkyl or -C_1-C_3 alkylene-C(O)-C_1-C_3 alkyl, may be prepared using general procedure as outlined in Scheme 3. Displacement of the chlorine atom of formula (7) with an alcohol of formula $R^{102}OH$ wherein R^{102} is C_1-C_4alkyl provides compounds of formula (1a). Displacement of the chlorine atom may be accomplished in a solvent such as, but not limited to, methanol or ethanol, and in the presence of a base such as, but not limited to, sodium or sodium hydride, and at a temperature from about 40 °C to about 80 °C. Displacement of the

chlorine atom of formula (7) with an amine of formula $R^{101}R^{103}NH$ wherein R^{101} is as defined above and R^{103} is hydrogen, or R^{101}, R^{103}, and the nitrogen atom to which they are attached form a heterocycloalkyl or heterocycloalkenyl, provides compounds of formula (1b). Displacement of the chlorine atom by $R^{101}R^{103}NH$ may be accomplished in a solvent such as, but not limited to, methanol or ethanol, and in the presence of a base such as, but not limited to, triethylamine or diisopropylethylamine, and at a temperature from about 60 °C to about 100 °C.

Utilizing reaction conditions such as those described in Scheme 1, intermediates (1a) and (1b) may be converted to target molecules (3a) and (3b) respectively by reacting with the appropriate boronic acids or derivatives thereof.

Alternatively, target molecules (3a) and (3b) may be synthesized from the reaction of (8) with $R^{102}OH$ and $R^{101}R^{103}NH$ using reaction conditions discussed above.

Scheme 3

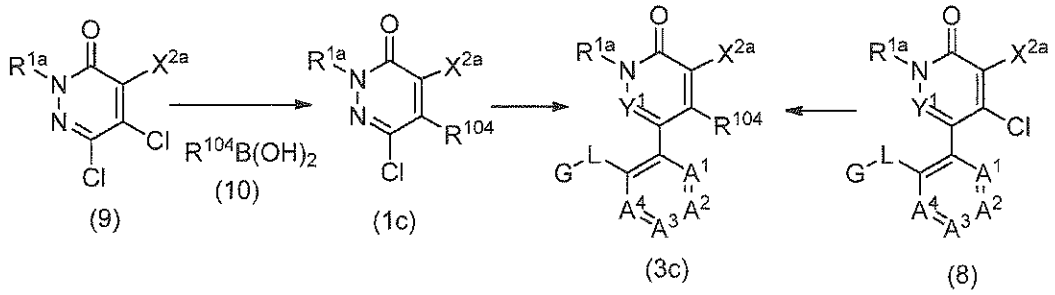


Compounds of formula (1) wherein X^{1a} is aryl, heteroaryl, or heterocycloalkenyl may be prepared using reaction conditions described in Scheme 4. Reaction of 5,6-dichloropyridazin-3(2H)-ones (9) with boronic acids of formula (10) wherein R^{104} is aryl, heteroaryl, or heterocycloalkenyl, or a derivative thereof (e.g., pinacol ester) under Suzuki coupling conditions as described in scheme 1 provides intermediates of formula (1c). Utilizing reaction conditions such as those described in Scheme 1, intermediates (1c) may be converted to target molecules (3c) by reacting with the appropriate boronic acids or derivatives thereof.

Alternatively, target molecules (3c) may be synthesized from the reaction of (8) with boronic acids of formula (10) wherein R^{104} is aryl, heteroaryl, or heterocycloalkenyl, or a

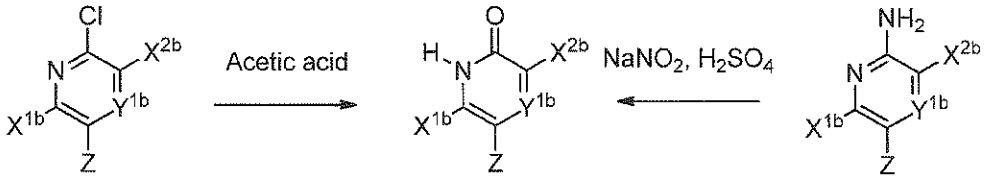
derivative thereof (e.g., pinacol ester) under Suzuki coupling conditions using reaction conditions discussed above.

Scheme 4



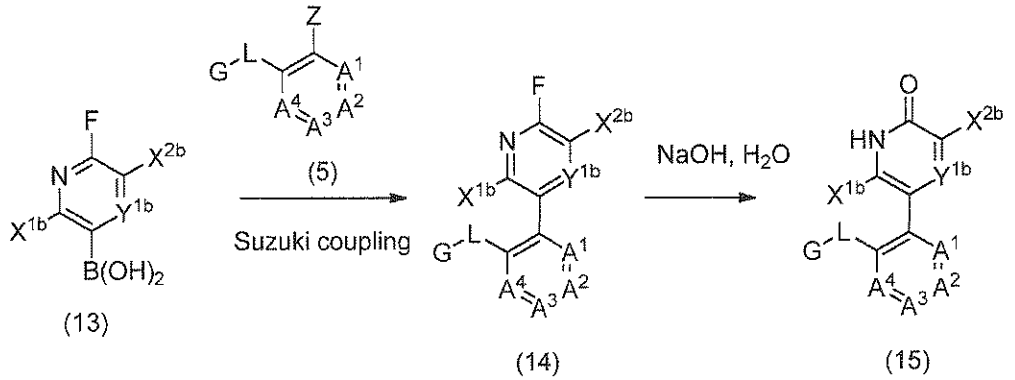
Compounds of formula (6) wherein X^2 is hydrogen may be prepared using general synthetic scheme as shown in Scheme 5. Hydrolysis of chloride (11) in an acid such as, but not limited to, acetic acid, and at a temperature from about 100 °C to about 150 °C provides compounds of formula (6a). Compounds of formula (6a) may also be prepared by reaction of compounds of formula (12) in the presence of sodium nitrite and an acid such as, but not limited to, sulfuric acid in a solvent such as water, and at a temperature from about 0 °C to about 25 °C.

Scheme 5



Compounds of general formula (I) wherein X^3 is L-G and J is IIb may be prepared using general procedure outlined in Scheme 6. Reaction of boronic acids (12), or a derivative thereof (e.g., pinacol ester) with compounds of formula (5) wherein Z is Br, Cl, I, or triflate under Suzuki coupling conditions as described in Scheme 1 provides compounds of formula (14). Hydrolysis of compounds of formula (14) in the presence of a base, such as, but not limited to, sodium hydroxide or potassium hydroxide, in a solvent such as water, dioxane, or tetrahydrofuran, or mixtures thereof, and at temperatures of 80 °C to about 140 °C, provides compounds of formula (15). Hydrolysis of compounds of formula (14) may also be accomplished by reaction in an acid, such as but not limited to acetic acid, and water at temperatures of about 80 °C to about 120 °C, to provide compounds of formula (15).

Scheme 6

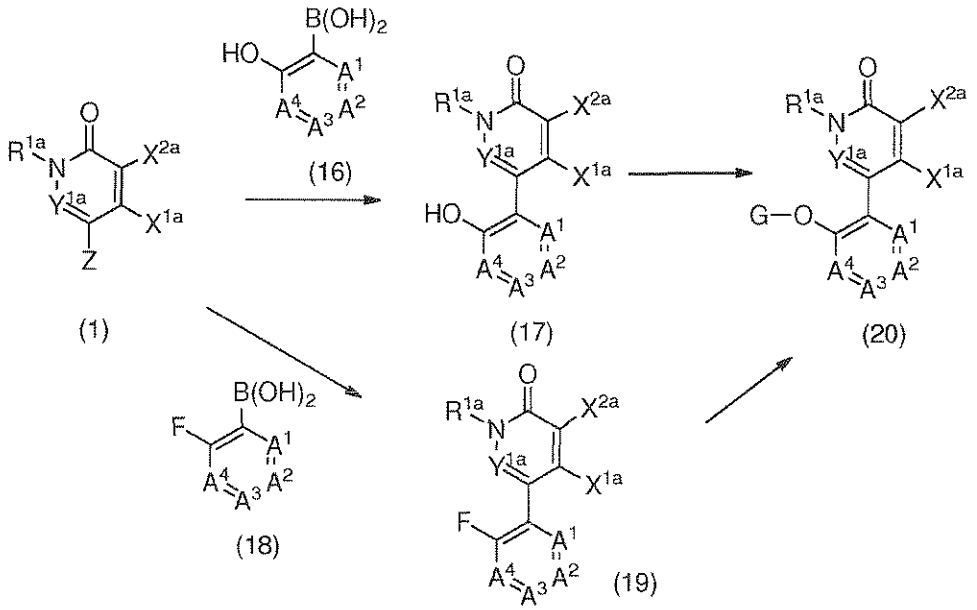


Compounds of general formula (I) wherein X^3 is L-G and L is –O- may be prepared as shown in Scheme 7.

Compounds of formula (17) may be prepared from reaction of (1) with a boronic acid of formula (16) or derivatives thereof (e.g. pinacol ester) using Suzuki coupling conditions as described in Scheme 1. Treatment of the resulting phenols of formula (17) with an appropriate halide of formula G-Z wherein Z is halogen such as Br, Cl, or F, in the presence of a base such as carbonate of cesium, potassium or sodium, in a solvent such as dimethylformamide or dimethylsulfoxide, and at temperatures ranging from about room temperature to about 100 °C provides compounds of formula (20). Alternatively, reaction of phenol (17) with an alcohol of formula G-OH in the presence of triphenylphosphine and in the presence of diisopropylazodicarboxylate or diethylazodicarboxylate, in a solvent such as tetrahydrofuran or dioxane, and at temperatures ranging from about room temperature to about 100 °C provides compounds of formula (20).

Alternatively, compounds of formula (20) may be obtained by (a) coupling of (1) wherein Z is triflate, Cl, Br, or I, with boronic acid (18) or derivative thereof using reaction conditions described in Scheme 1; and (b) displacement of the fluorine atom of the resulting intermediates (19) with an alcohol of formula G-OH. Displacement of the fluorine atom may be accomplished 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, carbonate of cesium, potassium, or sodium, or sodium hydride, and at a temperature from about 40 °C to about 120 °C.

Scheme 7

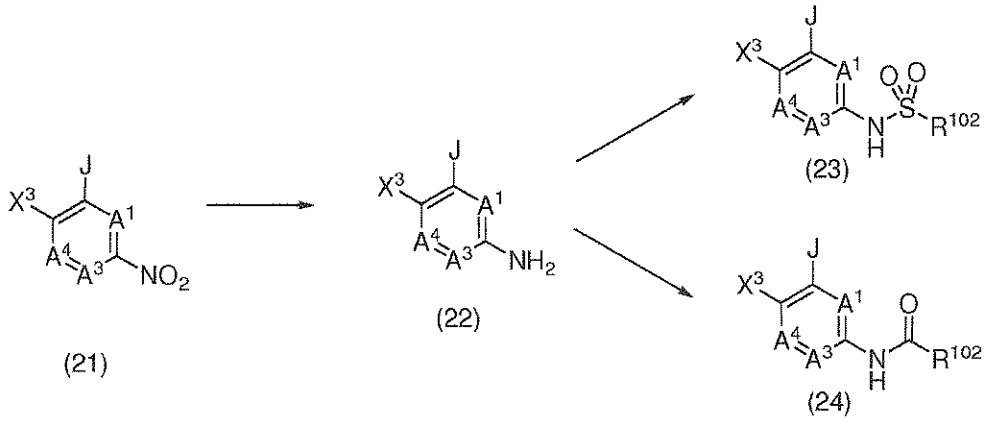


Compounds of general formula (I) wherein A^2 is CR^{18} and R^{18} is $NHC(O)R^{105}$ or $NHSO_2R^{106}$ wherein R^{105} is C_1-C_3 alkyl, and R^{106} is C_1-C_3 alkyl, C_1-C_3 haloalkyl, C_3-C_7 cycloalkyl, aryl, heteroaryl, C_1-C_3 alkylene-cycloalkyl, C_1-C_3 alkylene-heterocycloalkyl, C_1-C_3 alkylene-heteroaryl, or C_1-C_3 alkylene-aryl.

Reduction of the nitro compounds of formula (21) to the anilines of formula (22) may be achieved with iron powder in the presence of ammonium chloride in a solvent such as, but not limited to, tetrahydrofuran, ethanol, or water, or a mixture thereof, and at a temperature from about 80 °C to about 120 °C. Alternatively the reduction may be carried out with tin chloride in hydrochloric acid at a temperature from about 80 °C to about 120 °C. Transformation of (21) to (22) may also be conducted in the presence of a catalyst such as platinum oxide or palladium on charcoal, in a solvent such as ethanol or methanol and under hydrogen pressure. Treatment of aniline (22) with sulfonyl chlorides of formula $R^{106}SO_2Cl$, in the presence of a base such as triethylamine or diisopropylethylamine in a solvent such as dichloromethane or tetrahydrofuran and at a temperature from about 0 °C to about 40 °C provides sulfonamides (23).

Treatment of aniline (22) with carboxylic acids of formula $R^{105}COOH$ in the presence of a coupling agent such as HATU or EDAC and a base such as diisopropylethylaminde or triethylamine, and in a solvent such as tetrahydrofuran, dioxane, or dimethylformamide, at a temperature from about 0 °C to about 40 °C provides amides of formula (24).

Scheme 8



It can be appreciated that the synthetic schemes and specific examples as illustrated in the synthetic examples section are illustrative and are not to be read as limiting the scope of the invention as it is defined in the appended claims. All alternatives, modifications, and equivalents of the synthetic methods and specific examples are included within the scope of the claims.

Optimum reaction conditions and reaction times for each individual step can vary depending on the particular reactants employed and substituents present in the reactants used. Unless otherwise specified, solvents, temperatures and other reaction conditions can be readily selected by one of ordinary skill in the art. Specific procedures are provided in the Examples section. Reactions can be worked up 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 typically can be prepared from commercially available materials.

Routine experimentations, including appropriate manipulation of the reaction conditions, reagents and sequence of the synthetic route, protection of any chemical functionality that can 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 can be found in T. Greene and P. Wuts, Protecting Groups in Organic Synthesis (3rd ed.), John Wiley & Sons, NY (1999), which is incorporated herein by reference in its entirety. Synthesis of the compounds of the invention can be accomplished

by methods analogous to those described in the synthetic schemes described hereinabove and in specific examples.

Starting materials, if not commercially available, can be prepared by procedures 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 is required, it typically can be obtained by carrying out one of the procedures described herein using an optically active 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, precipitation, crystallization, or enzymatic resolution).

Similarly, when a pure geometric isomer of a compound is required, it typically can be prepared 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.

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 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 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, 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 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 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 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.

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.

Pharmaceutical Compositions

This invention also provides for pharmaceutical compositions comprising a 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 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), bucally 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 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, 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 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 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

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, 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 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 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 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% (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 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; f) absorption accelerators such as quaternary ammonium compounds; g) wetting agents such as cetyl alcohol and glycerol monostearate; h) absorbents 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 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 μg/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 LD_{50} 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.

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 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 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.

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.

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 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 conditions with a pharmaceutically acceptable carrier and any needed preservatives, buffers or propellants which may be required. Opthalmic 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 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, 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, bucally, intravaginally, 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.

A "bromodomain-mediated disorder or condition" is characterized by the participation of one or more bromodomains (e.g., BRD4) 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 (monocytic, myeloblastic, 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, Waldenström'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, 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.

Compounds of formula I, or pharmaceutically acceptable salts thereof, may be used to treat AIDS. In addition, compounds of formula I, or pharmaceutically acceptable salts thereof, may be used to treat obesity. Compounds of formula I, or pharmaceutically acceptable salts thereof, may be used to treat type II diabetes.

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-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 include, such as radiation, alkylating agents, angiogenesis inhibitors, antibodies, antimetabolites, antimitotics, 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 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

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, proteosome inhibitors, purine analogs, pyrimidine analogs, receptor tyrosine kinase inhibitors, 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. 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).

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'-OCH_3-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, 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.

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

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 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 EFGR or ErbB3 and EGFR.

Alkylating agents include altretamine, AMD-473, AP-5280, apaziquone, 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 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), 5-azacitidine, XELODA® (capecitabine), carmofur, 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, 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 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-((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 (obatoclax) and the like.

Bcr-Abl kinase inhibitors include DASATINIB® (BMS-354825), GLEEVEC® (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, 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.

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

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, PU24FCl, PU-3, radicicol, SNX-2112, STA-9090 VER49009 and 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-DM1, CR-011-vcMMAE, PSMA-ADC, MEDI-547, SGN-19Am SGN-35, 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 inhibitors such as GSK923295A and the like.

JAK-2 inhibitors include CEP-701 (lesaurtinib), XL019 and INCB018424 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.

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

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.

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.

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.

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

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, pirarbucin, pixantrone, rubitecan, sobuzoxane, SN-38, tafluposide, topotecan and the like.

Antibodies include AVASTIN® (bevacizumab), CD40-specific antibodies, chTNT-1/B, denosumab, ERBITUX® (cetuximab), HUMAX-CD4® (zanolimumab), IGF1R-specific antibodies, lintuzumab, PANOREX® (edrecolomab), RENCAREX® (WX G250), RITUXAN® (rituximab), ticilimumab, trastuzimab, CD20 antibodies types I and II and the like.

Hormonal therapies include ARIMIDEX® (anastrozole), AROMASIN® (exemestane), arzoxifene, CASODEX® (bicalutamide), CETROTIDE® (cetrorelix), 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), 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® (fosrelin, goserelin) and the like.

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.

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

Proteasome inhibitors include VELCADE® (bortezomib), MG132, NPI-0052, PR-171 and the like.

Examples of immunologicals include interferons and other immune-enhancing agents. 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-muHMFG1), PROVENGE® (sipuleucel-T), sargaramostim, 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 I:poly 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: 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), DIMERICINE® (T4N5 liposome lotion), discodermolide, DX-8951f (exatecan mesylate), enzastaurin, EPO906 (epithilone B), GARDASIL® (quadrivalent human papillomavirus (Types 6, 11, 16, 18) recombinant vaccine), GASTRIMMUNE®, GENASENSE®, GMK (ganglioside conjugate vaccine), GVAX® (prostate cancer vaccine), halofuginone, histerelin, hydroxycarbamide, ibandronic acid, IGN-101, IL-13-PE38, IL-13-PE38QQR (cintredekin 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), 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® (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 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-alphavbeta3 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 autoimmune disease, where examples of the agents include, such as methotrexate, 6-mercaptopurine, 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, nedocromil, ketotifen, ipratropium and oxitropium, cyclosporin, FK506, rapamycin, mycophenolate mofetil, leflunomide, NSAIDs, for example, ibuprofen, corticosteroids such as prednisolone, phosphodiesterase inhibitors, adensosine agonists, antithrombotic agents, complement inhibitors, adrenergic agents, agents which interfere with signalling by proinflammatory cytokines such as TNFα or IL-1 (e.g., NIK, IKK, p38 or MAP kinase inhibitors), IL-1β converting enzyme inhibitors, T-cell signalling inhibitors such as kinase inhibitors, metalloproteinase inhibitors, sulfasalazine, 6-mercaptopurines, 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-1RI, sIL-1RII, sIL-6R), antiinflammatory cytokines (e.g. IL-4, IL-10, IL-11, IL-13 and TGFβ), 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 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-18 BP, 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-1β 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 TNFα or IL-1 (e.g. NIK, IKK, or MAP kinase inhibitors); IL-1β converting enzyme inhibitors; TNFα 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 TGFβ). 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, (p75TNFRIgG (etanercept) and p55TNFRIgG (LENERCEPT™) 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-1β 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-β1a (AVONEX®; Biogen); interferon-β1b (BETASERON®; Chiron/Berlex); interferon α-n3) (Interferon Sciences/Fujimoto), interferon-α (Alfa Wassermann/J&J), interferon β1A-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 S1P1 agonist, NSAIDs, for example, ibuprofen, corticosteroids such as prednisolone, phosphodiesterase inhibitors, adensosine agonists, antithrombotic agents, complement inhibitors, adrenergic agents, agents which interfere with signalling by proinflammatory cytokines such as TNFα or IL-1 (e.g., NIK, IKK, p38 or MAP kinase inhibitors), IL-1β 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-1RI, sIL-1RII, sIL-6R) and antiinflammatory cytokines (e.g. IL-4, IL-10, IL-13 and TGFβ).

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, α-immunokine NNSO3, ABR-215062, AnergiX.MS, chemokine receptor antagonists, BBR-2778, calagualine, CPI-1189, LEM (liposome encapsulated mitoxantrone), THC.CBD (cannabinoid agonist), MBP-8298, mesopram (PDE4 inhibitor), MNA-715, anti-IL-6 receptor antibody, neurovax, pirfenidone 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, rofecoxib, sulfasalazine, methotrexate, azathioprine, minocyclin, prednisone, and anti-TNF antibodies, D2E7 (HUMIRA®), CA2 (infliximab), CDP 571, TNFR-Ig constructs, (p75TNFRIgG (ENBREL®) and p55TNFRIgG (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, 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, 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, cephalexin, 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 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, 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 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, PUVA, UVB, sulfasalazine, ABT-874 and ustekinamab.

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, 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, 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-1β 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-11 or anti-cytokine antibodies, for example, fonotolizumab (anti-IFNg antibody), or anti-receptor 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, (p75TNFRIgG (etanercept) and p55TNFRIgG (LENERCEPT™).

A compound of Formula (I) may also be co-administered with insulin for the treatment of type I diabetes.

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 compounds of the invention can also be co-administered with a therapeutically effective amount of one or more agents used in the treatment of obesity, where examples of the agents include orlistat.

The compounds of the invention can also be co-administered with a therapeutically effective amount of one or more agents used in the treatment of type II diabetes, where examples of the agents include, alpha glucosidase inhibitors, insulin, metformin, sulfonylureas (e.g,. carbutamide, acetohexamide, chlorpropamide, glibenclamide, glibornuride, gliclazide, glimepiride, glipizide, gliquidone, glisoxepide, glyclopyramide, tolbutamide, and tolazamide), nonsulfonylureas (e.g., nateglinide, and repaglinide), and thiazolidinediones (e.g., pioglitazone).

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

Examples

1. 2-methyl-6-(2-phenoxyphenyl)pyridazin-3(2H)-one.

1A. 6-chloro-2-methylpyridazin-3(2H)-one. A mixture of 6-chloropyridazin-3(2H)-one (5.04 g, 38.6 mmol) and iodomethane (2.88 mL, 46.3 mmol) in dimethylformamide (30 mL) was treated with Cs_2CO_3 (15.10 g, 46.3 mmol) at ambient temperature. The reaction mixture was stirred at ambient temperature for 4 hours. 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 $MgSO_4$, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel eluting with 20% ethyl acetate in hexanes to give 4.55 g (82%) of the title compound.

1B. 2-methyl-6-(2-phenoxyphenyl)pyridazin-3(2H)-one. A mixture of Example 1A (29 mg, 0.20 mmol), 2-phenoxyphenylboronic acid (0.056 g, 0.260 mmol, 1.3 equivalents),

$Pd(PPh_3)_4$ (0.011 g, 5 mol%) and cesium fluoride (0.091 g, 0.6 mmol) in DME (2 mL) and methanol (1 mL) was heated under microwave condition (120 °C, 40 min.). 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 $MgSO_4$, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel eluting with 30% ethyl acetate in hexanes to give the title compound (0.041 g, 74 % yield). ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.75 (d, J = 9.77 Hz, 1H), 7.66 (dd, J = 7.78, 1.68 hz, 1H), 7.45-7.49 (m, 1H), 7.35-7.40 (m, 2H), 7.26-7.30 (m, 2H), 7.11-7.15 (m, 1 H), 6.97-7.01 (m, 3H), 6.94 (d, J = 9.77 Hz, 1H), 3.68 (s, 3H). MS (ESI+) m/z 279.0 $(M+H)^+$.

2. 6-[2-(benzyloxy)phenyl]-2-methylpyridazin-3(2H)-one. Example 2 was prepared according to the procedure used for the preparation of Example 1B, substituting 2-(benzyloxy)phenylboronic acid for 2-phenoxyphenylboronic acid, to provide the title compound. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.78 (d, J = 9.77 Hz, 1H), 7.49 (dd, J = 7.48, 1.68 hz, 1H), 7.30-7.46 (m, 6H), 7.25 (d, J = 7.63 Hz, 1H), 7.06 (t, J = 7.02 Hz, 1H), 6.92 (d, J = 9.46 Hz, 1H), 5.19 (s, 2H), 3.70 (s, 3H). MS (ESI+) m/z 293.1 $(M+H)^+$.

3. 4-[2-(1-methyl-6-oxo-1,6-dihydropyridazin-3-yl)phenoxy]benzonitrile.

A mixture of 6-(2-hydroxyphenyl)-2-methylpyridazin-3(2H)-one (0.100 g, 0.495 mmol) (prepared according to the procedure reported in *Synthetic Communications*, 2002, *32*, 1675), 4-fluorobenzonitrile (0.072 g, 0.593 mmol), and sodium hydride (14.2 mg, 0.593 mmol) in N-methylpyrrolodone (4 mL) was heated at 130 °C for 16 hours. The reaction mixture was cooled to ambient temperature, taken up in ethyl acetate, and washed with 1 N aqueous sodium hydroxide solution followed by brine. The organic layer was separated, dried over anhydrous sodium sulfate, filtered, and evaporated under reduced pressure. The residue was purified by flash chromatography (silica gel, 30-100% ethyl acetate/hexane) to provide the title compound. 1H NMR (300 MHz, DMSO-d_6) δ 7.77 - 7.87 (m, 2 H) 7.71 - 7.76 (m, 1 H) 7.66 - 7.71 (m, 1 H) 7.52 - 7.61 (m, 1 H) 7.36 - 7.47 (m, 1 H) 7.22 (d, *J*=7.93 Hz, 1 H) 7.02 - 7.10 (m, 2 H) 6.89 - 6.97 (m, 1 H) 3.60 (s, 3 H). MS (ESI+) m/z 304.3 $(M+H)^+$.

4. 6-[2-(cyclopentyloxy)phenyl]-2-methylpyridazin-3(2H)-one. A mixture of 6-(2-hydroxyphenyl)-2-methylpyridazin-3(2H)-one (0.120 g, 0.593 mmol) (prepared according to the procedure reported in *Synthetic Communications*, 2002, *32*, 1675), 4- bromocyclopentane (0.097 g, 0.653 mmol), and sodium hydride (17.1 mg, 0.712 mmol) in N-methylpyrrolodone (4 mL) was stirred at ambient temperature for 72 h. The reaction mixture was taken up in

ethyl acetate, and washed with 1 N aqueous sodium hydroxide solution followed by brine. The organic layer was separated, dried over anhydrous sodium sulfate, filtered, and evaporated under reduced pressure. The residue was purified by flash chromatography (silica gel, 10-30% ethyl acetate/hexane) to provide the title compound. ^{1}H NMR (300 MHz, DMSO- d_6) δ 7.68 (d, J=9.49 Hz, 1 H) 7.47 (dd, J=7.80, 1.70 Hz, 1 H) 7.35 - 7.44 (m, 1 H) 7.12 (d, J=7.80 Hz, 1 H) 7.01 (t, J=6.95 Hz, 1 H) 6.94 (d, J=9.49 Hz, 1 H) 4.85 - 4.95 (m, 1 H) 3.70 (s, 3 H) 1.82 - 1.97 (m, 2 H) 1.52 - 1.77 (m, 6 H). MS (ESI+) m/z 271.3 $(M+H)^+$.

5. *N*-{4-(2,4-difluorophenoxy)-3-[1-methyl-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-3-yl]phenyl}methanesulfonamide.

5A. 5-bromo-1-methyl-4-(trifluoromethyl)pyridin-2(1H)-one. Example 5A was prepared according to the procedure used for the preparation of Example 1A, substituting 5-bromo-4-(trifluoromethyl)-1,2-dihydropyridin-2-ol for 6-chloropyridazin-3(2H)-one, to provide the title compound.

5B. 2-bromo-1-(2,4-difluorophenoxy)-4-nitrobenzene. 2-Bromo-1-fluoro-4-nitrobenzene (15 g, 68.2 mmol), 2,4-difluorophenol (7.82 ml, 82 mmol), and cesium carbonate (26.7 g, 82 mmol) were combined in DMSO (75 mL) then heated to 110°C for 1 hour. After cooling, to the reaction mixture was added water (1000 mL) and brine (1000 mL), and the mixture was extracted with ethyl acetate (3 x 200 mL). The combined organics were washed with brine, dried ($MgSO_4$), filtered, and concentrated under reduced pressure to give a crude solid which was used in the next step without additional purification.

5C. 3-bromo-4-(2,4-difluorophenoxy)aniline. A mixture of Example 5B (22.5 g, 68.2 mmol), iron powder (19.0 g, 341 mmol), and ammonium chloride (7.30 g, 136 mmol) in tetrahydrofuran (117 ml), ethanol (117 ml), and water (39.0 ml) was refluxed at 100°C for 2 hours. The mixture was cooled just below reflux, filtered through Celite. The filter cake was washed with warm MeOH (3x50 mL). The solution was concentrated under reduced pressure, neutralized to a pH of 8 with saturated $NaHCO_3$ (150 mL), and extracted with ethyl acetate (3x100 mL). The combined organics were washed with brine, dried ($MgSO_4$), filtered, concentrated, and purified by flash chromatography (silica gel, 0-15% ethyl acetate/hexane gradient) to provide the title compound (8.1 g, 85%).

5D. 4-(2,4-difluorophenoxy)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline. Example 5C (14.3 g, 47.7 mmol), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (24 g, 95 mmol), potassium acetate (10.3 g, 105 mmol), 1,3,5,7-tetramethyl-6-phenyl-2,4,8-trioxa-6-phosphaadamantane (1.39 g, 4.77 mmol), and

tris(dibenzylideneacetone)dipalladium(0) (1.31 g, 1.43 mmol) were degassed under argon for 30 minutes. Dioxane (200 mL), degassed with argon for 30 minutes, was then added by cannula transfer and the reaction mixture heated at 80°C for 22 hours. The cooled mixture was vacuum filtered through Celite, rinsed with ethyl acetate (100 mL), and washed with brine (150 mL) and water (150 mL). The aqueous phase was extracted with ethyl acetate (3 x 150 mL). The combined organics were washed with brine, dried ($MgSO_4$), gravity filtered, then concentrated under reduced pressure. Purification by flash chromatography (silica gel, 0-25% ethyl acetate/hexane gradient) afforded the title compound (14.2 g, 88%).

5E. 5-(5-amino-2-(2,4-difluorophenoxy)phenyl)-1-methyl-4-(trifluoromethyl)pyridin-2(1H)-one. Example 5E was prepared according to the procedure used for the preparation of Example 1B, substituting Example 5D for 2-phenoxyphenylboronic acid, and Example 5A for Example 1A, respectively, to provide the title compound.

5F. *N*-{4-(2,4-difluorophenoxy)-3-[1-methyl-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-3-yl]phenyl}methanesulfonamide. Example 5F was prepared according to the procedure used for the preparation of Example 22, substituting Example 5E for Example 20C to provide the title compound. ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.74 (s, 1H), 7.93 (s, 1H), 7.46-7.31 (m, 1H), 7.31-7.00 (m, 4H), 6.89-6.75 (m, 2H), 3.47 (s, 3H), 2.96 (s, 3H). MS (ESI+) m/z 475.3 $(M+H)^+$.

6. 2-methyl-6-[2-(pyridin-2-yloxy)phenyl]pyridazin-3(2H)-one. Example 6 was prepared according to the procedure used for the preparation of Example 3, substituting 2-fluoropyridine for 4-fluorobenzonitrile, to provide the title compound. ^{1}H NMR (300 MHz, DMSO- d_6) δ 8.08 (dd, *J*=5.35, 1.78 Hz, 1 H) 7.79 - 7.88 (dd, *J*=6.74, 1.59 Hz, 1 H) 7.63 - 7.68 (m, 1 H) 7.63 (d, *J*=9.52 Hz, 1 H) 7.47 - 7.55 (m, 1 H) 7.32 - 7.39 (m, 1 H) 7.20 (dd, *J*=8.33, 1.19 Hz, 1 H) 7.07 - 7.12 dd, *J*=4.76, 0.79 Hz, 1 H) 7.02 (d, *J*=8.33 Hz, 1 H) 6.89 (d, *J*=9.52 Hz, 1 H) 3.60 (s, 3 H). MS (ESI+) m/z 280.2 $(M+H)^+$.

7. 2-methyl-6-{2-[4-(trifluoromethyl)phenoxy]phenyl}pyridazin-3(2H)-one. Example 7 was prepared according to the procedure used for the preparation of Example 3, substituting 1-fluoro-4-(trifluoromethyl)benzene for 4-fluorobenzonitrile, to provide the title compound. ^{1}H NMR (300 MHz, DMSO- d_6) δ 7.66 - 7.76 (m, 4 H) 7.51 - 7.59 (m, 1 H) 7.36 - 7.43 (m, 1 H) 7.19 (dd, *J*=8.13, 0.99 Hz, 1 H) 7.11 (d, *J*=8.33 Hz, 2 H) 6.94 (d, *J*=9.52 Hz, 1 H) 3.62 (s, 3 H). MS (ESI+) m/z 347.0 $(M+H)^+$.

8. 2-methyl-6-{2-[4-(methylsulfonyl)phenoxy]phenyl}pyridazin-3(2H)-one. Example 8 was prepared according to the procedure used for the preparation of Example 3, substituting

1-fluoro-4-(methylsulfonyl)benzene for 4-fluorobenzonitrile, to provide the title compound. ^{1}H NMR (300 MHz, DMSO- d_6) δ 7.86 - 7.93 (m, 2 H) 7.71 - 7.77 (m, 1 H) 7.70 (d, *J*=9.49 Hz, 1 H) 7.53 - 7.60 (m, 1 H) 7.38 - 7.44 (m, 1 H) 7.21 (dd, *J*=8.14, 1.02 Hz, 1 H) 7.10 - 7.17 (m, 2 H) 6.94 (d, *J*=9.49 Hz, 1 H) 3.61 (s, 3 H) 3.17 (s, 3 H). MS (ESI+) m/z 357.2 $(M+H)^+$.

9. 2-methyl-6-(5-nitro-2-phenoxyphenyl)pyridazin-3(2H)-one.

9A. 6-(2-fluoro-5-nitrophenyl)-2-methylpyridazin-3(2H)-one. Example 1A (0.145 g, 1 mmol), 2-fluoro-5-nitrophenylboronic acid (0.294 g, 1.1 mmol), $Pd(PPh_3)_4$ (0.058 g, 0.05 mmol) and sodium carbonate (0.212 g, 2.0 mmol) were combined in toluene (4 mL), ethanol (1 mL), and water (1 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 0.19 g (76%) of the title compound.

9B. 2-methyl-6-(5-nitro-2-phenoxyphenyl)pyridazin-3(2H)-one. Phenol (0.045 g, 0.48 mmol), Example 9A (0.1 g, 0.4 mmol) and cesium carbonate (0.130 g, 0.4 mmol) were combined in DMSO (2 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, 60 % ethyl acetate in hexanes) afforded 0.09 g (70%) of the title compound. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.47 (d, J = 2.75 Hz, 1H), 8.28 (dd, J = 9.15, 2.75 Hz, 1H), 7.94 (d, J = 9.46 Hz, 1H), 7.49-7.53 (m, 2H), 7.31 (t, J = 7.48 Hz, 1H), 7.26 (d, J = 7.63 Hz, 2H), 7.04 (d, J = 9.46 HZ), 6.98 (d, J = 9.16 Hz, 1H), 3.76(s, 3H). MS (DCI+) m/z 324.1 $(M+H)^+$.

10. 6-(5-amino-2-phenoxyphenyl)-2-methylpyridazin-3(2H)-one. Example 9B (0.08 g, 0.247 mmol) and 10% palladium on carbon (0.023 g, 0.025 mmol) 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. The residue was purified by reverse phase HPLC (C18, CH_3CN/water (0.1%TFA), 0-100%) to afford the title compound (0.066 g, 90%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.72 (d, J = 9.77 Hz, 1H), 7.31-7.36 (m, 2H), 7.23 (d, J = 2.75 Hz, 1H), 7.31 (t, J = 7.08 Hz, 1H), 7.03 (dd, J = 8.85, 2.75 Hz, 1H), 6.92-6.94 (m, 4H), 3.67 (s, 3H). MS (DCI+) m/z 294.0 $(M+H)^+$.

11. 4-methyl-N-[3-(1-methyl-6-oxo-1,6-dihydropyridazin-3-yl)-4-phenoxyphenyl]benzenesulfonamide. A mixture of Example 10 (0.03 g, 0.102 mmol), 4-methylbenzene-1-sulfonyl chloride (0.019g, 0.102 mmol) and triethylamine (0.022g, 0.204 mmol) in dichloromethane (2 mL) was stirred for 2 hours. The solvent was removed under reduced pressure. The residue was purified by reverse phase HPLC (C18, CH_3CN/water (0.1%TFA), 0-100%) to afford the title compound (0.037 g, 80%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.30 (s, 1H), 7.66-7.69 (m, 3H), 7.31-7.36 (m, 2H), 7.31-7.39 (m, 5H), 7.16 (dd, J = 8.85, 2.75 Hz, 1H), 7.09 (t, J = 7.32 Hz, 1H), 6.89-6.92 (m, 4H), 3.66 (s, 3H), 2.35 (s, 3H). MS (DCI+) m/z 448.2 $(M+H)^+$.

12. N-[3-(1-methyl-6-oxo-1,6-dihydropyridazin-3-yl)-4-phenoxyphenyl]acetamide. Example 12 was prepared according to the procedure used for the preparation of Example 10, substituting acetic chloride for 4-methylbenzene-1-sulfonyl chloride, to provide the title compound. ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.11 (s, 1H), 7.89 (d, J = 2.75 Hz, 1H), 7.67-7.72 (m, 2H), 7.32-7.36 (m, 2H), 7.08 (t, J = 7.32 Hz, 1H), 7.00 (d, J = 8.85 Hz, 1H), 6.92-6.95 (m, 3H), 3.67 (s, 3H), 2.05 (s, 3H). MS (ESI+) m/z 336.2 $(M+H)^+$.

13. 3-(1-methyl-6-oxo-1,6-dihydropyridazin-3-yl)-4-phenoxybenzonitrile.

13A. 4-fluoro-3-(1-methyl-6-oxo-1,6-dihydropyridazin-3-yl)benzonitrile . Example 13A was prepared according to the procedure used for the preparation of Example 9A, substituting 4-fluoro-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzonitrile for 2-fluoro-5-nitrophenylboronic acid, to provide the title compound.

13B. 3-(1-methyl-6-oxo-1,6-dihydropyridazin-3-yl)-4-phenoxybenzonitrile. Example 13B was prepared according to the procedure used for the preparation of Example 9B, substituting Example 13A for Example 9A, to provide the title compound. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.10 (d, J = 2.14 Hz, 1H), 7.86-7.89 (m, 2H), 7.45-7.49 (m, 2H), 7.27 (t, J = 7.48 Hz, 1H), 7.18-7.21 (m, 2H), 7.01 (d, J = 9.46 Hz, 1H), 6.95 (d, J = 8.85 Hz, 1H), 3.73 (s, 3H). MS (DCI+) m/z 304.1 $(M+H)^+$.

14. 3-(1-methyl-6-oxo-1,6-dihydropyridazin-3-yl)-4-phenoxybenzamide. A mixture of Example 13B (0.030 g, 0.1 mmol) and lithium hydroxide monohydrate (0.042 g, 1 mmol) in dioxane (3 mL) and water (1 mL) was heated at 90 °C for 2 hours. After cooling to room temperature, the reaction mixture was partitioned between water and ethyl acetate. The aqueous layer was neutralized to pH 5 using 10% HCl. It was then extracted with additional ethyl acetate three times. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by reverse phase HPLC (C18, CH_3CN/water (0.1%TFA), 0-100%) to afford the title compound. ^{1}H NMR (500 MHz,

DMSO-d_6) δ 8.17 (d, J = 2.14 Hz, 1H), 8.03 (br s, 1H), 7.94 (dd, J = 8.54, 2.44 Hz, 1H), 7.82 (d, J = 9.77 Hz, 1H), 7.40-7.45 (m, 3H), 7.20 (t, J = 7.32 Hz, 1H), 7.08-7.11 (m 2H), 6.98 (d, J = 9.77 Hz, 1H), 6.94 (d, J = 8.54 Hz, 1H), 3.72 (s, 3H). MS (DCI+) m/z 322.1 $(M+H)^+$.

15. 3-(1-methyl-6-oxo-1,6-dihydropyridazin-3-yl)-4-phenoxybenzoic acid. The title compound was isolated as a by-product during the preparation of Example 14. ^{1}H NMR (500 MHz, DMSO-d_6) δ 13.04 (br s, 1H), 8.20 (d, J = 2.14 Hz, 1H), 7.98 (dd, J = 8.7, 2.29 Hz, 1H), 7.86 (d, J = 9.77 Hz, 1H), 7.44-7.48 (m, 2H), 7.24 (t, J = 7.48 Hz, 1H), 7.13-7.17 (m 2H), 6.99 (d, J = 9.77 Hz, 1H), 6.93 (d, J = 8.54 Hz, 1H), 3.74 (s, 3H). MS (DCI+) m/z 323.1 $(M+H)^+$.

16. N-[3-(1-methyl-6-oxo-1,6-dihydropyridazin-3-yl)-4-phenoxybenzyl]acetamide.

16A. 6-(5-(aminomethyl)-2-phenoxyphenyl)-2-methylpyridazin-3(2H)-one. Example 13B (0.1 g, 0.330 mmol) and solvent 7M NH_3-methanol (10 mL) were added to Ra-Ni 2800, water slurry (0.200 g, 3.41 mmol) in a 50 mL pressure bottle and stirred for 16 hours at 30 psi and room temperature. The mixture was filtered through a nylon membrane and the filtrate was cooncentrated. The residue was purified by reverse phase HPLC (C18, CH_3CN/water (0.1%TFA), 0-100%) to afford the title compound.

16B. N-[3-(1-methyl-6-oxo-1,6-dihydropyridazin-3-yl)-4-phenoxybenzyl]acetamide. Example 16B was prepared according to the procedure used for the preparation of Example 11, substituting acetic chloride for 4-methylbenzene-1-sulfonyl chloride, and Example 16A for Example 10, respectively, to provide the title compound. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.41 (t, J = 5.65, 1H), 7.72 (d, J = 9.77 Hz, 1H), 7.53 (d, J = 2.14 Hz, 1H), 7.34-7.38 (m, 3H), 7.11 (t, J = 7.32 Hz, 1H), 6.93-6.97 (m, 4H), 4.28 (d, J = 6.1 Hz, 2H), 3.68 (s, 3H), 1.88 (s, 3H). MS (ESI+) m/z 350.1 $(M+H)^+$.

17. 2,2,2-trifluoro-N-[3-(1-methyl-6-oxo-1,6-dihydropyridazin-3-yl)-4-phenoxybenzyl]acetamide. The title compound was isolated as a by-product during the preparation of Example 16B. ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.5 (t, J = 5.65, 1H), 7.75 (d, J = 9.46 Hz, 1H), 7.59 (d, J = 2.14 Hz, 1H), 7.35-7.39 (m, 3H), 7.13 (t, J = 7.48 Hz, 1H), 6.94-7.01 (m, 4H), 4.43 (d, J = 5.8 Hz, 2H), 3.69 (s, 3H). MS (ESI+) m/z 404.1 $(M+H)^+$.

18. 5-methoxy-2-methyl-6-(2-phenoxyphenyl)pyridazin-3(2H)-one.

18A. 5,6-dichloropyridazin-3(2H)-one. 3,4,6-Trichloropyridazine (12 g, 65.4 mmol) in acetic acid (45 mL) was heated at 130 °C for two hours. After cooling to room temperature, the reaction mixture was poured into ice water (200 mL). The solid was collected by filtration to give 3.7 g of the title compound.

18B. 5,6-dichloro-2-methylpyridazin-3(2H)-one. Example 18B was prepared according to the procedure used for the preparation of Example 1A, substituting Example 18A for 6-chloropyridazin-3(2H)-one, to provide the title compound.

18C. 6-chloro-5-methoxy-2-methylpyridazin-3(2H)-one. Methanol (80 mL) was cooled to 0 °C. To this solvent was added sodium (0.804 g, 35.0 mmol). All sodium was dissolved completely within 1 hour. To this solution was added Example 18B (6.2 g, 34.5 mmol). The reaction mixture was stirred at 50 °C for 2 hours. The solvent was removed, and the residue was triturated with water. The solid was collected by filtration to give 5.41 g (89%) of the title compound.

18D. 5-methoxy-2-methyl-6-(2-phenoxyphenyl)pyridazin-3(2H)-one. Example 18D was prepared according to the procedure used for the preparation of Example 1B, substituting Example 18C for Example 1A, to provide the title compound. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.60-7.64 (m, 1H), 7.40-7.47 (m, 2H), 7.32-7.38 (m, 2H), 7.21-7.25 (m, 1H), 7.10 (t, J = 7.32 Hz, 1H), 6.91-6.98 (m, 3H), 6.29 (s, 1H), 3.61 (s, 3H), 3.57 (s, 3H). MS (DCI+) m/z 309.1 $(M+H)^+$.

19. N-[3-(4-methoxy-1-methyl-6-oxo-1,6-dihydropyridazin-3-yl)phenyl]methanesulfonamide. A mixture of the product from Example 18C (0.053 g, 0.30 mmol), 3 -(methylsulfonylylamino)phenylboronic acid (Combi-Blocks 0.084 g, 0.390 mmol), tetrakis(tiriphenylphosphine) palladium(0) (0.017 g, 0.015 mmol) and sodium carbonate (2M, 0.300 mL, 0.600 mmol) in toluene (1.0 mL), ethanol (0.25 mL), and water (0.5 mL) was heated by microwave at 110 °C for 30 minutes. The reaction mixture was filtered through a 0.45um Nylon filter disk to remove solids and the filtrate was partitioned between ethyl acetate and brine. The organic layer was separated and concentrated. Purification by reverse phase HPLC (C18, 0-100 % CH_3CN/water (0.1% TFA)) afforded the title compound (0.048 g, 52%) ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.84 (s, 1 H) 7.50 (s, 1 H) 7.33 - 7.44 (m, 2 H) 7.22 - 7.31 (m, 1 H) 6.43 (s, 1 H) 3.83 (s, 3 H) 3.65 (s, 3 H) 3.00 (s, 3 H). MS (ESI+) m/z 310 $(M+H)^+$.

20. 6-(5-amino-2-phenoxyphenyl)-5-methoxy-2-methylpyridazin-3(2H)-one.

20A. 6-(2-fluoro-5-nitrophenyl)-5-methoxy-2-methylpyridazin-3(2H)-one. Example 20A was prepared according to the procedure used for the preparation of Example 9A, substituting Example 18C for Example 1A, to provide the title compound.

20B. 5-methoxy-2-methyl-6-(5-nitro-2-phenoxyphenyl)pyridazin-3(2H)-one. Example 20B was prepared according to the procedure used for the preparation of Example 9B, substituting Example 20A for Example 9A, to provide the title compound.

20C. 6-(5-amino-2-phenoxyphenyl)-5-methoxy-2-methylpyridazin-3(2H)-one. Example 20C was prepared according to the procedure used for the preparation of Example 10, substituting Example 20B for Example 9B, to provide the title compound. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.23-7.26 (m, 2H), 6.95 (t, J = 7.93 Hz, 1H), 6.76-6.81 (m, 3H), 6.64-6.67 (m, 1H), 6.56 (d, J = 2.75 Hz, 1H), 6.21 (s, 1H), 5.11 (s, 2H), 3.51 (s, 3H), 3.50 (s, 3H). MS (DCI+) m/z 324.1 $(M+H)^+$.

21. N-[3-(4-methoxy-1-methyl-6-oxo-1,6-dihydropyridazin-3-yl)-4-phenoxyphenyl]acetamide. Example 21 was prepared according to the procedure used for the preparation of Example 11, substituting acetic chloride for 4-methylbenzene-1-sulfonyl chloride, and substituting Example 20C for Example 10, respectively, to provide the title compound. ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.05 (s, 1H), 7.67 (d, J = 2.44 Hz, 1H), 7.59 (dd, J = 8.85, 2.44 Hz, 1H), 7.29-7.34 (m, 2H), 7.06 (t, J = 7.48 Hz, 1H), 6.97 (d, J = 8.85 Hz, 1H), 6.86-6.92 (m, 2H), 6.28 (s, 1H), 3.58 (s, 3H), 3.56 (s, 3H), 2.04 (s, 3H). MS (DCI+) m/z 366.0 $(M+H)^+$.

22. N-[3-(4-methoxy-1-methyl-6-oxo-1,6-dihydropyridazin-3-yl)-4-phenoxyphenyl]methanesulfonamide. A mixture of Example 20C (0.03 g, 0.093 mmol), methanesulfonyl chloride (0.021 g, 0.186 mmol), and triethylamine (0.036 g, 0.36 mmol) in dichloromethane (1mL) was stirred at room temperature for 1 hour. The solvent was removed, and the residue was taken up in dioxane (2 mL) and 1.0 N NaOH (1 mL). The reaction mixture was heated at 90 °C for 1 hour. The solvents were partially removed, and the residue was partitioned between water and ethyl acetate. The aqueous layer was neutralized with 10% HCl and extracted with additional ethyl acetate twice. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by reverse phase HPLC (C18, CH_3CN/water (0.1%TFA), 0-100%) to afford 0.025 g (68%) of the title compound. ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.77 (s, 1H), 7.29-7.35 (m, 1H), 7.22 (d, J = 2.75 Hz, 1H), 7.08 (t, J = 7.32 Hz, 1H), 6.99 (d, J = 8.85 Hz, 1H), 6.91-6.93 (m, 2H), 6.29 (s, 1H), 3.60 (s, 3H), 3.56 (s, 3H), 3.02 (s, 3H). MS (DCI+) m/z 402.2 $(M+H)^+$.

23. N-[3-(4-methoxy-1-methyl-6-oxo-1,6-dihydropyridazin-3-yl)-4-phenoxyphenyl]-N-methylmethanesulfonamide. The product from Example 22 (0.06 g, 0.149 mmol), potassium carbonate (0.027 g, 0.194 mmol) and methyl iodide (0.014 mL, 0.224 mmol) in

dimethylformamide (0.7 mL) was stirred for 1 hour and partitioned between ethyl acetate and brine. The organic layer was separated and concentrated. Purification by reverse phase HPLC (C18, 0-100 % CH_3CN/water (0.1% TFA)) afforded the title compound (0.030 g, 48%). ^1H NMR (300 MHz, DMSO-d_6) δ 7.43 - 7.51 (m, 2 H) 7.30 - 7.41 (m, 2 H) 7.13 (t, J=7.29 Hz, 1 H) 6.89 - 7.04 (m, 3 H) 6.32 (s, 1 H) 3.64 (s, 3 H) 3.58 (s, 3 H) 3.24 (s, 3 H) 2.98 (s, 3 H). MS (ESI+) m/z 416 $(M+H)^+$.

24. N-[3-(4-methoxy-1-methyl-6-oxo-1,6-dihydropyridazin-3-yl)-4-phenoxyphenyl]propane-1-sulfonamide. The product from Example 20 (0.039 g, 0.12 mmol) and triethylamine (0.025 mL, 0.18 mmol) in dichloromethane (0.5 mL) were treated with propanesulfonyl chloride (0.015 mL, 0.13 mmol) stirred for 3 hours and partitioned between ethyl acetate and brine. The organic layer was separated and concentrated. Purification by reverse phase HPLC (C18, 0-100 % CH_3CN/water (0.1% TFA)) afforded the title compound (0.023 g, 44%). ^1H NMR (300 MHz, DMSO-d_6) δ 9.84 (s, 1 H) 7.26 - 7.41 (m, 3 H) 7.21 (d, J=2.38 Hz, 1 H) 7.08 (t, J=7.34 Hz, 1 H) 6.98 (d, J=8.73 Hz, 1 H) 6.91 (d, J=7.54 Hz, 2 H) 6.30 (s, 1 H) 3.59 (s, 3 H) 3.56 (s, 3 H) 3.02 - 3.13 (m, 2 H) 1.63 - 1.81 (m, 2 H) 0.96 (t, J=7.34 Hz, 3 H). MS (ESI+) m/z 430 $(M+H)^+$.

25. 2,2,2-trifluoro-N-[3-(4-methoxy-1-methyl-6-oxo-1,6-dihydropyridazin-3-yl)-4-phenoxyphenyl]ethanesulfonamide. Example 25 was prepared according to the procedure of Example 24 substituting 2,2,2-trifluoroethanesulfonyl chloride for propanesulfonyl chloride to afford the title compound (0.040 g, 71%). ^1H NMR (300 MHz, DMSO-d_6) δ 10.46 (s, 1 H) 7.29 - 7.38 (m, 3 H) 7.25 (d, J=2.38 Hz, 1 H) 7.09 (t, J=7.34 Hz, 1 H) 6.99 (d, J=8.73 Hz, 1 H) 6.92 (d, J=7.54 Hz, 2 H) 6.30 (s, 1 H) 4.56 (q, J=9.78 Hz, 2 H) 3.60 (s, 3 H) 3.56 (s, 3 H). MS (ESI+) m/z 470 $(M+H)^+$.

26. N-[3-(4-methoxy-1-methyl-6-oxo-1,6-dihydropyridazin-3-yl)-4-phenoxyphenyl]cyclopentanesulfonamide. A mixture of the product from Example 20 (0.049 g, 0.15 mmol) cyclopentanesulfonyl chloride (0.03 g, 0.18 mmol) and cesium carbonate (0.073 g, 0.225 mmol) in dimethylformamide (0.75 mL) was heated at 80 °C for 30 minutes and partitioned between ethyl acetate and brine adjusting the pH to 2 with 1M HCl. The organic layer was separated and concentrated. Purification by reverse phase HPLC (C18, 0-100 % CH_3CN/water (0.1% TFA)) afforded the title compound (0.006 g, 8%). ^1H NMR (300 MHz, DMSO-d_6) δ 9.77 (s, 1 H) 7.26 - 7.37 (m, 3 H) 7.22 (d, J=2.78 Hz, 1 H) 7.07 (t, J=7.34 Hz, 1 H) 6.98 (d, J=9.12 Hz, 1 H) 6.90 (d, J=7.54 Hz, 2 H) 6.29 (s, 1 H) 3.59 (s, 3 H) 3.55 (s, 3 H) 1.81 - 1.98 (m, 4 H) 1.48 - 1.75 (m, 4 H). MS (ESI+) m/z 456 $(M+H)^+$.

27. N-[3-(4-methoxy-1-methyl-6-oxo-1,6-dihydropyridazin-3-yl)-4-phenoxyphenyl]-1-phenylmethanesulfonamide. Example 27 was prepared according to the procedure of Example 26 substituting alpha-toluenesulfonyl chloride for cyclopentanesulfonyl chloride to afford the title compound (0.025 g, 43%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.88 (s, 1 H) 7.30 - 7.40 (m, 7 H) 7.26 (dd, *J*=8.73, 2.78 Hz, 1 H) 7.13 (d, *J*=2.78 Hz, 1 H) 7.08 (t, *J*=7.34 Hz, 1 H) 6.95 (d, *J*=8.73 Hz, 1 H) 6.91 (d, *J*=7.54 Hz, 2 H) 6.29 (s, 1 H) 4.49 (s, 2 H) 3.61 (s, 3 H) 3.57 (s, 3 H). MS (ESI+) m/z 478 $(M+H)^+$.

28. 3,3,3-trifluoro-N-[3-(4-methoxy-1-methyl-6-oxo-1,6-dihydropyridazin-3-yl)-4-phenoxyphenyl]propane-1-sulfonamide. Example 28 was prepared according to the procedure of Example 24 substituting 3,3,3-trifluoropropane-1-sulfonyl chloride for propanesulfonyl chloride. Purification by chromatography (silica gel, 0-100% ethyl acetate in hexane) afforded the title compound (0.30 g, 41%). to afford the title compound (0.040 g, 71%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.04 (s, 1 H) 7.29 - 7.38 (m, 3 H) 7.25 (d, *J*=2.71 Hz, 1 H) 7.09 (t, *J*=7.46 Hz, 1 H) 6.99 (d, *J*=8.82 Hz, 1 H) 6.91 (d, *J*=7.80 Hz, 2 H) 6.29 (s, 1 H) 3.60 (s, 3 H) 3.56 (s, 3 H) 3.33 - 3.40 (m, 2 H) 2.67 - 2.85 (m, 2 H). MS (ESI+) m/z 484 $(M+H)^+$.

29. ethyl [3-(4-methoxy-1-methyl-6-oxo-1,6-dihydropyridazin-3-yl)-4-phenoxyphenyl]carbamate. A mixture of Example 20C (0.03 g, 0.093 mmol), ethyl carbonochloridate (0.015 g, 0.139 mmol), and triethylamine (0.028 g, 0.278 mmol) in dichloromethane (1mL) was stirred at room temperature for 1 hour. The solvent was removed, and the residue was purified by reverse phase HPLC (C18, CH_3CN/water (0.1%TFA), 0-100%) to afford 0.030 g (81%) of the title compound. ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.71 (s, 1H), 7.48-7.51 (m, 2H), 7.29-7.33 (m, 2H), 7.05 (t, J = 7.48 Hz, 1H), 6.96 (d, J = 8.85 Hz, 1H), 6.88 (d, J = 7.63 Hz, 2H), 6.27 (s, 1H), 4.12 (q, J = 7.02 Hz, 2H), 3.57 (s, 3H), 3.55 (s, 3H), 1.24 (t, J = 7.02 Hz, 3H). MS (DCI+) m/z 396.2 $(M+H)^+$.

30. 1-ethyl-3-[3-(4-methoxy-1-methyl-6-oxo-1,6-dihydropyridazin-3-yl)-4-phenoxyphenyl]urea. A mixture of Example 20C (0.03 g, 0.093 mmol), isocyanatoethane (0.019 g, 0.269 mmol), and triethylamine (0.027 g, 0.269 mmol) in dichloromethane (1mL) was stirred at 43 °C overnight. The solvent was removed, and the residue was purified by reverse phase HPLC (C18, CH_3CN/water (0.1%TFA), 0-100%) to afford 0.019 g (51%) of the title compound. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.54 (s, 1H), 7.52 (d, J = 2.44 Hz, 1H), 7.38 (dd, J = 8.85, 2.75 Hz, 1H), 7.28-7.31 (m, 2H), 7.03 (t, J = 7.32 Hz, 1H), 6.90 (d, J =

8.54 Hz, 1H), 6.87 (d, J = 7.63 Hz, 2H), 6.26 (s, 1H), 3.56 (s, 3H), 3.55 (s, 3H), 3.10 (q, J = 7.22 Hz, 2H), 1.05 (t, J = 7.17 Hz, 3H). MS (DCI+) m/z 395.2 $(M+H)^+$.

31. N'-[3-(4-methoxy-1-methyl-6-oxo-1,6-dihydropyridazin-3-yl)-4-phenoxyphenyl]-N,N-dimethylsulfuric diamide. Example 31 was prepared according to the procedure of Example 26 substituting dimethylsulfamoyl chloride for cyclopentanesulfonyl chloride to afford the title compound (0.013 g, 25%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.92 (s, 1 H) 7.26 - 7.35 (m, 3 H) 7.20 (d, *J*=2.78 Hz, 1 H) 7.06 (t, *J*=7.34 Hz, 1 H) 6.97 (d, *J*=8.72 Hz, 1 H) 6.89 (d, *J*=7.54 Hz, 2 H) 6.28 (s, 1 H) 3.59 (s, 3 H) 3.55 (s, 3 H) 2.73 (s, 6 H). MS (ESI+) m/z 432 $(M+H)^+$.

32. 4-[2-(4-methoxy-1-methyl-6-oxo-1,6-dihydropyridazin-3-yl)phenoxy]benzonitrile.

32A. 6-(2-hydroxyphenyl)-5-methoxy-2-methylpyridazin-3(2H)-one. Example 32A was prepared according to the procedure used for the preparation of Example 9A, substituting Example 18C for Example 1A, and substituting 2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol for 2-fluoro-5-nitrophenylboronic acid, respectively, to provide the title compound.

32B. 4-[2-(4-methoxy-1-methyl-6-oxo-1,6-dihydropyridazin-3-yl)phenoxy]benzonitrile. Example 32B was prepared according to the procedure used for the preparation of Example 9B, substituting Example 32A for phenol, and substituting 4-fluorobenzonitrile for Example 9A, respectively, to provide crude material. The crude mixture was purified by reverse phase HPLC (C18, CH_3CN/water (0.1%TFA), 0-100%) to afford the title compound. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.79-7.82 (m, 2H), 7.54-7.58 (m, 1H), 7.50 (dd, J = 7.78, 1.68 Hz, 1H), 7.35-7.38 (m, 1H), 7.20 (d, J = 8.24 Hz, 1H), 7.03-7.06 (m, 2H), 6.28 (s, 1H), 3.53 (s, 3H), 3.51 (s, 3H). MS (ESI+) m/z 334.2 $(M+H)^+$.

33. 6-[2-(4-fluorophenoxy)phenyl]-5-methoxy-2-methylpyridazin-3(2H)-one. A mixture of Example 32A (0.035 g, 0.015 mmol), 4-fluorophenylboronic acid (0.042 g, 0.03 mmol), copper (II) acetate (0.027 g, 0.015 mmol), triethylamine (0.076 g, 0.750 mmol) and molecular sieves 4Å (0.05 g) in dichloromethane (2 mL) was stirred overnight. The solid was removed by filtration, and the filtrate was concentrated. The residue was purified by reverse phase HPLC (C18, CH_3CN/water (0.1%TFA), 0-100%) to afford 0.019 g (31%) of the title compound. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.40-7.47 (m, 2H), 7.17-7.24 (m, 3H), 6.97-7.00 (m, 2H), 6.92 (d, J = 7.32 Hz, 1H), 6.31 (s, 1H), 3.64 (s, 3H), 3.58 (s, 3H). MS (ESI+) m/z 327.1 $(M+H)^+$.

34. 6-[2-(3-chloro-4-fluorophenoxy)phenyl]-5-methoxy-2-methylpyridazin-3(2H)-one. Example 34 was prepared according to the procedure used for the preparation of Example 33,

substituting 4-fluoro3-chlorophenylboronic acid for 4-fluorophenylboronic acid, to provide the title compound. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.37-7.52 (m, 3H), 7.26-7.30 (m, 1H), 7.14 (dd, J = 6.26, 2.9 Hz, 1H), 7.06 (d, J = 7.32 Hz, 1H), 6.93-6.97 (m, 1H), 6.31 (s, 1H), 3.62 (s, 3H), 3.57 (s, 3H). MS (ESI+) m/z 361.1 $(M+H)^+$.

35. 5-methoxy-6-[2-(4-methoxyphenoxy)phenyl]-2-methylpyridazin-3(2H)-one. Example 35 was prepared according to the procedure used for the preparation of Example 33, substituting 4-methoxyphenylboronic acid for 4-fluorophenylboronic acid, to provide the title compound. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.36-7.42 (m, 3H), 7.13-7.17 (m, 1H), 6.93 (s, 4H), 6.80 (d, J = 8.24 Hz, 1H), 6.32 (s, 1H), 3.73 (s, 3H), 3.69 (s, 3H), 3.60 (s, 3H). MS (ESI+) m/z 339.1 $(M+H)^+$.

36. 6-[2-(3-fluorophenoxy)phenyl]-5-methoxy-2-methylpyridazin-3(2H)-one. Example 36 was prepared according to the procedure used for the preparation of Example 33, substituting 3-fluorophenylboronic acid for 4-fluorophenylboronic acid, to provide the title compound. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.44-7.52 (m, 2H), 7.34-7.40 (m, 1H), 7.29 (t, J = 7.48 Hz, 1H), 7.08 (d, J = 8.24 Hz, 1H), 6.91-6.95 (m, 1H), 6.76 (dd, J = 9, 1.37 Hz, 2H), 6.32 (s, 1H), 3.59 (s, 3H), 3.56 (s, 3H). MS (DCI+) m/z 327.2 $(M+H)^+$.

37. 6-[2-(4-chlorophenoxy)phenyl]-5-methoxy-2-methylpyridazin-3(2H)-one. A mixture of Example 32A (0.035 g, 0.15 mmol), 1-chloro-4-iodobenzene (0.054 g, 0.225 mmol), copper(I) iodide (0.00714 g, 0.0038 mmol), picolinic acid (0.00923 g, 0.075 mmol) and tripotassium phosphate (0.064 g, 0.30 mmol) in toluene (1 mL) was degassed and back-filled with nitrogen three times. The reaction mixture was heated at 110 °C overnight. 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 $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by reverse phase HPLC (C18, CH_3CN/water (0.1%TFA), 0-100%) to afford 0.038 g (75%) of the title compound. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.37-7.50 (m, 1H), 7.24-7.28 (m, 1H), 7.04 (d, J = 8.24 Hz, 1H), 6.94-6.98 (m, 2H), 6.30 (s, 1H), 3.60 (s, 3H), 3.57 (s, 3H). MS (DCI+) m/z 343.2 $(M+H)^+$.

38. methyl {[1-methyl-6-oxo-3-(2-phenoxyphenyl)-1,6-dihydropyridazin-4-yl]oxy}acetate.

38A. ethyl 2-(3-chloro-1-methyl-6-oxo-1,6-dihydropyridazin-4-yloxy)acetate. Ethyl 2-hydroxyacetate (0.208 g, 2.0 mmol) in tetrahydrofuran (5 mL) was treated with sodium hydride (0.080 g, 2.0 mmol, 60% dispersion in mineral oil) for 5 minutes. To this solution was added Example 18B (0.179 g, 1.0 mmol). The reaction mixture was stirred at room

temperature overnight. 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 under reduced pressure. The residue was purified by flash column chromatography on silica gel eluting with 70% ethyl acetate in hexanes to afford 0.128 g (52%) of the title compound.

38B. methyl {[1-methyl-6-oxo-3-(2-phenoxyphenyl)-1,6-dihydropyridazin-4-yl]oxy}acetate. Example 38B was prepared according to the procedure used for the preparation of Example 1B, substituting Example 38A for Example 1A, to provide the title compound. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.60-7.64 (m, 1H), 7.40-7.47 (m, 2H), 7.32-7.38 (m, 2H), 7.21-7.25 (m, 1H), 7.10 (t, J = 7.32 Hz, 1H), 6.91-6.98 (m, 3H), 6.39 (s, 1H), 4.82 (s, 2H), 3.66 (s, 3H), 3.53 (s, 3H). MS (ESI+) m/z 367.1 $(M+H)^+$.

39. 6-[2-(cyclohexyloxy)phenyl]-5-methoxy-2-methylpyridazin-3(2H)-one. A mixture of the product from Example 32A (0.046 g, 0.2 mmol), cyclohexanol (0.022 mL, 0.210 mmol) and triphenylphosphine (0.055 g, 0.210 mmol) in tetrahydrofuran (0.1 mL) was sonicated until the solids dissolved. With continued sonication, diisopropyl azodicarboxylate (0.041 mL, 0.210 mmol) was added and sonication continued for 20 minutes. Purification by chromatography (silica gel, 0-70% ethyl acetate in hexane) afforded the title compound (0.030 g, 48%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.33 - 7.41 (m, 1 H) 7.21 (dd, *J*=7.54, 1.59 Hz, 1 H) 7.06 (d, *J*=8.33 Hz, 1 H) 6.95 (t, *J*=6.94 Hz, 1 H) 6.33 (s, 1 H) 4.28 - 4.44 (m, 1 H) 3.72 (s, 3 H) 3.60 (s, 3 H) 1.69 - 1.86 (m, 2 H) 1.49 - 1.62 (m, *J*=8.93, 6.15 Hz, 2 H) 1.16 - 1.49 (m, 6 H). MS (ESI+) m/z 315 $(M+H)^+$.

40. 5-methoxy-2-methyl-6-[2-(pyridin-2-ylmethoxy)phenyl]pyridazin-3(2H)-one. The product from Example 32A (0.046 g, 0.2 mmol), 2-(bromomethyl)pyridine hydrobromide (0.066 g, 0.260 mmol), and potassium carbonate (0.069 g, 0.500 mmol) were combined in dimethylformamide (1.0 mL) and stirred for 16 hours. The reaction mix was partitioned between ethyl acetate and water. The organic layer was separated and concentrated. Purification by chromatography (silica gel, 0-4% methanol in dichloromethane) afforded the title compound (0.030 g, 46%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.55 (d, *J*=3.97 Hz, 1 H) 7.78 - 7.87 (m, 1 H) 7.37 - 7.45 (m, 1 H) 7.22 - 7.35 (m, 3 H) 7.14 (d, *J*=7.93 Hz, 1 H) 7.04 (t, *J*=7.54 Hz, 1 H) 6.36 (s, 1 H) 5.18 (s, 2 H) 3.69 (s, 3 H) 3.61 (s, 3 H). MS (ESI+) m/z 324 $(M+H)^+$.

41. 6-[2-(1H-indazol-5-ylmethoxy)phenyl]-5-methoxy-2-methylpyridazin-3(2H)-one. Example 41 was prepared according to the procedure of Example 40 substituting 5-

(bromomethyl)-1H-indazole hydrobromide for 2-(bromomethyl)pyridine hydrobromide. Purification by reverse phase HPLC (C18, 0-100 % CH_3CN/water (0.1% TFA)) afforded the title compound (0.007 g, 10%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 13.07 (s, 1 H) 8.05 (s, 1 H) 7.70 (s, 1 H) 7.53 (d, *J*=8.72 Hz, 1 H) 7.37 - 7.46 (m, 1 H) 7.18 - 7.30 (m, 3 H) 7.01 (t, *J*=6.94 Hz, 1 H) 6.32 (s, 1 H) 5.19 (s, 2 H) 3.72 (s, 3 H) 3.58 (s, 3 H). MS (ESI+) m/z 363 $(M+H)^+$.

42. 6-[2-(2-cyclohexylethoxy)phenyl]-5-methoxy-2-methylpyridazin-3(2H)-one. Example 42 was prepared according to the procedure of Example 40 substituting (2-bromoethyl)cyclohexane for 2-(bromomethyl)pyridine hydrobromide and heating the reaction mixture at 50 °C for 6 hours. Purification by chromatography (silica gel, 0-100% ethyl acetate in hexane) afforded the title compound (0.038 g, 63%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.35 - 7.45 (m, 1 H) 7.21 (dd, *J*=7.54, 1.59 Hz, 1 H) 7.07 (d, *J*=7.54 Hz, 1 H) 6.98 (t, *J*=7.93 Hz, 1 H) 6.36 (s, 1 H) 3.97 (t, *J*=6.35 Hz, 2 H) 3.71 (s, 3 H) 3.60 (s, 3 H) 1.56 - 1.67 (m, 5 H) 1.46 (q, *J*=6.61 Hz, 2 H) 1.03 - 1.36 (m, 4 H) 0.72 - 0.98 (m, *J*=11.11 Hz, 2 H). MS (ESI+) m/z 343 $(M+H)^+$.

43. tert-butyl 4-{[2-(4-methoxy-1-methyl-6-oxo-1,6-dihydropyridazin-3-yl)phenoxy]methyl}piperidine-1-carboxylate. Example 43 was prepared according to the procedure of Example 40 substituting 4-bromomethyl-piperidine-1-carboxylic acid tert-butyl ester for 2-(bromomethyl)pyridine hydrobromide and heating the reaction mixture at 50 °C for 6 hours. Purification by chromatography (silica gel, 0-100% ethyl acetate in hexane) afforded the title compound (0.030 g, 31%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.35 - 7.44 (m, 1 H) 7.21 (dd, J=7.54, 1.98 Hz, 1 H) 7.07 (d, J=8.33 Hz, 1 H) 6.99 (t, J=7.34 Hz, 1 H) 6.33 (s, 1 H) 3.91 (d, J=12.69 Hz, 2 H) 3.83 (d, J=5.95 Hz, 2 H) 3.71 (s, 3 H) 3.60 (s, 3 H) 2.62 - 2.75 (m, 2 H) 1.70 - 1.87 (m, 1 H) 1.53 - 1.60 (m, 2 H) 1.38 (s, 9 H) 0.96 - 1.13 (m, 2 H). MS (ESI+) m/z 430 $(M+H)^+$.

44. 5-methoxy-2-methyl-6-[2-(piperidin-4-ylmethoxy)phenyl]pyridazin-3(2H)-one. The product from Example 43 (0.028 g, 0.065 mmol) in dichloromethane (1 mL) was treated with trifluoroacetic acid (0.3 mL, 3.89 mmol), stirred for 1 hour and concentrated. Purification by reverse phase HPLC (C18, 0-100 % CH_3CN/water (0.1% TFA)) afforded the TFA salt of the title compound (0.015 g, 51%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.47 (d, *J*=9.52 Hz, 1 H) 8.15 (d, *J*=7.54 Hz, 1 H) 7.38 - 7.46 (m, 1 H) 7.23 (dd, *J*=7.54, 1.59 Hz, 1 H) 7.10 (d, *J*=7.93 Hz, 1 H) 7.01 (t, *J*=7.14 Hz, 1 H) 6.34 (s, 1 H) 3.85 (d, *J*=6.35 Hz, 2 H) 3.61 (s, 3 H) 3.73 (s,

3 H) 3.24 - 3.31 (m, 2 H) 2.87 (q, *J*=11.24 Hz, 2 H) 1.87 - 2.02 (m, 1 H) 1.75 (d, *J*=12.70 Hz, 2 H) 1.23 - 1.41 (m, 2 H). MS (ESI+) m/z 330 $(M+H)^+$.

45. 5-methoxy-2-methyl-6-[2-(pyridin-4-ylmethoxy)phenyl]pyridazin-3(2H)-one. Example 45 was prepared according to the procedure of Example 40 substituting 4-(bromomethyl)pyridine hydrobromide for 2-(bromomethyl)pyridine hydrobromide. Purification by chromatography (silica gel, 0-6% methanol in dichloromethane) afforded the title compound (0.022 g, 38%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.51 - 8.59 (m, 2 H) 7.37 - 7.46 (m, 1 H) 7.21 - 7.32 (m, 3 H) 6.99 - 7.14 (m, 2 H) 6.37 (s, 1 H) 5.20 (s, 2 H) 3.70 (s, 3 H) 3.62 (s, 3 H). MS (ESI+) m/z 324 $(M+H)^+$.

46. 6-[2-(cyclopentylmethoxy)phenyl]-5-methoxy-2-methylpyridazin-3(2H)-one. Example 46 was prepared according to the procedure of Example 40 substituting iodomethylcyclopentane for 2-(bromomethyl)pyridine hydrobromide and heating the reaction mixture at 50 °C for 6 hours. Purification by reverse phase HPLC (C18, 0-100 % CH_3CN/water (0.1% TFA)) afforded the title compound (0.008 g, 14%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.35 - 7.44 (m, 1 H) 7.21 (dd, *J*=7.54, 1.59 Hz, 1 H) 7.05 (d, *J*=7.54 Hz, 1 H) 6.98 (t, *J*=7.93 Hz, 1 H) 6.34 (s, 1 H) 3.83 (d, *J*=6.35 Hz, 2 H) 3.71 (s, 3 H) 3.60 (s, 3 H) 2.08 - 2.23 (m, 1 H) 1.56 - 1.69 (m, 2 H) 1.42 - 1.52 (m, 4 H) 1.11 - 1.29 (m, 2 H). MS (ESI+) m/z 315 $(M+H)^+$.

47. 5-methoxy-2-methyl-6-[2-(tetrahydro-2H-pyran-4-ylmethoxy)phenyl]pyridazin-3(2H)-one. Example 47 was prepared according to the procedure of Example 40 substituting 4-(bromomethyl)tetrahydropyran for 2-(bromomethyl)pyridine hydrobromide and heating the reaction mixture at 50 °C for 6 hours. Purification by reverse phase HPLC (C18, 0-100 % CH_3CN/water (0.1% TFA)) afforded the title compound (0.025 g, 43%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.36 - 7.44 (m, 1 H) 7.21 (dd, *J*=7.46, 2.03 Hz, 1 H) 7.07 (d, *J*=7.80 Hz, 1 H) 6.99 (t, *J*=7.46 Hz, 1 H) 3.79 - 3.86 (m, 2 H) 6.34 (s, 1 H) 3.82 (d, *J*=6.44 Hz, 2 H) 3.71 (s, 3 H) 3.60 (s, 3 H) 3.21 - 3.31 (m, 2 H) 1.74 - 1.96 (m, 1 H) 1.49 (dd, *J*=12.72, 1.86 Hz, 2 H) 1.13 - 1.30 (m, 2 H). MS (ESI+) m/z 331 $(M+H)^+$.

48. methyl 1-[1-methyl-6-oxo-3-(2-phenoxyphenyl)-1,6-dihydropyridazin-4-yl]pyrrolidine-3-carboxylate.

48A. methyl 1-(3-chloro-1-methyl-6-oxo-1,6-dihydropyridazin-4-yl)pyrrolidine-3-carboxylate. A mixture of Example 18B (0.179 g, 1.0 mmol), methyl pyrrolidine-3-carboxylate, hydrochloric acid (0.364 g, 2.2 mmol), and triethylamine (0.405 g. 4.0 mmol) in

ethanol (5 mL) was heated under reflux for 16 hours. The solvent was removed, and the crude product was used directly for the next reaction.

48B. methyl 1-[1-methyl-6-oxo-3-(2-phenoxyphenyl)-1,6-dihydropyridazin-4-yl]pyrrolidine-3-carboxylate. Example 48B was prepared according to the procedure used for the preparation of Example 9A, substituting Example 48A for Example 1A, and substituting 2-phenoxyphenylboronic acid for 2-fluoro-5-nitrophenylboronic acid, respectively, to provide the title compound. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.43-7.48 (m, 2H), 7.33-7.36 (m, 2H), 7.32-7.38 (m, 1H), 7.11 (t, J = 7.32 Hz, 1H), 6.92-6.93 (m, 3H), 5.64 (s, 1H), 4.82 (s, 2H), 3.59 (s, 3H), 3.46 (s, 3H)3.00-3.15 (m, 5H), 1.99-2.06 (m, 2H). MS (DCI+) m/z 406.1 $(M+H)^+$.

49. ethyl 1-[1-methyl-6-oxo-3-(2-phenoxyphenyl)-1,6-dihydropyridazin-4-yl]pyrrolidine-3-carboxylate. Example 49 was isolated as a by-product during the formation of Example 48B. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.42-7.48 (m, 2H), 7.33-7.36 (m, 2H), 7.22 (t, J = 7.48 Hz, 1H), 7.12 (t, J = 7.32 Hz, 1H), 6.91-6.92 (m, 3H), 5.64 (s, 1H), 4.02-4.07 (s, 2H), 3.46 (s, 3H), 3.02-3.17 (m, 5H), 1.84-2.08 (m, 2H), 1.13 (t, J = 7.02 Hz, 3H). MS (DCI+) m/z 420.2 $(M+H)^+$.

50. methyl N-[1-methyl-6-oxo-3-(2-phenoxyphenyl)-1,6-dihydropyridazin-4-yl]glycinate.

50A. methyl 2-(3-chloro-1-methyl-6-oxo-1,6-dihydropyridazin-4-ylamino)acetate. A mixture of Example 18B (0.179 g, 1.0 mmol), 2-amino-N-methylacetamide, hydrochloric acid (0.374 g, 3 mmol), and triethylamine (0.506 g. 5.0 mmol) in ethanol (10 mL) was heated under reflux for 16 hours. After cooling, more 2-amino-N-methylacetamide, hydrochloric acid (0.374 g, 3 mmol), and triethylamine (0.506 g. 5.0 mmol) were added. The reaction mixture was heated under reflux overnight. The solvent was removed, and the residue was taken up to ethyl acetate. It was washed with water. The aqueous layer was extracted with additional ethyl acetate three times. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel eluting with 40-80% ethyl acetate in hexanes to afford 0.135 g (55%) of the title compound.

50B. methyl N-[1-methyl-6-oxo-3-(2-phenoxyphenyl)-1,6-dihydropyridazin-4-yl]glycinate. Example 50B was prepared according to the procedure used for the preparation of Example 1B, substituting Example 50A for Example 1A, to provide the title compound. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.47-7.50 (m, 2H), 7.40 (dd, J = 7.63, 1.83 Hz, 1H), 7.33-7.36 (m, 2H), 7.24-7.27 (m, 1H), 7.12 (t, J = 7.32 Hz, 1H), 7.05-7.06 (m, 3H), 6.92 (d, J = 7.63 Hz,

1H), 5.96 (t, J = 6.26, Hz, 1H), 5.62 (s, 1H), 3.90 (d, J = 5.8 Hz, 1H), 3.59 (s, 3H), 3.47 (s, 3H). MS (DCI+) m/z 366.2 $(M+H)^+$.

51. 2-methyl-5-(4-methyl-3-oxopiperazin-1-yl)-6-(2-phenoxyphenyl)pyridazin-3(2H)-one.

51A. 6-chloro-2-methyl-5-(4-methyl-3-oxopiperazin-1-yl)pyridazin-3(2H)-one. A mixture of Example 18B (0.179 g, 1.0 mmol), 1-methylpiperazin-2-one, hydrochloric acid (0.301 g, 2 mmol), and triethylamine (0.405 g. 4.0 mmol) in ethanol (10 mL) was heated under reflux for 16 hours. The solvent was removed, and the residue was purified by flash column chromatography on silica gel eluting with 1-5 % methanol in ethyl acetate to afford 0.21 g (82%) of the title compound.

51B. 2-methyl-5-(4-methyl-3-oxopiperazin-1-yl)-6-(2-phenoxyphenyl)pyridazin-3(2H)-one. Example 50B was prepared according to the procedure used for the preparation of Example 1B, substituting Example 51A for Example 1A, to provide the title compound. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.54 (dd, J = 7.63, 1.83 Hz, 1H), 7.46-7.49 (m, 1H), 7.31-7.35 (m, 2H), 7.28 (t, J = 7.63 Hz, 1H), 7.1 (t, J = 7.32 Hz, 1H), 7.01 (d, J = 8.24 Hz, 1H), 6.98-6.91 (m, 2H), 6.14 (s, 1H), 3.51 (s, 3H), 3.34 (br s, 2H), 3.09 (br 2, 2H), 2.93 (br s, 2H), 2.78 (s, 3H). MS (ESI+) m/z 391.1 $(M+H)^+$.

52. 6-(biphenyl-2-yl)-2-methylpyridazin-3(2H)-one.

52A. 2-(1-methyl-6-oxo-1,6-dihydropyridazin-3-yl)phenyl trifluoromethanesulfonate. A mixture of 6-(2-hydroxyphenyl)-2-methylpyridazin-3(2H)-one (1.24 g, 6.13 mmol), 1,1,1-trifluoro-N-phenyl-N-(trifluoromethylsulfonyl)methanesulfonamide (2.41 g, 6.75 mmol), and triethylamine (0.745 g, 7.36 mmol) in dichloromethane (35 mL) was stirred at ambient temperature for 16 h. The reaction mixture was concentrated under reduced pressure, and the residue purified by flash chromatography (silica gel, 10-30% ethyl acetate/hexane gradient) to provide the title compound.

Example 52B. 6-(biphenyl-2-yl)-2-methylpyridazin-3(2H)-one. A mixture of Example 52A (0.232 g, 0.694 mmol), phenylboronic acid (0.102 g, 0.833 mmol) and $PdCl_2$(dppf) (0.025 g, 0.035 mmol) in dioxane (4 mL) and 2M aqueous sodium carbonate (2 mL) was heated at 70 °C for 4 hours. The reaction mixture was cooled to ambient temperature, partitioned between ethyl acetate and brine, and the organic layer separated, dried (anhydrous sodium sulfate), filtered, anc concentrated. The residue was purified by flash chromatography (silica gel, 10-50% ethyl acetate/hexane gradient) to provide the title compound. ^{1}H NMR (300 MHz,

DMSO- d_6) δ 7.43 - 7.63 (m, 4 H) 7.30 - 7.39 (m, 3 H) 7.18 - 7.26 (m, 2 H) 6.83 (d, J = 9.51 Hz, 1 H) 6.67 (d, J = 9.51 Hz ,1 H) 3.64 (s, 3 H). MS (ESI+) m/z 263.1 $(M+H)^+$.

53. 2'-(1-methyl-6-oxo-1,6-dihydropyridazin-3-yl)biphenyl-3-carbonitrile. Example 53 was prepared according to the procedure used for the preparation of Example 52B, substituting 3-cyanophenylboronic acid for phenylboronic acid, to provide the title compound. ^{1}H NMR (300 MHz, DMSO- d_6) δ 7.78 - 7.83 (m, 1 H) 7.75 (t, J=1.53 Hz, 1 H) 7.43 - 7.66 (m, 6 H) 7.04 (d, J=9.49 Hz, 1 H) 6.76 (d, J=9.49 Hz, 1 H) 3.57 (s, 3 H). MS (ESI+) m/z 288.3 $(M+H)^+$.

54. 5-(2-fluoropyridin-4-yl)-2-methyl-6-(2-phenoxyphenyl)pyridazin-3(2H)-one.

54A. 6-chloro-5-(2-fluoropyridin-4-yl)-2-methylpyridazin-3(2H)-one. Example 54A was prepared according to the procedure used for the preparation of Example 9A, substituting Example 18B for Example 1A, and substituting 2-fluoropyridin-4-ylboronic acid for 2-fluoro-5-nitrophenylboronic acid, respectively, to provide the title compound.

54B. 5-(2-fluoropyridin-4-yl)-2-methyl-6-(2-phenoxyphenyl)pyridazin-3(2H)-one. Example 54B was prepared according to the procedure used for the preparation of Example 9A, substituting Example 54A for Example 1A, and substituting 2-phenoxyphenylboronic acid for 2-fluoro-5-nitrophenylboronic acid, respectively, to provide the title compound. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.13 (d, J = 5.13 Hz, 1H), 7.64 (dd, J = 7.51, 1.65 Hz, 1H), 7.37-7.41 (m, 2H), 7.24-7.27 (m, 3H), 7.07-7.10 (m, 2H), 6.99 (s, 1H), 6.63 (d, J = 8.43 Hz, 1H), 6.38-6.39 (m, 2H), 3.73 (s, 3H). MS (ESI+) m/z 374.1 $(M+H)^+$.

55. 2-methyl-5-(2-oxo-1,2-dihydropyridin-4-yl)-6-(2-phenoxyphenyl)pyridazin-3(2H)-one. Example 54B (0.032 g, 0.086 mmol) in acetic acid (4 mL) and water (1 mL) was heated at 100 °C overnight. The solvents were removed under reduced pressure. The residue was purified by reverse phase HPLC (C18, CH_3CN/water (0.1%TFA), 0-100%) to afford 0.028 g (88%) of the title compound. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.56 (dd, J = 7.63, 1.53 Hz, 1H), 7.37-7.41 (m, 1H), 7.27-7.29 (m, 2H), 7.21-7.25 (m, 2H), 7.10 (t, J = 7.48 Hz, 1H), 6.98 (s, 1H), 6.70 (d, J = 7.32 Hz, 1H), 6.93-6.95 (m, 2H), 6.07 (d, J = 1.22 Hz, 1H), 5.92 (dd, J = 6.71, 1.83 Hz, 1H), 3.69 (s, 3H). MS (DCI+) m/z 372.2 $(M+H)^+$.

56. 2-methyl-5-(1-methyl-2-oxo-1,2-dihydropyridin-4-yl)-6-(2-phenoxyphenyl)pyridazin-3(2H)-one. Example 56 was prepared according to the procedure used for the preparation of Example 1A, substituting Example 55 for 6-chloropyridazin-3(2H)-one, except that the crude product was purified by reverse phase HPLC (C18, CH_3CN/water (0.1%TFA), 0-100%) to provide the title compound. ^{1}H NMR (500 MHz,

DMSO-d_6) δ 7.58 (dd, J = 7.63, 1.53 Hz, 1H), 7.51 (d, J = 7.02 Hz, 1H), 7.38-7.41 (m, 1H), 7.23-7.30 (m, 3H), 7.08 (t, J = 7.32 Hz, 1H), 6.98 (s, 1H), 6.74 (d, J = 7.32 Hz, 1H), 6.59-6.61 (m, 2H), 6.10 (d, J = 1.83 Hz, 1H), 5.94 (dd, J = 6.71, 1.83 Hz, 1H), 3.70 (s, 3H), 3.35 (s, 3H). MS (DCI+) m/z 386.2 $(M+H)^+$.

57. 5-(2-methoxypyridin-4-yl)-2-methyl-6-(2-phenoxyphenyl)pyridazin-3(2H)-one. Methanol (2 mL) was cooled to 0 °C. To this solvent was added sodium (0.0248 g, 1.08 mmol). All sodium was dissolved completely within 10 minutes. To this solution was added Example 54B (0.08 g, 0.216 mmol). The reaction mixture was stirred at 60 °C for 10 hours. The solvent was removed, and the residue was purified by reverse phase HPLC (C18, CH_3CN/water (0.1%TFA), 0-100%) to provide the title compound. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.03 (d, J = 5.19 Hz, 1H), 7.61 (dd, J = 7.63, 1.83 Hz, 1H), 7.35-7.39 (m, 1H), 7.21-7.27 (m, 3H), 7.08 (t, J = 7.32 Hz, 1H), 7.03 (s, 1H), 6.70 (dd, J = 5.19, 1.53 Hz, 1H), 6.56-6.62 (m, 2H), 6.36-6.40 (m, 2H), 3.76 (s, 3H), 3.72 (s, 3H). MS (DCI+) m/z 386.2 $(M+H)^+$.

58. N-{3-[4-(2-methoxypyridin-4-yl)-1-methyl-6-oxo-1,6-dihydropyridazin-3-yl]-4-phenoxyphenyl}methanesulfonamide.

58A. 6-chloro-5-(2-methoxypyridin-4-yl)-2-methylpyridazin-3(2H)-one. Example 58A was prepared according to the procedure used for the preparation of Example 57, substituting Example 54A for Example 54B, to provide the title compound.

58B. 6-(2-fluoro-5-nitrophenyl)-5-(2-methoxypyridin-4-yl)-2-methylpyridazin-3(2H)-one. Example 54B was prepared according to the procedure used for the preparation of Example 9A, substituting Example 58A for Example 1A, to provide the title compound.

58C. 5-(2-methoxypyridin-4-yl)-2-methyl-6-(5-nitro-2-phenoxyphenyl)pyridazin-3(2H)-one. Example 54B was prepared according to the procedure used for the preparation of Example 9B, substituting Example 58B for Example 9A, to provide the title compound.

58D. 6-(5-amino-2-phenoxyphenyl)-5-(2-methoxypyridin-4-yl)-2-methylpyridazin-3(2H)-one. Example 58D was prepared according to the procedure used for the preparation of Example 10, substituting Example 58D for Example 9B, to provide the title compound.

58E. N-{3-[4-(2-methoxypyridin-4-yl)-1-methyl-6-oxo-1,6-dihydropyridazin-3-yl]-4-phenoxyphenyl}methanesulfonamide. Example 58D was prepared according to the procedure used for the preparation of Example 22, substituting Example 58E for Example 20C, to provide the title compound. ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.76 (s, 1H), 8.04 (d, J = 5.19 Hz, 1H), 7.43 (d, J = 2.75 Hz, 1H), 7.19-7.24 (m, 3H), 7.05 (t, J = 7.32 Hz, 1H), 7.02

(s, 1H), 6.72 (dd, J = 5.34, 1.37 Hz, 1H), 6.68 (d, J = 8.85 Hz, 1H), 6.57 (s, 1H), 6.40 (d, J = 7.63 Hz, 2H), 3.77 (s, 3H), 3.70 (s, 3H), 2.99 (s, 3H). MS (ESI+) m/z 479.0 $(M+H)^+$.

59. ethyl 3-[1-methyl-6-oxo-3-(2-phenoxyphenyl)-1,6-dihydropyridazin-4-yl]benzoate. Example 18B (0.090 g, 0.5 mmol), 3-(ethoxycarbonyl)phenylboronic acid (0.107 g, 0.55 mmol), $Pd(PPh_3)_4$ (0.058 g, 0.05 mmol) and sodium carbonate (0.106 g, 1.0 mmol) were combined in toluene (4 mL), ethanol (1 mL) and water (1 mL) and the mixture was degassed and left under nitrogen. The reaction mixture was heated at 90 °C for 2 hours, and then cooled to room temperature. To this solution was he added 2-phenoxyphenylboronic acid (0.150 g, 1.4 mmol). The reaction mixture was heated under reflux overnight. After cooling to room temperature, the mixture 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 ($MgSO_4$), filtered and concentrated. The crude product was purified by flash chromatography (silica gel, 20-50% ethyl acetate in hexanes) to provide crude material, which was further purified by reverse HPLC (C18, CH_3CN/water (0.1%TFA), 0-100%) to afford 0.11 g (52%) of the title compound. ^1H NMR (500 MHz, DMSO-d_6) δ 7.90-7.92 (m, 1H), 7.67 (s, 1H), 7.61 (dd, J = 7.63, 1.83 Hz, 1H), 7.40-7.46 (m, 2H), 7.19-7.24 (m, 3H), 7.32-7.35 (m, 1H), 7.17-7.23 (m, 3H), 7.03 (t, J = 7.32 Hz, 1H), 7.00 (s, 1H), 6.56 (d, J = 8.24 Hz, 1H), 6.32 (d, J = 7.63 Hz, 2H), 4.21 (q, J = 7.12 Hz, 2H), 3.73 (s, 3H), 1.23 (t, J = 7.02 Hz, 3H). MS (DCI+) m/z 427.1 $(M+H)^+$.

60. 2-methyl-5-{3-[(4-methylpiperazin-1-yl)methyl]phenyl}-6-(2-phenoxyphenyl)pyridazin-3(2H)-one. Syntheses were performed using a Personal Chemistry Ermy's optimizer microwave. . Each microwave tube was charged with a stir bar and 0.1 equivalent of $PdCl_2(PPh_3)_2$ (15mg). . In the microwave tube, a solution of Example 18B (39mg, 0.22mmol) dissolved in dioxane (1.0 mL) was added, followed by the addition of 1-methyl-4-(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl)piperazine (82 mg, 0.26mmol) in dioxane(0.7mL). Then, 434 μL of 1M aqueous solution of Cs_2CO_3 was added. The resulting mixture was heated in the microwave for 1800 seconds at 150 °C. In the microwave vial with the previous mixture a solution of 2-phenoxyphenylboronic acid (26mg, 0.12 mmol) in dioxane(0.5 mL), was added, along with 0.1equivalent of $PdCl_2(PPh_3)_2$ (9 mg) and 246 μL of 1M aqueous solution of Cs_2CO_3. This was capped and placed back in the microwave to heat for 1800 seconds at 150 °C. The reaction mixture was filtered, and concentrated to dryness. The residues were dissolved in 1:1 DMSO/MeOH. Purification by reverse phase HPLC (C18, CH_3CN/water (0.1%TFA), 0-100% gradient) provided the title

compound as TFA salt. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.67 (dd, J = 7.63, 1.53 Hz, 1H), 7.29-7.39 (m, 4H), 7.22-7.26 (m, 3H), 7.01-7.15 (m, 3H), 6.94 (s, 1H), 6.91 (s, 1H), 6.54 (d, J = 7.93 Hz, 1H), 6.32 (d, J = 7.63 Hz, 1H), 3.73 (s, 3H), 3.52 (s, 2H), 2.77 (s, 3H). MS (ESI) m/z 467 $(M+H)^+$.

61. 2-methyl-5-{4-[(4-methylpiperazin-1-yl)methyl]phenyl}-6-(2-phenoxyphenyl)pyridazin-3(2H)-one. Example 61 was prepared according to the procedure used for the preparation of Example 60, substituting 1-methyl-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl)piperazine for 1-methyl-3-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl)piperazine, to provide the title compound as TFA salt. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.59 (dd, J = 7.63, 1.83 Hz, 1H), 7.31-7.35 (m, 1H), 7.14-7.24 (m, 7H), 7.07 (t, J = 7.48 Hz, 1H), 6.91 (s, 1H), 6.51 (d, J = 8.24 Hz, 1H), 6.31 (d, J = 8.54 Hz, 2H), 3.71 (s, 3H), 3.40 (br s, 2H), 2.96 (br s, 4H), 2.77 (s, 3H). MS (ESI) m/z 467.1 $(M+H)^+$.

62. N-[3-(1-methyl-4-{4-[(4-methylpiperazin-1-yl)methyl]phenyl}-6-oxo-1,6-dihydropyridazin-3-yl)-4-phenoxyphenyl]methanesulfonamide.

62A. 6-chloro-2-methyl-5-(4-((4-methylpiperazin-1-yl)methyl)phenyl)pyridazin-3(2H)-one. Example 62A was prepared according to the procedure used for the preparation of Example 9A, substituting Example 18B for Example 1A, and substituting 1-methyl-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl)piperazine for 2-fluoro-5-nitrophenylboronic acid, respectively, to provide the title compound.

62B. 6-(2-fluoro-5-nitrophenyl)-2-methyl-5-(4-((4-methylpiperazin-1-yl)methyl)phenyl)pyridazin-3(2H)-one. Example 62B was prepared according to the procedure used for the preparation of Example 9A, substituting Example 62A for Example 1A, to provide the title compound.

62C. 2-methyl-5-(4-((4-methylpiperazin-1-yl)methyl)phenyl)-6-(5-nitro-2-phenoxyphenyl)pyridazin-3(2H)-one. Example 62C was prepared according to the procedure used for the preparation of Example 9B, substituting Example 62B for Example 9A, to provide the title compound.

62D. 6-(5-amino-2-phenoxyphenyl)-2-methyl-5-(4-((4-methylpiperazin-1-yl)methyl)phenyl)pyridazin-3(2H)-one. Example 58D was prepared according to the procedure used for the preparation of Example 10, substituting Example 62D for Example 9B, to provide the title compound.

62E. N-[3-(1-methyl-4-{4-[(4-methylpiperazin-1-yl)methyl]phenyl}-6-oxo-1,6-dihydropyridazin-3-yl)-4-phenoxyphenyl]methanesulfonamide. Example 62E was

prepared according to the procedure used for the preparation of Example 22, substituting Example 62D for Example 20C, to provide the title compound. ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.74 (s, 1H), 7.38 (d, J = 2.75 Hz, 1H), 7.14-7.25 (m, 7H), 7.05 (t, J = 7.32 Hz, 1H), 6.91 (s, 1H), 6.59 (d, J = 8.85 Hz, 1H), 6.36 (d, J = 7.63 Hz, 2H), 4.21 (q, J = 7.12 Hz, 2H), 3.69 (s, 3H), 3.64 (s, 2H), 2.97 (br s, 4H), 2.77 (s, 3H). MS (ESI+) m/z 560.2 $(M+H)^+$.

63. N-{3-[1-methyl-4-(4-methylphenyl)-6-oxo-1,6-dihydropyridazin-3-yl]-4-phenoxyphenyl}methanesulfonamide.

63A. 6-(5-amino-2-phenoxyphenyl)-2-methyl-5-p-tolylpyridazin-3(2H)-one. The title compound was isolated as a by-product in preparation of Example 62D.

63B. N-{3-[1-methyl-4-(4-methylphenyl)-6-oxo-1,6-dihydropyridazin-3-yl]-4-phenoxyphenyl}methanesulfonamide. Example 63B was prepared according to the procedure used for the preparation of Example 22, substituting Example 63A for Example 20C, to provide the title compound. ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.72 (s, 1H), 7.36 (d, J = 2.75 Hz, 1H), 7.16-7.22 (m, 3H), 7.02-7.08 (m, 5 H), 6.87 (s, 1H), 6.61 (d, J = 8.85 Hz, 1H), 6.35 (d, J = 7.63 Hz, 2H), 3.86 (s, 3H), 2.95 (s, 2H), 2.29 (s, 3H). MS (ESI+) m/z 462.1 $(M+H)^+$.

64. 5-(3-amino-4-methylphenyl)-2-methyl-6-(2-phenoxyphenyl)pyridazin-3(2H)-one. Example 64 was prepared according to the procedure used for the preparation of Example 60, substituting 3-amino-4-methylphenylboronic acid for 1-methyl-3-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl)piperazine, to provide the title compound as TFA salt. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.57 (dd, J =7.63, 1.53 Hz, 1 H) 7.33 - 7.40 (m, 1 H) 7.20 - 7.26 (m, 3 H) 7.00 - 7.11 (m, 2 H) 6.90 (d, J =1.53 Hz, 1 H) 6.86 (s, 1 H) 6.68 (dd, J =7.93, 1.53 Hz, 1 H) 6.59 (d, J =7.63 Hz, 1 H) 6.38 (d, J =7.63 Hz, 2 H) 3.70 (s, 3 H) 2.19 (s, 3 H). MS (ESI) m/z 384 $(M+H)^+$.

65. 4-[1-methyl-6-oxo-3-(2-phenoxyphenyl)-1,6-dihydropyridazin-4-yl]benzaldehyde.

65A. 4-(3-chloro-1-methyl-6-oxo-1,6-dihydropyridazin-4-yl)benzaldehyde. 4-formylphenylboronic acid (1.18 g, 7.88 mmol), Example 18B (1.34 g, 7.5 mmol), bis(triphenylphosphine)palladium(II) chloride (0.26 g, 0.375 mmol) and sodium carbonate (7.50 mL, 15.00 mmol) were combined in 1,2-dimethoxyethane (18 mL) and water (12 mL), sparged with nitrogen for 15 minutes and heated at 90 °C for 16 hours under nitrogen. The reaction mixture was partitioned between ethyl acetate and water. The ethyl acetate layer was washed with brine, dried (Na_2SO_4), treated with mercaptopropyl silica gel for 30 minutes,

filtered and concentrated. Purification by chromatography (silica gel, 20-70% ethyl acetate in hexane) afforded the title compound (1.2 g, 64%). MS (APCI+) m/z 249 $(M+H)^+$.

Example 65B. 4-[1-methyl-6-oxo-3-(2-phenoxyphenyl)-1,6-dihydropyridazin-4-yl]benzaldehyde. The product from Example 65A (0.249 g, 1.0 mmol), 2-phenoxyphenylboronic acid (0.257 g, 1.2 mmol), bis(triphenylphosphine)palladium(II) chloride (0.035 g, 0.05 mmol) and sodium carbonate (1.0 mL, 2.0 mmol) were combined in 1,2-dimethoxyethane (4.0 mL), sparged with argon for 15 minutes and heated at 120 °C for 60 minutes under argon. The mixture was cooled and partitioned between ethyl acetate and water. The organic layer was washed with brine, dried (Na_2SO_4), treated with mercaptopropyl silica gel for twenty minutes, filtered and concentrated. Purification by chromatography (silica gel, 0-70% ethyl acetate in hexane) afforded the title compound (0.38 g, 94%). ^1H NMR (300 MHz, DMSO-d_6) δ 9.98 (d, 1 H) 7.76 (d, J=8.48 Hz, 2 H) 7.62 (dd, J=7.46, 1.70 Hz, 1 H) 7.34 - 7.39 (m, 3 H) 7.15 - 7.26 (m, 3 H) 7.05 (d, J=7.12 Hz, 1 H) 7.01 (s, 1 H) 6.56 (d, J=8.14 Hz, 1 H) 6.32 (d, J=7.80 Hz, 2 H) 3.71 - 3.73 (m, 3 H). MS (ESI+) m/z 383 $(M+H)^+$.

66. 2-methyl-5-[4-(morpholin-4-ylmethyl)phenyl]-6-(2-phenoxyphenyl)pyridazin-3(2H)-one. A mixture of the product from Example 65B (0.048 g, 0.125 mmol), morpholine (0.016 mL, 0.188 mmol) and acetic acid (7.16 µl, 0.125 mmol) in dichloroethane (0.625 mL)was treated with sodium triacetoxyborohydride (0.034 g, 0.163 mmol) and stirred for two hours. The reaction mixture was partitioned between ethyl acetate and 5% aqueous sodium bicarbonate. The organic layer was separated, dried (Na_2SO_4) and concentrated. Purification by reverse phase HPLC (C18, 0-100 % CH_3CN/water (0.1% TFA)) afforded the title compound as the trifluoroacetic acid salt (0.050 g, 70%). ^1H NMR (300 MHz, DMSO-d_6) δ 9.87 (s, 1 H) 7.61 (dd, J=7.46, 1.70 Hz, 1 H) 7.34 - 7.40 (m, 3 H) 7.17 - 7.29 (m, 5 H) 7.07 (t, J=7.46 Hz, 1 H) 6.94 (s, 1 H) 6.55 (d, J=8.14 Hz, 1 H) 6.35 (d, J=7.80 Hz, 2 H) 4.33 (s, 2 H) 3.90 - 4.04 (m, 2 H) 3.71 (s, 3 H) 3.55 - 3.67 (m, 2 H) 3.02 - 3.27 (m, 4 H). MS (ESI+) m/z 454 $(M+H)^+$.

67. 2-methyl-6-(2-phenoxyphenyl)-5-[4-(piperidin-1-ylmethyl)phenyl]pyridazin-3(2H)-one. Example 67 was prepared according to the procedure of Example 66 substituting piperidine for morpholine. Purification by reverse phase HPLC (C18, 0-100 % CH_3CN/water (0.1% TFA)) afforded the title compound as the trifluoroacetic acid salt (0.050 g, 71%). ^1H NMR (300 MHz, DMSO-d_6) δ 9.30 (s, 1 H) 7.61 (dd, J=7.80, 1.70 Hz, 1 H) 7.31 - 7.40 (m, 3 H) 7.18 - 7.28 (m, 5 H) 7.08 (t, J=7.46 Hz, 1 H) 6.95 (s, 1 H) 6.53 (d, J=8.14 Hz, 1 H) 6.36 (d,

J=7.46 Hz, 2 H) 4.27 (d, *J*=5.09 Hz, 2 H) 3.75 - 3.77 (s, 3 H) 3.28 (d, *J*=11.87 Hz, 2 H) 2.81 - 2.95 (m, 2 H) 1.75 - 1.90 (m, 2 H) 1.50 - 1.74 (m, 3 H) 1.26 - 1.45 (m, 1 H). MS (ESI+) m/z 452 $(M+H)^+$.

68. 2-methyl-5-{4-[(4-methylpiperidin-1-yl)methyl]phenyl}-6-(2-phenoxyphenyl)pyridazin-3(2H)-one. Example 68 was prepared according to the procedure of Example 66 substituting 4-methylpiperidine for morpholine. Purification by reverse phase HPLC (C18, 0-100 % CH_3CN/water (0.1% TFA)) afforded the title compound as the trifluoroacetic acid salt (0.050 g, 69%). ^1H NMR (300 MHz, DMSO-d_6) δ 9.24 (s, 1 H) 7.61 (dd, *J*=7.54, 1.59 Hz, 1 H) 7.31 - 7.42 (m, 3 H) 7.18 - 7.28 (m, 5 H) 7.08 (t, *J*=7.34 Hz, 1 H) 6.95 (s, 1 H) 6.53 (d, *J*=8.33 Hz, 1 H) 6.35 (d, *J*=7.54 Hz, 2 H) 4.26 (d, *J*=4.76 Hz, 2 H) 3.72 (s, 3 H) 3.29 (d, *J*=11.90 Hz, 2 H) 2.83 - 3.00 (m, 2 H) 1.18 - 1.87 (m, 5 H) 0.91 (d, *J*=6.35 Hz, 3 H). MS (ESI+) m/z 466 $(M+H)^+$.

69. 5-{4-[(diethylamino)methyl]phenyl}-2-methyl-6-(2-phenoxyphenyl)pyridazin-3(2H)-one. Example 69 was prepared according to the procedure of Example 66 substituting diethylamine for morpholine. Purification by reverse phase HPLC (C18, 0-100 % CH_3CN/water (0.1% TFA)) afforded the title compound as the trifluoroacetic acid salt (0.048 g, 69%). ^1H NMR (300 MHz, DMSO-d_6) δ 9.27 (s, 1 H) 7.60 (dd, *J*=7.54, 1.98 Hz, 1 H) 7.30 - 7.44 (m, 3 H) 7.18 - 7.29 (m, 5 H) 7.08 (t, *J*=7.34 Hz, 1 H) 6.96 (s, 1 H) 6.54 (d, *J*=7.93 Hz, 1 H) 6.37 (d, *J*=7.54 Hz, 2 H) 4.30 (d, *J*=5.16 Hz, 2 H) 3.71 (s, 3 H) 3.00 - 3.09 (m, 4 H) 1.21 (t, *J*=7.14 Hz, 6 H). MS (ESI+) m/z 440 $(M+H)^+$.

70. 2-methyl-6-(2-phenoxyphenyl)-5-[4-(piperazin-1-ylmethyl)phenyl]pyridazin-3(2H)-one.

70A. tert-butyl 4-(4-(1-methyl-6-oxo-3-(2-phenoxyphenyl)-1,6-dihydropyridazin-4-yl)benzyl)piperazine-1-carboxylate. Example 70A was prepared according to the procedure of Example 66 substituting 1-Boc-piperazine for morpholine and used in the next step without further purification (0.052 g, 75%).

Example 70B. 2-methyl-6-(2-phenoxyphenyl)-5-[4-(piperazin-1-ylmethyl)phenyl]pyridazin-3(2H)-one. The product from Example 70A (0.052 g, 0.094 mmol) and trifluoroacetic acid (0.5 mL) in dichloromethane (1 mL) was stirred for 1 h and concentrated. Purification by reverse phase HPLC (C18, 0-100 % CH_3CN/water (0.1% TFA)) afforded the title compound as the bis-trifluoroacetic acid salt (0.024 g, 37%). ^1H NMR (300 MHz, DMSO-d_6) δ 8.70 (s, 2 H) 7.59 (dd, *J*=7.54, 1.59 Hz, 1 H) 7.14 - 7.38 (m, 8 H) 7.06 (t,

J=7.34 Hz, 1 H) 6.90 (s, 1 H) 6.53 (d, *J*=8.33 Hz, 1 H) 6.32 (d, *J*=7.54 Hz, 2 H) 3.82 (s, 1 H) 3.71 (s, 3 H) 3.19 (s, 4 H) 2.80 (s, 4 H). MS (ESI+) m/z 453 $(M+H)^+$.

71. 2-methyl-6-(2-phenoxyphenyl)-5-[4-(pyrrolidin-1-ylmethyl)phenyl]pyridazin-3(2H)-one. Example 71 was prepared according to the procedure of Example 66 substituting pyrrolidine for morpholine. Purification by reverse phase HPLC (C18, 0-100 % CH_3CN/water (0.1% ammonium acetate)) afforded the title compound (0.048 g, 87%). ^1H NMR (300 MHz, DMSO-d_6) δ 9.27 (s, 1 H) 7.58 (dd, *J*=7.46, 1.70 Hz, 1 H) 7.27 - 7.37 (m, 1 H) 7.15 - 7.23 (m, 5 H) 7.04 - 7.12 (m, 3 H) 6.90 (s, 1 H) 6.46 (d, *J*=7.46 Hz, 1 H) 6.28 (d, *J*=7.46 Hz, 2 H 3.71 (s, 2 H) 3.55 (s, 3 H) 2.42 (s, 4 H) 1.67 - 1.74 (m, 4 H). MS (ESI+) m/z 438 $(M+H)^+$.

72. 5-[4-(1-hydroxyethyl)phenyl]-2-methyl-6-(2-phenoxyphenyl)pyridazin-3(2H)-one. To a solution of the product of Example 65B (0.09 g, 0.235 mmol) in tetrahydrofuran (10 mL) was added dropwise methylmagnesium bromide (0.26 mL of a 1M solution in tetrahydrofuran, 0.26 mmol). The reaction mixture was stirred at ambient temperature for 3 hours under nitrogen gas. The reaction mixture was quenched by the addition of ethyl acetate and then washed with saturated aqueous sodium chloride solution. The organic phase was dried with anhydrous Na_2SO_4 and filtered. The solvent was evaporated under reduced pressure, and the resulting residue was purified by flash chromatography (silica gel. 0-100% ethyl acetate/hexane gradient) to provide the title compound (0.030 g, 18 % yield). ^1H NMR (400 MHz, DMSO-d_6) δ 7.53 (d, *J* = 7.6 Hz, 1 H), 7.26-7.01 (m, 9 H), 6.88 (s, 1 H), 6.53 (d, *J* = 7.6 Hz, 1 H), 6.29 (d, *J* = 7.6 Hz, 2 H), 4.88 (q, *J* = 6.4 Hz, 1 H), 3.87 (s, 3 H), 1.50 (d, *J* = 6.4 Hz, 3 H). MS (ESI+): m/z 399.2 (M +H).

73. 5-[4-(1-hydroxy-2-methylpropyl)phenyl]-2-methyl-6-(2-phenoxyphenyl)pyridazin-3(2H)-one. Example 73 was prepared according to the procedure used for the preparation of Example 72, substituting isopropylmagnesium bromide for methylmagnesium bromide, to provide the title compound. ^1H NMR (400 MHz, DMSO-d_6) δ 7.57 (dd, *J* = 7.6, 1.6, Hz, 1 H), 7.30 (t, *J* = 6.4 Hz, 1 H), 7.23-7.16 (m, 5 H), 7.11-7.08 (m, 3 H), 6.90 (s, 1 H), 6.44 (d, *J* = 8.4 Hz, 1 H), 6.31 (d, *J* = 7.6 Hz, 2 H), 5.14 (d, *J* = 4.8 Hz, 1 H), 4.24 (t, *J* =4.2 Hz, 1 H), 3.71 (s, 3 H), 1.79 (q, *J* = 6.4 Hz, 1 H), 0.83 (d, *J* = 6.4 Hz, 3 H), 0.77 (d, *J* = 6.8 Hz, 3 H). . MS (ESI+) m/z 427.1 (M +H).

74. 5-{4-[cyclopentyl(hydroxy)methyl]phenyl}-2-methyl-6-(2-phenoxyphenyl)pyridazin-3(2H)-one. Example 74 was prepared according to the procedure used for the preparation of Example 72, substituting cyclopentylmagnesium bromide for methylmagnesium bromide, to

provide the title compound. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (dd, J = 7.6, 1.6 Hz, 1 H), 7.26-7.02 (m, 8 H), 6.90 (s, 1 H), 6.52 (d, J = 7.6 Hz, 1 H), 6.35 (d, J = 7.6 Hz, 2 H), 4.39 (d, J = 7.6 Hz, 1 H), 3.86 (s, 3 H), 2.22-2.16 (m, 1 H), 1.87-1.82 (m, 2 H), 1.65-1.41 (m, 5 H), 1.19-1.14 (m, 1 H). MS (ESI) m/z 453.1 (M +H).

75. 5-[4-(1-hydroxypropyl)phenyl]-2-methyl-6-(2-phenoxyphenyl)pyridazin-3(2H)-one. Example 75 was prepared according to the procedure used for the preparation of Example 72, substituting ethylmagnesium bromide for methylmagnesium bromide, to provide the title compound. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.58 (dd, J = 7.6, 1.9 Hz, 1 H), 7.29 (dd, J = 7.6, 1.6 Hz, 1 H), 7.22-7.18 (m, 5 H), 7.10-7.07 (m, 3 H), 6.90 (s, 1 H), 6.43 (d, J = 8.0 Hz, 1 H), 6.26 (d, J = 8.0 Hz, 2 H).5.15 (brs, 1 H), 4.43 (t, J = 6.4 Hz, 1 H), 3.71 (s, 3 H), 1.63-1.56 (dt, J = 7.2, 14.0 Hz, 2 H), 0.85 (t, J = 7.2 Hz, 3 H). MS (ESI+) m/z 412.9 (M).

76. 5-{4-[hydroxy(phenyl)methyl]phenyl}-2-methyl-6-(2-phenoxyphenyl)pyridazin-3(2H)-one. Example 76 was prepared according to the procedure used for the preparation of Example 72, substituting phenylmagnesium bromide for methylmagnesium bromide, to provide the title compound. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.57 (d, J = 6.0 Hz, 1 H), 7.39 (d, J = 7.2 Hz, 2 H), 7.35-7.16 (m, 7 H), 7.07 (d, J = 8.0 Hz, 2 H), 7.02-7.00 (m, 3 H), 6.87 (s, 1 H), 6.39 (d, J = 7.6 Hz, 1 H), 6.16 (dd, J = 6.4, 2.4 Hz, 2 H), 5.92 (d, J = 4.4 Hz, 1 H), 5.68 (d, J = 4.0 Hz, 1 H), 3.70 (s, 3 H). MS (ESI) m/z 461.2 (M +H).

77. 5-[4-(1-hydroxybut-3-en-1-yl)phenyl]-2-methyl-6-(2-phenoxyphenyl)pyridazin-3(2H)-one. To a solution of the product of Example 65B (0.2 g, 0.523 mmol) in dimethylformamide (10 mL) was added indium (0.523 mmol, 0.060 g), and to the mixture was added dropwise 3-bromoprop-1-ene (0.070 g, 0.575 mmol). The reaction mixture was stirred at ambient temperature for 2 days under nitrogen gas. The reaction mixture was quenched by the addition of ethyl acetate and then washed with saturated aqueous sodium chloride solution. The organic phase was dried with anhydrous Na_2SO_4 and filtered. The solvent was evaporated under reduced pressure, and the resulting residue was purified by reverse phase HPLC (C18, CH_3CN/water (10 mM NH_4CO_3), 35-75%) to provide the title compound (0.30 g, 39 % yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.57 (d, J = 5.6 Hz, 1 H), 7.32 (t, J = 6.8 Hz, 1 H), 7.22-7.13 (m, 5 H), 7.11-7.06 (m, 3 H), 6.89 (s, 1 H), 6.47 (d, J = 5.6 Hz, 1 H), 6.27 (d, J = 8.0 Hz, 2 H), 5.78-5.74 (m, 1 H), 5.29 (d, J = 4.8 Hz, 1 H), 5.04-5.00 (m, 2 H), 4.58-4.56 (m, 1 H), 3.71 (s, 3 H), 2.38-2.35 (m, 2 H). MS (ESI+) m/z 425.2 (M +H).

78. 5-[4-(methoxymethyl)phenyl]-2-methyl-6-(2-phenoxyphenyl)pyridazin-3(2H)-one.

78A. 6-chloro-5-(4-(methoxymethyl)phenyl)-2-methylpyridazin-3(2H)-one. A mixture of Example 18B (121 mg, 0.726 mmol), 4-(methoxymethyl)phenylboronic acid, (100 mg, 0.559 mmol), $Pd(Ph_3P)_4$ (32 mg, 0.028 mmol) and sodium carbonate (118 mg, 1.12 mmol) in toluene (4 mL), ethanol (1 mL) and water (1 mL) was stirred at 85 °C for 16 hours. The reaction mixture was concentrated and purified by preparatory-thin layer chromatography (silica, 3:1 petroleum ether/ethyl acetate) to afford the title compound (107 mg, 0.404 mmol, 72.4 % yield). MS (ESI+) m/z 265 $(M+H)^+$.

Example 78B. 5-[4-(methoxymethyl)phenyl]-2-methyl-6-(2-phenoxyphenyl)pyridazin-3(2H)-one. A mixture of 2-phenoxyphenylboronic acid (323 mg, 1.511 mmol), Example 78A (100 mg, 0.378 mmol), potassium carbonate (157 mg, 1.133 mmol) and $Pd(dppf)Cl_2$ (30.9 mg, 0.038 mmol) in 1,4-dioxane (2 mL) and water (0.5 mL) was heated in a microwave reactor at 100 °C for 1 hour. The mixture was diluted with ethyl acetate (100 mL) and washed with brine (4 x 30 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by preparative-TLC (silica, 100/1 dichloromethane/methanol) followed by preparative HPLC (C18, water (10 mM NH_4HCO_3)/acetonitrile, 35-75% gradient) to afford the title compound (73 mg, 49 % yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.80 (s, 1 H), 8.64 (s, 1 H), 8.63 (d, J = 4.4 Hz, 1 H), 7.76-7.80 (m, 2 H), 7.34-7.43 (m, 2 H), 6.70 (br s, 1 H), 6.25-6.28 (m, 1 H), 3.46 (s, 3 H), 2.25 (s, 3 H), 2.04 (s, 3 H), 2.03 (s, 3 H). MS (ESI+) m/z 399 $(M+H)^+$.

79. 5-[4-(hydroxymethyl)phenyl]-2-methyl-6-(2-phenoxyphenyl)pyridazin-3(2H)-one.

79A. 6-chloro-5-(4-(hydroxymethyl)phenyl)-2-methylpyridazin-3(2H)-one. Example 79A was prepared according to the procedure used for the preparation of Example 78A, substituting 4-(hydroxymethyl)phenylboronic acid for 4-(methoxymethyl)phenylboronic acid, to provide the title compound.

Example 79B. 5-[4-(hydroxymethyl)phenyl]-2-methyl-6-(2-phenoxyphenyl)pyridazin-3(2H)-one. Example 79B was prepared according to the procedure used for the preparation of Example 78B, substituting Example 79A for Example 78A, to provide the title compound. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.80 (s, 1 H), 8.64 (s, 1 H), 8.63 (d, J = 4.4 Hz, 1 H), 7.76-7.80 (m, 2 H), 7.34-7.43 (m, 2 H), 6.70 (br s, 1 H), 6.25-6.28 (m, 1 H), 3.46 (s, 3 H), 2.25 (s, 3 H), 2.04 (s, 3 H), 2.03 (s, 3 H). MS (ESI+) m/z 385 $(M+H)^+$.

80. 4-[1-methyl-6-oxo-3-(2-phenoxyphenyl)-1,6-dihydropyridazin-4-yl]benzyl acetate.

80A. 4-(3-chloro-1-methyl-6-oxo-1,6-dihydropyridazin-4-yl)benzyl acetate. Example 80A was prepared according to the procedure used for the preparation of Example 78A,

substituting 4-(acetoxymethyl)phenylboronic acid for 4-(methoxymethyl)phenylboronic acid, to provide the title compound.

Example 80B. 4-[1-methyl-6-oxo-3-(2-phenoxyphenyl)-1,6-dihydropyridazin-4-yl]benzyl acetate. Example 80B was prepared according to the procedure used for the preparation of Example 78B, substituting Example 80A for Example 78A, to provide the title compound. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.80 (s, 1 H), 8.64 (s, 1 H), 8.63 (d, J = 4.4 Hz, 1 H), 7.76-7.80 (m, 2 H), 7.34-7.43 (m, 2 H), 6.70 (br s, 1 H), 6.25-6.28 (m, 1 H), 3.46 (s, 3 H), 2.25 (s, 3 H), 2.04 (s, 3 H), 2.03 (s, 3 H). MS (ESI+) m/z 427 $(M+H)^+$.

81. tert-butyl 4-[1-methyl-6-oxo-3-(2-phenoxyphenyl)-1,6-dihydropyridazin-4-yl]-3,6-dihydropyridine-1(2H)-carboxylate.

81A. tert-butyl 4-(3-chloro-1-methyl-6-oxo-1,6-dihydropyridazin-4-yl)-5,6-dihydropyridine-1(2H)-carboxylate. A mixture of tert-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5,6- dihydropyridine -1(2H)-carboxylate (1.73 g, 5.59 mmol), 5,6-dichloro-2-methylpyridazin-3(2H)-one (1.00 g, 5.59 mmol), $Pd(Ph_3P)_4$ (0.323 g, 0.279 mmol), and sodium carbonate (1.18 g, 11.2 mmol) in toluene (40 mL), ethanol (10 mL) and water (10 mL) was stirred at 85 °C for 16 hours. The reaction mixture was diluted with ethyl acetate (10 mL), filtered through Celite and concentrated under reduced pressure. The resulting residue was purified by flash chromatography (silica gel, 2:1, petroleum ether/ethyl acetate) to afford the title compound (1.4 g, 74 % yield).

Example 81B. tert-butyl 4-[1-methyl-6-oxo-3-(2-phenoxyphenyl)-1,6-dihydropyridazin-4-yl]-3,6-dihydropyridine-1(2H)-carboxylate. A mixture of 2-phenoxyphenylboronic acid (197 mg, 0.921 mmol), Example 81A (100 mg, 0.307 mmol), potassium carbonate (127 mg, 0.921 mmol) and $Pd(dppf)Cl_2$ (25.1 mg, 0.031 mmol) in dioxane (3 mL) and water (0.75 mL) was heated under microwave conditions at 130 °C for 2 hours. The reaction mixture was diluted with ethyl acetate (20 mL) and washed with brine (2 x 10 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (silica gel, 6:1 to 3:1 gradient, petroleum ether/ethyl acetate) to afford the title compound (0.070 g, 47 % yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (d, J = 7.2 Hz, 1 H), 7.37-7.27 (m, 3 H), 7.18 (t, J = 7.2 Hz, 1 H), 7.08 (t, J = 7.2 Hz, 1 H), 6.87 (t, J = 7.2 Hz, 3 H), 6.73 (s, 1 H), 5.56 (s, 1 H), 3.81-3.77 (m, 5 H), 3.38 (s, 2 H), 2.09 (s, 2 H), 1.46 (s, 9 H). MS (ESI+) m/z 460.0 $(M+H)^+$.

82. 2-methyl-6-(2-phenoxyphenyl)-5-(1,2,3,6-tetrahydropyridin-4-yl)pyridazin-3(2H)-one. Example 81B (0.3 g, 0.650 mmol) was dissolved in the solution of HCl in dioxane (2M,

10 mL) and the mixture was stirred at room temperature for 2 hours. The solvent was evaporated under reduced pressure. The crude material was purified via flash chromatography (Redi-Sep C-18 column, 0-100% acetonitrile /Water (NH_4OAc buffer) to provide the title compound. ^1H NMR (400 MHz, CD_3OD) δ 7.51-7.44 (m, 2 H), 7.33-7.26 (m, 3 H), 7.08 (t, J = 7.2 Hz, 1 H), 7.01 (d, J = 8.4 Hz, 1 H), 6.91-6.89 (m, 2 H), 6.81 (s, 1 H), 5.69 (s, 1 H), 3.72 (s, 3 H), 3.39-3.38 (m, 2 H), 2.94 (t, J = 5.6 Hz, 2 H), 2.24-2.23 (m, 2 H). MS (ESI+) m/z 360.1 $(M+H)^+$.

83. 2-methyl-5-(1-methyl-1,2,3,6-tetrahydropyridin-4-yl)-6-(2-phenoxyphenyl)pyridazin-3(2H)-one. Sodium cyanoborohydride (0.027 g, 0.422 mmol) was added to a solution of Example 82 (0.070 g, 0.18 mmol), formaldehyde (37% solution) (0.131 mL, 1.759 mmol) and acetic acid (0.013 mL, 0.229 mmol) in methanol (2 mL) and the reaction mixture was stirred at ambient temperature for 16 hours. The reaction mixture was neutralized with aqueous saturated aqueous sodium bicarbonate solution, and methanol was evaporated under reduced pressure. The residue was diluted with water and extracted with ethyl acetate (2 x 25 mL). The combined organic layers were combined, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by preparative-TLC (silica, 15:1 CH_2Cl_2/MeOH) to provide the title compound. ^1H NMR (400 MHz, CD_3OD) δ 7.37-7.31 (m, 2 H), 7.21-7.12 (m, 3 H), 6.96 (t, J = 7.2 Hz, 1 H), 6.85 (d, J = 8.4 Hz, 1 H), 6.80-6.77 (m, 2 H), 6.68 (s, 1 H), 5.52-5.51 (m, 1 H), 3.61 (s, 3 H), 2.82-2.81 (m, 2 H), 2.38 (t, J = 5.6 Hz, 2 H), 2.19 (s, 3 H), 2.15-2.14 (m, 2 H). MS (ESI+) m/z 373.9 $(M+H)^+$.

84. 5-(1-acetyl-1,2,3,6-tetrahydropyridin-4-yl)-2-methyl-6-(2-phenoxyphenyl)pyridazin-3(2H)-one. Acetyl chloride (0.021 g, 0.264 mmol) was added to a solution of Example 82 (0.070 g, 0.18 mmol) and triethylamine (0.049 mL, 0.35 mmol) in tetrahydrofuran (2 mL). The reaction mixture was stirred at ambient temperature for 16 hours. The crude reaction mixture was diluted with ethyl acetate (20 mL) and washed with water (15 mL) and brine (15 mL), filtered and concentrated. The crude residue was purified by preparative-TLC (silica gel, 20:1 dichloromethane/methanol) to afford the title compound. ^1H NMR (400 MHz, $CDCl_3$) δ 7.45-7.27 (m, 4 H), 7.20 (t, J = 7.2 Hz, 1 H), 7.08 (d, J = 7.2 Hz, 1 H), 6.92-6.83 (m, 3 H), 6.74 (s, 1 H), 5.60-5.55 (m, 1 H), 3.99-3.98 (m, 1 H), 3.86-3.85 (m, 1 H), 3.78-3.77 (m, 3 H), 3.60-3.57 (m, 1 H), 3.40 (t, J = 5.6 Hz, 1 H), 2.15-2.13 (m, 2 H), 2.06-2.05 (m, 3 H). MS (ESI+) m/z 462.0 $(M+H)^+$.

85. 2-methyl-5-[1-(methylsulfonyl)-1,2,3,6-tetrahydropyridin-4-yl]-6-(2-phenoxyphenyl)pyridazin-3(2H)-one. Methanesulfonyl chloride (0.026 g, 0.226 mmol) was added to a solution of Example 82 (0.06 g, 0.15 mmol) and triethylamine (0.042 mL, 0.30 mmol) in tetrahydrofuran (2 mL). The reaction mixture was stirred at ambient temperature for 16 h. The crude reaction mixture was diluted with ethyl acetate (20 mL), washed with water (15 mL) and brine (15 mL), filtered and concentrated. The crude material was purified by preparative TLC (silica gel, 20:1 dichloromethane/methanol) to afford the title compound. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43-7.27 (m, 4 H), 7.21-7.17 (m, 1 H , 7.09 (t, J = 7.6 Hz, 1 H), 6.92-6.89 (m, 3 H), 6.73 (s, 1 H), 5.60-5.59 (m, 1 H), 3.78 (s, 3 H), 3.70-3.69 (m, 2 H), 3.27 (t, J = 5.6 Hz, 2 H), 2.76 (s, 3 H), 2.23-2.22 (m, 2 H). MS (ESI+) m/z 438.0 $(M+H)^+$.

86. tert-butyl 4-[1-methyl-6-oxo-3-(2-phenoxyphenyl)-1,6-dihydropyridazin-4-yl]piperidine-1-carboxylate. To a solution of Example 81B (0.090 g, 0.20 mmol) in methanol (4 mL) was added Pd/C (0.021 g, 0.020 mmol) under argon, and the reaction was degassed with hydrogen three times and stirred under an atmosphere of hydrogen at 20 °C for 6 hours. The reaction mixture was filtered through Celite and concentrated to afford the title compound (0.09 g, 100 % yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43-7.27 (m, 4 H), 7.24-7.21 (m, 1 H), 7.09 (t, J = 7.6 Hz, 1 H), 6.98 (d, J = 7.6 Hz, 1 H), 6.91-6.89 (m, 2 H), 6.76 (s, 1 H), 4.15-4.07 (m, 2 H), 3.74 (s, 3 H), 2.58-2.45 (m, 3 H), 1.77-1.47 (m, 4 H), 1.44 (s, 9 H). MS (ESI+) m/z 406.0 $(M+H)^+$.

87. 2-methyl-6-(2-phenoxyphenyl)-5-(piperidin-4-yl)pyridazin-3(2H)-one. Example 86 (0.3 g, 0.650 mmol) was dissolved in the solution of HCl in dioxane (2M, 10 mL) and the reaction mixture was stirred at ambient temperature for 2 hours. The solvent was evaporated under reduced pressure and the residue was purified by flash chromatography (Redi-Sep C-18 column, 0-100% acetonitrile/water (NH_4OAc buffer) to provide the title compound. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52-7.43 (m, 2 H), 7.35-7.27 (m, 3 H), 7.10 (t, J = 7.2 Hz, 1 H), 7.04 (d, J = 8.4 Hz, 1 H), 6.93-6.91 (m, 2 H), 6.87 (s, 1 H), 3.71 (s, 3 H), 3.35-3.32 (m, 1 H), 3.16-3.06 (m, 2 H), 2.64-2.44 (m, 3 H), 1.77-1.67 (m, 3 H), 1.45-1.41 (m, 1 H). MS (ESI+) m/z 362.0 $(M+H)^+$.

88. 2-methyl-5-(1-methylpiperidin-4-yl)-6-(2-phenoxyphenyl)pyridazin-3(2H)-one. Sodium cyanoborohydride (0.027 g, 0.422 mmol) was added to a solution of Example 87 (0.070 g, 0.18 mmol), formaldehyde (37% solution) (0.131 mL, 1.759 mmol) and acetic acid (0.013 mL, 0.229 mmol) in methanol (2 mL) and the reaction mixture was stirred at ambient

temperature for 16 hours. The reaction mixture was neutralized with aqueous saturated sodium bicarbonate solution, and methanol was evaporated under reduced pressure. The residue was diluted with water and extracted with ethyl acetate (2 x 25 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by preparative TLC (silica, 15:1 dichloromethane/methanol) to afford the title compound (38 mg, 57.5 % yield). ^{1}H NMR (400 MHz, CD_3OD) δ 7.52-7.42 (m, 2 H), 7.35-7.27 (m, 3 H),7.12-7.08 (m, 1 H), 7.05-7.03 (m, 1 H), 6.92-6.88 (m, 2 H), 6.87 (s, 1 H), 3.71 (s, 3 H), 2.99-2.87 (m, 2 H), 2.48-2.41 (m, 1 H), 2.29 (s, 3 H), 2.00-1.48 (m, 6 H). MS (ESI+) m/z 376.0 $(M+H)^+$.

89. 5-(1-acetylpiperidin-4-yl)-2-methyl-6-(2-phenoxyphenyl)pyridazin-3(2H)-one. Acetyl chloride (0.021 g, 0.264 mmol) was added to a solution of Example 87 (0.070 g, 0.18 mmol) and Et_3N (0.049 mL, 0.352 mmol) in tetrahydrofuran (2 mL). The reaction mixture was stirred at ambient temperature for 16 hours. The crude material was diluted with ethyl acetate (20 mL), washed with water (15 mL) and brine (15 mL), filtered and concentrated. The crude residue was purified by preparative TLC (silica gel, 20:1 dichloromethane/lmethanol) to afford the title compound. (49 mg, 0.121 mmol, 69.0 % yield). ^{1}HNMR (400 MHz, CD_3OD) δ 7.45-7.25 (m, 5 H), 7.11-7.08 (m, 1 H),7.01 (d, J = 8.0 Hz, 1 H), 6.91-6.89 (m, 2 H), 6.74 (s, 1 H), 4.74-4.61 (m, 1 H), 3.88-3.79 (m, 1 H), 3.74 (s, 3 H), 2.96-2.81 (m, 1 H), 2.62-2.55 (m, 1 H), 2.43-2.25 (m, 1 H), 2.07 (d, J = 5.2 Hz, 3 H), 1.93-1.83 (m, 1 H), 1.63-1.53 (m, 2 H), 1.32-1.24 (m, 1 H). MS (ESI+) m/z 404.0 $(M+H)^+$.

90. 2-methyl-5-[1-(methylsulfonyl)piperidin-4-yl]-6-(2-phenoxyphenyl)pyridazin-3(2H)-one. Methanesulfonyl chloride (0.026 g, 0.226 mmol) was added to a solution of Example 87 (0.060 g, 0.15 mmol) and triethylamine (0.042 mL, 0.302 mmol) in tetrahydrofuran (2 mL). The reaction mixture was stirred at ambient temperature for 16 hours. The crude material was diluted with ethyl acetate (20 mL), washed with water (15 mL) and brine (15 mL), filtered and concentrated. The crude material was purified by preparative TLC (silica gel, 20:1 dichloromethane/methanol) to afford the title compound (46 mg, 69.4 % yield). ^{1}H NMR (400 MHz, CD_3OD) δ 7.46-7.44 (m, 1 H), 7.38-7.36 (m, 1H), 7.32-7.23 (m, 3H), 7.09 (t, J = 7.6 Hz, 1H), 7.02 (d, J = 8.0 Hz, 1H), 6.89-6.87 (m, 2 H), 6.79 (s, 1 H), 3.91-3.76 (m, 2 H), 3.73 (s, 3 H), 2.76 (s, 3 H), 2.50-2.42 (m, 2 H), 1.94-1.48 (m, 5 H). MS (ESI+) m/z 440.0 $(M+H)^+$.

91. 2-methyl-5-[4-(5-methyl-1,3,4-oxadiazol-2-yl)phenyl]-6-(2-phenoxyphenyl)pyridazin-3(2H)-one.

91A. 6-chloro-2-methyl-5-(4-(5-methyl-1,3,4-oxadiazol-2-yl)phenyl)pyridazin-3(2H)-one. Example 91A was prepared according to the procedure used for the preparation of Example 78A, substituting 4-(5-methyl-1,3,4-oxadiazol-2-yl)phenylboronic acid for 4-(methoxymethyl)phenylboronic acid, to provide the title compound.

Example 91B. 2-methyl-5-[4-(5-methyl-1,3,4-oxadiazol-2-yl)phenyl]-6-(2-phenoxyphenyl)pyridazin-3(2H)-one. Example 91B was prepared according to the procedure used for the preparation of Example 78B, substituting Example 91A for Example 78A, to provide the title compound. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.80 (s, 1 H), 8.64 (s, 1 H), 8.63 (d, J = 4.4 Hz, 1 H), 7.76-7.80 (m, 2 H), 7.34-7.43 (m, 2 H), 6.70 (br s, 1 H), 6.25-6.28 (m, 1 H), 3.46 (s, 3 H), 2.25 (s, 3 H), 2.04 (s, 3 H), 2.03 (s, 3 H). MS (ESI+) m/z 437 $(M+H)^+$.

92. methyl 3-{4-[1-methyl-6-oxo-3-(2-phenoxyphenyl)-1,6-dihydropyridazin-4-yl]phenyl}propanoate.

92A. methyl 3-(4-(3-chloro-1-methyl-6-oxo-1,6-dihydropyridazin-4-yl)phenyl)propanoate. Example 92A was prepared according to the procedure used for the preparation of Example 78A, substituting 4-(3-methoxy-3-oxopropyl)phenylboronic acid for 4-(methoxymethyl)phenylboronic acid, to provide the title compound.

Example 92B

methyl 3-{4-[1-methyl-6-oxo-3-(2-phenoxyphenyl)-1,6-dihydropyridazin-4-yl]phenyl}propanoate. Example 92B was prepared according to the procedure used for the preparation of Example 78B, substituting Example 92A for Example 78A, to provide the title compound. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.80 (s, 1 H), 8.64 (s, 1 H), 8.63 (d, J = 4.4 Hz, 1 H), 7.76-7.80 (m, 2 H), 7.34-7.43 (m, 2 H), 6.70 (br s, 1 H), 6.25-6.28 (m, 1 H), 3.46 (s, 3 H), 2.25 (s, 3 H), 2.04 (s, 3 H), 2.03 (s, 3 H). MS (ESI+) m/z 441 $(M+H)^+$.

93. 5-(4-benzylphenyl)-2-methyl-6-(2-phenoxyphenyl)pyridazin-3(2H)-one.

93A. 5-(4-benzylphenyl)-6-chloro-2-methylpyridazin-3(2H)-one. Example 93A was prepared according to the procedure used for the preparation of Example 78A, substituting 4-benzylphenylboronic acid for 4-(methoxymethyl)phenylboronic acid, to provide the title compound.

Example 93B. 5-(4-benzylphenyl)-2-methyl-6-(2-phenoxyphenyl)pyridazin-3(2H)-one. Example 93B was prepared according to the procedure used for the preparation of Example 78B, substituting Example 93A for Example 78A, to provide the title compound. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.80 (s, 1 H), 8.64 (s, 1 H), 8.63 (d, J = 4.4 Hz, 1 H), 7.76-7.80 (m,

2 H), 7.34-7.43 (m, 2 H), 6.70 (br s, 1 H), 6.25-6.28 (m, 1 H), 3.46 (s, 3 H), 2.25 (s, 3 H), 2.04 (s, 3 H), 2.03 (s, 3 H). MS (ESI+) m/z 445 $(M+H)^+$.

94. {4-[1-methyl-6-oxo-3-(2-phenoxyphenyl)-1,6-dihydropyridazin-4-yl]phenyl}acetonitrile.

94A. 2-(4-(3-chloro-1-methyl-6-oxo-1,6-dihydropyridazin-4-yl)phenyl)acetonitrile. Example 94A was prepared according to the procedure used for the preparation of Example 78A, substituting 4-(cyanomethyl)phenylboronic acid for 4-(methoxymethyl)phenylboronic acid, to provide the title compound.

Example 94B. {4-[1-methyl-6-oxo-3-(2-phenoxyphenyl)-1,6-dihydropyridazin-4-yl]phenyl}acetonitrile. Example 94B was prepared according to the procedure used for the preparation of Example 78B, substituting Example 94A for Example 78A, to provide the title compound. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.80 (s, 1 H), 8.64 (s, 1 H), 8.63 (d, J = 4.4 Hz, 1 H), 7.76-7.80 (m, 2 H), 7.34-7.43 (m, 2 H), 6.70 (br s, 1 H), 6.25-6.28 (m, 1 H), 3.46 (s, 3 H), 2.25 (s, 3 H), 2.04 (s, 3 H), 2.03 (s, 3 H). MS (ESI+) m/z 394 $(M+H)^+$.

95. 5-[4-(5,6-dihydro-4H-1,3-oxazin-2-yl)phenyl]-2-methyl-6-(2-phenoxyphenyl)pyridazin-3(2H)-one.

95A. 6-chloro-5-(4-(5,6-dihydro-4H-1,3-oxazin-2-yl)phenyl)-2-methylpyridazin-3(2H)-one. Example 95A was prepared according to the procedure used for the preparation of Example 78A, substituting 4-(5,6-dihydro-4H-1,3-oxazin-2-yl)phenylboronic acid for 4-(methoxymethyl)phenylboronic acid, to provide the title compound.

Example 95B. 5-[4-(5,6-dihydro-4H-1,3-oxazin-2-yl)phenyl]-2-methyl-6-(2-phenoxyphenyl)pyridazin-3(2H)-one. Example 95B was prepared according to the procedure used for the preparation of Example 78B, substituting Example 95A for Example 78A, to provide the title compound. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.80 (s, 1 H), 8.64 (s, 1 H), 8.63 (d, J = 4.4 Hz, 1 H), 7.76-7.80 (m, 2 H), 7.34-7.43 (m, 2 H), 6.70 (br s, 1 H), 6.25-6.28 (m, 1 H), 3.46 (s, 3 H), 2.25 (s, 3 H), 2.04 (s, 3 H), 2.03 (s, 3 H). MS (ESI+) m/z 438 $(M+H)^+$.

96. 2-methyl-5-[4-(2-methylpropyl)phenyl]-6-(2-phenoxyphenyl)pyridazin-3(2H)-one.

96A. 6-chloro-5-(4-isobutylphenyl)-2-methylpyridazin-3(2H)-one. Example 96A was prepared according to the procedure used for the preparation of Example 78A, substituting 4-isobutylphenylboronic acid for 4-(methoxymethyl)phenylboronic acid, to provide the title compound.

Example 96B. 2-methyl-5-[4-(2-methylpropyl)phenyl]-6-(2-phenoxyphenyl)pyridazin-3(2H)-one. Example 96B was prepared according to the procedure used for the preparation

of Example 78B, substituting Example 96A for Example 78A, to provide the title compound. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.80 (s, 1 H), 8.64 (s, 1 H), 8.63 (d, J = 4.4 Hz, 1 H), 7.76-7.80 (m, 2 H), 7.34-7.43 (m, 2 H), 6.70 (br s, 1 H), 6.25-6.28 (m, 1 H), 3.46 (s, 3 H), 2.25 (s, 3 H), 2.04 (s, 3 H), 2.03 (s, 3 H). MS (ESI+) m/z 411 $(M+H)^+$.

97. ethyl {4-[1-methyl-6-oxo-3-(2-phenoxyphenyl)-1,6-dihydropyridazin-4-yl]phenyl}acetate.

97A. ethyl 2-(4-(3-chloro-1-methyl-6-oxo-1,6-dihydropyridazin-4-yl)phenyl)acetate. Example 97A was prepared according to the procedure used for the preparation of Example 78A, substituting 4-(2-ethoxy-2-oxoethyl)phenylboronic acid for 4-(methoxymethyl)phenylboronic acid, to provide the title compound.

Example 97B. ethyl {4-[1-methyl-6-oxo-3-(2-phenoxyphenyl)-1,6-dihydropyridazin-4-yl]phenyl}acetate. Example 97B was prepared according to the procedure used for the preparation of Example 78B, substituting Example 97A for Example 78A, to provide the title compound. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.80 (s, 1 H), 8.64 (s, 1 H), 8.63 (d, J = 4.4 Hz, 1 H), 7.76-7.80 (m, 2 H), 7.34-7.43 (m, 2 H), 6.70 (br s, 1 H), 6.25-6.28 (m, 1 H), 3.46 (s, 3 H), 2.25 (s, 3 H), 2.04 (s, 3 H), 2.03 (s, 3 H). MS (ESI+) m/z 441 $(M+H)^+$.

98. N-{4-[1-methyl-6-oxo-3-(2-phenoxyphenyl)-1,6-dihydropyridazin-4-yl]benzyl}methanesulfonamide.

98A. N-(4-(3-chloro-1-methyl-6-oxo-1,6-dihydropyridazin-4-yl)benzyl)ethanesulfonamide. Example 98A was prepared according to the procedure used for the preparation of Example 78A, substituting 4-(ethylsulfonamidomethyl)phenylboronic acid for 4-(methoxymethyl)phenylboronic acid, to provide the title compound.

Example 98B. N-{4-[1-methyl-6-oxo-3-(2-phenoxyphenyl)-1,6-dihydropyridazin-4-yl]benzyl}methanesulfonamide. Example 98B was prepared according to the procedure used for the preparation of Example 78B, substituting Example 98A for Example 78A, to provide the title compound. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.80 (s, 1 H), 8.64 (s, 1 H), 8.63 (d, J = 4.4 Hz, 1 H), 7.76-7.80 (m, 2 H), 7.34-7.43 (m, 2 H), 6.70 (br s, 1 H), 6.25-6.28 (m, 1 H), 3.46 (s, 3 H), 2.25 (s, 3 H), 2.04 (s, 3 H), 2.03 (s, 3 H). MS (ESI+) m/z 462 $(M+H)^+$.

99. N-{4-[1-methyl-6-oxo-3-(2-phenoxyphenyl)-1,6-dihydropyridazin-4-yl]benzyl}acetamide.

99A. N-(4-(3-chloro-1-methyl-6-oxo-1,6-dihydropyridazin-4-yl)benzyl)acetamide. Example 99A was prepared according to the procedure used for the preparation of Example

78A, substituting 4-(acetamidomethyl)phenylboronic acid for 4-(methoxymethyl)phenylboronic acid, to provide the title compound.

Example 99B. N-{4-[1-methyl-6-oxo-3-(2-phenoxyphenyl)-1,6-dihydropyridazin-4-yl]benzyl}acetamide. Example 99B was prepared according to the procedure used for the preparation of Example 78B, substituting Example 99A for Example 78A, to provide the title compound. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.80 (s, 1 H), 8.64 (s, 1 H), 8.63 (d, J = 4.4 Hz, 1 H), 7.76-7.80 (m, 2 H), 7.34-7.43 (m, 2 H), 6.70 (br s, 1 H), 6.25-6.28 (m, 1 H), 3.46 (s, 3 H), 2.25 (s, 3 H), 2.04 (s, 3 H), 2.03 (s, 3 H). MS (ESI+) m/z 426 $(M+H)^+$.

100. N-(2-{4-[1-methyl-6-oxo-3-(2-phenoxyphenyl)-1,6-dihydropyridazin-4-yl]phenyl}ethyl)acetamide.

100A. N-(4-(3-chloro-1-methyl-6-oxo-1,6-dihydropyridazin-4-yl)phenethyl)acetamide. Example 100A was prepared according to the procedure used for the preparation of Example 78A, substituting 4-(2-acetamidoethyl)phenylboronic acid for 4-(methoxymethyl)phenylboronic acid, to provide the title compound.

Example 100B. N-(2-{4-[1-methyl-6-oxo-3-(2-phenoxyphenyl)-1,6-dihydropyridazin-4-yl]phenyl}ethyl)acetamide. Example 100B was prepared according to the procedure used for the preparation of Example 78B, substituting Example 100A for Example 78A, to provide the title compound. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.80 (s, 1 H), 8.64 (s, 1 H), 8.63 (d, J = 4.4 Hz, 1 H), 7.76-7.80 (m, 2 H), 7.34-7.43 (m, 2 H), 6.70 (br s, 1 H), 6.25-6.28 (m, 1 H), 3.46 (s, 3 H), 2.25 (s, 3 H), 2.04 (s, 3 H), 2.03 (s, 3 H). MS (ESI+) m/z 440 $(M+H)^+$.

101. 5-[4-(3-hydroxypropyl)phenyl]-2-methyl-6-(2-phenoxyphenyl)pyridazin-3(2H)-one.

101A. 6-chloro-5-(4-(3-hydroxypropyl)phenyl)-2-methylpyridazin-3(2H)-one. Example 101A was prepared according to the procedure used for the preparation of Example 78A, substituting 4-(3-hydroxypropyl)phenylboronic acid for 4-(methoxymethyl)phenylboronic acid, to provide the title compound.

Example 101B. 5-[4-(3-hydroxypropyl)phenyl]-2-methyl-6-(2-phenoxyphenyl)pyridazin-3(2H)-one. Example 101B was prepared according to the procedure used for the preparation of Example 78B, substituting Example 101A for Example 78A, to provide the title compound. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.80 (s, 1 H), 8.64 (s, 1 H), 8.63 (d, J = 4.4 Hz, 1 H), 7.76-7.80 (m, 2 H), 7.34-7.43 (m, 2 H), 6.70 (br s, 1 H), 6.25-6.28 (m, 1 H), 3.46 (s, 3 H), 2.25 (s, 3 H), 2.04 (s, 3 H), 2.03 (s, 3 H). MS (ESI+) m/z 413 $(M+H)^+$.

102. methyl 4-[1-methyl-6-oxo-3-(2-phenoxyphenyl)-1,6-dihydropyridazin-4-yl]benzoate. Example 102 was prepared according to the procedure used for the preparation

of Example 105, substituting 4-(methoxycarbonyl)phenylboronic acid in 1,4-dioxane for N-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetamide, to provide the title compound. %). ^{1}H NMR (500 MHz, DMSO-d_6/D_2O) δ 7.81 (d, J = 8.24 Hz, 2 H) 7.62 (dd, J = 7.63, 1.53 Hz, 1 H) 7.36 - 7.40 (m, 1 H) 7.24 - 7.32 (m, 3 H) 7.20 (t, J = 7.93 Hz, 2 H) 7.06 (t, J = 7.48 Hz, 1 H) 7.01 (s, 1 H) 6.58 (d, J = 8.24 Hz, 1 H) 6.32 (d, J = 7.63 Hz, 2 H) 3.86 (s, 3 H) 3.74 (s, 3 H)MS (ESI+) m/z 413.3 $(M+H)^+$.

103. 2-methyl-5-(1-methyl-1H-pyrazol-4-yl)-6-(2-phenoxyphenyl)pyridazin-3(2H)-one. Example 103 was prepared according to the procedure used for the preparation of Example 105, substituting 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole for N-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetamide, to provide the title compound. ^{1}H NMR (500 MHz, DMSO-d_6/D_2O) δ 7.58 (s, 1 H) 7.44 - 7.54 (m, 2 H) 7.26 - 7.33 (m, 3 H) 7.08 - 7.13 (m, 1 H) 7.00 (s, 1 H) 6.96 (s, 1 H) 6.79 (d, J = 8.24 Hz, 1 H) 6.49 - 6.59 (m, 2 H) 3.75 (s, 3 H) 3.65 (s, 3 H). MS (ESI+) m/z 359.2 $(M+H)^+$.

104. 2-methyl-6-(2-phenoxyphenyl)-5-(pyridin-4-yl)pyridazin-3(2H)-one. Example 104 was prepared according to the procedure used for the preparation of Example 105, substituting pyridin-4-yl-boronic acid for N-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetamide, to provide the title compound. ^{1}H NMR (500 MHz, DMSO-d_6/D_2O) δ 7.67 (dd, J = 7.48, 1.68 Hz, 1 H) 7.52 (d, J = 6.10 Hz, 1 H) 7.43 (d, J = 6.41 Hz, 3 H) 7.23 - 7.34 (m, 4 H) 7.12 (s, 1 H) 7.07 - 7.11 (m, 1 H) 6.63 (d, J = 8.24 Hz, 1 H) 6.38 (d, J = 7.93 Hz, 2 H) 3.75 (s, 3 H)MS (ESI+) m/z 356.2 $(M+H)^+$.

105. N-{4-[1-methyl-6-oxo-3-(2-phenoxyphenyl)-1,6-dihydropyridazin-4-yl]phenyl}acetamide. A 4mL microwave vial was charged with a stir bar, a solution of Example 18B (40 mg, 0.22 mmol) in dioxane (1mL), a solution of N-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetamide monomer (87 mg, 1.5 equivalents,0.34 mmol) in dioxane (1 mL), cesium carbonate (145 mg, 2 eq, 0.44 mmol) in water (.45 mL) with Silicat resin (82 mg, 0.1 eq, 0.27 loading). This was placed in parallel dual model microwave system Anton Parr and was allowed to heat at 135 °C for 30 minutes. Upon completion, the crude material was filtered, dried, and purified by reverse phase HPLC (C18, 0-100 % CH_3CN/water (0.1% TFA)) to afford *N*-(4-(3-chloro-1-methyl-6-oxo-1,6-dihydropyridazin-4-yl)phenyl)acetamide intermediate (35 mg, 0.13 mmol) which was then dissolved in dioxane (1mL) to which was added excess 2-pheoxyphenyl boronic acid (45 mg, 1.6 equivalents, 0.20mmol) in dioxane, cesium carbonate (41 mg, 1 equivalent, 0.12 mmol) in water (0.130 mL) and with Silicat resin (93 mg, 0.2 eq, 0.27 loading). This was again placed in parallel

dual model microwave system Anton Parr and was allowed to heat at 135 °C for 30 minutes. Upon completion, the crude material was filtered, dried, and purified by reverse phase HPLC (C18, 0-100 % CH_3CN/water (0.1% TFA)) to afford the title compound. ^1H NMR (400 MHz, DMSO-d_6/D_2O) δ 7.58 (dd, J = 7.5, 1.7 Hz, 1H), 7.48–7.32 (m, 3H), 7.25–7.16 (m, 3H), 7.06 (t, J = 7.9 Hz, 3H), 6.89 (s, 1H), 6.57 (d, J = 7.7 Hz, 1H), 6.36 (d, J = 7.7 Hz, 2H), 3.70 (s, 3H), 2.06 (s, 3H). MS (ESI+) m/z 412 $(M+H)^+$.

106. N-{3-[1-methyl-6-oxo-3-(2-phenoxyphenyl)-1,6-dihydropyridazin-4-yl]phenyl}acetamide. Example 106 was prepared according to the procedure used for the preparation of Example 105, substituting N-(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetamide for N-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetamide, to provide the title compound. ^1H NMR (400 MHz, DMSO-d_6/D_2O) δ 7.65 – 7.52 (m, 2H), 7.47 (s, 1H), 7.40 – 7.28 (m, 1H), 7.22 (dd, J = 11.0, 4.5 Hz, 3H), 7.15 (t, J = 7.9 Hz, 1H), 7.06 (t, J = 7.4 Hz, 1H), 6.85 (s, 1H), 6.72 (d, J = 7.9 Hz, 1H), 6.56 (d, J = 7.6 Hz, 1H), 6.42 – 6.29 (m, 2H), 3.71 (s, 3H), 1.99 (s, 3H). MS (ESI+) m/z 412 $(M+H)^+$.

107. 5-(4-ethoxy-3-fluorophenyl)-2-methyl-6-(2-phenoxyphenyl)pyridazin-3(2H)-one. Example 107 was prepared according to the procedure used for the preparation of Example 105, substituting 4-ethoxy-3-fluorophenylboronic acid for N-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetamide, to provide the title compound. ^1H NMR (400 MHz, DMSO-d_6/D_2O) δ 7.60 (dd, J = 7.5, 1.7 Hz, 1H), 7.44 – 7.31 (m, 1H), 7.24 (dd, J = 15.9, 8.1 Hz, 3H), 7.13 – 6.96 (m, 2H), 6.96 – 6.80 (m, 3H), 6.64 (t, J = 8.7 Hz, 1H), 6.42 (dd, J = 25.2, 7.7 Hz, 2H), 4.10 (q, J = 7.0 Hz, 2H), 3.70 – 3.69 (m, 3H), 1.34 (t, J = 7.0 Hz, 3H). MS (ESI+) m/z 417 $(M+H)^+$.

108. N,N-dimethyl-4-[1-methyl-6-oxo-3-(2-phenoxyphenyl)-1,6-dihydropyridazin-4-yl]benzamide. Example 108 was prepared according to the procedure used for the preparation of Example 105, substituting 4-(dimethylcarbamoyl)phenylboronic acid for N-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetamide, to provide the title compound. ^1H NMR (400 MHz, DMSO-d_6/D_2O) δ 7.68 – 7.51 (m, 1H), 7.42 – 7.33 (m, 1H), 7.33 – 7.24 (m, 3H), 7.24 – 7.17 (m, 4H), 7.08 (t, J = 7.4 Hz, 1H), 6.98 (d, J = 2.5 Hz, 1H), 6.59 – 6.46 (m, 1H), 6.39 – 6.26 (m, 2H), 3.75 (d, J = 9.9 Hz, 3H), 2.98 (s, 3H), 2.90 (s, 3H). MS (ESI+) m/z 426 $(M+H)^+$.

109. N,N-dimethyl-3-[1-methyl-6-oxo-3-(2-phenoxyphenyl)-1,6-dihydropyridazin-4-yl]benzamide. Example 109 was prepared according to the procedure used for the preparation of Example 105, substituting 3-(dimethylcarbamoyl)phenylboronic acid for N-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetamide, to provide the title

compound. ^{1}H NMR (400 MHz, DMSO-d_6/D_2O) δ 7.60 (dd, J = 7.5, 1.7 Hz, 1H), 7.44 – 7.32 (m, 2H), 7.32 – 7.18 (m, 3H), 7.10 (dd, J = 18.1, 10.7 Hz, 1H), 6.96 (s, 1H), 6.54 (d, J = 7.8 Hz, 1H), 6.41 (d, J = 7.7 Hz, 1H), 3.72 (d, J = 2.4 Hz, 3H), 2.54 (dd, J = 9.3, 7.5 Hz, 6H). MS (ESI+) m/z 426 $(M+H)^+$.

110. 2-methyl-5-[3-(2-methylpropoxy)phenyl]-6-(2-phenoxyphenyl)pyridazin-3(2H)-one. Example 110 was prepared according to the procedure used for the preparation of Example 105, substituting 3-isobutoxyphenylboronic acid for N-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetamide, to provide the title compound. ^{1}H NMR (400 MHz, DMSO-d_6/D_2O) δ 7.59 (dd, J = 7.5, 1.7 Hz, 1H), 7.44 – 7.29 (m, 1H), 7.29 – 7.12 (m, 4H), 7.07 (t, J = 7.4 Hz, 1H), 7.00 – 6.84 (m, 2H), 6.74 (t, J = 12.2 Hz, 1H), 6.68 – 6.59 (m, 1H), 6.55 (t, J = 9.7 Hz, 1H), 6.44 – 6.27 (m, 2H), 3.73 (s, 3H), 3.42 (d, J = 6.6 Hz, 2H), 1.81 (td, J = 13.3, 6.7 Hz, 1H), 0.91 – 0.81 (m, 6H). MS (ESI+) m/z 427 $(M+H)^+$.

111. 5-[3-fluoro-4-(propan-2-yloxy)phenyl]-2-methyl-6-(2-phenoxyphenyl)pyridazin-3(2H)-one. Example 111 was prepared according to the procedure used for the preparation of Example 105, substituting 3-fluoro-4-isopropoxyphenylboronic acid for N-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetamide, to provide the title compound. ^{1}H NMR (400 MHz, DMSO-d_6/D_2O) δ 7.66 – 7.56 (m, 1H), 7.49 – 7.33 (m, 1H), 7.31 – 7.15 (m, 3H), 7.14 – 6.86 (m, 6H), 6.60 (t, J = 8.3 Hz, 1H), 6.42 – 6.32 (m, 2H), 4.71 – 4.55 (m, 1H), 3.73 (d, J = 10.4 Hz, 3H), 1.29 (d, J = 6.0 Hz, 6H). MS (ESI+) m/z 430 $(M+H)^+$.

112. 4-[1-methyl-6-oxo-3-(2-phenoxyphenyl)-1,6-dihydropyridazin-4-yl]benzenesulfonamide. Example 112 was prepared according to the procedure used for the preparation of Example 105, substituting 4-sulfamoylphenylboronic acid for N-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetamide, to provide the title compound. ^{1}H NMR (400 MHz, DMSO-d_6/D_2O) δ 7.72 – 7.59 (m, 3H), 7.49 – 7.30 (m, 3H), 7.32 – 7.19 (m, 4H), 7.18 – 7.05 (m, 1H), 7.06 – 6.91 (m, 1H), 6.53 (dd, J = 8.2, 0.6 Hz, 1H), 6.32 – 6.17 (m, 2H), 3.73 (d, J = 10.4 Hz, 3H). MS (ESI+) m/z 434 $(M+H)^+$.

113. 5-(1-benzyl-1H-pyrazol-4-yl)-2-methyl-6-(2-phenoxyphenyl)pyridazin-3(2H)-one. Example 113 was prepared according to the procedure used for the preparation of Example 105, substituting 1-benzyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole for N-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetamide, to provide the title compound. ^{1}H NMR (400 MHz, DMSO-d_6/D_2O) δ 7.58 – 7.40 (m, 3H), 7.35 – 7.27 (m, 3H), 7.26 – 7.22 (m, 1H), 7.22 – 7.10 (m, 4H), 7.10 – 7.00 (m, 2H), 6.70 – 6.56 (m, 1H), 6.44 – 6.28 (m, 2H), 5.21 (s, 2H), 3.66 (s, 3H).MS (ESI+) m/z 435 $(M+H)^+$.

114. N-cyclopropyl-4-[1-methyl-6-oxo-3-(2-phenoxyphenyl)-1,6-dihydropyridazin-4-yl]benzamide. Example 114 was prepared according to the procedure used for the preparation of Example 105, substituting 4-(cyclopropylcarbamoyl)phenylboronic acid for N-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetamide, to provide the title compound. ^{1}H NMR (400 MHz, DMSO-d_6/D_2O) δ 7.72 – 7.51 (m, 3H), 7.42 – 7.30 (m, 1H), 7.23 (dt, J = 10.8, 4.5 Hz, 3H), 7.06 (t, J = 7.4 Hz, 1H), 6.97 (d, J = 6.2 Hz, 1H), 6.57 (d, J = 7.8 Hz, 1H), 6.32 (d, J = 7.7 Hz, 2H), 3.72 (s, 3H), 2.94 – 2.74 (m, 1H), 0.84 – 0.66 (m, 2H), 0.63 – 0.45 (m, 2H). MS (ESI+) m/z 438 $(M+H)^+$.

115. 5-(3,5-dimethyl-1H-pyrazol-4-yl)-2-methyl-6-(2-phenoxyphenyl)pyridazin-3(2H)-one. Example 115 was prepared according to the procedure used for the preparation of Example 105, substituting 3,5-dimethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole for N-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetamide, to provide the title compound. ^{1}H NMR (400 MHz, DMSO-d_6/D_2O) δ 7.54 (dd, J = 7.6, 1.7 Hz, 1H), 7.43 – 7.27 (m, 3H), 7.27 – 7.08 (m, 2H), 6.76 (s, 1H), 6.57 (d, J = 8.3 Hz, 1H), 6.49 (dd, J = 8.5, 0.9 Hz, 2H), 3.72 – 3.71 (m, 3H), 1.72 (s, 6H). MS (ESI+) m/z 373 $(M+H)^+$.

116. 5-(6-methoxypyridin-3-yl)-2-methyl-6-(2-phenoxyphenyl)pyridazin-3(2H)-one. Example 116 was prepared according to the procedure used for the preparation of Example 105, substituting 6-methoxypyridin-3-ylboronic acid for N-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetamide, to provide the title compound. ^{1}H NMR (400 MHz, DMSO-d_6/D_2O) δ 8.04 – 7.90 (m, 1H), 7.62 (dd, J = 7.5, 1.7 Hz, 1H), 7.47 – 7.37 (m, 2H), 7.33 – 7.20 (m, 3H), 7.08 (dd, J = 10.6, 4.2 Hz, 1H), 6.98 (s, 1H), 6.80 – 6.63 (m, 2H), 6.48 – 6.28 (m, 2H), 3.83 (s, 3H), 3.71 – 3.71 (m, 3H). MS (ESI+) m/z 386 $(M+H)^+$.

117. 5-(4-ethoxyphenyl)-2-methyl-6-(2-phenoxyphenyl)pyridazin-3(2H)-one. Example 117 was prepared according to the procedure used for the preparation of Example 105, substituting 4-ethoxyphenylboronic acid for N-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetamide, to provide the title compound. ^{1}H NMR (400 MHz, DMSO-d_6/D_2O) δ 7.68 – 7.48 (m, 1H), 7.42 – 7.27 (m, 1H), 7.28 – 7.14 (m, 3H), 7.07 (t, J = 8.1 Hz, 3H), 6.86 (s, 1H), 6.83 – 6.72 (m, 2H), 6.57 (d, J = 7.7 Hz, 1H), 6.36 (d, J = 7.7 Hz, 2H), 4.01 (q, J = 7.0 Hz, 2H), 3.70 (s, 3H), 1.32 (t, J = 7.0 Hz, 3H). MS (ESI+) m/z 399 $(M+H)^+$.

118. 5-(isoquinolin-4-yl)-2-methyl-6-(2-phenoxyphenyl)pyridazin-3(2H)-one. Example 118 was prepared according to the procedure used for the preparation of Example 105, substituting isoquinolin-4-ylboronic acid for N-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetamide, to provide the title compound. ^{1}H NMR (400 MHz, DMSO-d_6/D_2O) δ 9.48 – 9.17 (m, 1H), 8.34 – 8.22 (m, 1H), 8.22 – 8.09 (m, 1H), 7.86 – 7.77 (m, 1H), 7.77 –

7.64 (m, 2H), 7.63 – 7.49 (m, 1H), 7.25 – 7.14 (m, 3H), 7.14 – 7.08 (m, 1H), 7.08 – 6.90 (m, 2H), 6.51 – 6.35 (m, 1H), 6.32 – 6.09 (m, 2H), 3.80 (s, 3H). MS (ESI+) m/z 406 (M+H)+.

119. N-{4-[1-methyl-6-oxo-3-(2-phenoxyphenyl)-1,6-dihydropyridazin-4-yl]phenyl}methanesulfonamide. Example 119 was prepared according to the procedure used for the preparation of Example 105, substituting 4-(methylsulfonamido)phenylboronic acid for N-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetamide, to provide the title compound. ^{1}H NMR (400 MHz, DMSO-d_6/D_2O) δ 7.63 – 7.55 (m, 1H), 7.43 – 7.31 (m, 2H), 7.30 – 7.19 (m, 2H), 7.19 – 7.10 (m, 2H), 7.10 – 7.03 (m, 2H), 7.04 (d, J = 2.1 Hz, 1H), 6.91 (s, 1H), 6.63 – 6.46 (m, 1H), 6.40 – 6.19 (m, 1H), 3.71 (d, J = 3.1 Hz, 3H), 3.03 (s, 3H). MS (ESI+) m/z 448 (M+H)+.

120. N-{3-[1-methyl-6-oxo-3-(2-phenoxyphenyl)-1,6-dihydropyridazin-4-yl]phenyl}methanesulfonamide. Example 120 was prepared according to the procedure used for the preparation of Example 105, substituting 3-(methylsulfonamido)phenylboronic acid for N-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetamide, to provide the title compound. ^{1}H NMR (400 MHz, DMSO-d_6/D_2O) δ 7.57 (dd, J = 7.5, 1.7 Hz, 1H), 7.40 – 7.31 (m, 1H), 7.31 – 7.21 (m, 4H), 7.18 (t, J = 8.4 Hz, 1H), 7.15 – 7.02 (m, 2H), 6.90 (d, J = 5.3 Hz, 2H), 6.55 (d, J = 8.3 Hz, 1H), 6.39 (d, J = 7.6 Hz, 2H), 3.72 (s, 3H), 2.69 (s, 3H). MS (ESI+) m/z 448 (M+H)+.

121. N-{5-[1-methyl-6-oxo-3-(2-phenoxyphenyl)-1,6-dihydropyridazin-4-yl]pyridin-3-yl}acetamide. Example 121 was prepared according to the procedure used for the preparation of Example 105, substituting 5-acetamidopyridin-3-ylboronic acid for N-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetamide, to provide the title compound. ^{1}H NMR (400 MHz, DMSO-d_6/D_2O) δ 8.69 (d, J = 2.2 Hz, 1H), 8.00 (d, J = 1.9 Hz, 1H), 7.90 (t, J = 2.1 Hz, 1H), 7.61 (dd, J = 7.6, 1.7 Hz, 1H), 7.45 – 7.34 (m, 1H), 7.34 – 7.18 (m, 3H), 7.16 – 7.03 (m, 1H), 7.01 (s, 1H), 6.64 (d, J = 7.6 Hz, 1H), 6.40 (d, J = 0.8 Hz, 1H), 3.73 (s, 3H), 2.03 (s, 3H). MS (ESI+) m/z 413 (M+H)+.

122. N-methyl-5-[1-methyl-6-oxo-3-(2-phenoxyphenyl)-1,6-dihydropyridazin-4-yl]pyridine-3-carboxamide. Example 122 was prepared according to the procedure used for the preparation of Example 105, substituting 5-(methylcarbamoyl)pyridin-3-ylboronic acid for N-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetamide, to provide the title compound. ^{1}H NMR (400 MHz, DMSO-d_6/D_2O) δ 8.91 (d, J = 2.0 Hz, 1H), 8.40 (d, J = 2.2 Hz, 1H), 8.02 (t, J = 2.1 Hz, 1H), 7.65 (dd, J = 7.6, 1.7 Hz, 1H), 7.49 – 7.34 (m, 1H), 7.33 – 7.16 (m, 3H), 7.12 (s, 1H), 7.06 (dd, J = 10.6, 4.1 Hz, 1H), 6.64 – 6.52 (m, 1H), 6.38 – 6.24 (m, 2H), 3.74 (d, J = 2.8 Hz, 3H), 2.77 (s, 3H). MS (ESI+) m/z 413 (M+H)+.

123. 2-methyl-6-(2-phenoxyphenyl)-5-[6-(propan-2-yloxy)pyridin-3-yl]pyridazin-3(2H)-one. Example 123 was prepared according to the procedure used for the preparation of Example 105, substituting 6-isopropoxypyridin-3-ylboronic acid for N-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetamide, to provide the title compound. ^{1}H NMR (400 MHz, DMSO-d_6/D_2O) δ 7.92 (d, J = 2.3 Hz, 1H), 7.62 (dd, J = 7.5, 1.7 Hz, 1H), 7.48 – 7.32 (m, 2H), 7.32 – 7.17 (m, 3H), 7.08 (t, J = 7.4 Hz, 1H), 7.02 – 6.84 (m, 1H), 6.59 (dd, J = 12.5, 4.3 Hz, 2H), 6.52 – 6.29 (m, 2H), 5.32 – 5.02 (m, 1H), 3.72 (d, J = 1.5 Hz, 3H), 1.28 (d, J = 6.2 Hz, 6H). MS (ESI+) m/z 414 (M+H)+.

124. 5-(3-acetyl-2-fluorophenyl)-2-methyl-6-(2-phenoxyphenyl)pyridazin-3(2H)-one. Example 124 was prepared according to the procedure used for the preparation of Example 105, substituting 3-acetyl-2-fluorophenylboronic acid for N-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetamide, to provide the title compound. ^{1}H NMR (400 MHz, DMSO-d_6/D_2O) δ 7.74 (dd, J = 10.3, 4.5 Hz, 1H), 7.60 (dd, J = 7.6, 1.7 Hz, 1H), 7.40 – 7.29 (m, 2H), 7.30 – 7.17 (m, 4H), 7.14 – 7.00 (m, 2H), 6.60 (d, J = 7.7 Hz, 1H), 6.41 (d, J = 7.7 Hz, 2H), 3.76 (s, 3H), 2.24 (d, J = 4.5 Hz, 3H). MS (ESI+) m/z 415 (M+H)+.

125. 5-(2,6-dimethoxypyridin-3-yl)-2-methyl-6-(2-phenoxyphenyl)pyridazin-3(2H)-one. Example 125 was prepared according to the procedure used for the preparation of Example 105, substituting 2,6-dimethoxypyridin-3-ylboronic acid for N-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetamide, to provide the title compound. ^{1}H NMR (400 MHz, DMSO-d_6/D_2O) δ 7.59 – 7.45 (m, 1H), 7.37 – 7.30 (m, 2H), 7.30 – 7.22 (m, 3H), 7.22 – 7.15 (m, 1H), 7.09 (q, J = 7.0 Hz, 1H), 6.89 (d, J = 7.6 Hz, 1H), 6.67 (dd, J = 12.5, 4.9 Hz, 1H), 6.47 (dd, J = 8.5, 0.9 Hz, 2H), 6.26 (d, J = 8.1 Hz, 1H), 3.81 (s, 3H), 3.69 (s, 3H), 3.44 (d, J = 6.9 Hz, 3H). MS (ESI+) m/z 416 $(M+H)^+$.

126. methyl 2-[1-methyl-6-oxo-3-(2-phenoxyphenyl)-1,6-dihydropyridazin-4-yl]benzoate. Example 126 was prepared according to the procedure used for the preparation of Example 105, substituting methyl 2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoate for N-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetamide, to provide the title compound. ^{1}H NMR (400 MHz, DMSO-d_6/D_2O) δ 7.77 – 7.67 (m, 1H), 7.63 – 7.46 (m, 2H), 7.41 – 7.32 (m, 1H), 7.33 – 7.21 (m, 4H), 7.20 – 7.03 (m, 2H), 6.85 (s, 1H), 6.50 – 6.44 (m, 1H), 6.43 (d, J = 7.7 Hz, 2H), 3.72 (s, 3H), 3.63 (s, 3H). MS (ESI+) m/z 413 $(M+H)^+$.

127. N-methyl-4-[1-methyl-6-oxo-3-(2-phenoxyphenyl)-1,6-dihydropyridazin-4-yl]benzamide. Example 127 was prepared according to the procedure used for the preparation of Example 105, substituting N-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide for N-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-

yl)phenyl)acetamide, to provide the title compound. ^{1}H NMR (400 MHz, DMSO-d_6/D_2O) δ 7.67 (d, J = 8.4 Hz, 2H), 7.61 (dd, J = 7.5, 1.7 Hz, 1H), 7.47 – 7.32 (m, 1H), 7.27 – 7.21 (m, 4H), 7.18 (d, J = 8.4 Hz, 2H), 7.06 (t, J = 7.4 Hz, 1H), 6.97 (s, 1H), 6.56 (d, J = 7.7 Hz, 1H), 6.42 – 6.22 (m, 2H), 3.73 (s, 3H), 2.79 (s, 3H). MS (ESI+) m/z 412 $(M+H)^+$.

128. N-methyl-3-[1-methyl-6-oxo-3-(2-phenoxyphenyl)-1,6-dihydropyridazin-4-yl]benzamide. Example 128 was prepared according to the procedure used for the preparation of Example 105, substituting N-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide for N-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetamide, to provide the title compound. ^{1}H NMR (400 MHz, DMSO-d_6/D_2O) δ 7.90 – 7.76 (m, 1H), 7.71 (t, J = 1.6 Hz, 1H), 7.59 (dd, J = 7.5, 1.7 Hz, 1H), 7.39 – 7.24 (m, 2H), 7.26 – 7.14 (m, 4H), 7.09 – 7.02 (m, 1H), 7.01 (s, 1H), 6.52 (dd, J = 8.2, 0.7 Hz, 1H), 6.31 (dd, J = 8.6, 0.9 Hz, 2H), 3.74 (s, 3H), 2.74 (s, 3H). MS (ESI+) m/z 412 $(M+H)^+$.

129. 2-methyl-5-[1-(3-methylbutyl)-1H-pyrazol-4-yl]-6-(2-phenoxyphenyl)pyridazin-3(2H)-one. Example 129 was prepared according to the procedure used for the preparation of Example 105, substituting 1-isopentyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole for N-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetamide, to provide the title compound. ^{1}H NMR (400 MHz, DMSO-d_6/D_2O) δ 7.57 – 7.44 (m, 3H), 7.37 – 7.22 (m, 3H), 7.23 – 7.08 (m, 2H), 7.03 (s, 1H), 6.72 (d, J = 7.8 Hz, 1H), 6.54 (dd, J = 11.9, 10.8 Hz, 2H), 4.02 (t, J = 7.0 Hz, 2H), 3.66 (s, 3H), 1.54 (q, J = 6.9 Hz, 2H), 1.42 – 1.23 (m, 1H), 0.82 (d, J = 6.6 Hz, 6H). MS (ESI+) m/z 415 $(M+H)^+$.

130. 2-methyl-6-(2-phenoxyphenyl)-5-[2-(propan-2-yloxy)pyridin-3-yl]pyridazin-3(2H)-one. Example 130 was prepared according to the procedure used for the preparation of Example 105, substituting 2-isopropoxy-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine for N-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetamide, to provide the title compound. ^{1}H NMR (400 MHz, DMSO-d_6/D_2O) δ 8.21 – 8.03 (m, 1H), 7.63 – 7.47 (m, 1H), 7.42 – 7.24 (m, 4H), 7.24 – 7.15 (m, 1H), 7.15 – 7.04 (m, 1H), 6.97 – 6.89 (m, 1H), 6.89 – 6.80 (m, 1H), 6.66 – 6.49 (m, 1H), 6.44 (dd, J = 8.6, 1.0 Hz, 2H), 5.10 – 4.80 (m, 1H), 3.71 (t, J = 2.2 Hz, 3H), 0.99 (d, J = 6.1 Hz, 6H). MS (ESI+) m/z 414 $(M+H)^+$.

131. 5-(1,3-benzothiazol-5-yl)-2-methyl-6-(2-phenoxyphenyl)pyridazin-3(2H)-one. Example 131 was prepared according to the procedure used for the preparation of Example 105, substituting 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzo[d]thiazole for N-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetamide, to provide the title compound. ^{1}H NMR (400 MHz, DMSO-d_6/D_2O) δ 8.03 (d, J = 8.4 Hz, 1H), 7.83 (d, J = 1.5 Hz, 1H), 7.72 – 7.53 (m, 1H), 7.37 – 7.25 (m, 4H), 6.98 (ddd, J = 15.3, 10.8, 4.4 Hz, 3H),

6.90 – 6.71 (m, 2H), 6.53 (d, J = 7.5 Hz, 1H), 6.34 – 6.01 (m, 2H), 3.75 (s, 3H). MS (ESI+) m/z 412 $(M+H)^+$.

132. 5-(5-acetyl-2-fluorophenyl)-2-methyl-6-(2-phenoxyphenyl)pyridazin-3(2H)-one. Example 132 was prepared according to the procedure used for the preparation of Example 105, substituting 1-(4-fluoro-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)ethanone for N-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetamide, to provide the title compound. ^{1}H NMR (400 MHz, DMSO-d_6/D_2O) δ 8.05 – 7.90 (m, 1H), 7.72 (dd, J = 7.2, 2.2 Hz, 1H), 7.59 (dd, J = 7.6, 1.6 Hz, 1H), 7.38 – 7.29 (m, 1H), 7.29 – 7.17 (m, 4H), 7.14 – 7.00 (m, 2H), 6.60 (d, J = 7.7 Hz, 1H), 6.40 (s, 1H), 3.76 (s, 3H), 2.34 (d, J = 24.6 Hz, 3H). MS (ESI+) m/z 415 $(M+H)^+$.

133. 5-(2,3-dihydro-1,4-benzodioxin-6-yl)-2-methyl-6-(2-phenoxyphenyl)pyridazin-3(2H)-one. Example 133 was prepared according to the procedure used for the preparation of Example 105, substituting 2-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane for N-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetamide, to provide the title compound. ^{1}H NMR (400 MHz, DMSO-d_6/D_2O) δ 7.57 (dd, J = 7.6, 1.7 Hz, 1H), 7.43 – 7.32 (m, 1H), 7.29 – 7.20 (m, 3H), 7.09 (dd, J = 10.6, 4.1 Hz, 1H), 6.84 (s, 1H), 6.69 (t, J = 7.6 Hz, 1H), 6.64 – 6.54 (m, 3H), 6.44 – 6.26 (m, 2H), 4.30 – 4.20 (m, 2H), 4.16 (d, J = 2.5 Hz, 2H), 3.71 (s, 3H). MS (ESI+) m/z 413 $(M+H)^+$.

134. 5-[3-(1-methoxyethyl)phenyl]-2-methyl-6-(2-phenoxyphenyl)pyridazin-3(2H)-one. Example 134 was prepared according to the procedure used for the preparation of Example 105, substituting 2-(3-(1-methoxyethyl)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane for N-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetamide, to provide the title compound. ^{1}H NMR (400 MHz, DMSO-d_6/D_2O) δ 7.59 (dd, J = 7.5, 1.7 Hz, 1H), 7.38 – 7.30 (m, 3H), 7.24 – 7.16 (m, 3H), 7.07 (t, J = 7.4 Hz, 1H), 7.00 (s, 1H), 6.95 (s, 1H), 6.57 – 6.37 (m, 1H), 6.30 (dd, J = 8.5, 0.9 Hz, 2H), 4.14 (q, J = 6.4 Hz, 1H), 3.74 (s, 3H), 2.89 (s, 3H), 1.07 (d, J = 6.4 Hz, 3H). MS (ESI+) m/z 413 $(M+H)^+$.

135. 5-[4-(1-methoxyethyl)phenyl]-2-methyl-6-(2-phenoxyphenyl)pyridazin-3(2H)-one. Example 135 was prepared according to the procedure used for the preparation of Example 105, substituting 2-(4-(1-methoxyethyl)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane for N-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetamide, to provide the title compound. ^{1}H NMR (400 MHz, DMSO-d_6/D_2O) δ 7.61 (dd, J = 7.5, 1.7 Hz, 1H), 7.42 – 7.27 (m, 1H), 7.28 – 7.18 (m, 4H), 7.18 – 7.04 (m, 4H), 6.94 (s, 1H), 6.42 (d, J = 8.2 Hz, 1H), 6.24 (d, J = 7.7 Hz, 2H), 4.33 (q, J = 6.4 Hz, 1H), 3.74 (s, 3H), 3.16 (d, J = 11.7 Hz, 3H), 1.33 (d, J = 6.4 Hz, 3H). MS (ESI+) m/z 469 $(M+H)^+$.

136. 5-(3-ethoxy-2-fluorophenyl)-2-methyl-6-(2-phenoxyphenyl)pyridazin-3(2H)-one. Example 136 was prepared according to the procedure used for the preparation of Example 105, substituting 2-(3-ethoxy-2-fluorophenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane for N-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetamide, to provide the title compound. ^{1}H NMR (400 MHz, DMSO-d_6/D_2O) δ 7.53 (dd, J = 7.6, 1.7 Hz, 1H), 7.38 – 7.31 (m, 1H), 7.31 – 7.23 (m, 2H), 7.19 (dt, J = 7.5, 3.7 Hz, 1H), 7.11 (dd, J = 11.6, 4.3 Hz, 2H), 7.03 – 6.93 (m, 2H), 6.62 – 6.52 (m, 2H), 6.50 – 6.33 (m, 2H), 4.09 – 3.88 (m, 2H), 3.73 (s, 3H), 1.26 (t, J = 7.0 Hz, 3H). MS (ESI+) m/z 413 $(M+H)^+$.

137. 5-(2,1,3-benzothiadiazol-5-yl)-2-methyl-6-(2-phenoxyphenyl)pyridazin-3(2H)-one. Example 137 was prepared according to the procedure used for the preparation of Example 105, substituting 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzo[c][1,2,5]thiadiazole for N-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetamide, to provide the title compound. ^{1}H NMR (400 MHz, DMSO-d_6/D_2O) δ 7.99 – 7.88 (m, 1H), 7.86 – 7.82 (m, 1H), 7.77 – 7.59 (m, 1H), 7.50 – 7.42 (m, 1H), 7.41 – 7.33 (m, 1H), 7.32 – 7.26 (m, 1H), 7.14 (s, 1H), 7.00 – 6.87 (m, 3H), 6.70 – 6.52 (m, 1H), 6.30 – 6.06 (m, 2H), 3.77 (s, 3H). MS (ESI+) m/z 413 $(M+H)^+$.

138. 5-[5-(benzylamino)pyridin-3-yl]-2-methyl-6-(2-phenoxyphenyl)pyridazin-3(2H)-one. Example 138 was prepared according to the procedure used for the preparation of Example 105, substituting N-benzyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-3-amine for N-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetamide, to provide the title compound. ^{1}H NMR (400 MHz, DMSO-d_6/D_2O) δ 7.99 – 7.87 (m, 1H), 7.66 – 7.58 (m, 1H), 7.55 – 7.47 (m, 1H), 7.43 – 7.36 (m, 1H), 7.36 – 7.28 (m, 2H), 7.28 – 7.20 (m, 6H), 7.17 – 7.03 (m, 1H), 6.98 – 6.85 (m, 2H), 6.74 – 6.62 (m, 1H), 6.52 – 6.22 (m, 2H), 4.14 (s, 2H), 3.71 (d, J = 17.5 Hz, 3H). MS (ESI+) m/z 461 $(M+H)^+$.

139. 2-methyl-5-[3-(morpholin-4-yl)phenyl]-6-(2-phenoxyphenyl)pyridazin-3(2H)-one. Example 139 was prepared according to the procedure used for the preparation of Example 105, substituting 4-(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)morpholine for N-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetamide, to provide the title compound. ^{1}H NMR (400 MHz, DMSO-d_6/D_2O) δ 7.58 – 7.42 (m, 1H), 7.39 – 7.30 (m, 1H), 7.28 – 7.18 (m, 3H), 7.16 – 7.10 (m, 1H), 7.10 – 7.03 (m, 1H), 6.96 – 6.89 (m, 1H), 6.86 (s, 1H), 6.69 – 6.55 (m, 3H), 6.51 – 6.31 (m, 2H), 3.70 (s, 3H), 3.65 (dd, J = 13.7, 8.9 Hz, 4H), 2.96 – 2.73 (m, 4H). MS (ESI+) m/z 440 $(M+H)^+$.

140. 2-methyl-6-(2-phenoxyphenyl)-5-[6-(2,2,2-trifluoroethoxy)pyridin-3-yl]pyridazin-3(2H)-one. Example 140 was prepared according to the procedure used for the preparation

of Example 105, substituting 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-(2,2,2-trifluoroethoxy)pyridine for N-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetamide, to provide the title compound. ^{1}H NMR (400 MHz, DMSO-d_6/D_2O) δ 8.02 – 7.91 (m, 1H), 7.60 – 7.45 (m, 2H), 7.41 – 7.33 (m, 1H), 7.32 – 7.16 (m, 3H), 7.13 – 6.97 (m, 1H), 6.93 (s, 1H), 6.84 – 6.76 (m, 1H), 6.75 – 6.63 (m, 1H), 6.55 – 6.32 (m, 2H), 4.92 (q, J = 9.0 Hz, 2H), 3.70 (s, 3H). MS (ESI+) m/z 453 $(M+H)^+$.

141. 2-methyl-5-[3-(morpholin-4-ylmethyl)phenyl]-6-(2-phenoxyphenyl)pyridazin-3(2H)-one. Example 141 was prepared according to the procedure used for the preparation of Example 105, substituting 4-(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl)morpholine for N-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetamide, to provide the title compound. ^{1}H NMR (400 MHz, DMSO-d_6/D_2O) δ 7.59 – 7.52 (m, 1H), 7.50 – 7.43 (m, 1H), 7.43 – 7.33 (m, 2H), 7.31 – 7.27 (m, 1H), 7.27 – 7.18 (m, 4H), 7.12 – 7.02 (m, 1H), 6.93 (d, J = 3.4 Hz, 1H), 6.68 – 6.59 (m, 1H), 6.52 – 6.42 (m, 2H), 4.30 – 4.07 (m, 2H), 3.76 – 3.71 (m, 4H), 3.70 (s, 3H), 3.00 – 2.81 (m, 4H). MS (ESI+) m/z 454 $(M+H)^+$.

142. 2-methyl-6-(2-phenoxyphenyl)-5-[3-(thiomorpholin-4-ylcarbonyl)phenyl]pyridazin-3(2H)-one. Example 142 was prepared according to the procedure used for the preparation of Example 105, substituting (3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)(thiomorpholino)methanone for N-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetamide, to provide the title compound. ^{1}H NMR (400 MHz, DMSO-d_6/D_2O) δ 7.54 – 7.44 (m, 1H), 7.42 – 7.31 (m, 3H), 7.31 – 7.23 (m, 3H), 7.23 – 7.15 (m, 2H), 7.16 – 7.09 (m, 1H), 7.09 – 7.00 (m, 2H), 6.97 – 6.85 (m, 2H), 6.65 (t, J = 7.1 Hz, 1H), 6.51 (d, J = 7.9 Hz, 2H), 3.70 (s, 3H), 3.61 – 3.42 (m, 4H), 3.26 (s, 4H). MS (ESI+) m/z 484 $(M+H)^+$.

143. 5-[5-(cyclopentylamino)pyridin-3-yl]-2-methyl-6-(2-phenoxyphenyl)pyridazin-3(2H)-one. Example 143 was prepared according to the procedure used for the preparation of Example 105, substituting N-cyclopentyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-3-amine for N-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetamide, to provide the title compound. ^{1}H NMR (400 MHz, DMSO-d_6/D_2O) δ 8.04 – 7.90 (m, 1H), 7.74 – 7.61 (m, 1H), 7.61 – 7.48 (m, 1H), 7.46 – 7.32 (m, 1H), 7.36 – 7.19 (m, 3H), 7.15 – 7.04 (m, 1H), 6.99 (s, 1H), 6.96 – 6.88 (m, 1H), 6.81 – 6.64 (m, 1H), 6.59 – 6.28 (m, 2H), 3.71 (s, 3H), 3.55 – 3.40 (m, 1H), 1.95 – 1.72 (m, 2H), 1.71 – 1.40 (m, 4H), 1.44 – 1.21 (m, 2H). MS (ESI+) m/z 439 $(M+H)^+$.

144. N-cyclopropyl-5-[1-methyl-6-oxo-3-(2-phenoxyphenyl)-1,6-dihydropyridazin-4-yl]pyridine-3-carboxamide. Example 144 was prepared according to the procedure used for the preparation of Example 105, substituting N-cyclopropyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)nicotinamide for N-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetamide, to provide the title compound. ^{1}H NMR (400 MHz, DMSO-d_6/D_2O) δ 8.96 – 8.76 (m, 1H), 8.56 – 8.26 (m, 1H), 7.97 (t, J = 2.1 Hz, 1H), 7.65 – 7.48 (m, 1H), 7.48 – 7.33 (m, 1H), 7.23 (dd, J = 10.9, 4.4 Hz, 3H), 7.12 – 6.93 (m, 2H), 6.77 – 6.58 (m, 1H), 6.50 – 6.33 (m, 2H), 3.72 (s, 3H), 2.97 – 2.74 (m, 1H), 0.87 – 0.67 (m, 2H), 0.62 – 0.46 (m, 2H). MS (ESI+) m/z 439 $(M+H)^+$.

145. N-cyclopentyl-5-[1-methyl-6-oxo-3-(2-phenoxyphenyl)-1,6-dihydropyridazin-4-yl]pyridine-3-carboxamide. Example 145 was prepared according to the procedure used for the preparation of Example 105, substituting N-cyclopentyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)nicotinamide for N-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetamide, to provide the title compound. ^{1}H NMR (400 MHz, DMSO-d_6/D_2O) δ 8.89 (d, J = 2.0 Hz, 1H), 8.38 (d, J = 2.2 Hz, 1H), 8.00 (t, J = 2.1 Hz, 1H), 7.57 (dd, J = 7.5, 1.7 Hz, 1H), 7.42 – 7.32 (m, 2H), 7.28 – 7.17 (m, 3H), 6.98 (d, J = 7.7 Hz, 1H), 6.65 (d, J = 8.2 Hz, 1H), 6.54 – 6.37 (m, 2H), 4.19 (dd, J = 13.4, 6.7 Hz, 1H), 3.73 (s, 3H), 2.07 – 1.80 (m, 2H), 1.78 – 1.61 (m, 2H), 1.61 – 1.38 (m, 4H). MS (ESI+) m/z 467 $(M+H)^+$.

146. N,N-diethyl-3-[1-methyl-6-oxo-3-(2-phenoxyphenyl)-1,6-dihydropyridazin-4-yl]benzenesulfonamide. Example 146 was prepared according to the procedure used for the preparation of Example 105, substituting N,N-diethyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzenesulfonamide for N-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetamide, to provide the title compound. ^{1}H NMR (400 MHz, DMSO-d_6/D_2O) δ 7.85 – 7.70 (m, 1H), 7.60 – 7.51 (m, 3H), 7.49 (d, J = 10.8 Hz, 1H), 7.39 – 7.31 (m, 1H), 7.29 – 7.18 (m, 3H), 7.16 – 6.99 (m, 1H), 6.92 (s, 1H), 6.73 – 6.59 (m, 1H), 6.50 (dd, J = 9.8, 4.2 Hz, 2H), 3.71 (s, 3H), 2.94 (q, J = 7.1 Hz, 4H), 0.99 (t, J = 7.1 Hz, 6H). MS (ESI+) m/z 490 $(M+H)^+$.

147. 2-methyl-5-[4-(morpholin-4-ylcarbonyl)phenyl]-6-(2-phenoxyphenyl)pyridazin-3(2H)-one. Example 147 was prepared according to the procedure used for the preparation of Example 105, substituting morpholino(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)methanone for N-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetamide, to provide the title compound. ^{1}H NMR (400 MHz, DMSO-d_6/D_2O) δ 7.57 – 7.47 (m, 1H), 7.39 – 7.32 (m, 1H), 7.30 – 7.26 (m, 2H), 7.26 – 7.19 (m, 5H), 7.15 –

7.00 (m, 1H), 6.90 (s, 1H), 6.62 (dd, J = 8.3, 5.2 Hz, 1H), 6.49 – 6.40 (m, 2H), 3.71 (s, 3H), 3.65 – 3.55 (m, 4H), 3.51 – 3.35 (m, 4H). MS (ESI+) m/z 468 $(M+H)^+$.

148. N-cyclohexyl-N-methyl-3-[1-methyl-6-oxo-3-(2-phenoxyphenyl)-1,6-dihydropyridazin-4-yl]benzamide. Example 148 was prepared according to the procedure used for the preparation of Example 105, substituting N-cyclohexyl-N-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide for N-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetamide, to provide the title compound. ^{1}H NMR (400 MHz, DMSO-d_6/D_2O) δ 7.56 – 7.43 (m, 1H), 7.36 (dd, J = 9.2, 5.7 Hz, 1H), 7.32 – 7.28 (m, 2H), 7.27 – 7.21 (m, 2H), 7.20 – 7.12 (m, 1H), 7.12 – 7.02 (m, 2H), 6.88 (s, 1H), 6.62 (d, J = 8.2 Hz, 1H), 6.52 (t, J = 5.5 Hz, 1H), 3.69 (s, 3H), 2.58 – 2.43 (m, 1H), 1.87 – 1.65 (m, 2H), 1.64 – 1.33 (m, 4H), 1.26 – 0.76 (m, 3H). MS (ESI+) m/z 494 $(M+H)^+$.

149. 2-methyl-5-[4-(morpholin-4-yl)phenyl]-6-(2-phenoxyphenyl)pyridazin-3(2H)-one. Example 149 was prepared according to the procedure used for the preparation of Example 105, substituting 4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)morpholine for N-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetamide, to provide the title compound. ^{1}H NMR (400 MHz, DMSO-d_6/D_2O) δ 7.64 – 7.39 (m, 1H), 7.39 – 7.30 (m, 1H), 7.25 – 7.13 (m, 4H), 7.09 – 6.96 (m, 3H), 6.80 – 6.72 (m, 3H), 6.69 – 6.56 (m, 1H), 6.51 – 6.32 (m, 2H), 3.77 – 3.70 (m, 4H), 3.70 – 3.62 (s, 3H), 3.19 – 3.03 (m, 4H). MS (ESI+) m/z 440 $(M+H)^+$.

150. N-[3-(dimethylamino)propyl]-4-[1-methyl-6-oxo-3-(2-phenoxyphenyl)-1,6-dihydropyridazin-4-yl]benzamide. Example 150 was prepared according to the procedure used for the preparation of Example 105, substituting N-(3-(dimethylamino)propyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide for N-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetamide, to provide the title compound. ^{1}H NMR (400 MHz, DMSO-d_6/D_2O) δ 7.75 – 7.63 (m, 2H), 7.58 – 7.45 (m, 1H), 7.42 – 7.30 (m, 1H), 7.30 – 7.15 (m, 5H), 7.08 – 6.98 (m, 1H), 6.96 – 6.82 (m, 1H), 6.69 – 6.60 (m, 1H), 6.55 – 6.43 (m, 2H), 3.78 – 3.65 (m, 3H), 3.45 – 3.32 (m, 2H), 3.17 – 3.06 (m, 2H), 2.81 (s, 6H), 2.06 – 1.79 (m, 2H). MS (ESI+) m/z 483 $(M+H)^+$.

151. 2-methyl-6-(2-phenoxyphenyl)-5-[6-(piperazin-1-yl)pyridin-3-yl]pyridazin-3(2H)-one. Example 151 was prepared according to the procedure used for the preparation of Example 105, substituting 1-(5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-yl)piperazine for N-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetamide, to provide the title compound. ^{1}H NMR (400 MHz, DMSO-d_6/D_2O) δ 7.98 – 7.86 (m, 1H), 7.59 – 7.46 (m, 1H), 7.42 – 7.36 (m, 1H), 7.36 – 7.29 (m, 1H), 7.28 – 7.16 (m, 3H), 7.12 – 6.97 (m,

1H), 6.85 (s, 1H), 6.81 – 6.66 (m, 2H), 6.59 – 6.42 (m, 2H), 3.77 – 3.70 (m, 4H), 3.67 (s, 3H), 3.23 – 3.12 (m, 4H). MS (ESI+) m/z 440 $(M+H)_+$.

152. 3-fluoro-N,N-dimethyl-5-[1-methyl-6-oxo-3-(2-phenoxyphenyl)-1,6-dihydropyridazin-4-yl]benzamide. Example 152 was prepared according to the procedure used for the preparation of Example 105, substituting 3-fluoro-N,N-dimethyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide for N-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetamide, to provide the title compound. ^{1}H NMR (400 MHz, DMSO-d_6/D_2O) δ 7.64 – 7.46 (m, 1H), 7.42 – 7.31 (m, 1H), 7.28 – 7.21 (m, 2H), 7.21 – 7.14 (m, 2H), 7.14 – 7.04 (m, 2H), 6.96 (dd, J = 4.3, 3.0 Hz, 2H), 6.75 – 6.64 (m, 1H), 6.54 (t, J = 5.4 Hz, 2H), 3.70 (s, 3H), 2.90 – 2.64 (m, 6H). MS (ESI+) m/z 444 $(M+H)^+$.

153. 2-methyl-5-[2-(morpholin-4-yl)pyridin-4-yl]-6-(2-phenoxyphenyl)pyridazin-3(2H)-one. Example 153 was prepared according to the procedure used for the preparation of Example 105, substituting 4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-yl)morpholine for N-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetamide, to provide the title compound. ^{1}H NMR (400 MHz, DMSO-d_6/D_2O) δ 8.01 – 7.81 (m, 1H), 7.64 – 7.49 (m, 1H), 7.43 – 7.31 (m, 1H), 7.27 – 7.14 (m, 3H), 7.11 – 7.02 (m, 1H), 6.97 (s, 1H), 6.81 – 6.65 (m, 1H), 6.55 – 6.41 (m, 4H), 3.71 (s, 3H), 3.63 – 3.55 (m, 4H), 3.25 (s, 4H). MS (ESI+) m/z 441 $(M+H)^+$.

154. 2-methyl-5-{3-[(4-methylpiperidin-1-yl)carbonyl]phenyl}-6-(2-phenoxyphenyl)pyridazin-3(2H)-one. Example 154 was prepared according to the procedure used for the preparation of Example 105, substituting (4-methylpiperidin-1-yl)(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)methanone for N-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetamide, to provide the title compound. ^{1}H NMR (400 MHz, DMSO-d_6/D_2O) δ 7.52 – 7.46 (m, 1H), 7.39 – 7.30 (m, 2H), 7.30 – 7.25 (m, 2H), 7.25 – 7.21 (m, 1H), 7.21 – 7.15 (m, 1H), 7.10 – 7.01 (m, 2H), 6.89 (s, 1H), 6.66 – 6.59 (m, 1H), 6.55 – 6.46 (m, 2H), 3.70 (s, 3H), 2.88 – 2.67 (m, 2H), 1.66 – 1.48 (m, 2H), 0.98 – 0.78 (m, 4H). MS (ESI+) m/z 480 $(M+H)^+$.

155. 2-fluoro-N,N-dimethyl-5-[1-methyl-6-oxo-3-(2-phenoxyphenyl)-1,6-dihydropyridazin-4-yl]benzamide. Example 155 was prepared according to the procedure used for the preparation of Example 105, substituting 2-fluoro-N,N-dimethyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide for N-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetamide, to provide the title compound. ^{1}H NMR (400 MHz, DMSO-d_6/D_2O) δ 7.54 – 7.46 (m, 1H), 7.40 – 7.33 (m, 1H), 7.33 – 7.27 (m, 1H), 7.28 – 7.23 (m, 2H), 7.23 – 7.18 (m, 1H), 7.18 – 7.12 (m, 1H), 7.11 – 7.03 (m, 2H), 6.93 – 6.87 (m, 1H),

6.74 – 6.66 (m, 1H), 6.63 – 6.54 (m, 2H), 3.68 (s, 3H), 3.09 – 2.81 (m, 3H), 2.78 – 2.55 (m, 3H). MS (ESI+) m/z 444 $(M+H)^+$.

156. 2-methyl-6-(2-phenoxyphenyl)-5-[3-(pyrrolidin-1-ylsulfonyl)phenyl]pyridazin-3(2H)-one. Example 156 was prepared according to the procedure used for the preparation of Example 105, substituting 1-(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenylsulfonyl)pyrrolidine for N-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetamide, to provide the title compound. ^{1}H NMR (400 MHz, DMSO-d_6/D_2O) δ 7.86 – 7.68 (m, 1H), 7.66 – 7.44 (m, 4H), 7.44 – 7.29 (m, 1H), 7.30 – 7.15 (m, 3H), 7.13 – 6.97 (m, 1H), 6.99 – 6.89 (m, 1H), 6.72 – 6.61 (m, 1H), 6.57 – 6.40 (m, 2H), 3.71 (d, J = 4.0 Hz, 3H), 3.07 – 2.78 (m, 4H), 1.71 – 1.47 (m, 4H). MS (ESI+) m/z 488 $(M+H)^+$.

157. 2-methyl-6-(2-phenoxyphenyl)-5-[3-(piperidin-1-ylcarbonyl)phenyl]pyridazin-3(2H)-one. Example 157 was prepared according to the procedure used for the preparation of Example 105, substituting piperidin-1-yl(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)methanone for N-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetamide, to provide the title compound. ^{1}H NMR (400 MHz, DMSO-d_6/D_2O) δ 7.53 – 7.46 (m, 1H), 7.40 – 7.31 (m, 3H), 7.31 – 7.25 (m, 2H), 7.25 – 7.15 (m, 3H), 7.11 – 7.01 (m, 2H), 6.89 (d, J = 3.9 Hz, 1H), 6.67 – 6.57 (m, 1H), 6.55 – 6.43 (m, 2H), 3.70 (s, 3H), 3.25 – 3.18 (m, 4H), 1.73 – 1.46 (m, 2H), 1.48 – 1.23 (m, 4H). MS (ESI+) m/z 466 $(M+H)^+$.

158. N,N-diethyl-4-[1-methyl-6-oxo-3-(2-phenoxyphenyl)-1,6-dihydropyridazin-4-yl]benzamide. Example 158 was prepared according to the procedure used for the preparation of Example 105, substituting N,N-diethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide for N-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetamide, to provide the title compound. ^{1}H NMR (400 MHz, DMSO-d_6/D_2O) δ 7.55 – 7.45 (m, 1H), 7.38 – 7.32 (m, 1H), 7.30 – 7.18 (m, 7H), 7.12 – 7.00 (m, 1H), 6.96 – 6.80 (m, 1H), 6.71 – 6.59 (m, 1H), 6.47 (s, 1H), 3.70 (s, 3H), 3.35 – 3.29 (m, 4H), 1.21 – 0.92 (m, 6H). MS (ESI+) m/z 454 $(M+H)^+$.

159. N-methyl-4-[1-methyl-6-oxo-3-(2-phenoxyphenyl)-1,6-dihydropyridazin-4-yl]benzenesulfonamide. Example 159 was prepared according to the procedure used for the preparation of Example 105, substituting N-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzenesulfonamide for N-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetamide, to provide the title compound. ^{1}H NMR (400 MHz, DMSO-d_6/D_2O) δ 7.75 – 7.61 (m, 2H), 7.58 – 7.47 (m, 1H), 7.40 – 7.32 (m, 3H), 7.27 – 7.15 (m, 3H), 7.12 – 6.98 (m, 1H), 6.96 – 6.84 (m, 1H), 6.65 – 6.58 (m, 1H), 6.46 – 6.35 (m, 2H), 3.72 (s, 3H), 2.47 – 2.44 (m, 3H). MS (ESI+) m/z 448 $(M+H)^+$.

160. N,N-diethyl-3-[1-methyl-6-oxo-3-(2-phenoxyphenyl)-1,6-dihydropyridazin-4-yl]benzamide. Example 160 was prepared according to the procedure used for the preparation of Example 105, substituting N,N-diethyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide for N-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetamide, to provide the title compound. ^{1}H NMR (400 MHz, DMSO-d_6/D_2O) δ 7.48 (dd, J = 7.6, 1.7 Hz, 1H), 7.36 – 7.28 (m, 4H), 7.29 – 7.20 (m, 3H), 7.17 (t, J = 7.0 Hz, 1H), 7.03 – 6.92 (m, 1H), 6.98 – 6.86 (m, 2H), 6.63 (d, J = 8.3 Hz, 1H), 6.52 (d, J = 8.3 Hz, 2H), 3.70 (s, 3H), 3.14 (s, 4H), 0.98 (t, J = 6.9 Hz, 6H). MS (ESI+) m/z 454 $(M+H)^+$.

161. 2-methyl-5-[4-(4-methylpiperazin-1-yl)phenyl]-6-(2-phenoxyphenyl)pyridazin-3(2H)-one. Example 161 was prepared according to the procedure used for the preparation of Example 105, substituting 1-methyl-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)piperazine for N-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetamide, to provide the title compound. ^{1}H NMR (400 MHz, DMSO-d_6/D_2O) δ 7.62 – 7.43 (m, 1H), 7.41 – 7.29 (m, 1H), 7.28 – 7.14 (m, 3H), 7.04 (dd, J = 8.0, 5.8 Hz, 3H), 6.84 (d, J = 8.8 Hz, 2H), 6.78 (s, 1H), 6.66 (d, J = 8.2 Hz, 1H), 6.46 (d, J = 8.4 Hz, 2H), 3.67 (s, 3H), 3.31 (d, J = 20.1 Hz, 8H), 2.88 (s, 3H). MS (ESI+) m/z 453 $(M+H)^+$.

162. 2-methyl-5-(6-{[2-(morpholin-4-yl)ethyl]amino}pyridin-3-yl)-6-(2-phenoxyphenyl)pyridazin-3(2H)-one. Example 162 was prepared according to the procedure used for the preparation of Example 105, substituting N-(2-morpholinoethyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-amine for N-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetamide, to provide the title compound. ^{1}H NMR (400 MHz, DMSO-d_6/D_2O) δ 7.83 (d, J = 2.3 Hz, 1H), 7.57 – 7.45 (m, 1H), 7.45 – 7.31 (m, 1H), 7.27 – 7.16 (m, 4H), 7.06 (td, J = 7.2, 3.5 Hz, 1H), 6.84 (d, J = 3.5 Hz, 1H), 6.76 (d, J = 8.1 Hz, 1H), 6.62 – 6.51 (m, 2H), 6.51 – 6.39 (m, 1H), 3.86 – 3.76 (m, 4H), 3.66 (s, 3H), 3.63 (t, J = 6.1 Hz, 2H), 3.27 (dd, J = 6.8, 3.6 Hz, 6H). MS (ESI+) m/z 484 $(M+H)^+$.

163. N-[3-(dimethylamino)propyl]-3-[1-methyl-6-oxo-3-(2-phenoxyphenyl)-1,6-dihydropyridazin-4-yl]benzamide. Example 163 was prepared according to the procedure used for the preparation of Example 105, substituting N-(3-(dimethylamino)propyl)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide for N-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetamide, to provide the title compound. ^{1}H NMR (400 MHz, DMSO-d_6/D_2O) δ 7.89 – 7.76 (m, 1H), 7.71 – 7.65 (m, 1H), 7.57 – 7.43 (m, 1H), 7.39 – 7.30 (m, 2H), 7.29 – 7.17 (m, 4H), 7.09 – 7.00 (m, 1H), 6.93 (s, 1H), 6.68 – 6.55 (m, 1H), 6.54 – 6.32 (m, 2H), 3.71 (s, 3H), 3.35 – 3.27 (m, 2H), 3.13 – 2.99 (m, 2H), 2.52 (dt, J = 3.6, 1.8 Hz, 6H), 2.01 – 1.81 (m, 2H). MS (ESI+) m/z 483 $(M+H)^+$.

164. 5-[6-(benzylamino)pyridin-3-yl]-2-methyl-6-(2-phenoxyphenyl)pyridazin-3(2H)-one. Example 164 was prepared according to the procedure used for the preparation of Example 105, substituting N-benzyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-amine for N-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetamide, to provide the title compound. ^{1}H NMR (400 MHz, DMSO-d_6/D_2O) δ 7.70 (t, J = 12.0 Hz, 1H), 7.53 (dd, J = 7.5, 1.7 Hz, 1H), 7.44 – 7.35 (m, 1H), 7.37 – 7.30 (m, 5H), 7.30 – 7.17 (m, 4H), 7.05 (t, J = 7.4 Hz, 1H), 6.87 (d, J = 4.4 Hz, 1H), 6.81 – 6.68 (m, 1H), 6.62 (d, J = 9.0 Hz, 1H), 6.53 (s, 1H), 4.51 (d, J = 5.4 Hz, 2H), 3.70 (d, J = 21.2 Hz, 3H). MS (ESI+) m/z 461 $(M+H)^+$.

165. N-(2-cyanoethyl)-4-[1-methyl-6-oxo-3-(2-phenoxyphenyl)-1,6-dihydropyridazin-4-yl]benzamide. Example 165 was prepared according to the procedure used for the preparation of Example 105, substituting N-(2-cyanoethyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide for N-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetamide, to provide the title compound. ^{1}H NMR (400 MHz, DMSO-d_6/D_2O) δ 7.75 – 7.63 (m, 2H), 7.61 – 7.46 (m, 1H), 7.43 – 7.31 (m, 1H), 7.30 – 7.15 (m, 5H), 7.13 – 6.95 (m, 1H), 6.89 (d, J = 9.4 Hz, 1H), 6.75 – 6.53 (m, 1H), 6.53 – 6.27 (m, 2H), 3.71 (s, 3H), 3.58 – 3.42 (m, 2H), 2.76 (t, J = 6.5 Hz, 2H) MS (ESI+) m/z 451 $(M+H)^+$.

166. 2-methyl-5-[5-methyl-6-(morpholin-4-yl)pyridin-3-yl]-6-(2-phenoxyphenyl)pyridazin-3(2H)-one. Example 166 was prepared according to the procedure used for the preparation of Example 105, substituting 4-(3-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-yl)morpholine for N-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetamide, to provide the title compound. ^{1}H NMR (400 MHz, DMSO-d_6/D_2O) δ 7.94 – 7.77 (m, 1H), 7.66 – 7.49 (m, 1H), 7.49 – 7.33 (m, 1H), 7.29 – 7.16 (m, 5H), 7.14 – 7.02 (m, 1H), 6.89 (d, J = 3.7 Hz, 1H), 6.68 (d, J = 7.8 Hz, 1H), 6.54 – 6.35 (m, 2H), 3.74 – 3.70 (m, 3H), 3.70 (s, 3H), 3.17 – 3.00 (m, 4H), 2.04 (s, 3H). MS (ESI+) m/z 455 $(M+H)^+$.

167. N,N-diethyl-3-fluoro-5-[1-methyl-6-oxo-3-(2-phenoxyphenyl)-1,6-dihydropyridazin-4-yl]benzamide. Example 167 was prepared according to the procedure used for the preparation of Example 105, substituting N,N-diethyl-3-fluoro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide for N-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetamide, to provide the title compound. ^{1}H NMR (400 MHz, DMSO-d_6/D_2O) δ 7.55 – 7.47 (m, 1H), 7.43 – 7.31 (m, 1H), 7.30 – 7.22 (m, 2H), 7.19 (tt, J = 7.2, 2.4 Hz, 1H), 7.15 – 7.10 (m, 1H), 7.10 – 7.03 (m, 2H), 6.95 (d, J = 3.9 Hz, 1H), 6.89 (d, J = 5.9 Hz, 1H), 6.72 – 6.64 (m, 1H), 6.61 – 6.52 (m, 2H), 3.70 (s, 3H), 3.24 – 3.04 (m, 4H), 1.21 – 0.82 (m, 6H). MS (ESI+) m/z 472 $(M+H)^+$.

168. N-tert-butyl-4-[1-methyl-6-oxo-3-(2-phenoxyphenyl)-1,6-dihydropyridazin-4-yl]benzamide. Example 168 was prepared according to the procedure used for the preparation of Example 105, substituting N-tert-butyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide for N-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetamide, to provide the title compound. ^{1}H NMR (400 MHz, DMSO-d_6/D_2O) δ 7.71 – 7.59 (m, 2H), 7.57 – 7.47 (m, 1H), 7.44 – 7.27 (m, 1H), 7.20 (t, J = 7.7 Hz, 5H), 7.07 – 6.98 (m, 1H), 6.89 – 6.80 (m, 1H), 6.71 – 6.56 (m, 1H), 6.53 – 6.25 (m, 2H), 3.69 (s, 3H), 1.39 (s, 9H). MS (ESI+) m/z 454 $(M+H)^+$.

169. N-cyclopentyl-4-[1-methyl-6-oxo-3-(2-phenoxyphenyl)-1,6-dihydropyridazin-4-yl]benzamide. Example 169 was prepared according to the procedure used for the preparation of Example 105, substituting N-cyclopentyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide for N-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetamide, to provide the title compound. ^{1}H NMR (400 MHz, DMSO-d_6/D_2O) δ 7.69 (d, J = 8.3 Hz, 2H), 7.52 (dd, J = 7.5, 1.7 Hz, 1H), 7.44 – 7.28 (m, 1H), 7.20 (dd, J = 11.6, 5.3 Hz, 5H), 7.04 (t, J = 7.4 Hz, 1H), 6.88 (s, 1H), 6.66 (d, J = 8.2 Hz, 1H), 6.45 (d, J = 7.8 Hz, 2H), 4.37 – 4.08 (m, 1H), 3.70 (s, 3H), 1.90 (dd, J = 8.0, 4.9 Hz, 2H), 1.65 (d, J = 40.3 Hz, 2H), 1.60 – 1.37 (m, 4H) MS (ESI+) m/z 466 $(M+H)^+$.

170. 4-[1-methyl-6-oxo-3-(2-phenoxyphenyl)-1,6-dihydropyridazin-4-yl]-N-(2-methylpropyl)benzamide. Example 170 was prepared according to the procedure used for the preparation of Example 105, substituting N-isobutyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide for N-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetamide, to provide the title compound. ^{1}H NMR (400 MHz, DMSO-d_6/D_2O) δ 7.77 – 7.60 (m, 2H), 7.56 – 7.48 (m, 1H), 7.39 – 7.30 (m, 1H), 7.27 – 7.13 (m, 5H), 7.13 – 6.96 (m, 1H), 6.89 (s, 1H), 6.66 (dd, J = 11.3, 4.7 Hz, 1H), 6.52 – 6.32 (m, 2H), 3.70 (s, 3H), 3.11 (d, J = 6.9 Hz, 2H), 2.05 – 1.74 (m, 1H), 0.90 (d, J = 6.7 Hz, 6H). MS (ESI+) m/z 454 $(M+H)^+$.

171. N-(3-methoxypropyl)-4-[1-methyl-6-oxo-3-(2-phenoxyphenyl)-1,6-dihydropyridazin-4-yl]benzamide. Example 171 was prepared according to the procedure used for the preparation of Example 105, substituting N-(3-methoxypropyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide for N-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetamide, to provide the title compound. ^{1}H NMR (400 MHz, DMSO-d_6/D_2O) δ 7.67 (d, J = 8.3 Hz, 2H), 7.52 (dd, J = 7.6, 1.7 Hz, 1H), 7.43 – 7.30 (m, 1H), 7.32 – 7.17 (m, 5H), 7.04 (t, J = 7.4 Hz, 1H), 6.89 (s, 1H), 6.65 (d, J = 8.2 Hz, 1H), 6.44 (d, J

= 7.8 Hz, 2H), 3.70 (s, 3H), 3.40 (t, J = 6.4 Hz, 2H), 3.32 (t, J = 6.7 Hz, 2H), 3.25 (s, 3H), 1.78 (p, J = 6.6 Hz, 2H). MS (ESI+) m/z 470 $(M+H)^+$.

172. 2-methyl-5-{1-[2-(morpholin-4-yl)ethyl]-1H-pyrazol-4-yl}-6-(2-phenoxyphenyl)pyridazin-3(2H)-one. Example 172 was prepared according to the procedure used for the preparation of Example 105, substituting 4-(2-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazol-1-yl)ethyl)morpholine for N-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetamide, to provide the title compound. ^{1}H NMR (400 MHz, DMSO-d_6/D_2O) δ 7.66 (s, 1H), 7.56 – 7.39 (m, 2H), 7.35 – 7.21 (m, 3H), 7.14 (s, 1H), 7.07 (t, J = 7.4 Hz, 1H), 6.97 (s, 1H), 6.90 (d, J = 8.2 Hz, 1H), 6.68 – 6.53 (m, 2H), 4.45 (t, J = 6.5 Hz, 2H), 3.86 – 3.74 (m, 4H), 3.62 (s, 3H), 3.50 (t, J = 6.5 Hz, 2H), 3.18 (dd, J = 9.3, 4.3 Hz, 4H). MS (ESI+) m/z 458 $(M+H)^+$.

173. N-(2-methoxyethyl)-4-[1-methyl-6-oxo-3-(2-phenoxyphenyl)-1,6-dihydropyridazin-4-yl]benzamide. Example 173 was prepared according to the procedure used for the preparation of Example 105, substituting N-(2-methoxyethyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide for N-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetamide, to provide the title compound. ^{1}H NMR (400 MHz, DMSO-d_6/D_2O) δ 7.68 (d, J = 8.3 Hz, 2H), 7.52 (dd, J = 7.6, 1.7 Hz, 1H), 7.41 – 7.28 (m, 1H), 7.26 – 7.14 (m, 5H), 7.04 (t, J = 7.4 Hz, 1H), 6.89 (s, 1H), 6.65 (d, J = 8.2 Hz, 1H), 6.44 (d, J = 8.2 Hz, 2H), 3.70 (s, 3H), 3.54 – 3.40 (m, 4H), 3.29 (s, 3H). MS (ESI+) m/z 456 $(M+H)^+$.

174. 2-methyl-5-[2-(4-methylpiperazin-1-yl)pyridin-4-yl]-6-(2-phenoxyphenyl)pyridazin-3(2H)-one. Example 174 was prepared according to the procedure used for the preparation of Example 105, substituting 1-methyl-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-yl)piperazine for N-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetamide, to provide the title compound. ^{1}H NMR (400 MHz, DMSO-d_6/D_2O) δ 8.02 (d, J = 5.2 Hz, 1H), 7.55 (dd, J = 7.6, 1.7 Hz, 1H), 7.45 – 7.32 (m, 1H), 7.23 (q, J = 8.3 Hz, 3H), 7.08 (t, J = 7.4 Hz, 1H), 6.96 (s, 1H), 6.69 (d, J = 8.2 Hz, 1H), 6.62 (s, 1H), 6.53 – 6.42 (m, 3H), 3.71 (s, 3H), 3.26 – 3.24 (m, 4H), 3.20 (s, 4H), 2.84 (s, 3H). MS (ESI+) m/z 454 $(M+H)^+$.

175. 2-methyl-5-[3-(morpholin-4-ylcarbonyl)phenyl]-6-(2-phenoxyphenyl)pyridazin-3(2H)-one. Example 175 was prepared according to the procedure used for the preparation of Example 105, substituting morpholino(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)methanone for N-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetamide, to provide the title compound. ^{1}H NMR (400 MHz, DMSO-d_6/D_2O) δ 7.51 (dd, J = 7.5, 1.7 Hz, 1H), 7.44 – 7.29 (m, 4H), 7.26 – 7.19 (m, 2H), 7.13 (s, 1H), 7.06 (t,

J = 7.4 Hz, 1H), 6.90 (s, 1H), 6.63 (d, J = 8.3 Hz, 1H), 6.50 (d, J = 7.9 Hz, 2H), 3.70 (s, 3H), 3.55 – 3.44 (m, 4H), 3.27 (s, 4H). MS (ESI+) m/z 468 $(M+H)^+$.

176. 2-methyl-5-[3-(5-methyl-1,3,4-oxadiazol-2-yl)phenyl]-6-(2-phenoxyphenyl)pyridazin-3(2H)-one. Example 176 was prepared according to the procedure used for the preparation of Example 105, substituting 2-methyl-5-(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-1,3,4-oxadiazole for N-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetamide, to provide the title compound. ^{1}H NMR (400 MHz, DMSO-d_6/D_2O) δ 7.98 – 7.85 (m, 1H), 7.73 – 7.64 (m, 1H), 7.59 – 7.52 (m, 1H), 7.46 (t, J = 7.8 Hz, 1H), 7.39 – 7.29 (m, 3H), 7.28 – 7.12 (m, 4H), 7.03 – 6.90 (m, 2H), 6.64 (dd, J = 13.1, 8.2 Hz, 1H), 6.47 (d, J = 8.3 Hz, 2H), 3.71 (d, J = 8.3 Hz, 3H), 2.53 (s, 3H). MS (ESI+) m/z 437 $(M+H)^+$.

177. N-cyclopropyl-3-[1-methyl-6-oxo-3-(2-phenoxyphenyl)-1,6-dihydropyridazin-4-yl]benzamide. Example 177 was prepared according to the procedure used for the preparation of Example 105, substituting N-cyclopropyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide for N-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetamide, to provide the title compound. ^{1}H NMR (400 MHz, DMSO-d_6/D_2O) δ 7.85 – 7.73 (m, 1H), 7.66 (t, J = 1.6 Hz, 1H), 7.50 (dd, J = 7.6, 1.7 Hz, 1H), 7.39 – 7.26 (m, 2H), 7.26 – 7.13 (m, 4H), 7.04 (t, J = 7.4 Hz, 1H), 6.93 (s, 1H), 6.61 (d, J = 8.2 Hz, 1H), 6.52 – 6.27 (m, 2H), 3.71 (s, 3H), 2.92 – 2.75 (m, 1H), 0.78 – 0.61 (m, 2H), 0.60 – 0.44 (m, 2H). MS (ESI+) m/z 438 $(M+H)^+$.

178. 2-methyl-6-(2-phenoxyphenyl)-5-[4-(pyrrolidin-1-ylsulfonyl)phenyl]pyridazin-3(2H)-one. Example 178 was prepared according to the procedure used for the preparation of Example 105, substituting 1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenylsulfonyl)pyrrolidine for N-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetamide, to provide the title compound. ^{1}H NMR (400 MHz, DMSO-d_6/D_2O) δ 7.74 – 7.58 (m, 2H), 7.52 (dd, J = 7.6, 1.7 Hz, 1H), 7.44 – 7.29 (m, 3H), 7.27 – 7.16 (m, 3H), 7.06 (t, J = 7.4 Hz, 1H), 6.95 (s, 1H), 6.63 (d, J = 8.3 Hz, 1H), 6.49 (d, J = 7.8 Hz, 2H), 3.71 (s, 3H), 3.14 (t, J = 6.8 Hz, 4H), 1.80 – 1.56 (m, 4H). MS (ESI+) m/z 488 $(M+H)^+$.

179. 2-methyl-5-[6-(morpholin-4-yl)pyridin-3-yl]-6-(2-phenoxyphenyl)pyridazin-3(2H)-one. Example 179 was prepared according to the procedure used for the preparation of Example 105, substituting 4-(5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-yl)morpholine for N-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetamide, to provide the title compound. ^{1}H NMR (400 MHz, DMSO-d_6/D_2O) δ 7.87 (d, J = 2.5 Hz, 1H), 7.53 (dd, J = 7.5, 1.7 Hz, 1H), 7.44 – 7.35 (m, 1H), 7.32 (dd, J = 9.0, 2.5 Hz, 1H), 7.24 (ddd,

J = 11.6, 6.2, 3.0 Hz, 3H), 7.05 (t, J = 7.4 Hz, 1H), 6.85 (s, 1H), 6.74 (d, J = 8.2 Hz, 1H), 6.68 (d, J = 9.0 Hz, 1H), 6.52 (d, J = 7.9 Hz, 2H), 3.69 (s, J = 4.0 Hz, 3H), 3.68 (d, J = 1.8 Hz, 4H), 3.56 – 3.37 (m, 4H). MS (ESI+) m/z 441 $(M+H)^+$.

180. 2-methyl-6-(2-phenoxyphenyl)-5-{4-[4-(propan-2-yl)piperazin-1-yl]phenyl}pyridazin-3(2H)-one. Example 180 was prepared according to the procedure used for the preparation of Example 105, substituting 1-isopropyl-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)piperazine for N-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetamide, to provide the title compound. ^{1}H NMR (400 MHz, DMSO-d_6/D_2O) δ 7.50 (dd, J = 7.6, 1.7 Hz, 1H), 7.42 – 7.30 (m, 1H), 7.26 – 7.15 (m, 4H), 7.05 (t, J = 7.4 Hz, 3H), 6.86 (t, J = 13.8 Hz, 2H), 6.78 (s, 1H), 6.66 (d, J = 7.7 Hz, 1H), 6.46 (d, J = 7.8 Hz, 2H), 3.68 (d, J = 4.7 Hz, 4H), 3.53 (dt, J = 13.2, 6.5 Hz, 4H), 3.33 (s, 2H), 3.20 (s, 2H), 1.32 (d, J = 6.6 Hz, 6H). MS (ESI+) m/z 481 $(M+H)^+$.

181. N,N-diethyl-2-fluoro-5-[1-methyl-6-oxo-3-(2-phenoxyphenyl)-1,6-dihydropyridazin-4-yl]benzamide. Example 181 was prepared according to the procedure used for the preparation of Example 105, substituting N,N-diethyl-2-fluoro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide for N-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetamide, to provide the title compound. ^{1}H NMR (400 MHz, DMSO-d_6/D_2O) δ 7.53 – 7.45 (m, 1H), 7.39 – 7.29 (m, 3H), 7.29 – 7.22 (m, 2H), 7.22 – 7.13 (m, 2H), 7.06 (dd, J = 14.2, 6.8 Hz, 1H), 7.04 – 6.98 (m, 1H), 6.90 (s, 1H), 6.69 (d, J = 8.2 Hz, 1H), 6.58 (d, J = 8.2 Hz, 2H), 3.68 (s, 3H), 3.38 (s, 2H), 2.91 (s, 2H), 1.07 (s, 3H), 0.88 (s, 3H). MS (ESI+) m/z 472 $(M+H)^+$.

182. N-benzyl-4-[1-methyl-6-oxo-3-(2-phenoxyphenyl)-1,6-dihydropyridazin-4-yl]benzamide. Example 182 was prepared according to the procedure used for the preparation of Example 105, substituting N-benzyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide for N-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetamide, to provide the title compound. ^{1}H NMR (400 MHz, DMSO-d_6/D_2O) δ 7.73 (d, J = 8.3 Hz, 2H), 7.53 (dd, J = 7.5, 1.7 Hz, 1H), 7.38 – 7.30 (m, 4H), 7.29 – 7.13 (m, 6H), 7.02 (t, J = 7.4 Hz, 1H), 6.90 (s, 1H), 6.64 (d, J = 8.2 Hz, 1H), 6.43 (d, J = 7.7 Hz, 2H), 4.48 (s, 2H), 3.70 (s, 3H). MS (ESI+) m/z 488 $(M+H)^+$.

183. 2-methyl-6-(2-phenoxyphenyl)-5-[4-(pyrrolidin-1-ylcarbonyl)phenyl]pyridazin-3(2H)-one. Example 183 was prepared according to the procedure used for the preparation of Example 105, substituting pyrrolidin-1-yl(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)methanone for N-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetamide, to provide the title compound. ^{1}H NMR (400 MHz, DMSO-d_6/D_2O) δ

7.52 (dd, J = 7.5, 1.7 Hz, 1H), 7.41 – 7.28 (m, 3H), 7.25 – 7.14 (m, 5H), 7.06 (t, J = 7.4 Hz, 1H), 6.90 (s, 1H), 6.61 (d, J = 8.3 Hz, 1H), 6.46 (d, J = 7.7 Hz, 2H), 3.71 (s, 3H), 3.40 (s, 4H), 1.85 (t, J = 6.7 Hz, 4H). MS (ESI+) m/z 452 $(M+H)^+$.

184. 2-methyl-6-(2-phenoxyphenyl)-5-[6-(piperidin-1-yl)pyridin-3-yl]pyridazin-3(2H)-one. Example 184 was prepared according to the procedure used for the preparation of Example 105, substituting 2-(piperidin-1-yl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine for N-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetamide, to provide the title compound. ^{1}H NMR (400 MHz, DMSO-d_6/D_2O) δ 7.82 (d, J = 2.5 Hz, 1H), 7.56 – 7.45 (m, 1H), 7.38 (d, J = 7.6 Hz, 1H), 7.31 – 7.16 (m, 4H), 7.05 (t, J = 7.3 Hz, 1H), 6.83 (s, 1H), 6.72 (d, J = 8.2 Hz, 1H), 6.65 (d, J = 9.1 Hz, 1H), 6.52 (d, J = 8.3 Hz, 2H), 3.67 (s, 3H), 3.63 – 3.40 (m, 4H), 1.63 (d, J = 5.1 Hz, 2H), 1.56 (d, J = 5.3 Hz, 4H). MS (ESI+) m/z 439 $(M+H)^+$.

185. N-cyclohexyl-4-[1-methyl-6-oxo-3-(2-phenoxyphenyl)-1,6-dihydropyridazin-4-yl]benzamide. Example 185 was prepared according to the procedure used for the preparation of Example 105, substituting N-cyclohexyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide for N-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetamide, to provide the title compound. ^{1}H NMR (400 MHz, DMSO-d_6/D_2O) δ 7.68 (d, J = 8.3 Hz, 2H), 7.52 (dd, J = 7.6, 1.7 Hz, 1H), 7.40 – 7.29 (m, 1H), 7.29 – 7.15 (m, 5H), 7.04 (t, J = 7.4 Hz, 1H), 6.88 (s, 1H), 6.66 (d, J = 8.2 Hz, 1H), 6.45 (d, J = 7.9 Hz, 2H), 3.75 (d, J = 4.0 Hz, 1H), 3.70 (s, 3H), 1.91 – 1.69 (m, 4H), 1.60 (d, J = 12.5 Hz, 1H), 1.42 – 1.26 (m, 4H), 1.16 (d, J = 8.0 Hz, 1H). MS (ESI+) m/z 480 $(M+H)^+$.

186. N-[2-(dimethylamino)ethyl]-3-[1-methyl-6-oxo-3-(2-phenoxyphenyl)-1,6-dihydropyridazin-4-yl]benzamide. Example 186 was prepared according to the procedure used for the preparation of Example 105, substituting N-(2-(dimethylamino)ethyl)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide for N-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetamide, to provide the title compound. ^{1}H NMR (400 MHz, DMSO-d_6/D_2O) δ 7.81 (d, J = 7.7 Hz, 1H), 7.72 (s, 1H), 7.51 (dd, J = 7.5, 1.7 Hz, 1H), 7.40 – 7.29 (m, 2H), 7.29 – 7.14 (m, 4H), 7.04 (t, J = 7.4 Hz, 1H), 6.92 (s, 1H), 6.63 (d, J = 8.2 Hz, 1H), 6.46 (d, J = 7.8 Hz, 2H), 3.71 (s, 3H), 3.57 (dt, J = 23.4, 5.9 Hz, 2H), 3.27 (d, J = 5.9 Hz, 2H), 2.56 – 2.40 (m, 5H). MS (ESI+) m/z 469 $(M+H)^+$.

187. 2-methyl-6-(2-phenoxyphenyl)-5-{4-[(phenylamino)methyl]phenyl}pyridazin-3(2H)-one. Example 187 was prepared according to the procedure used for the preparation of Example 105, substituting N-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl)aniline for N-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetamide, to

provide the title compound. ^{1}H NMR (400 MHz, DMSO-d_6/D_2O) δ 7.49 (dd, J = 7.6, 1.7 Hz, 1H), 7.39 – 7.26 (m, 1H), 7.23 (d, J = 8.2 Hz, 2H), 7.21 – 7.13 (m, 3H), 7.12 – 7.00 (m, 5H), 6.82 (s, 1H), 6.58 (dd, J = 16.0, 7.6 Hz, 4H), 6.42 (t, J = 11.7 Hz, 2H), 4.27 (s, 2H), 3.70 (d, J = 8.9 Hz, 3H). MS (ESI+) m/z 460 $(M+H)^+$.

188. 2-methyl-5-[2-(4-methylpiperazin-1-yl)pyrimidin-5-yl]-6-(2-phenoxyphenyl)pyridazin-3(2H)-one. Example 188 was prepared according to the procedure used for the preparation of Example 105, substituting 2-(4-methylpiperazin-1-yl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrimidine for N-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetamide, to provide the title compound. ^{1}H NMR (400 MHz, DMSO-d_6/D_2O) δ 8.17 (s, 2H), 7.57 (dd, J = 7.6, 1.7 Hz, 1H), 7.43 (td, J = 8.1, 1.7 Hz, 1H), 7.26 (dd, J = 15.8, 8.1 Hz, 3H), 7.06 (t, J = 7.4 Hz, 1H), 6.93 (s, 1H), 6.81 (d, J = 8.3 Hz, 1H), 6.55 (d, J = 8.4 Hz, 2H), 3.98 (s, 4H), 3.67 (s, 3H), 3.26 (s, 4H), 2.87 (s, 3H). MS (ESI+) m/z 455 $(M+H)^+$.

189. methyl {4-[1-methyl-6-oxo-3-(2-phenoxyphenyl)-1,6-dihydropyridazin-4-yl]phenyl}acetate. Example 189 was prepared according to the procedure used for the preparation of Example 105, substituting methyl 2-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetate for N-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetamide, to provide the title compound. ^{1}H NMR (500 MHz, DMSO-d_6/D_2O) δ 7.61 (dd, J = 7.5, 1.6 Hz, 1H), 7.42 – 7.30 (m, 1H), 7.22 (t, J = 7.6 Hz, 3H), 7.15 (d, J = 8.2 Hz, 2H), 7.13 – 7.03 (m, 3H), 6.92 (s, 1H), 6.45 (d, J = 8.3 Hz, 1H), 6.28 – 6.15 (m, 2H), 3.73 (d, J = 2.8 Hz, 3H), 3.69 (s, 2H), 3.64 (s, 3H). MS (ESI+) m/z 427 $(M+H)^+$.

190. 5-(5-ethoxypyridin-3-yl)-2-methyl-6-(2-phenoxyphenyl)pyridazin-3(2H)-one. Example 190 was prepared according to the procedure used for the preparation of Example 105, substituting 3-ethoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine for N-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetamide, to provide the title compound. ^{1}H NMR (500 MHz, DMSO-d_6/D_2O) δ 8.26 (d, J = 2.7 Hz, 1H), 7.98 (d, J = 1.5 Hz, 1H), 7.66 (dd, J = 7.6, 1.6 Hz, 1H), 7.45 – 7.35 (m, 1H), 7.33 – 7.16 (m, 4H), 7.14 – 7.04 (m, 2H), 6.63 (d, J = 8.3 Hz, 1H), 6.40 – 6.31 (m, 2H), 3.83 (q, J = 7.0 Hz, 2H), 3.75 (s, 3H), 1.19 (t, J = 7.0 Hz, 3H). MS (ESI+) m/z 400 $(M+H)^+$.

191. 2-methyl-5-[4-(methylamino)phenyl]-6-(2-phenoxyphenyl)pyridazin-3(2H)-one. Example 191 was prepared according to the procedure used for the preparation of Example 105, substituting N-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline for N-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetamide, to provide the title compound. ^{1}H NMR (500 MHz, DMSO-d_6/D_2O) δ 7.55 (dd, J = 7.5, 1.6 Hz, 1H), 7.40 – 7.30

(m, 1H), 7.22 (dd, J = 15.1, 7.8 Hz, 3H), 7.11 – 7.00 (m, 1H), 6.93 (t, J = 19.3 Hz, 2H), 6.80 (s, 1H), 6.66 – 6.51 (m, 3H), 6.50 – 6.31 (m, 2H), 3.69 (d, J = 9.5 Hz, 3H), 2.71 (s, 3H). MS (ESI+) m/z 384 $(M+H)^+$.

192. 5-[2-(dimethylamino)pyrimidin-5-yl]-2-methyl-6-(2-phenoxyphenyl)pyridazin-3(2H)-one. Example 192 was prepared according to the procedure used for the preparation of Example 105, substituting N,N-dimethyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrimidin-2-amine for N-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetamide, to provide the title compound. ^{1}H NMR (500 MHz, DMSO-d_6/D_2O) δ 8.04 (s, 2H), 7.70 – 7.57 (m, 1H), 7.44 (dt, J = 31.2, 11.8 Hz, 1H), 7.36 – 7.30 (m, 1H), 7.25 (dd, J = 22.7, 15.2 Hz, 2H), 7.12 – 7.05 (m, 1H), 6.97 (d, J = 10.5 Hz, 1H), 6.78 (t, J = 7.4 Hz, 1H), 6.57 – 6.41 (m, 2H), 3.69 (s, 3H), 3.08 (s, 6H). MS (ESI+) m/z 400 $(M+H)^+$.

193. {3-[1-methyl-6-oxo-3-(2-phenoxyphenyl)-1,6-dihydropyridazin-4-yl]phenyl}acetonitrile. Example 193 was prepared according to the procedure used for the preparation of Example 105, substituting 2-(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetonitrile for N-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetamide, to provide the title compound. ^{1}H NMR (500 MHz, DMSO-d_6/D_2O) δ 7.60 (dd, J = 7.5, 1.6 Hz, 1H), 7.60 (dd, J = 7.5, 1.6 Hz, 1H), 7.36 (dd, J = 10.6, 4.8 Hz, 2H), 7.36 (dd, J = 10.6, 4.8 Hz, 2H), 7.32 – 7.15 (m, 5H), 7.30 – 7.17 (m, 5H), 7.14 – 7.01 (m, 2H), 7.11 – 7.02 (m, 2H), 6.93 (s, 1H), 6.93 (s, 1H), 6.56 (d, J = 8.2 Hz, 1H), 6.56 (d, J = 8.2 Hz, 1H), 6.35 – 6.32 (m, 2H), 6.41 – 6.20 (m, 2H), 3.84 (s, 2H), 3.84 (s, 2H), 3.73 – 3.73 (m, 3H). MS (ESI+) m/z 394 $(M+H)^+$.

194. 2-methyl-5-(1-methyl-1H-pyrrol-2-yl)-6-(2-phenoxyphenyl)pyridazin-3(2H)-one. Example 194 was prepared according to the procedure used for the preparation of Example 105, substituting 1-methyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrrole for N-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetamide, to provide the title compound. ^{1}H NMR (500 MHz, DMSO-d_6/D_2O) δ 7.54 (dd, J = 7.5, 1.6 Hz, 1H), 7.41 – 7.32 (m, 1H), 7.27 (t, J = 7.9 Hz, 2H), 7.22 (t, J = 7.5 Hz, 1H), 7.11 (t, J = 7.4 Hz, 1H), 6.81 (dd, J = 4.5, 2.6 Hz, 2H), 6.56 (d, J = 8.2 Hz, 1H), 6.39 (d, J = 7.7 Hz, 2H), 5.95 (dd, J = 3.6, 2.8 Hz, 1H), 5.55 (dd, J = 3.7, 1.7 Hz, 1H), 3.71 (s, 3H), 3.28 (s, 3H). MS (ESI+) m/z 358 $(M+H)^+$.

195. 2-methyl-6-(2-phenoxyphenyl)-5-(pyridin-3-yl)pyridazin-3(2H)-one. Example 195 was prepared according to the procedure used for the preparation of Example 105, substituting 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine for N-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetamide, to provide the title compound. ^{1}H NMR (500 MHz, DMSO-d_6/D_2O) δ 8.73 – 8.64 (m, 1H), 8.54 (d, J = 1.6 Hz, 1H), 7.96 – 7.79

(m, 1H), 7.66 (dd, J = 7.6, 1.6 Hz, 1H), 7.57 (dd, J = 8.0, 5.2 Hz, 1H), 7.47 – 7.34 (m, 1H), 7.34 – 7.19 (m, 3H), 7.12 – 7.03 (m, 1H), 6.61 (d, J = 8.3 Hz, 1H), 6.44 – 6.29 (m, 2H), 3.75 (s, 3H). MS (ESI+) m/z 356 $(M+H)^+$.

196. 2-methyl-5-(6-methylpyridin-3-yl)-6-(2-phenoxyphenyl)pyridazin-3(2H)-one. Example 196 was prepared according to the procedure used for the preparation of Example 105, substituting 2-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine for N-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetamide, to provide the title compound. ^{1}H NMR (500 MHz, DMSO-d_6/D_2O) δ 8.51 (d, J = 1.9 Hz, 1H), 7.92 (t, J = 2.8 Hz, 1H), 7.68 (dd, J = 7.6, 1.5 Hz, 1H), 7.57 (d, J = 8.3 Hz, 1H), 7.44 (td, J = 8.3, 1.7 Hz, 1H), 7.35 – 7.20 (m, 3H), 7.14 (s, 1H), 7.09 (t, J = 7.4 Hz, 1H), 6.70 (d, J = 8.2 Hz, 1H), 6.52 – 6.37 (m, 2H), 3.75 (s, 3H), 2.61 (s, 3H). MS (ESI+) m/z 370 $(M+H)^+$.

197. 5-(3-methoxyphenyl)-2-methyl-6-(2-phenoxyphenyl)pyridazin-3(2H)-one. Example 197 was prepared according to the procedure used for the preparation of Example 105, substituting 2-(3-methoxyphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane for N-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetamide, to provide the title compound. ^{1}H NMR (500 MHz, DMSO-d_6/D_2O) δ 7.60 (dd, J = 7.5, 1.6 Hz, 1H), 7.42 – 7.32 (m, 1H), 7.28 – 7.15 (m, 4H), 7.15 – 7.03 (m, 1H), 7.00 – 6.85 (m, 2H), 6.75 (t, J = 10.4 Hz, 1H), 6.69 – 6.61 (m, 1H), 6.55 (d, J = 8.3 Hz, 1H), 6.44 – 6.21 (m, 2H), 3.73 (s, 3H), 3.50 (s, 3H). MS (ESI+) m/z 385 $(M+H)^+$.

198. 2-methyl-5-(4-methyl-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazin-7-yl)-6-(2-phenoxyphenyl)pyridazin-3(2H)-one. Example 198 was prepared according to the procedure used for the preparation of Example 105, substituting 4-methyl-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazine for N-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetamide, to provide the title compound. ^{1}H NMR (500 MHz, DMSO-d_6/D_2O) δ 7.63 (dd, J = 7.6, 1.6 Hz, 1H), 7.50 – 7.42 (m, 1H), 7.35 (d, J = 2.0 Hz, 1H), 7.33 – 7.23 (m, 3H), 7.08 (t, J = 7.4 Hz, 1H), 6.93 (s, 1H), 6.81 (dd, J = 18.5, 5.1 Hz, 2H), 6.58 – 6.44 (m, 2H), 4.14 (s, 2H), 3.71 (s, 3H), 3.55 (t, J = 4.2 Hz, 2H), 3.07 (s, 3H). MS (ESI+) m/z 403 $(M+H)^+$.

199. 5-(4-fluoro-3-methoxyphenyl)-2-methyl-6-(2-phenoxyphenyl)pyridazin-3(2H)-one. Example 199 was prepared according to the procedure used for the preparation of Example 105, substituting 2-(4-fluoro-3-methoxyphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane for N-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetamide, to provide the title compound. ^{1}H NMR (500 MHz, DMSO-d_6/D_2O) δ 7.63 (dd, J = 7.6, 1.6 Hz, 1H), 7.48 – 7.34 (m, 1H), 7.31 – 7.17 (m, 3H), 7.10 (dt, J = 14.6, 7.9 Hz, 2H), 6.98 (s, 1H), 6.82 – 6.72 (m,

2H), 6.64 (d, J = 8.3 Hz, 1H), 6.51 – 6.34 (m, 2H), 3.73 (s, 3H), 3.45 (s, 3H). MS (ESI+) m/z 403 $(M+H)^+$.

200. 5-(2-aminopyridin-4-yl)-2-methyl-6-(2-phenoxyphenyl)pyridazin-3(2H)-one. Example 200 was prepared according to the procedure used for the preparation of Example 105, substituting 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-amine for N-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetamide, to provide the title compound. ^{1}H NMR (500 MHz, DMSO-d_6/D_2O) δ 7.75 (dd, J = 8.9, 3.5 Hz, 1H), 7.69 – 7.62 (m, 1H), 7.50 – 7.40 (m, 1H), 7.37 – 7.25 (m, 3H), 7.14 – 7.07 (m, 2H), 6.83 – 6.76 (m, 1H), 6.76 – 6.71 (m, 1H), 6.64 – 6.52 (m, 3H), 3.74 (d, J = 1.6 Hz, 5H). MS (ESI+) m/z 371 $(M+H)^+$.

201. 5-(3-acetylphenyl)-2-methyl-6-(2-phenoxyphenyl)pyridazin-3(2H)-one. Example 201 was prepared according to the procedure used for the preparation of Example 105, substituting 1-(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)ethanone for N-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetamide, to provide the title compound. ^{1}H NMR (500 MHz, DMSO-d_6/D_2O) δ 7.99 – 7.83 (m, 1H), 7.74 – 7.60 (m, 2H), 7.47 – 7.39 (m, 2H), 7.36 (td, J = 8.0, 1.7 Hz, 1H), 7.26 (dd, J = 7.5, 0.7 Hz, 1H), 7.19 (dd, J = 10.7, 5.2 Hz, 2H), 7.10 – 6.99 (m, 2H), 6.57 (d, J = 8.2 Hz, 1H), 6.28 (d, J = 7.7 Hz, 2H), 3.74 (d, J = 9.2 Hz, 3H), 2.33 (s, 3H). MS (ESI+) m/z 397 $(M+H)^+$.

202. N-ethyl-4-[1-methyl-6-oxo-3-(2-phenoxyphenyl)-1,6-dihydropyridazin-4-yl]benzamide. Example 202 was prepared according to the procedure used for the preparation of Example 105, substituting N-ethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide for N-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetamide, to provide the title compound. ^{1}H NMR (500 MHz, DMSO-d_6/D_2O) δ 7.68 (d, J = 8.4 Hz, 2H), 7.61 (dt, J = 9.5, 4.7 Hz, 1H), 7.38 (ddd, J = 9.1, 6.7, 1.8 Hz, 1H), 7.26 – 7.18 (m, 4H), 7.13 – 7.03 (m, 1H), 6.97 (d, J = 5.9 Hz, 1H), 6.57 (d, J = 8.2 Hz, 1H), 6.41 – 6.21 (m, 2H), 3.73 (s, 3H), 3.29 (q, J = 7.2 Hz, 2H), 1.12 (t, J = 7.2 Hz, 3H). MS (ESI+) m/z 426 $(M+H)^+$.

203. 5-(3-fluoro-4-methoxyphenyl)-2-methyl-6-(2-phenoxyphenyl)pyridazin-3(2H)-one. Example 203 was prepared according to the procedure used for the preparation of Example 105, substituting 2-(3-fluoro-4-methoxyphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane for N-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetamide, to provide the title compound. ^{1}H NMR (500 MHz, DMSO-d_6/D_2O) δ 7.60 (dd, J = 7.5, 1.6 Hz, 1H), 7.47 – 7.36 (m, 1H), 7.25 (ddd, J = 15.1, 11.1, 8.0 Hz, 3H), 7.06 (dt, J = 17.8, 8.3 Hz, 2H), 6.99 – 6.86 (m, 3H), 6.64 (d, J = 8.3 Hz, 1H), 6.43 – 6.30 (m, 2H), 3.83 (s, 3H), 3.71 (s, 3H). MS (ESI+) m/z 403 $(M+H)^+$.

204. 5-(1,5-dimethyl-1H-pyrazol-4-yl)-2-methyl-6-(2-phenoxyphenyl)pyridazin-3(2H)-one. Example 204 was prepared according to the procedure used for the preparation of Example 105, substituting 1,5-dimethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole for N-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetamide, to provide the title compound. ^{1}H NMR (500 MHz, DMSO-d_6/D_2O) δ 7.62 – 7.53 (m, 1H), 7.48 – 7.35 (m, 1H), 7.32 – 7.24 (m, 4H), 7.10 (q, J = 7.5 Hz, 1H), 6.77 – 6.69 (m, 2H), 6.67 (s, 1H), 6.49 – 6.31 (m, 3H), 3.71 (d, J = 2.0 Hz, 3H), 3.59 (d, J = 9.4 Hz, 3H), 1.83 (s, 3H). MS (ESI+) m/z 373 $(M+H)^+$.

205. 2-methyl-5-(2-methylpyridin-4-yl)-6-(2-phenoxyphenyl)pyridazin-3(2H)-one. Example 205 was prepared according to the procedure used for the preparation of Example 105, substituting 2-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine for N-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetamide, to provide the title compound. ^{1}H NMR (500 MHz, DMSO-d_6/D_2O) δ 8.62 – 8.45 (m, 1H), 7.83 – 7.62 (m, 1H), 7.57 – 7.49 (m, 1H), 7.48 – 7.38 (m, 1H), 7.36 – 7.30 (m, 2H), 7.30 – 7.22 (m, 3H), 7.18 – 7.07 (m, 2H), 6.73 – 6.66 (m, 1H), 6.49 – 6.33 (m, 2H), 3.79 – 3.74 (m, 3H), 2.40 (s, 3H). MS (ESI+) m/z 370 $(M+H)^+$.

206. 2-methyl-5-[1-(2-methylpropyl)-1H-pyrazol-4-yl]-6-(2-phenoxyphenyl)pyridazin-3(2H)-one. Example 206 was prepared according to the procedure used for the preparation of Example 105, substituting 1-isobutyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole for N-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetamide, to provide the title compound. ^{1}H NMR (500 MHz, DMSO-d_6/D_2O) δ 7.65 – 7.44 (m, 3H), 7.40 – 7.21 (m, 3H), 7.11 (dd, J = 13.6, 6.2 Hz, 2H), 7.02 (d, J = 9.8 Hz, 1H), 6.77 (t, J = 9.9 Hz, 1H), 6.66 – 6.51 (m, 2H), 3.81 (d, J = 7.0 Hz, 2H), 3.65 (s, 3H), 2.09 – 1.88 (m, 1H), 0.76 (d, J = 6.7 Hz, 6H). MS (ESI+) m/z 401 $(M+H)^+$.

207. 2-methyl-5-(4-methylpyridin-3-yl)-6-(2-phenoxyphenyl)pyridazin-3(2H)-one. Example 207 was prepared according to the procedure used for the preparation of Example 105, substituting 4-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine for N-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetamide, to provide the title compound. ^{1}H NMR (500 MHz, DMSO-d_6/D_2O) δ 8.54 (d, J = 5.6 Hz, 1H), 8.45 (s, 1H), 7.69 – 7.51 (m, 2H), 7.39 – 7.28 (m, 3H), 7.20 (dd, J = 18.3, 10.8 Hz, 1H), 7.16 – 7.08 (m, 2H), 6.56 (dd, J = 12.3, 8.1 Hz, 3H), 3.76 (d, J = 7.5 Hz, 3H), 2.19 (s, 3H). MS (ESI+) m/z 370 $(M+H)^+$.

208. 2-methyl-5-(1-methyl-1H-indol-5-yl)-6-(2-phenoxyphenyl)pyridazin-3(2H)-one. Example 208 was prepared according to the procedure used for the preparation of Example

105, substituting 1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indole for N-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetamide, to provide the title compound. ^{1}H NMR (500 MHz, DMSO-d_6/D_2O) δ 7.58 (dd, J = 7.5, 1.6 Hz, 1H), 7.46 (dd, J = 7.6, 1.6 Hz, 1H), 7.38 – 7.18 (m, 4H), 7.15 – 7.03 (m, 2H), 7.03 – 6.94 (m, 1H), 6.95 – 6.87 (m, 1H), 6.55 (dd, J = 21.5, 8.2 Hz, 1H), 6.39 – 6.28 (m, 1H), 6.28 – 6.17 (m, 1H), 3.81 – 3.74 (m, 3H), 3.71 (s, 3H). MS (ESI+) m/z 408 $(M+H)^+$.

209. 5-[3-(dimethylamino)phenyl]-2-methyl-6-(2-phenoxyphenyl)pyridazin-3(2H)-one. Example 209 was prepared according to the procedure used for the preparation of Example 105, substituting N,N-dimethyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline for N-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetamide, to provide the title compound. ^{1}H NMR (500 MHz, DMSO-d_6/D_2O) δ 7.60 (dd, J = 7.5, 1.6 Hz, 1H), 7.44 – 7.30 (m, 1H), 7.27 – 7.13 (m, 4H), 7.07 (t, J = 7.4 Hz, 1H), 6.94 (d, J = 12.7 Hz, 1H), 6.91 (dd, J = 8.3, 2.2 Hz, 1H), 6.63 (d, J = 7.8 Hz, 1H), 6.58 (s, 1H), 6.53 (d, J = 8.2 Hz, 1H), 6.34 – 6.15 (m, 2H), 3.73 (s, 3H), 2.70 (s, 6H). MS (ESI+) m/z 398 $(M+H)^+$.

210. 5-(2-fluoro-5-methoxyphenyl)-2-methyl-6-(2-phenoxyphenyl)pyridazin-3(2H)-one. Example 210 was prepared according to the procedure used for the preparation of Example 105, substituting 2-(2-fluoro-5-methoxyphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane for N-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetamide, to provide the title compound. ^{1}H NMR (500 MHz, DMSO-d_6/D_2O) δ 7.63 – 7.46 (m, 1H), 7.43 – 7.31 (m, 1H), 7.31 – 7.24 (m, 2H), 7.19 (dd, J = 11.6, 4.1 Hz, 1H), 7.10 (t, J = 7.4 Hz, 1H), 7.04 (t, J = 9.3 Hz, 1H), 7.00 (d, J = 5.2 Hz, 1H), 6.94 – 6.84 (m, 1H), 6.69 – 6.54 (m, 2H), 6.46 (dd, J = 9.4, 8.5 Hz, 2H), 3.73 (s, 3H), 3.47 (s, 3H). MS (ESI+) m/z 403 $(M+H)^+$.

211. 2-methyl-5-(5-methylfuran-2-yl)-6-(2-phenoxyphenyl)pyridazin-3(2H)-one. Example 211 was prepared according to the procedure used for the preparation of Example 105, substituting 4,4,5,5-tetramethyl-2-(5-methylfuran-2-yl)-1,3,2-dioxaborolane for N-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetamide, to provide the title compound. ^{1}H NMR (500 MHz, DMSO-d_6/D_2O) δ 7.61 – 7.42 (m, 2H), 7.37 – 7.21 (m, 3H), 7.11 (t, J = 7.4 Hz, 1H), 7.03 (s, 1H), 6.89 (d, J = 8.3 Hz, 1H), 6.84 – 6.65 (m, 2H), 6.26 – 6.10 (m, 1H), 5.72 (d, J = 3.4 Hz, 1H), 3.63 (s, 3H), 2.27 (s, 3H). MS (ESI+) m/z 359 $(M+H)^+$.

212. 5-(1-ethyl-1H-pyrazol-4-yl)-2-methyl-6-(2-phenoxyphenyl)pyridazin-3(2H)-one. Example 212 was prepared according to the procedure used for the preparation of Example 105, substituting 1-ethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole for N-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetamide, to provide the title compound. ^{1}H NMR (500 MHz, DMSO-d_6/D_2O) δ 7.62 – 7.56 (m, 1H), 7.57 – 7.45 (m, 2H),

7.35 – 7.21 (m, 3H), 7.19 – 7.02 (m, 2H), 7.04 – 6.93 (m, 2H), 6.79 – 6.66 (m, 1H), 6.56 – 6.30 (m, 2H), 4.15 – 3.97 (m, 2H), 3.66 (s, 3H), 1.28 (t, J = 7.3 Hz, 3H). MS (ESI+) m/z 373 $(M+H)^+$.

213. 5-(3-methoxypyridin-4-yl)-2-methyl-6-(2-phenoxyphenyl)pyridazin-3(2H)-one. Example 213 was prepared according to the procedure used for the preparation of Example 105, substituting 3-methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine for N-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetamide, to provide the title compound. ^{1}H NMR (500 MHz, DMSO-d_6/D_2O) δ 8.37 – 8.24 (m, 2H), 7.55 (d, J = 5.1 Hz, 1H), 7.48 – 7.27 (m, 4H), 7.27 – 7.08 (m, 2H), 7.01 (s, 1H), 6.67 (d, J = 8.3 Hz, 1H), 6.61 (d, J = 8.0 Hz, 2H), 3.74 (s, 3H), 3.48 (s, 3H). MS (ESI+) m/z 386 $(M+H)^+$.

214. 2-methyl-5-(1-methyl-1H-indol-2-yl)-6-(2-phenoxyphenyl)pyridazin-3(2H)-one. Example 214 was prepared according to the procedure used for the preparation of Example 105, substituting 1-methyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indole for N-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetamide, to provide the title compound. ^{1}H NMR (500 MHz, DMSO-d_6/D_2O) δ 7.74 – 7.56 (m, 1H), 7.44 (d, J = 7.9 Hz, 1H), 7.42 – 7.33 (m, 1H), 7.28 – 7.19 (m, 2H), 7.12 – 7.05 (m, 1H), 7.03 – 6.92 (m, 3H), 6.51 (d, J = 8.2 Hz, 1H), 6.25 – 6.11 (m, 2H), 6.07 (s, 1H), 3.77 (s, 3H), 3.34 (s, 3H). MS (ESI+) m/z 408 $(M+H)^+$.

215. N,N-dimethyl-5-[1-methyl-6-oxo-3-(2-phenoxyphenyl)-1,6-dihydropyridazin-4-yl]pyridine-3-carboxamide. Example 215 was prepared according to the procedure used for the preparation of Example 105, substituting N,N-dimethyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)nicotinamide for N-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetamide, to provide the title compound. ^{1}H NMR (500 MHz, DMSO-d_6/D_2O) δ 8.60 (d, J = 1.9 Hz, 1H), 8.48 (d, J = 2.1 Hz, 1H), 7.70 – 7.59 (m, 3H), 7.43 – 7.33 (m, 1H), 7.27 (td, J = 7.5, 2.7 Hz, 4H), 7.16 – 7.03 (m, 3H), 6.57 (d, J = 8.3 Hz, 1H), 6.46 – 6.30 (m, 3H), 3.74 (s, 3H), 3.05 (d, J = 124.7 Hz, 6H). MS (ESI+) m/z 427 $(M+H)^+$.

216. 5-[5-(dimethylamino)pyridin-3-yl]-2-methyl-6-(2-phenoxyphenyl)pyridazin-3(2H)-one. Example 216 was prepared according to the procedure used for the preparation of Example 105, substituting N,N-dimethyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-3-amine for N-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetamide, to provide the title compound. ^{1}H NMR (500 MHz, DMSO-d_6/D_2O) δ 8.06 (t, J = 5.6 Hz, 1H), 7.84 (d, J = 7.4 Hz, 1H), 7.73 – 7.65 (m, 1H), 7.55 – 7.43 (m, 1H), 7.32 (t, J = 6.3 Hz, 1H), 7.31 – 7.24 (m, 3H), 7.21 (s, 1H), 7.15 – 7.01 (m, 1H), 6.76 (dd, J = 9.6, 5.6 Hz, 1H), 6.45 – 6.27 (m, 2H), 3.76 (d, J = 3.2 Hz, 3H), 2.79 (s, 6H). MS (ESI+) m/z 399 $(M+H)^+$.

217. 5-butyl-2-methyl-6-(2-phenoxyphenyl)pyridazin-3(2H)-one.

217A. 5-butyl-6-chloro-2-methylpyridazin-3(2H)-one. A mixture of Example 18B (0.537 g, 3 mmol), (E)-ethyl 3-(tributylstannyl)acrylate (1.226 g, 3.15 mmol), and tetrakis (0.173 g, 0.150 mmol) in dioxane (20 mL) was heated at 80 °C overnight. The solvent was removed under reduced pressure, and the residue was purified by flash chromatography on silica gel eluting with 10% ethyl acetate in hexanes to give 0.15 g (25%) of the title compound.

217B. 5-butyl-2-methyl-6-(2-phenoxyphenyl)pyridazin-3(2H)-one. Example 217B was prepared according to the procedure used for the preparation of Example 1B, substituting Example 217A for Example 1A, to provide the title compound. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.32-7.50 (m, 4H), 7.24-7.28 (m, 1H), 7.11 (t, J = 7.32 Hz, 1H), 6.98 (d, J = 7.32 Hz, 1H), 6.92 (d, J = 7.63 Hz, 2H), 6.77 (s, 1H), 3.57 (s, 3H), 2.23-2.26 (m, 2H), 1.33-1.38 (m, 2H), 0.72 (t, J = 7.32 Hz, 3H). MS (DCI+) m/z 355.2 $(M+H)^+$.

218. methyl 1-methyl-6-oxo-3-(2-phenoxyphenyl)-1,6-dihydropyridazine-4-carboxylate.

218A. methyl 3-chloro-6-oxo-1,6-dihydropyridazine-4-carboxylate. Methyl 3,6-dichloropyridazine-4-carboxylate (12 g, 58.0 mmol) in acetic acid (45 mL) was heated at 130 °C for two hours. After cooling to room temperature, the solvent was removed under reduced pressure to give a white solid (10 g), which contained 45% of the desired product. The crude product was used directly for the next step.

218B. methyl 3-chloro-1-methyl-6-oxo-1,6-dihydropyridazine-4-carboxylate. Example 218B was prepared according to the procedure used for the preparation of Example 1A, substituting Example 218A for 6-chloropyridazin-3(2H)-one, to provide the title compound.

218C. methyl 1-methyl-6-oxo-3-(2-phenoxyphenyl)-1,6-dihydropyridazine-4-carboxylate. Example 218C was prepared according to the procedure used for the preparation of Example 1B, substituting Example 218B for Example 1A, to provide the title compound. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.56 (dd, J = 7.63, 1.83 Hz, 1H), 7.42-7.46 (m, 1H), 7.33-7.38 (m, 2H), 7.24-7.28 (m, 1H), 7.23 (s, 1H), 7.13 (t, J = 7.48 Hz, 1H), 6.87-6.89 (m, 3H), 3.71 (s, 3H), 3.63 (s, 3H). MS (DCI+) m/z 337.1 $(M+H)^+$.

219. methyl (2E)-3-[1-methyl-6-oxo-3-(2-phenoxyphenyl)-1,6-dihydropyridazin-4-yl]prop-2-enoate.

219A. (E)-ethyl 3-(3-chloro-1-methyl-6-oxo-1,6-dihydropyridazin-4-yl)acrylate. Example 219A was prepared according to the procedure used for the preparation of Example 9A, substituting Example 18B for Example 1A, and substituting (E)-ethyl 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)acrylate for 2-fluoro-5-nitrophenylboronic acid, respectively, to provide the title compound.

219B. methyl (2E)-3-[1-methyl-6-oxo-3-(2-phenoxyphenyl)-1,6-dihydropyridazin-4-yl]prop-2-enoate. Example 219B was prepared according to the procedure used for the preparation of Example 1B, substituting Example 219A for Example 1A, to provide the title compound. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.44-7.53 (m, 3H), 7.26-7.36 (m, 3H), 7.11-7.15 (m, 2H), 6.89-6.92 (m, 3H), 6.73 (d, J = 16.17 Hz, 1H), 3.69 (s, 3H), 3.67 (s, 3H). MS (DCI+) m/z 363.1 $(M+H)^+$.

220. methyl 3-[1-methyl-6-oxo-3-(2-phenoxyphenyl)-1,6-dihydropyridazin-4-yl]propanoate. Example 219B was prepared according to the procedure used for the preparation of Example 10, substituting Example 219B for Example 9B, to provide the title compound. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.46-7.50 (m, 1H), 7.43 (dd, J = 7.48, 1.68 Hz, 1H), 7.34-7.37 (m, 2H), 7.26 (t, J = 7.48 Hz, 1H), 7.13 (t, J = 7.48 hz, 1H), 6.93-6.97 (m, 3H), 6.80 (s, 1H), 3.58 (s, 3H), 3.54 (s, 3H), 2.55-2.63 (m 4H). MS (DCI+) m/z 365.1 $(M+H)^+$.

221. 5-acetyl-2-methyl-6-(2-phenoxyphenyl)pyridazin-3(2H)-one.

221A. 6-chloro-5-(1-ethoxyvinyl)-2-methylpyridazin-3(2H)-one. Example 218C was prepared according to the procedure used for the preparation of Example 217A, substituting tributyl(1-ethoxyvinyl)stannane for (E)-ethyl 3-(tributylstannyl)acrylate, to provide the title compound.

221B. 5-(1-ethoxyvinyl)-2-methyl-6-(2-phenoxyphenyl)pyridazin-3(2H)-one. Example 221B was prepared according to the procedure used for the preparation of Example 1B, substituting Example 221A for Example 1A, to provide the title compound.

221C. 5-acetyl-2-methyl-6-(2-phenoxyphenyl)pyridazin-3(2H)-one. Example 221B (0.11 g, 0.316 mmol) in tetrahydrofuran (5 mL) was treated with 1.0 N HCl (1.3 mL, 1.3 mmol). The reaction mixture was heated at 60 °C for one hour. The solvent was removed, and the residue was purified by reverse phase HPLC (C18, CH_3CN/water (0.1%TFA), 0-100%) to provide 0.085 g (84%) of the title compound. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.54 (dd, J = 7.63, 1.83 Hz, 1H), 7.36-7.42 (m, 4H), 7.22-7.26 (m, 1H), 7.16 (t, J = 7.32 Hz, 1H), 6.90 (d, J = 7.63 Hz, 2H), 6.75 (d, J = 8.24 Hz, 1H), 3.71(s, 3H), 2.41 (s, 3H). MS (DCI+) m/z 321.0 $(M+H)^+$.

222. 6-(2-benzylphenyl)-2-methylpyridazin-3(2H)-one. A mixture of 2-(1-methyl-6-oxo-1,6-dihydropyridazin-3-yl)phenyl trifluoromethanesulfonate (0.232 g, 0.694 mmol), 2-benzyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (0.182 g, 0.833 mmol), cesium fluoride (0.211, 1.39 mmol) and $PdCl_2$(dppf) (0.025 g, 0.035 mmol) in dioxane (5 mL) was heated at 75 °C for 16 hours. The reaction mixture was cooled to ambient temperature and

concentrated under reduced pressure. The residue was purified by flash chromatography (silica gel, 10-50% ethyl acetate/hexane gradient) to provide the title compound. 1H NMR (300 MHz, DMSO-d_6) δ 7.29 - 7.46 (m, 5 H) 7.15 - 7.23 (m, 2 H) 7.07 - 7.15 (m, 1 H) 6.94 - 7.00 (m, 2 H) 6.89 (d, J=9.49 Hz, 1 H) 4.09 (s, 2 H) 3.65 (s, 3 H). MS (ESI+) m/z 277.3 $(M+H)^+$.

223. 1-methyl-5-(2-phenoxyphenyl)pyridin-2(1H)-one. Example 223 was prepared according to the procedure used for the preparation of Example 1B, substituting 5-bromo-1-methylpyridin-2(1H)-one for Example 1A, to provide the title compound. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.91 (d, J = 2.44 Hz, 1H), 7.63 (dd, J = 9.31, 2.59 Hz, 1H), 7.48 (dd, J = 7.63, 1.83 Hz, 1H), 7.232-7.37 (m, 3H), 7.23-7.27 (m, 1H), 7.08 (t, J = 7.48 Hz, 1H), 6.92-6.98 (m, 3H), 3.44(s, 3H). MS (DCI+) m/z 278.1 $(M+H)^+$.

224. N-[3-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-4-phenoxyphenyl]methanesulfonamide. A mixture of 1-methyl-5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-1H-pyridine-2-one (Synchem Inc. 0.056 g, 0.24 mmol), the product from Example 261C (0.068 g, 0.2 mmol), tetrakis(tiriphenylphosphine) palladium(0) (0.012 g, 0.01 mmol) and sodium carbonate 2M (0.2 mL, 0.40 mmol) in toluene (1 mL), ethanol (0.25 mL) and water (0.5 mL) was heated by microwave at 110 °C for 30 minutes. The reaction mixture was filtered through a 0.45μm Nylon filter disk to remove solids and the filtrate was partitioned between ethyl acetate and brine. The organic layer was separated and concentrated. Purification by reverse phase HPLC (C18, 0-100 % CH_3CN/water (0.1% TFA)) afforded the title compound (0.028 g, 37%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.73 (s, 1 H) 7.88 (d, J=2.38 Hz, 1 H) 7.56 (dd, J=9.52, 2.78 Hz, 1 H) 7.28 - 7.36 (m, 2 H) 7.26 (d, J=2.78 Hz, 1 H) 7.16 - 7.22 (m, 1 H) 7.05 (t, J=7.34 Hz, 1 H) 7.00 (d, J=8.73 Hz, 1 H) 6.90 (d, J=7.93 Hz, 2 H) 6.35 - 6.40 (m, 1 H) 3.44 (s, 3 H) 3.03 (s, 3 H). MS (ESI+) m/z 371 $(M+H)^+$.

225. methyl {[3-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-4-phenoxyphenyl]sulfamoyl}acetate.

225A. 5-(2-fluoro-5-nitrophenyl)-1-methylpyridin-2(1H)-one. Example 225A was prepared according to the procedure used for the preparation of Example 9A, substituting 5-bromo-1-methylpyridin-2(1H)-one for Example 1A, to provide the title compound.

225B. 1-methyl-5-(5-nitro-2-phenoxyphenyl)pyridin-2(1H)-one. Example 225B was prepared according to the procedure used for the preparation of Example 9B, substituting Example 225A for Example 9A, to provide the title compound.

225C. 5-(5-amino-2-phenoxyphenyl)-1-methylpyridin-2(1H)-one. Example 225B was prepared according to the procedure used for the preparation of Example 10, substituting Example 225B for Example 9B, to provide the title compound.

225D. methyl {[3-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-4-phenoxyphenyl]sulfamoyl}acetate. A mixture of Example 225C (0.04 g, 0.137 mmol), 2,2,2-trifluoroethanesulfonyl chloride (0.062 g, 0.342 mmol), and triethylamine (0.055 g, 0.4 mmol) in dichloromethane (3mL) was stirred at room temperature for 1 hour. The solvent was removed, and the residue was taken up in dioxane (1 mL), methanol (1 mL) and 1.0 N NaOH (1 mL). The reaction mixture was heated at 90 °C for 1 hour. The solvents were partially removed under reduced pressure, and the residue was partitioned between water and ethyl acetate. The aqueous layer was neutralized with 10% HCl and extracted with additional ethyl acetate twice. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by reverse phase HPLC (C18, CH_3CN/water (0.1%TFA), 0-100%) to afford 0.026 g (19%) of the title compound. ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.18 (s, 1H), 7.88 (d, J = 2.44 Hz, 1H), 7.56 (dd, J = 9.31, 2.59 Hz, 1H), 7.29-7.36 (m, 3H), 7.20 (dd, J = 8.7, 2.59 Hz, 1H), 7.06 (t, J = 7.32 Hz, 1H), 7.01 (d, J = 8.54 Hz, 1H), 6.91 (d, J = 7.93 Hz, 2H), 6.39 (d, J = 9.46 Hz, 1H), 4.30 (s, 2H), 3.67 (s, 3H), 3.44 (s, 3H). MS (ESI+) m/z 429.1 $(M+H)^+$.

226. {[3-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-4-phenoxyphenyl]sulfamoyl}acetic acid. Example 226 was obtained as a by-product in the synthesis of Example 225D. ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.06 (s, 1H), 7.87 (d, J = 2.44 Hz, 1H), 7.56 (dd, J = 9.31, 2.59 Hz, 1H), 7.29-7.34 (m, 3H), 7.20 (dd, J = 8.7, 2.59 Hz, 1H), 7.06 (t, J = 7.32 Hz, 1H), 7.00 (d, J = 8.85 Hz, 1H), 6.91 (d, J = 7.93 Hz, 2H), 6.39 (d, J = 9.46 Hz, 1H), 4.15 (s, 2H), 3.44 (s, 3H). MS (ESI+) m/z 415.0 $(M+H)^+$.

227. 1-methyl-N-[3-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-4-phenoxyphenyl]-1H-imidazole-4-sulfonamide. The product from Example 225C (0.044 g, 0.15 mmol), 1-methyl-1H-imidazole-4-sulfonyl chloride (0.033 g, 0.180 mmol) and triethylamine (0.042 mL, 0.30 mmol) were combined in dichloromethane (0.75 mL), heated at 60 °C for 2 hours and concentrated. Purification by chromatography (silica gel, 0-3% methanol in dichloromethane) afforded the title compound (0.038 g, 56%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.21 (s, 1 H) 7.84 (d, *J*=1.36 Hz, 1 H) 7.75 - 7.78 (m, 2 H) 7.48 (dd, *J*=9.49, 2.71 Hz, 1 H) 7.25 - 7.35 (m, 2 H) 7.21 (d, *J*=2.71 Hz, 1 H) 7.09 (dd, *J*=8.82, 2.71 Hz, 1 H) 7.03 (t, *J*=7.46 Hz, 1 H) 6.89 (d,

J=8.82 Hz, 1 H) 6.83 (d, *J*=7.80 Hz, 2 H) 6.37 (d, *J*=9.49 Hz, 1 H) 3.67 (s, 3 H) 3.43 (s, 3 H). MS (ESI+) m/z 437 $(M+H)^+$.

228. N-[3-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-4-phenoxyphenyl]-1H-imidazole-4-sulfonamide. The product from Example 225C (0.044 g, 0.15 mmol), 1H-imidazole-4-sulfonyl chloride (0.03 g, 0.180 mmol) and triethylamine (0.042 mL, 0.30 mmol) were combined in dimethylformamide (0.75 mL) and heated at 60 °C for 24 hours. The reaction mix was partitioned between ethyl acetate and brine. The organic layer was separated and concentrated. Purification by reverse phase HPLC (C18, 0-100 % CH_3CN/water (0.1% TFA)) afforded the title compound as the trifluoroacetic acid salt (0.004 g, 4%). ^1H NMR (300 MHz, DMSO-d_6) δ 12.66 - 12.79 (m, 1 H) 10.18 - 10.21 (m, 1 H) 7.83 (d, *J*=6.35 Hz, 2 H) 7.76 (d, *J*=2.38 Hz, 1 H) 7.47 (dd, *J*=9.32, 2.58 Hz, 1 H) 7.26 - 7.32 (m, 2 H) 7.20 (d, *J*=2.78 Hz, 1 H) 7.09 (dd, *J*=8.73, 2.38 Hz, 1 H) 7.02 (t, *J*=7.34 Hz, 1 H) 6.88 (d, *J*=8.73 Hz, 1 H) 6.82 (d, *J*=7.54 Hz, 2 H) 6.36 (d, *J*=9.52 Hz, 1 H) 3.30 - 3.57 (m, 3 H). MS (ESI+) m/z 423 $(M+H)^+$.

229. 2,2,2-trifluoro-N-[3-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-4-phenoxyphenyl]ethanesulfonamide. A mixture of Example 225C (0.04 g, 0.137 mmol), 2,2,2-trifluoroethanesulfonyl chloride (0.037 g, 0.205 mmol), and triethylamine (0.042 g, 0.41 mmol) in dichloromethane (3mL) was stirred at room temperature for 1 hour. The solvent was removed, and the residue was purified by reverse phase HPLC (C18, CH_3CN/water (0.1%TFA), 0-100%) to afford 0.035 g (59%) of the title compound. ^1H NMR (500 MHz, DMSO-d_6) δ 10.46 (s, 1H), 7.89 (d, J = 2.44 Hz, 1H), 7.58 (dd, J = 9.46, 2.44 Hz, 1H), 7.28-7.35 (m, 3H), 7.19 (dd, J = 8.7, 2.59 Hz, 1H), 7.07 (t, J = 7.32 Hz, 1H), 7.01 (d, J = 8.85 Hz, 1H), 6.91 (d, J = 7.63 Hz, 2H), 6.39 (d, J = 9.46 Hz, 1H), 4.58 (q, J = 9.97 Hz, 2H), 3.44 (s, 3H). MS (ESI+) m/z 439.1 $(M+H)^+$.

230. N-methyl-N'-[3-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-4-phenoxyphenyl]sulfuric diamide. Example 230 was prepared according to the procedure used for the preparation of Example 229, substituting methylsulfamoyl chloride for 2,2,2-trifluoroethanesulfonyl chloride, to provide the title compound. ^1H NMR (500 MHz, DMSO-d_6) δ 9.72 (s, 1H), 7.85 (d, J = 2.44 Hz, 1H), 7.55 (dd, J = 9.46, 2.75 Hz, 1H), 7.28-7.36 (m, 3H), 7.22 (d, J = 2.75 Hz, 1H), 7.13 (dd, J = 8.7, 2.59 Hz, 1H), 7.03 (t, J = 7.32 Hz, 1H), 6.99 (d, J = 8.54 Hz, 1H), 6.86 (d, J = 7.63 Hz, 2H), 6.37 (d, J = 9.16 Hz, 1H), 3.43 (s, 6H). MS (ESI+) m/z 386.1 $(M+H)^+$.

231. N-{3-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-4-[4-(trifluoromethyl)phenoxy]phenyl}methanesulfonamide.

231A. 1-methyl-5-(5-nitro-2-(4-(trifluoromethyl)phenoxy)phenyl)pyridin-2(1H)-one. Example 231A was prepared according to the procedure used for the preparation of Example 9B, substituting 4-(trifluoromethyl)phenol for phenol, and substituting Example 225A for Example 9A, respectively, to provide the title compound.

231B. 5-(5-amino-2-(4-(trifluoromethyl)phenoxy)phenyl)-1-methylpyridin-2(1H)-one. Example 231B was prepared according to the procedure used for the preparation of Example 10, substituting Example 231A for Example 9B, to provide the title compound.

231C. N-{3-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-4-[4-(trifluoromethyl)phenoxy]phenyl}methanesulfonamide. Example 231C was prepared according to the procedure used for the preparation of Example 22, substituting Example 231B for Example 20C, to provide the title compound. ^{1}H NMR (300 MHz, DMSO-d_6) δ9.84 (s, 1H), 7.87 (d, J = 2.6 Hz, 1H), 7.69 - 7.62 (m, 2H), 7.51 (dd, J = 9.4, 2.6 Hz, 1H), 7.29 (d, J = 2.5 Hz, 1H), 7.28 - 7.20 (m, 1H), 7.17 (d, J = 8.6 Hz, 1H), 7.07 - 6.99 (m, 2H), 6.37 (dd, J = 9.4, 0.6 Hz, 1H), 3.42 (s, 3H), 3.06 (s, 3H). MS (ESI+) m/z 439.0 $(M+H)^+$

232. N-[4-(4-fluorophenoxy)-3-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)phenyl]methanesulfonamide.

232A. 5-(2-(4-fluorophenoxy)-5-nitrophenyl)-1-methylpyridin-2(1H)-one. Example 232A was prepared according to the procedure used for the preparation of Example 9B, substituting 4-fluorophenol for phenol, and substituting Example 225A for Example 9A, respectively, to provide the title compound.

232B. 5-(5-amino-2-(4-fluorophenoxy)phenyl)-1-methylpyridin-2(1H)-one. Example 232B was prepared according to the procedure used for the preparation of Example 10, substituting Example 232A for Example 9B, to provide the title compound.

232C. N-[4-(4-fluorophenoxy)-3-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)phenyl]methanesulfonamide. Example 232C was prepared according to the procedure used for the preparation of Example 22, substituting Example 232B for Example 20C, to provide the title compound. ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.72 (s, 1H), 7.89 (d, J = 2.6 Hz, 1H), 7.57 (dd, J = 9.4, 2.6 Hz, 1H), 7.29 - 7.06 (m, 4H), 7.00 - 6.91 (m, 3H), 6.39 (d, J = 9.3 Hz, 1H), 3.45 (s, 3H) 3.02 (s, 3H). MS (ESI+) m/z 389.1 $(M+H)^+$

233. N-[4-(4-chlorophenoxy)-3-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)phenyl]methanesulfonamide.

233A. 5-(2-(4-chlorophenoxy)-5-nitrophenyl)-1-methylpyridin-2(1H)-one. Example 233A was prepared according to the procedure used for the preparation of Example 9B,

substituting 4-chlorophenol for phenol, and substituting Example 225A for Example 9A, respectively, to provide the title compound.

233B. 5-(5-amino-2-(4-chlorophenoxy)phenyl)-1-methylpyridin-2(1H)-one. Example 233B was prepared according to the procedure used for the preparation of Example 10, substituting Example 233A for Example 9B, to provide the title compound.

233C. N-[4-(4-chlorophenoxy)-3-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)phenyl]methanesulfonamide. Example 233C was prepared according to the procedure used for the preparation of Example 22, substituting Example 233B for Example 20C, to provide the title compound. ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.76 (s, 1H), 7.87 (d, J = 2.6 Hz, 1H), 7.45 (dd, 1H), 7.39 7.32 (m, 2H), 7.26 (d, J = 2.6 Hz, 1H), 7.20 (dd, J = 8.7, 2.7 Hz, 1H), 7.05 (d, J = 8.7 Hz, 1H), 6.95 6.88 (m, 2H), 6.38 (d, J = 9.4 Hz, 1H), 3.44 (s, 3H), 3.04 (s, 3H). MS (ESI+) m/z 405.0 $(M+H)^+$

234. N-[3-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-4-(pyridin-3-yloxy)phenyl]methanesulfonamide.

234A. 1-methyl-5-(5-nitro-2-(pyridin-3-yloxy)phenyl)pyridin-2(1H)-one. Example 234A was prepared according to the procedure used for the preparation of Example 9B, substituting pyrindin-3-ol for phenol, and substituting Example 225A for Example 9A, respectively, to provide the title compound.

234B. 5-(5-amino-2-(pyridin-3-yloxy)phenyl)-1-methylpyridin-2(1H)-one. Example 234A (340.4 mg, 1.053 mmol), iron (294 mg, 5.26 mmol), and ammonium chloride (113 mg, 2.106 mmol) were combined in ethanol (12 mL), tetrahydrofuran (12 mL), and water (4 mL), then allowed to reflux at 100 °C for 2 hours. The mixture was cooled just below reflux, vacuum filtered through diatomaceous earth, the filter cake was washed with warm methanol (3x35 mL). The filtrate was concentrated under reduced pressure and the residue was partitioned between saturated aqueous $NaHCO_3$ and ethyl acetate. The combined organics were washed with brine, dried ($MgSO_4$), gravity filtered, and concentrated to give the title compound.

234C. N-[3-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-4-(pyridin-3-yloxy)phenyl]methanesulfonamide. Example 234C was prepared according to the procedure used for the preparation of Example 22, substituting Example 234B for Example 20C, to provide the title compound. ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.79 (s, 1H), 8.37 - 8.24 (m, 2H), 7.89 (d, J = 2.6 Hz, 1H), 7.56 (dd, J = 9.4, 2.6 Hz, 1H), 7.43 - 7.17 (m, 4H),

7.10 (d, J = 8.6 Hz, 1H), 6.38 (d, J = 9.6 Hz, 1H), 3.44 (s, 3H), 3.05 (s, 3H). MS (ESI+) m/z 372.1 $(M+H)^+$

235. N-[4-(2-chlorophenoxy)-3-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)phenyl]methanesulfonamide.

235A. 5-(2-(2-chlorophenoxy)-5-nitrophenyl)-1-methylpyridin-2(1H)-one. Example 235A was prepared according to the procedure used for the preparation of Example 9B, substituting 2-chlorophenol for phenol, and substituting Example 225A for Example 9A, respectively, to provide the title compound.

235B. 5-(5-amino-2-(2-chlorophenoxy)phenyl)-1-methylpyridin-2(1H)-one. Example 235B was prepared according to the procedure used for the preparation of Example 234B, substituting Example 235A for Example 234A, to provide the title compound.

235C. N-[4-(2-chlorophenoxy)-3-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)phenyl]methanesulfonamide. Example 235C was prepared according to the procedure used for the preparation of Example 22, substituting Example 235B for Example 20C, to provide the title compound. ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.75 (s, 1H), 7.91 (d, J = 2.6 Hz, 1H), 7.59 (dd, J = 9.4, 2.6 Hz, 1H), 7.53 (dd, J = 7.9, 1.6 Hz, 1H), 7.31 - 7.21 (m, 2H), 7.19 (dd, J = 8.7, 2.7 Hz, 1H), 7.16 - 7.06 (m, 1H), 6.94 (d, J = 8.7 Hz, 1H), 6.88 (dd, J = 8.1, 1.5 Hz, 1H), 6.39 (d, J = 9.4 Hz, 1H), 3.45 (s, 3H), 3.03 (s, 3H). MS (ESI+) m/z 405.1 $(M+H)^+$

236. N-{3-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-4-[2-(trifluoromethyl)phenoxy]phenyl}methanesulfonamide.

236A. 1-methyl-5-(5-nitro-2-(2-(trifluoromethyl)phenoxy)phenyl)pyridin-2(1H)-one. Example 236A was prepared according to the procedure used for the preparation of Example 9B, substituting 2-(trifluoromethyl)phenol for phenol, and substituting Example 225A for Example 9A, respectively, to provide the title compound.

236B. 5-(5-amino-2-(2-(trifluoromethyl)phenoxy)phenyl)-1-methylpyridin-2(1H)-one. Example 236B was prepared according to the procedure used for the preparation of Example 234B, substituting Example 236A for Example 234A, to provide the title compound.

236C. N-{3-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-4-[2-(trifluoromethyl)phenoxy]phenyl}methanesulfonamide. Example 236C was prepared according to the procedure used for the preparation of Example 22, substituting Example 236B for Example 20C, to provide the title compound. ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.83 (s, 1H), 7.84 (d, J = 2.6 Hz, 1H), 7.72 (dd, J = 7.8, 1.6 Hz, 1H), 7.56 (dd, J = 8.0, 1.6 Hz, 1H), 7.50 (dd, J = 9.4, 2.6 Hz, 1H), 7.32 - 7.17 (m, 3H), 7.07 (d, J = 8.7 Hz, 1H), 6.80 (d, J =

8.4 Hz, 1H), 6.36 (d, J = 9.3 Hz, 1H), 3.41 (s, 3H), 3.06 (s, 3H). MS (ESI+) m/z 439.1 $(M+H)^+$

237. N-[4-(2-cyanophenoxy)-3-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)phenyl]methanesulfonamide.

237A. 2-(2-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-4-nitrophenoxy)benzonitrile. Example 237A was prepared according to the procedure used for the preparation of Example 9B, substituting 2-hydroxybenzonitrile for phenol, and substituting Example 225A for Example 9A, respectively, to provide the title compound.

237B. 2-(4-amino-2-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)phenoxy)benzonitrile. Example 237B was prepared according to the procedure used for the preparation of Example 234B, substituting Example 237A for Example 234A, to provide the title compound.

237C. N-[4-(2-cyanophenoxy)-3-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)phenyl]methanesulfonamide. Example 237C was prepared according to the procedure used for the preparation of Example 22, substituting Example 237B for Example 20C, to provide the title compound. ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.89 (s, 1H), 7.88 (d, J = 2.6 Hz, 1H), 7.82 (dd, J = 7.7, 1.7 Hz, 1H), 7.61 - 7.45 (m, 2H), 7.30 (dd, J = 2.2, 0.9 Hz, 1H), 7.27 - 7.06 (m, 3H), 6.78 (d, J = 8.0 Hz, 1H), 6.36 (d, J = 9.3 Hz, 1H), 3.43 (s, 3H), 3.07 (s, 3H). MS (ESI+) m/z 396.1 $(M+H)^+$.

238. N-[4-(2-methoxyphenoxy)-3-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)phenyl]methanesulfonamide.

238A. 5-(2-(2-methoxyphenoxy)-5-nitrophenyl)-1-methylpyridin-2(1H)-one. Example 238A was prepared according to the procedure used for the preparation of Example 9B, substituting 2-methoxyphenol for phenol, and substituting Example 225A for Example 9A, respectively, to provide the title compound.

238B. 5-(5-amino-2-(2-methoxyphenoxy)phenyl)-1-methylpyridin-2(1H)-one. Example 238B was prepared according to the procedure used for the preparation of Example 234B, substituting Example 238A for Example 234A, to provide the title compound.

238C. N-[4-(2-methoxyphenoxy)-3-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)phenyl]methanesulfonamide. Example 238C was prepared according to the procedure used for the preparation of Example 22, substituting Example 238B for Example 20C, to provide the title compound. ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.58 (s, 1H), 7.93 (d, J = 2.6 Hz, 1H), 7.69 (dd, J = 9.4, 2.6 Hz, 1H), 7.21 (d, J = 2.6 Hz, 1H), 7.18 - 7.05 (m, 3H), 6.99 - 6.88 (m, 2H), 6.67 (d, J = 8.7 Hz, 1H), 6.42 (d, J = 9.3 Hz, 1H), 3.76 (s, 3H), 3.47 (s, 3H), 2.99 (s, 3H). MS (ESI+) m/z 401.1 $(M+H)^+$

239. N-[4-(2-fluorophenoxy)-3-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)phenyl]methanesulfonamide.

239A. 5-(2-(2-fluorophenoxy)-5-nitrophenyl)-1-methylpyridin-2(1H)-one. Example 239A was prepared according to the procedure used for the preparation of Example 9B, substituting 2-fluorophenol for phenol, and substituting Example 225A for Example 9A, respectively, to provide the title compound.

239B. 5-(5-amino-2-(2-fluorophenoxy)phenyl)-1-methylpyridin-2(1H)-one. Example 239B was prepared according to the procedure used for the preparation of Example 234B, substituting Example 239A for Example 234A, to provide the title compound.

239C. N-[4-(2-fluorophenoxy)-3-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)phenyl]methanesulfonamide. Example 239C was prepared according to the procedure used for the preparation of Example 22, substituting Example 239B for Example 20C, to provide the title compound. ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.71 (s, 1H), 7.90 (d, J = 2.6 Hz, 1H), 7.59 (dd, J = 9.4, 2.6 Hz, 1H), 7.38 - 7.23 (m, 2H), 7.20 - 7.09 (m, 3H), 7.06 - 6.96 (m, 1H), 6.92 (d, J = 8.7 Hz, 1H), 6.41 (d, J = 9.3 Hz, 1H), 3.46 (s, 3H), 3.02 (s, 3H). MS (ESI+) m/z 389.1 $(M+H)^+$.

240. N-[4-(2,4-difluorophenoxy)-3-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)phenyl]methanesulfonamide.

240A. 5-(2-(2,4-difluorophenoxy)-5-nitrophenyl)-1-methylpyridin-2(1H)-one. Example 239A was prepared according to the procedure used for the preparation of Example 9B, substituting 2,4-difluorophenol for phenol, and substituting Example 225A for Example 9A, respectively, to provide the title compound.

240B. 5-(5-amino-2-(2,4-difluorophenoxy)phenyl)-1-methylpyridin-2(1H)-one. Example 240B was prepared according to the procedure used for the preparation of Example 234B, substituting Example 240A for Example 234A, to provide the title compound.

240C. N-[4-(2,4-difluorophenoxy)-3-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)phenyl]methanesulfonamide. Example 240C was prepared according to the procedure used for the preparation of Example 22, substituting Example 240B for Example 20C, to provide the title compound. ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.69 (s, 1H), 7.90 (d, J = 2.6 Hz, 1H), 7.60 (dd, J = 9.4, 2.6 Hz, 1H), 7.49 - 7.38 (m, 1H), 7.24 (d, J = 2.6 Hz, 1H), 7.19 - 7.01 (m, 3H), 6.88 (d, J = 8.7 Hz, 1H), 6.43 (d, J = 9.3 Hz, 1H), 3.47 (s, 3H) 3.01 (s, 3H). MS (ESI+) m/z 407.1 $(M+H)^+$

241. N-[4-(2,4-difluorophenoxy)-3-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)phenyl]ethanesulfonamide. Example 241 was prepared according to the procedure used

for the preparation of Example 22, substituting ethanesulfonyl chloride for methanesulfonyl chloride, and substituting Example 240B for Example 20C, respectively, to provide the title compound. ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.77 (s, 1H), 7.89 (d, J = 2.6 Hz, 1H), 7.59 (dd, J = 9.3, 2.6 Hz, 1H), 7.43 (ddd, J = 11.3, 8.7, 2.8 Hz, 1H), 7.24 (d, J = 2.7 Hz, 1H), 7.19-7.01 (m, 3H), 6.87 (d, J = 8.7 Hz, 1H), 6.43 (d, J = 9.3 Hz, 1H), 3.46 (s, 3H), 3.11 (q, J = 7.3 Hz, 2H), 1.22 (t, J = 7.3 Hz, 3H). MS (ESI+) m/z 421.1 $(M+H)^+$.

242. N-[4-(3,5-difluorophenoxy)-3-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)phenyl]methanesulfonamide.

242A. 5-(2-(3,5-difluorophenoxy)-5-nitrophenyl)-1-methylpyridin-2(1H)-one. Example 242A was prepared according to the procedure used for the preparation of Example 9B, substituting 3,5-difluorophenol for phenol, and substituting Example 225A for Example 9A, respectively, to provide the title compound.

242B. 5-(5-amino-2-(3,5-difluorophenoxy)phenyl)-1-methylpyridin-2(1H)-one. Example 242B was prepared according to the procedure used for the preparation of Example 234B, substituting Example 242A for Example 234A, to provide the title compound.

242C. N-[4-(3,5-difluorophenoxy)-3-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)phenyl]methanesulfonamide. Example 242C was prepared according to the procedure used for the preparation of Example 22, substituting Example 242B for Example 20C, to provide the title compound. ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.83 (s, 1H), 7.87 (d, J = 2.6 Hz, 1H), 7.52 (dd, J = 9.4, 2.6 Hz, 1H), 7.30 - 7.19 (m, 2H), 7.16 (d, J = 8.6 Hz, 1H), 6.91 (tt, J = 9.3, 2.3 Hz, 1H), 6.67 - 6.57 (m, 2H), 6.39 (d, J = 9.3 Hz, 1H), 3.44 (s, 3H), 3.06 (s, 3H). MS (ESI+) m/z 407.1 $(M+H)^+$

243. N-[4-(3-chlorophenoxy)-3-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)phenyl]methanesulfonamide.

243A. 5-(2-(3-chlorophenoxy)-5-nitrophenyl)-1-methylpyridin-2(1H)-one. Example 243A was prepared according to the procedure used for the preparation of Example 9B, substituting 3-chlorophenol for phenol, and substituting Example 225A for Example 9A, respectively, to provide the title compound.

243B. 5-(5-amino-2-(3-chlorophenoxy)phenyl)-1-methylpyridin-2(1H)-one. Example 243B was prepared according to the procedure used for the preparation of Example 234B, substituting Example 243A for Example 234A, to provide the title compound.

243C. N-[4-(3-chlorophenoxy)-3-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)phenyl]methanesulfonamide. Example 243C was prepared according to the procedure used for the preparation of Example 22, substituting Example 243B for Example 20C, to

provide the title compound. ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.80 (s, 1H), 7.89 (d, J = 2.6 Hz, 1H), 7.54 (dd, J = 9.4, 2.7 Hz, 1H), 7.33 (t, J = 8.1 Hz, 1H), 7.27 (d, J = 2.6 Hz, 1H), 7.21 (dd, J = 8.6, 2.7 Hz, 1H), 7.14 - 7.05 (m, 2H), 6.97 (t, J = 2.2 Hz, 1H), 6.85 (ddd, J = 8.3, 2.4, 0.9 Hz, 1H), 6.38 (d, J = 9.3 Hz, 1H), 3.44 (s, 3H), 3.05 (s, 3H). MS (ESI+) m/z 405.1 $(M+H)^+$

244. N-{3-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-4-[3-(trifluoromethyl)phenoxy]phenyl}methanesulfonamide.

244A. 1-methyl-5-(5-nitro-2-(3-(trifluoromethyl)phenoxy)phenyl)pyridin-2(1H)-one. Example 244A was prepared according to the procedure used for the preparation of Example 9B, substituting 3-(trifluoromethyl)phenol for phenol, and substituting Example 225A for Example 9A, respectively, to provide the title compound.

244B. 5-(5-amino-2-(3-(trifluoromethyl)phenoxy)phenyl)-1-methylpyridin-2(1H)-one. Example 244B was prepared according to the procedure used for the preparation of Example 234B, substituting Example 244A for Example 234A, to provide the title compound.

244C. N-{3-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-4-[3-(trifluoromethyl)phenoxy]phenyl}methanesulfonamide. Example 244C was prepared according to the procedure used for the preparation of Example 22, substituting Example 244B for Example 20C, to provide the title compound. ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.82 (s, 1H), 7.90 (d, J = 2.6 Hz, 1H), 7.58 - 7.48 (m, 2H), 7.44 - 7.36 (m, 1H), 7.28 (d, J = 2.6 Hz, 1H), 7.26 - 7.08 (m, 4H), 6.37 (d, J = 9.3 Hz, 1H), 3.44 (s, 3H), 3.05 (s, 3H). MS (ESI+) m/z 439.1 $(M+H)^+$.

245. N-[4-(3-cyanophenoxy)-3-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)phenyl]methanesulfonamide.

245A. 3-(2-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-4-nitrophenoxy)benzonitrile. Example 245A was prepared according to the procedure used for the preparation of Example 9B, substituting 3-hydroxybenzonitrile for phenol, and substituting Example 225A for Example 9A, respectively, to provide the title compound.

245B. 3-(4-amino-2-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)phenoxy)benzonitrile. Example 245B was prepared according to the procedure used for the preparation of Example 234B, substituting Example 245A for Example 234A, to provide the title compound.

245C. N-[4-(3-cyanophenoxy)-3-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)phenyl]methanesulfonamide. Example 245C was prepared according to the procedure used for the preparation of Example 22, substituting Example 245B for Example 20C, o provide the title compound. ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.81 (s, 1H), 7.88 (d, J = 2.6

Hz, 1H), 7.57 - 7.46 (m, 3H), 7.39 - 7.34 (m, 1H), 7.30 - 7.18 (m, 3H), 7.10 (d, J = 8.6 Hz, 1H), 6.37 (d, J = 9.3 Hz, 1H), 3.44 (s, 3H), 3.05 (s, 3H). MS (ESI+) m/z 396.1 $(M+H)^+$.

246. N-[4-(3-fluorophenoxy)-3-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)phenyl]methanesulfonamide.

246A. 5-(2-(3-fluorophenoxy)-5-nitrophenyl)-1-methylpyridin-2(1H)-one. Example 246A was prepared according to the procedure used for the preparation of Example 9B, substituting 3-fluorophenol for phenol, and substituting Example 225A for Example 9A, respectively, to provide the title compound.

246B. 5-(5-amino-2-(3-fluorophenoxy)phenyl)-1-methylpyridin-2(1H)-one. Example 246B was prepared according to the procedure used for the preparation of Example 234B, substituting Example 246A for Example 234A, to provide the title compound.

246C. N-[4-(3-fluorophenoxy)-3-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)phenyl]methanesulfonamide. Example 246C was prepared according to the procedure used for the preparation of Example 22, substituting Example 246B for Example 20C, to provide the title compound. ^{1}H NMR (300 MHz, DMSO-d_6) 9.79 (s, 1H), 7.88 (d, J = 2.6 Hz, 1H), 7.54 (dd, J = 9.4, 2.6 Hz, 1H), 7.34 (td, J = 8.1, 6.8 Hz, 1H), 7.27 (d, J = 2.6 Hz, 1H), 7.21 (dd, J = 8.6, 2.6 Hz, 1H), 7.10 (d, J = 8.6 Hz, 1H), 6.88 (tdd, J = 8.5, 2.4, 0.9 Hz, 1H), 6.79 - 6.67 (m, 2H), 6.38 (d, J = 9.3 Hz, 1H), 3.43 (s, 3H) 3.05 (s, 3H). MS (ESI+) m/z 389.1 $(M+H)^+$.

247. N-[4-(cyclohexyloxy)-3-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)phenyl]methanesulfonamide.

247A. 5-(2-(cyclohexyloxy)-5-nitrophenyl)-1-methylpyridin-2(1H)-one. Cyclohexanol (48.4 mg, 0.483 mmol) and sodium hydride (56.4 mg, 1.410 mmol) were combined in anhydrous tetrahydrofuran (5 mL). Bubbling occurred and the opaque mixture was stirred at ambient temperature for 1 hour. Example 225A (100 mg, 0.403 mmol) was added and the mixture heated to 50 °C for 2 hours. Cold water (10 mL) was added and the aqueous extracted with ethyl acetate. The combined organics were washed with brine, dried ($MgSO_4$), filtered, and concentrated to give the title compound.

247B. 5-(5-amino-2-(cyclohexyloxy)phenyl)-1-methylpyridin-2(1H)-one. Example 247B was prepared according to the procedure used for the preparation of Example 234B, substituting Example 247A for Example 234A, to provide the title compound.

247C. N-[4-(cyclohexyloxy)-3-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)phenyl]methanesulfonamide. Example 247C was prepared according to the procedure

used for the preparation of Example 22, substituting Example 247B for Example 20C, to provide the title compound. ^{1}H NMR (300 MHz, DMSO-d_6) 1H NMR 9.40 (s, 1H), 7.83 (d, J = 2.6 Hz, 1H), 7.61 (dd, J = 9.3, 2.6 Hz, 1H), 7.15 - 7.04 (m, 3H), 6.42 (d, J = 9.3 Hz, 1H), 4.39 - 4.27 (m, 1H), 3.48 (s, 3H), 2.94 (s, 3H), 1.96 - 1.20 (m, 10H). MS (ESI+) m/z 377.1 $(M+H)^+$.

248. N-[4-(cyclopentyloxy)-3-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)phenyl]methanesulfonamide.

248A. 5-(2-(cyclopentyloxy)-5-nitrophenyl)-1-methylpyridin-2(1H)-one. Example 248A was prepared according to the procedure used for the preparation of Example 247A, substituting cyclopentanol for cyclohexanol, to provide the title compound.

248B. 5-(5-amino-2-(cyclopentyloxy)phenyl)-1-methylpyridin-2(1H)-one. Example 248B was prepared according to the procedure used for the preparation of Example 234B, substituting Example 248A for Example 234A, to provide the title compound.

248C. N-[4-(cyclopentyloxy)-3-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)phenyl]methanesulfonamide. Example 248C was prepared according to the procedure used for the preparation of Example 22, substituting Example 248B for Example 20C, to provide the title compound. ^{1}H NMR (300 MHz, DMSO-d_6) 9.39 (s, 1H), 7.80 (d, J = 2.6 Hz, 1H), 7.55 (dd, J = 9.3, 2.6 Hz, 1H), 7.16 - 7.09 (m, 2H), 7.08 - 7.01 (m, 1H), 6.41 (d, J = 9.3 Hz, 1H), 4.83 - 4.75 (m, 1H), 3.47 (s, 3H), 2.93 (s, 3H), 1.90 - 1.75 (m, 2H), 1.76 - 1.35 (m, 6H). MS (ESI+) m/z 363.1 $(M+H)^+$.

249. N-[3-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-4-(tetrahydrofuran-3-yloxy)phenyl]methanesulfonamide.

249A. 1-methyl-5-(5-nitro-2-(tetrahydrofuran-3-yloxy)phenyl)pyridin-2(1H)-one. Example 249A was prepared according to the procedure used for the preparation of Example 247A, substituting tetrahydrofuran-3-ol for cyclohexanol, to provide the title compound.

249B. 5-(5-amino-2-(tetrahydrofuran-3-yloxy)phenyl)-1-methylpyridin-2(1H)-one. Example 249B was prepared according to the procedure used for the preparation of Example 234B, substituting Example 249A for Example 234A, to provide the title compound.

249C. N-[3-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-4-(tetrahydrofuran-3-yloxy)phenyl]methanesulfonamide. Example 249C was prepared according to the procedure used for the preparation of Example 22, substituting Example 249B for Example 20C, to provide the title compound. ^{1}H NMR (300 MHz, DMSO-d_6) 9.43 (s, 1H), 7.82 (d, J = 2.6 Hz, 1H), 7.57 (dd, J = 9.4, 2.6 Hz, 1H), 7.21 - 7.09 (m, 2H), 7.09 - 7.02 (m, 1H), 6.42 (d,

J = 9.3 Hz, 1H), 5.06 - 4.98 (m, 1H), 3.89 - 3.76 (m, 4H), 3.47 (s, 3H), 2.95 (s, 3H), 2.30 - 2.10 (m, 1H), 2.00 - 1.87 (m, 1H). MS (ESI+) m/z 365.1 $(M+H)^+$.

250. N-[3-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-4-(tetrahydro-2H-pyran-4-ylmethoxy)phenyl]methanesulfonamide.

250A. 1-methyl-5-(5-nitro-2-((tetrahydro-2H-pyran-4-yl)methoxy)phenyl)pyridin-2(1H)-one. Example 250A was prepared according to the procedure used for the preparation of Example 247A, substituting (tetrahydro-2H-pyran-4-yl)methanol for cyclohexanol, to provide the title compound.

250B. 5-(5-amino-2-((tetrahydro-2H-pyran-4-yl)methoxy)phenyl)-1-methylpyridin-2(1H)-one. Example 250B was prepared according to the procedure used for the preparation of Example 234B, substituting Example 250A for Example 234A, to provide the title compound.

250C. N-[3-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-4-(tetrahydro-2H-pyran-4-ylmethoxy)phenyl]methanesulfonamide. Example 250C was prepared according to the procedure used for the preparation of Example 22, substituting Example 250B for Example 20C, to provide the title compound. ^{1}H NMR (300 MHz, DMSO-d_6) 9.41 (s, 1H), 7.83 (d, J = 2.6 Hz, 1H), 7.57 (dd, J = 9.3, 2.6 Hz, 1H), 7.17 - 7.03 (m, 3H), 6.42 (d, J = 9.3 Hz, 1H), 3.87 (d, J = 4.0 Hz, 2H), 3.83 (d, J = 6.1 Hz, 2H), 3.47 (s, 3H), 3.41 - 3.17 (m, 2H), 2.93 (s, 3H), 2.04 - 1.86 (m, 1H), 1.64 - 1.54 (m, 2H), 1.39 - 1.20 (m, 2H). MS (ESI+) m/z 393.1 $(M+H)^+$.

251. N-[3-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-4-phenoxyphenyl]-1H-pyrrole-2-carboxamide. A mixture of 1H-pyrrole-2-carboxylic acid (0.018 g, 0.164 mmol), oxalyl chloride (0.035 g, 0.274 mmol) and dimethylformamide (1 drop) in dichloromethane (3 mL) was stirred at ambient temperature for 1 hour. The solvent was evaporated under reduced pressure and the residue treated with toluene (2 mL) and then evaporated under reduced pressure. The residue was dissolved in dichloromethane (2 mL) and was then added to a solution of Example 225C (0.040 g, 0.137 mmol) and triethylamine (0.055 g, 0.547 mmol) in dichloromethane (3 mL). The reaction mixture was stirred at ambient temperature for 2 hours. The reaction mixture was concentrated under reduced pressure. The residue was purified by reverse phase HPLC (C18, CH_3CN/water (0.1%TFA), 0-100%) to afford the title compound (0.035 g, 66%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.64 (s, 1H), 9.85 (s, 1H), 7.90 (d, J = 2.75 Hz, 1H), 7.82 (d, J = 2.75 Hz, 1H), 7.76 (dd, J = 8.85, 2.75 Hz, 1H), 7.60 (dd, J = 9.31, 2.59 Hz, 1H), 7.29-7.33 (m, 2H), 6.97-7.01 (m, 3H), 6.97-6.98 (m, 1H), 6.89 (d, J = 7.63 Hz, 2H), 6.38 (d, J = 9.46 Hz, 1H), 6.17-6.19 (m, 1H), 3.44 (s, 3H). MS (ESI+) m/z 386.1 $(M+H)^+$.

252. tert-butyl (2-{[3-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-4-phenoxyphenyl]amino}-2-oxoethyl)carbamate. The product from Example 225C (0.058 g, 0.2 mmol), Boc-glycine (0.042 g, 0.240 mmol), triethylamine (0.098 mL, 0.70 mmol) and HATU (0.091 g, 0.240 mmol) were combined in DMSO (1.2 mL), stirred for 1 hour and partitioned between ethyl acetate and brine. The organic layer was separated and concentrated. Purification by chromatography (silica gel, 1-4% methanol in dichloromethane) afforded the title compound (0.071 g, 79%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.00 (s, 1 H) 7.86 (d, J=2.71 Hz, 1 H) 7.70 (d, J=2.37 Hz, 1 H) 7.48 - 7.59 (m, 2 H) 7.27 - 7.34 (m, 2 H) 6.97 - 7.08 (m, 3 H) 6.87 (d, J=7.80 Hz, 2 H) 6.37 (d, J=9.49 Hz, 1 H) 3.72 (d, J=6.10 Hz, 2 H) 3.43 (s, 3 H) 1.40 (s, 9 H). MS (ESI+) m/z 448 $(M+H)^+$.

253. N-[3-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-4-phenoxyphenyl]glycinamide. The product from Example 252 (0.071 g, 0.158 mmol) and trifluoroacetic acid (0.5 mL) in dichloromethane (1 mL) was stirred for 1 h and concentrated. Purification by reverse phase HPLC (C18, 0-100 % CH_3CN/water (0.1% TFA)) afforded the title compound as the trifluoroacetic acid salt (0.060 g, 81%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.49 (s, 1 H) 8.08 (s, 2 H) 7.86 (d, J=2.37 Hz, 1 H) 7.63 (d, J=2.37 Hz, 1 H) 7.51 - 7.58 (m, 2 H) 7.29 - 7.36 (m, 2 H) 6.99 - 7.10 (m, 2 H) 6.89 (d, J=7.46 Hz, 2 H) 6.39 (d, J=9.49 Hz, 1 H) 3.79 (q, J=5.54 Hz, 2 H) 3.44 (s, 3 H). MS (ESI+) m/z 350 $(M+H)^+$.

254. 1-methyl-5-[2-phenoxy-5-(pyridin-2-ylamino)phenyl]pyridin-2(1H)-one. A mixture of Example 225C (0.035 g, 0.120 mmol), 2-bromopyridine (0.023 g, 0.144 mmol), 2'-(dicyclohexylphosphino)-N,N-dimethylbiphenyl-2-amine (0.0071 g, 0.018 mmol), tris(dibenzylideneacetone)dipalladium(0) (0.0055 g, 0.006 mmol), and Cs_2CO_3 (0.055 g, 0.168 mmol) in dioxane (1 mL) was degassed and back-filled with nitrogen several times. The reaction mixture was heated at 100 °C overnight. After cooling to room temperature, the reaction mixture 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 $MgSO_4$, filtered, and concentrated. The residue was purified by reverse phase HPLC (C18, CH_3CN/water (0.1%TFA), 0-100%) to afford 0.019 g (33%) of the title compound as a TFA salt. ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.46 (s, 1H), 9.86 (br s, 1H), 8.08 (dd, J = 5.49, 1.22 Hz, 1H), 7.91 (d, J = 2.44 Hz, 1H), 7.75 (t, J = 7.02 Hz, 1H), 7.67 (d, J = 2.75 Hz, 1H), 7.61 (dd, J = 9.46, 2.75 Hz, 1H), 7.57 (dd, J = 8.7, 2.59 Hz, 1H), 7.30-7.35 (m, 2H), 7.02-7.07 (m, 2H), 6.98 (d, J = 8.54 Hz, 1H), 6.90 (d, J = 7.93 Hz, 2H), 6.84-6.87 (m, 1H), 6.38 (d, J = 9.46 Hz, 1H), 3.43 (s, 3H). MS (ESI+) m/z 370.2 $(M+H)^+$.

255. N-ethyl-3-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-4-phenoxybenzenesulfonamide.

255A. 3-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-4-phenoxybenzene-1-sulfonyl chloride. Under ice-cooling, thionyl chloride (2 mL) was added dropwise over 20 minutes to water (8 mL). The mixture was stirred overnight for 12 hours to give a SO_2 containing solution. Separately, Example 225C (0.3 g, 1.026 mmol) was added to concentrated HCl (8 mL) and dioxane (6 mL) at 0 °C. The solution was stirred for 5 minutes. To this suspension/solution was added sodium nitrite (0.078 g, 1.129 mmol) in water (2 mL) dropwise at 0 °C. The solution was stirred at 0 °C for three hours. To the SO_2 containing solution was added copper(I) chloride (0.020 g, 0.205 mmol). Then, to this solution was added the diazotized Example 225C at 0 °C. The solution was stirred for 30 minutes. The reaction mixture was extracted with ethyl acetate. The solvent was removed, and the residue was taken up into tetrahydrofuran which was used directly for the next reaction.

255B. N-ethyl-3-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-4-phenoxybenzenesulfonamide. A quater of tetrahydrofuran solution containing Example 255A was treated with excess ethyl amine in tetrahydrofuran. The solution was stirred at ambient temperature for three hours. The solvent was removed, and the residue was purified by reverse phase HPLC (C18, CH_3CN/water (0.1%TFA), 0-100%) to afford 0.010 g of the title compound. ^1H NMR (500 MHz, DMSO-d_6) δ 8.00 (d, J = 2.44 Hz, 1H), 7.82 (d, J = 2.44 Hz, 1H), 7.71 (dd, J = 2.59, 1.37 Hz, 1H), 7.69 (d, J = 2.14 Hz, 1H), 7.51 (t, J = 5.8 Hz, 1H), 7.41-7.45 (m, 3H), 7.21 (t, J = 7.32 Hz, 1H), 7.11 (d, J = 7.63 Hz, 2H), 6.99 (d, J = 8.54 Hz, 1H), 6.44 (d, J = 9.46 Hz, 1H), 3.49 (s, 3H), 2.77-2.84 (m, 2H), 1.00 (t, J = 7.17 Hz, 3H). MS (ESI+) m/z 385.2 $(M+H)^+$.

256. 3-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-4-phenoxybenzenesulfonamide. A quater of tetrahydrofuran solution containing Example 255A was treated with excess concentrated ammonium hydroxide. The solution was stirred at for three hours. The solvent was removed, and the residue was purified by reverse phase HPLC (C18, CH_3CN/water (0.1%TFA), 0-100%) to afford 0.010 g of the title compound. ^1H NMR (500 MHz, DMSO-d_6) δ 7.98 (d, J = 2.75 Hz, 1H), 7.88 (d, J = 2.44 Hz, 1H), 7.74 (dd, J = 8.7, 2.29 Hz, 1H), 7.6 (dd, J = 9.46, 2.75 Hz, 1H), 7.40-7.44 (m, 2H), 7.34 (s, 2H), 7.20 (t, J = 7.32 Hz, 1H), 7.08 (d, J = 7.63 Hz, 2H), 7.00 (d, J = 8.54 Hz, 1H), 6.45 (d, J = 9.46 Hz, 1H), 3.49 (s, 3H). MS (ESI+) m/z 357.2 $(M+H)^+$.

257. N-[2-methyl-5-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-4-phenoxyphenyl]methanesulfonamide.

257A. 5-(2-fluoro-4-methyl-5-nitrophenyl)-1-methylpyridin-2(1H)-one. 4-bromo-5-fluoro-2-nitrotoluene (Aldrich, 0.234 g, 1.0 mmol), 1-methyl-5-(4,4,5,5-tetramethyl-[1,3,2]dioxaboralan-2-yl)-1H-pyridin-2-one (Synchem, Inc.0.235 g, 1.0 mmol), bis(triphenylphosphine)palladium(II) chloride (0.035 g, 0.05 mmol) and sodium carbonate 2M (1.5 mL, 3.0 mmol) were combined in DME (4 mL) and water (4.0 mL), sparged with nitrogen and heated by microwave at 120 °C for 30 minutes. The reaction mixture was partitioned between ethyl acetate and water. The ethyl acetate layer was washed with brine, dried (Na_2SO_4), treated with mercaptopropyl silica gel for 30 minutes, filtered and concentrated to afford the title compound (0.262 g, 99%).

257B. 1-methyl-5-(4-methyl-5-nitro-2-phenoxyphenyl)pyridin-2(1H)-one. The product from Example 257A (0.262 g, 1.0 mmol), phenol (0.104 g, 1.1 mmol) and cesium carbonate (0.358 g, 1.1 mmol) were combined in DMSO (5 mL) and heated at 100 °C for 30 minutes under nitrogen. The reaction mixture was partitioned between ethyl acetate and water. The organic layer was washed with brine, dried (Na_2SO_4), filtered and concentrated to afford the title compound (0.31 g, 92%).

257C. 5-(5-amino-4-methyl-2-phenoxyphenyl)-1-methylpyridin-2(1H)-one. The product from Example 257B (0.336 g, 1.0 mmol), iron (0.279 g, 5.0 mmol), and ammonium chloride (0.080 g, 1.5 mmol) were combined in a solvent mixture of ethanol (9 mL), tetrahydrofuran (9 mL) and water (3 mL) and heated at 95 °C with vigorous stirring for 1.5 hours. The mixture was cooled, filtered through Celite and the Celite 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. Purification by chromatography (silica gel, 0-4% methanol in dichloromethane) afforded the title compound (0.186 g, 61%).

Example 257D. N-[2-methyl-5-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-4-phenoxyphenyl]methanesulfonamide. A solution of the product from Example 257C (0.060 g, 0.196 mmol) and triethylamine (0.068 mL, 0.49 mmol) in dichloromethane (3 mL) was treated with methanesulfonyl chloride (0.035 mL, 0.45 mmol), stirred for 2 hours and concentrated. The residue was dissolved in a mixture of dioxane (2 mL) and 1M sodium hydroxide (2 mL) and heated for 1 hour at 90 °C. The mixture was cooled, diluted with ethyl acetate, brought to pH 7 with 1 M HCl and the organic layer was separated, dried (Na_2SO_4), filtered and concentrated. Purification by chromatography (silica gel, 0-4% methanol in dichloromethane) afforded the title compound (0.039 g, 52%). ^1H NMR (300 MHz, DMSO-

d_6) δ 9.11 (s, 1 H) 7.86 (d, *J*=2.78 Hz, 1 H) 7.58 (dd, *J*=9.52, 2.78 Hz, 1 H) 7.29 - 7.39 (m, 3 H) 7.08 (t, *J*=7.34 Hz, 1 H) 6.93 (d, *J*=7.93 Hz, 2 H) 6.87 (s, 1 H) 6.37 (d, *J*=9.52 Hz, 1 H) 3.44 (s, 3 H) 3.03 (s, 3 H) 2.27 (s, 3 H). MS (ESI+) m/z 385 $(M+H)^+$.

258. 4-methoxy-1-methyl-5-(2-phenoxyphenyl)pyridin-2(1H)-one.

258A. 5-chloro-4-methoxy-1-methylpyridin-2(1H)-one. 5-Chloro-4-hydroxypyridin-2(1H)-one (1.27 g, 8.73 mmol) in dimethylformamide was cooled to 0 °C. To this solution was added sodium hydride (0.254 g, 21.81 mmol). After the end of bubbling, iodomethane (3.1 g, 21.81 mmol) was added to the solution. The solution was stirred for 6 hours at 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 $MgSO_4$, filtered, and concentrated. The residue was purified by flash chromatography on silica gel eluting with 40% ethyl acetate in hexanes to afford 0.2 g (6.6%) of the title compound.

258B. 4-methoxy-1-methyl-5-(2-phenoxyphenyl)pyridin-2(1H)-one. A mixture of Example 258A (0.035 g, 0.2 mmol), 2-phenoxyphenylboronic acid (0.064 g, 0.30 mmol), 2'-(dicyclohexylphosphino)-N,N-dimethylbiphenyl-2-amine (0.016 g, 0.040 mmol), palladium(II) acetate (0.0045 g, 0.02 mmol) and CsF (0.091 g, 0.6 mmol) in dioxane (1 mL) in a 4 mL vial was degassed and back-filled with nitrogen four times. The reaction mixture was heated at 90 °C overnight. The mixture was filtered through a pad of filtering agent. The filtrate was concentrated. The residue was then purified by reverse HPLC (C18, CH_3CN/water (0.1%TFA), 0-100%) to afford 0.030 g (48%) of the title compound. ^1H NMR (500 MHz, DMSO-d_6) δ 7.57 (m, 1H), 7.30-7.37 (m, 4H), 7.16-7.20 (m, 1H), 7.07 (t, J = 7.32 Hz, 1H), 6.90-6.92.(m, 3H), 5.79 (s, 1H), 3.54 (s, 3H), 3.34 (s, 3H). MS (ESI+) m/z 308.1 $(M+H)^+$.

259. N-[3-(4-methoxy-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-4-phenoxyphenyl]methanesulfonamide.

259A. 5-(2-fluoro-5-nitrophenyl)-4-methoxy-1-methylpyridin-2(1H)-one. Example 259A was prepared according to the procedure used for the preparation of Example 258B, substituting 2-fluoro-5-nitrophenylboronic acid for 2-phenoxyphenylboronic acid, to provide the title compound.

259B. 4-methoxy-1-methyl-5-(5-nitro-2-phenoxyphenyl)pyridin-2(1H)-one. Example 259B was prepared according to the procedure used for the preparation of Example 9B, substituting Example 259A for Example 9A, to provide the title compound.

259C. 5-(5-amino-2-phenoxyphenyl)-4-methoxy-1-methylpyridin-2(1H)-one. Example 259C was prepared according to the procedure used for the preparation of Example 10, substituting Example 259B for Example 9B, to provide the title compound.

259D. N-[3-(4-methoxy-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-4-phenoxyphenyl]methanesulfonamide. Example 259D was prepared according to the procedure used for the preparation of Example 22, substituting Example 259C for Example 20C, to provide the title compound. ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.70 (s, 1H), 7.58 (s, 1H), 7.29-7.33 (m, 2H), 7.20 (dd, J = 8.85, 2.75 Hz, 1H), 7.13 (d, J = 2.75 Hz, 1H), 7.04 (t, J = 7.48 Hz, 1H), 6.94 (d, J = 8.85 Hz, 1H), 6.88 (d, J = 7.63 Hz, 2H), 5.79 (s, 1H), 3.53 (s, 3H), 3.33 (s, 3H), 3.02 (s, 3H). MS (ESI+) m/z 401.0 $(M+H)^+$.

260. 3-methyl-5-(2-phenoxyphenyl)pyridin-2(1H)-one. 2-Phenoxylphenylboronic acid (0.072 g, 0.335 mmol), 5-bromo-3-methylpyridin-2(1H)-one (0.060 g, 0.319 mmol), bis(triphenylphosphine)palladium(II) chloride (0.009 g, 0.013 mmol) and 2M sodium carbonate (0.64 mL, 1.28 mmol) were combined in 1,2-dimethoxyethane (1.6 mL) and ethanol (1.6 mL), sparged with nitrogen for 15 minutes and heated by microwave at 120 °C for 30 minutes. The reaction mixture was partitioned between ethyl acetate and water. The ethyl acetate layer was washed with brine, dried (Na_2SO_4), filtered and concentrated. Purification by reverse phase HPLC (C18, 0-100 % CH_3CN/water (0.1% TFA)) afforded the title compound as the trifluoroacetic acid salt (0.020 g, 23%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.60 (s, 1 H) 6.75 - 7.63 (m, 11 H) 1.97 (m, 3 H) MS (APCI+) m/z 278 $(M+H)^+$.

261. N-[3-(5-methyl-6-oxo-1,6-dihydropyridin-3-yl)-4-phenoxyphenyl]methanesulfonamide.

261A. 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 ($MgSO_4$), filtered and concentrated to afford the title compound (3.43 g, quantitative yield).

261B. 3-bromo-4-phenoxyaniline. Example 261A (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 hours. 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 $NaHCO_3$ and ethyl acetate (3 x 125 mL). The combined organics were washed with brine, dried ($MgSO_4$), gravity filtered then concentrated to afford the title compound (2.86, 93%).

261C. N-(3-bromo-4-phenoxyphenyl)methanesulfonamide. Example 261B (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 hour. The solution was neutralized to a pH of 7 with saturated aqueous NH_4Cl (200 mL). The aqueous phase was extracted with ethyl acetate (3x125 mL). The combined organics were washed with brine, dried ($MgSO_4$), filtered, then concentrated. The residue was purified by flash chromatography (silica gel, 0-25% ethyl acetate/hexane gradient,) to afford the title compound (2.79 g, 75%).

261D. N-(3-(6-fluoro-5-methylpyridin-3-yl)-4-phenoxyphenyl)methanesulfonamide. A mixture of 2-fluoro-3-methylpyridine-5-boronic acid (Combi-Blocks 0.088 g, 0.566 mmol), the product from Example 261C (0.149 g, 0.435 mmol), tetrakis(tiriphenylphosphine) palladium(0) (0.025 g, 0.022 mmol) and sodium carbonate (0.435 mL, 0.871 mmol) in toluene (2.4 mL), ethanol (0.62 mL) and water (1.24 mL) was heated by microwave at 110 °C for 30 minutes. The reaction mixture was filtered through a 0.45um Nylon filter disk to remove solids and the filtrate was partitioned between ethyl acetate and brine. The organic layer was separated and concentrated. Purification by chromatography (silica gel, 0-60% ethyl acetate in hexane) afforded the title compound (0.133 g, 82%). MS (ESI+) m/z 373 $(M+H)^+$.

Example 261E. N-[3-(5-methyl-6-oxo-1,6-dihydropyridin-3-yl)-4-phenoxyphenyl]methanesulfonamide. The product from Example 261D (0.12 g, 0.322 mmol) and sodium hydroxide (1M, 6.0 mL, 6.00 mmol) were combined in dioxane (1.611 mL) and heated at 140 °C for 3 hours. The reaction mixture was partitioned into ethyl acetate and water adjusting the pH to 6. The ethyl acetate layer was washed with brine, dried (Na_2SO_4), filtered and concentrated. Purification by reverse phase HPLC (C18, 0-100 % CH_3CN/water (0.1% TFA)) afforded the title compound (0.027 g, 22%). ^1H NMR (300 MHz, DMSO-d_6) δ 11.60 (s, 1 H) 9.70 (s, 1 H) 7.48 (s, 1 H) 7.36 (s, 1 H) 7.31 (t, J=7.93 Hz, 2 H)

7.25 (d, *J*=2.38 Hz, 1 H) 7.14 - 7.20 (m, 1 H) 7.04 (t, *J*=7.34 Hz, 1 H) 6.99 (d, *J*=8.73 Hz, 1 H) 6.88 (d, *J*=7.93 Hz, 2 H) 3.02 (s, 3 H) 1.95 (s, 3 H). MS (ESI+) m/z 371 $(M+H)^+$.

262. N-[3-(5-methyl-6-oxo-1,6-dihydropyridin-3-yl)-4-phenoxyphenyl]acetamide.

262A. 3-(6-fluoro-5-methylpyridin-3-yl)-4-phenoxyaniline. The product from Example 261B (0.792 g, 3.0 mmol), 2-fluoro-3-methylpyridine-5-boronic acid (Combi-Blocks 0.604 g, 3.9 mmol), tetrakis(triphenylphosphune)palladium(0) (0.173 g, 0.15 mmol) and sodium carbonate (4.50 mL, 9.0 mmol) were combined in toluene (10 mL), ethanol (2.5 mL) and water (2.5 mL), sparged with nitrogen for 10 minutes and heated by microwave at 120 °C for 60 minutes. The reaction mixture was partitioned between ethyl acetate and brine. The organic layer was separated, dried (Na_2SO_4), filtered and concentrated. Purification by chromatography (silica gel, 0-60% ethyl acetate in hexane) afforded the title compound (0.742 g, 84%).

262B. N-(3-(6-fluoro-5-methylpyridin-3-yl)-4-phenoxyphenyl)acetamide. The product from Example 262A (0.059 g, 0.2 mmol) in acetic anhydride (0.5 mL) was heated by microwave at 100 °C for 20 minutes and concentrated. Purification by chromatography (silica gel, 0-4% methanol in dichloromethane) afforded the title compound (0.050 g, 72%).

Example 262C. N-[3-(5-methyl-6-oxo-1,6-dihydropyridin-3-yl)-4-phenoxyphenyl]acetamide. The product from Example 262B (0.045 g, 0.134 mmol) in acetic acid (1.4 mL) / water (0.35 mL) was heated at 100 °C for 16 hours and concentrated. Purification by reverse phase HPLC (C18, 0-100 % CH_3CN/water (0.1% TFA)) afforded the title compound (0.030 g, 66%). ^1H NMR (300 MHz, DMSO-d_6) δ 11.56 (s, 1 H) 10.01 (s, 1 H) 7.67 (d, *J*=2.78 Hz, 1 H) 7.52 (dd, *J*=8.73, 2.78 Hz, 1 H) 7.44 - 7.48 (m, *J*=1.59 Hz, 1 H) 7.26 - 7.35 (m, 3 H) 7.02 (t, *J*=7.34 Hz, 1 H) 6.96 (d, *J*=8.73 Hz, 1 H) 6.84 (d, *J*=7.54 Hz, 2 H) 2.05 (s, 3 H) 1.95 (s, 3 H). MS (ESI+) m/z 335 $(M+H)^+$.

263. N-[4-(2,4-difluorophenoxy)-3-(5-methyl-6-oxo-1,6-dihydropyridin-3-yl)phenyl]methanesulfonamide.

263A. 2-bromo-1-(2,4-difluorophenoxy)-4-nitrobenzene. Example 263A was prepared according to the procedure used for the preparation of Example 9B, substituting 2-bromo-1-fluoro-4-nitrobenzene for Example 9A, and substituting 2,4-difluorophenol for phenol, respectively, to provide the title compound.

263B. 3-bromo-4-(2,4-difluorophenoxy)aniline. Example 263B was prepared according to the procedure used for the preparation of Example 234B, substituting Example 263A for Example 234A, to provide the title compound.

263C. 4-(2,4-difluorophenoxy)-3-(6-fluoro-5-methylpyridin-3-yl)aniline. Example 263C was prepared according to the procedure used for the preparation of Example 9A, substituting Example 263B for Example 1A, and substituting 6-fluoro-5-methylpyridin-3-ylboronic acid for 2-fluoro-5-nitrophenylboronic acid, respectively, to provide the title compound.

263D. N-(4-(2,4-difluorophenoxy)-3-(6-fluoro-5-methylpyridin-3-yl)phenyl)methanesulfonamide. Example 263C was prepared according to the procedure used for the preparation of Example 22, substituting Example 263C for Example 20C, to provide the title compound.

263E. N-[4-(2,4-difluorophenoxy)-3-(5-methyl-6-oxo-1,6-dihydropyridin-3-yl)phenyl]methanesulfonamide. Example 263E was prepared according to the procedure used for the preparation of Example 55, substituting Example 263D for Example 54B, to provide the title compound. ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.63 (br s, 1H), 9.68 (s, 1H), 7.51-7.53 (m, 1H), 7.40-7.46 (m, 2H), 7.24 (d, J = 2.75 Hz, 1H), 7.01-7.15 (m, 3H), 6.89 (d, J = 8.54 Hz, 1H), 3.01 (s, 3H), 1.99 (s, 3H). MS (DCI+) m/z 407.0 $(M+H)^+$.

264. N-[4-(2,4-difluorophenoxy)-3-(5-methyl-6-oxo-1,6-dihydropyridin-3-yl)phenyl]ethanesulfonamide.

264A. N-(4-(2,4-difluorophenoxy)-3-(6-fluoro-5-methylpyridin-3-yl)phenyl)ethanesulfonamide. Example 264A was prepared according to the procedure used for the preparation of Example 22, substituting Example 263C for Example 20C, and substituting ethanesulfonyl chloride for methanesulfonyl chloride, respectively, to provide the title compound.

264B. N-[4-(2,4-difluorophenoxy)-3-(5-methyl-6-oxo-1,6-dihydropyridin-3-yl)phenyl]ethanesulfonamide. Example 264B was prepared according to the procedure used for the preparation of Example 55, substituting Example 264A for Example 54B, to provide the title compound. ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.67 (br s, 1H), 9.75 (s, 1H), 7.49-7.51 (m, 1H), 7.41-7.46 (m, 1H), 7.38 (d, J = 2.44 Hz, 1H), 7.23 (d, J = 2.44 Hz, 1H), 7.14 (dd, J = 8.85, 2.75 Hz, 1H), 7.01-7.10 (m, 2H), 6.88 (d, J = 8.85 Hz, 1H), 3.11 (q, J = 7.32 Hz, 2H), 1.21 (t, J = 7.32 Hz, 3H). MS (DCI+) m/z 421.0 $(M+H)^+$.

265. N-[4-(2,4-difluorophenoxy)-3-(5-methyl-6-oxo-1,6-dihydropyridin-3-yl)phenyl]acetamide. Example 265 was prepared according to the procedure used for the preparation of Example 55, substituting Example 263C for Example 54B, to provide the title compound. ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.63 (br s, 1H), 10.00 (s, 1H), 7.65 (d, J = 2.44 Hz, 1H), 7.46-7.50 (m, 2H), 7.39-7.44 (m, 1H), 7.36 (d, J = 2.44 Hz, 1H), 7.01-7.04 (m, 2H), 6.87 (d, J = 8.85 Hz, 1H), 2.04 (s, 3H), 1.98 (s, 3H). MS (DCI+) m/z 371.1 $(M+H)^+$.

266. N-{4-[(4,4-difluorocyclohexyl)oxy]-3-(5-methyl-6-oxo-1,6-dihydropyridin-3-yl)phenyl}methanesulfonamide.

266A. 2-bromo-1-(4,4-difluorocyclohexyloxy)-4-nitrobenzene. Example 266A was prepared according to the procedure used for the preparation of Example 247A, substituting 2-bromo-1-fluoro-4-nitrobenzene for Example 225A, and substituting 4,4-difluorocyclohexanol for cyclohexanol, respectively, to provide the title compound.

266B. 3-bromo-4-(4,4-difluorocyclohexyloxy)aniline. Example 266B was prepared according to the procedure used for the preparation of Example 10, substituting Example 266A for Example 9B, and substituting platinum on carbon for palladium on carbon, respectively, to provide the title compound.

266C. 4-(4,4-difluorocyclohexyloxy)-3-(6-fluoro-5-methylpyridin-3-yl)aniline. Example 266C was prepared according to the procedure used for the preparation of Example 9A, substituting Example 266B for Example 1A, and substituting 6-fluoro-5-methylpyridin-3-ylboronic acid for 2-fluoro-5-nitrophenylboronic acid, respectively, to provide the title compound.

266D. N-(4-(4,4-difluorocyclohexyloxy)-3-(6-fluoro-5-methylpyridin-3-yl)phenyl)methanesulfonamide. Example 266D was prepared according to the procedure used for the preparation of Example 22, substituting Example 266C for Example 20C, to provide the title compound.

266E. N-{4-[(4,4-difluorocyclohexyl)oxy]-3-(5-methyl-6-oxo-1,6-dihydropyridin-3-yl)phenyl}methanesulfonamide. Example 266E was prepared according to the procedure used for the preparation of Example 55, substituting Example 266D for Example 54B, to provide the title compound. ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.63 (bs, 1H), 9.42 (s, 1H), 7.52 (dd, J = 2.6, 1.1 Hz, 1H), 7.34 (d, J = 2.2 Hz, 1H), 7.25 7.00 (m, 3H), 4.57 (d, J = 3.3 Hz, 1H), 2.94 (s, 3H), 2.00 (s, 3H), 1.98-1.74 (m, 8H). MS (ESI+) m/z 413.1 $(M+H)^+$.

267. N-{4-[(4,4-difluorocyclohexyl)oxy]-3-(5-methyl-6-oxo-1,6-dihydropyridin-3-yl)phenyl}ethanesulfonamide.

267A. N-(4-(4,4-difluorocyclohexyloxy)-3-(6-fluoro-5-methylpyridin-3-yl)phenyl)ethanesulfonamide. Example 267A was prepared according to the procedure used for the preparation of Example 22, substituting Example 266C for Example 20C, and substituting ethanesulfonyl chloride for methanesulfonyl chloride, respectively, to provide the title compound.

267B. N-{4-[(4,4-difluorocyclohexyl)oxy]-3-(5-methyl-6-oxo-1,6-dihydropyridin-3-yl)phenyl}ethanesulfonamide. Example 267B was prepared according to the procedure

used for the preparation of Example 55, substituting Example 267A for Example 54B, to provide the title compound. ^{1}H NMR (300 MHz, DMSO-d_6) d 11.62 (bs, 1H), 9.51 (s, 1H), 7.50 (dd, J = 2.5, 1.1 Hz, 1H), 7.33 (d, J = 2.1 Hz, 1H), 7.12 (s, 3H), 4.56 (d, J = 3.2 Hz, 1H), 3.04 (q, J = 7.4 Hz, 2H), 2.00 (s, 3H), 1.95 1.70 (m, 8H), 1.20 (t, J = 7.3 Hz, 3H). MS (ESI+) m/z 427.1 $(M+H)^+$.

268. N-{4-(2,4-difluorophenoxy)-3-[1-methyl-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-3-yl]phenyl}ethanesulfonamide. Example 268 was prepared according to the procedure used for the preparation of Example 22, substituting ethanesulfonyl chloride for methanesulfonyl chloride, and substituting Example 5E for Example 20C, respectively, to provide the title compound. ^{1}H NMR (300 MHz, DMSO-d_6) δ1H 9.82 (s, 1H), 7.93 (s, 1H), 7.46-7.34 (m, 1H), 7.34-7.12 (m, 2H), 7.13-6.95 (m, 2H), 6.85 (d, J = 8.8 Hz, 2H), 3.47 (s, 3H), 3.06 (q, J = 7.4 Hz, 2H), 1.19 (t, J = 7.3 Hz, 3H). MS (ESI+) m/z 489.1 $(M+H)^+$.

269. N-[3-(4-chloro-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-4-(2,4-difluorophenoxy)phenyl]methanesulfonamide.

269A. 5-bromo-4-chloropyridin-2-ol. 5-Bromo-4-chloropyridin-2-amine (2.01 g, 9.69 mmol) was dissolved in 75 % (v/v) sulfuric acid (40.2 ml, 566 mmol) and then chilled in an ice bath. Sodium nitrite (2.21 g, 32.0 mmol) dissolved in water (20.1 ml, 1116 mmol) was added dropwise and the reaction mixture was then stirred for 3 hours. The mixture was concentrated under reduced pressure and aqueous ammonia (15 mL) was added dropwise. The resulting white precipitate was collected via vacuum filtration and the filter cake washed with cold water (100 mL) then dried in a vacuum oven for 24 hours to give 1.94 g (95%) of the title compound.

269B. 5-bromo-4-chloro-1-methylpyridin-2(1H)-one. Example 269B was prepared according to the procedure used for the preparation of Example 1A, substituting Example 269A for 6-chloropyridazin-3(2H)-one, to provide the title compound.

269C. 5-(5-amino-2-(2,4-difluorophenoxy)phenyl)-4-chloro-1-methylpyridin-2(1H)-one. Example 269C was prepared according to the procedure used for the preparation of Example 1B, substituting Example 5D for 2-phenoxyphenylboronic acid, and Example 269B for Example 1A, respectively, to provide the title compound.

269D. N-[3-(4-chloro-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-4-(2,4-difluorophenoxy)phenyl]methanesulfonamide. Example 269D was prepared according to the procedure used for the preparation of Example 22, substituting Example 269C for Example 20C, to provide the title compound. ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.82-9.74 (m,

1H), 7.93 (s, 1H), 7.48-7.35 (m, 1H), 7.27-7.01 (m, 4H), 6.90 (d, J = 8.8 Hz, 1H), 6.65-6.44 (m, 1H), 3.46-3.41 (m, 3H), 3.01 (s, 3H). MS (ESI+) m/z 441.1 $(M+H)^+$.

270. N-[4-(2,4-difluorophenoxy)-3-(4-methoxy-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)phenyl]methanesulfonamide.

270A. 5-bromo-4-methoxy-1-methylpyridin-2(1H)-one. Example 270A was prepared according to the procedure used for the preparation of Example 18C, substituting Example 269B for Example 18B, to provide the title compound.

270B. 5-(5-amino-2-(2,4-difluorophenoxy)phenyl)-4-methoxy-1-methylpyridin-2(1H)-one. Example 270B was prepared according to the procedure used for the preparation of Example 1B, substituting Example 5D for 2-phenoxyphenylboronic acid, and Example 270A for Example 1A, respectively, to provide the title compound.

270C. N-[4-(2,4-difluorophenoxy)-3-(4-methoxy-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)phenyl]methanesulfonamide. Example 270C was prepared according to the procedure used for the preparation of Example 22, substituting 270B for Example 20C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.69 (s, 1H), 7.62 (s, 1H), 7.43-7.32 (m, 1H), 7.18 (dd, J = 8.7, 2.7 Hz, 1H), 7.15-6.97 (m, 3H), 6.88 (d, J = 8.7 Hz, 1H), 5.82 (s, 1H), 3.60 (s, 3H), 3.36 (s, 3H), 3.01 (s, 3H).

MS (ESI+) m/z 437.1 $(M+H)^+$.

271. N-[4-(2,4-difluorophenoxy)-3-(4-methoxy-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)phenyl]ethanesulfonamide. Example 271 was prepared according to the procedure used for the preparation of Example 22, substituting Example 270B for Example 20C and substituting ethanesulfonyl chloride for methanesulfonyl chloride, respectively to provide the title compound. ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.76 (s, 1H), 7.62 (s, 1H), 7.43-7.32 (m, 1H), 7.18 (dd, J = 8.7, 2.7 Hz, 1H), 7.14-6.96 (m, 3H), 6.87 (d, J = 8.7 Hz, 1H), 5.81 (s, 1H), 3.60 (s, 3H), 3.36 (s, 3H), 3.10 (q, J = 7.3 Hz, 2H), 1.22 (t, J = 7.3 Hz, 3H). MS (ESI+) m/z 451.1 $(M+H)^+$.

272. N-[4-(2,4-difluorophenoxy)-3-{4-[4-(hydroxymethyl)phenyl]-1-methyl-6-oxo-1,6-dihydropyridin-3-yl}phenyl]methanesulfonamide. Example 272 was prepared according to the procedure used for the preparation of Example 1B, substituting 4-(hydroxymethyl)phenylboronic acid for 2-phenoxyphenylboronic acid, and Example 269D for Example 1A, respectively. The reaction mixture was heated at 140°C, instead of 120°C, to provide the title compound. ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.62 (s, 1H), 7.87-7.76 (m, 1H), 7.43-7.29 (m, 1H), 7.21-6.94 (m, 6H), 6.96-6.85 (m, 1H), 6.63-6.54 (m, 1H), 6.45-6.25

(m, 1H), 6.14 (td, J = 9.2, 5.6 Hz, 1H), 4.48-4.42 (m, 2H), 3.49 (s, 3H), 2.87-2.76 (m, 3H). MS (ESI+) m/z 513.1 $(M+H)^+$.

273. N-[4-(2,4-difluorophenoxy)-3-(1-methyl-4-{4-[(4-methylpiperazin-1-yl)methyl]phenyl}-6-oxo-1,6-dihydropyridin-3-yl)phenyl]methanesulfonamide. Example 273 was prepared according to the procedure used for the preparation of Example 1B, substituting 1-methyl-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl)piperazine for 2-phenoxyphenylboronic acid, and substituting Example 269D for Example 1A, respectively. The reaction mixture was heated at 140°C, instead of 120°C, to provide the title compound. ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.66 (s, 1H), 7.83 (s, 1H), 7.41-7.28 (m, 1H), 7.20 (d, J = 8.3 Hz, 2H), 7.13 (d, J = 2.8 Hz, 1H), 7.09 (d, J = 8.7 Hz, 2H), 7.06 (dd, J = 8.9, 3.0 Hz, 1H), 6.99-6.87 (m, 1H), 6.57 (d, J = 8.7 Hz, 1H), 6.37 (s, 1H), 6.31 (td, J = 9.2, 5.8 Hz, 1H), 3.58 (m, 2H), 3.49 (s, 3H), 3.45-3.21 (m, 4H), 2.87 (s, 3H), 2.74 (s, 3H), 2.43-2.27 (m, 4H). MS (ESI+) m/z 595.1 $(M+H)^+$

274. N-[4-(2,4-difluorophenoxy)-3-{1-methyl-4-[4-(morpholin-4-yl)phenyl]-6-oxo-1,6-dihydropyridin-3-yl}phenyl]methanesulfonamide. Example 274 was prepared according to the procedure used for the preparation of Example 1B, substituting 4-morpholinophenyl boronic acid for 2-phenoxyphenylboronic acid, and substituting Example 269D for Example 1A, respectively. The reaction mixture was heated at 140 °C instead of 120 °C, to provide the title compound. ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.62 (s, 1H), 7.75 (s, 1H), 7.40-7.28 (m, 1H), 7.13 (d, J = 2.7 Hz, 1H), 7.07 (dd, J = 8.7, 2.7 Hz, 1H), 6.97 (s, 1H), 6.96-6.86 (m, 2H), 6.88-6.74 (m, 2H), 6.62 (d, J = 8.7 Hz, 1H), 6.34-6.24 (m, 2H), 3.75-3.66 (m, 4H), 3.47 (s, 3H), 3.13-3.06 (m, 4H), 2.86 (s, 3H). MS (ESI+) m/z 568.2 $(M+H)^+$

275. 5-[2-(cyclopropylmethoxy)-5-(ethylsulfonyl)phenyl]-4-methoxy-1-methylpyridin-2(1H)-one.

275A. (3-bromo-4-fluorophenyl)(ethyl)sulfane. A mixure of 3-bromo-4-fluorobenzenethiol (3.89 g, 18.8 mmol) and 5.0 M sodium hydroxide (3.95 mL, 19.7 mmol) in methanol (50 mL) was stirred at 0 °C for 10 minutes. To this solution was added iodoethane (1.80 mL, 22.5 mmol). The reaction mixture was stirred at ambient temperature for 6 hours. The solvent was removed under reduced pressure, and the residue 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 $MgSO_4$, filtered, and concentrated to provide the title compound (4.35 g, 98 % yield).

275B. 2-bromo-4-(ethylsulfonyl)-1-fluorobenzene. Example 275A (4.4 g, 18.7 mmol) in dichloromethane (300 mL) was treated with mCPBA (10.2 g, 41.2 mmol). The reaction was

stirred at ambient temperature for 6 hours. The solvent was removed under reduced pressure, and the residue was taken up into ethyl acetate and was washed with saturated aqueous $NaHCO_3$ solution (150 mL). The aqueous layer was then extracted with additional ethyl acetate three times. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by flash chromatography (silica gel, 15% ethyl acetate in hexane to afford the title compound (4.4 g, 88 % yield).

275C. 2-bromo-1-(cyclopropylmethoxy)-4-(ethylsulfonyl)benzene. Example 275C was prepared according to the procedure used for the preparation of Example 247A, substituting Example 275B for Example 225A, and substituting cyclopropylmethanol for cyclohexanol, respectively, to provide the title compound.

275D. 2-(2-(cyclopropylmethoxy)-5-(ethylsulfonyl)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane. Example 275D was prepared according to the procedure used for the preparation of Example 5D, substituting Example 275C for Example 5C, to provide the title compound.

275E. 5-[2-(cyclopropylmethoxy)-5-(ethylsulfonyl)phenyl]-4-methoxy-1-methylpyridin-2(1H)-one. Example 275E was prepared according to the procedure used for the preparation of Example 1B, substituting Example 275D for 2-phenoxyphenylboronic acid, and substituting Example 270A for Example 1A, respectively, to provide the title compound. ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.79 (dd, J = 8.6, 2.4 Hz, 1H), 7.61 (d, J = 2.4 Hz, 2H), 7.23 (d, J = 8.7 Hz, 1H), 5.89 (s, 1H), 3.93 (d, J = 6.7 Hz, 2H), 3.67 (s, 3H), 3.39 (s, 3H), 3.25 (q, J = 7.3 Hz, 2H), 1.20-1.06 (m, 4H), 0.61-0.44 (m, 2H), 0.37-0.24 (m, 2H). MS (ESI+) m/z 378.1 $(M+H)^+$.

276. 5-{2-(2,4-difluorophenoxy)-5-[(methylsulfonyl)amino]phenyl}-N,1-dimethyl-2-oxo-1,2-dihydropyridine-4-carboxamide.

276A. methyl 5-bromo-1-methyl-2-oxo-1,2-dihydropyridine-4-carboxylate. Example 276A was prepared according to the procedure used for the preparation of Example 1A, substituting methyl 5-bromo-2-hydroxyisonicotinate for 6-chloropyridazin-3(2H)-one, to provide the title compound.

276B. Methyl 5-(5-amino-2-(2,4-difluorophenoxy)phenyl)-1-methyl-2-oxo-1,2-dihydropyridine-4-carboxylate. Example 276B was prepared according to the procedure used for the preparation of Example 1B, substituting Example 5D for 2-phenoxyphenylboronic acid, and Example 276A for Example 1A, respectively, to provide the title compound.

276C. 5-(2-(2,4-difluorophenoxy)-5-(methylsulfonamido)phenyl)-1-methyl-2-oxo-1,2-dihydropyridine-4-carboxylic acid. Example 276C was prepared according to the procedure used for the preparation of Example 22, substituting Example 276B for Example 20C to provide the title compound.

276D.5-{2-(2,4-difluorophenoxy)-5-[(methylsulfonyl)amino]phenyl}-N,1-dimethyl-2-oxo-1,2-dihydropyridine-4-carboxamide. Example 276C (23 mg, 0.051 mmol) and oxalyl chloride (8.94 μL, 0.102 mmol) were combined in dichloromethane (5 mL) and 1 drop of dimethylformamide. After stirring at ambient temperature for 2 hours, the solution was concentrated under reduced pressure. The residue was treated with 2.0 N methylamine in tetrahydrofuran (0.383 mL, 0.766 mmol) and stirred at ambient temperature for 1 hour. To this mixture was ddded 1:1 brine/water (20 mL) and the mixture was extracted with ethyl acetate. The combined organics were washed with brine, dried ($MgSO_4$), filtered, and concentrated. Purification by reverse phase chromatography (C18, CH_3CN/water 0.1% TFA) afforded 18.8 mg (79 %) of the title compound. ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.67 (s, 1H), 8.39-8.32 (m, 1H), 7.78 (s, 1H), 7.46-7.34 (m, 1H), 7.17-7.00 (m, 4H), 6.73 (d, J = 8.6 Hz, 1H), 6.45 (s, 1H), 3.47 (s, 3H), 2.99 (s, 3H). MS (ESI+) m/z 464.1 $(M+H)^+$.

277. N-[4-(2,4-difluorophenoxy)-3-(4-ethoxy-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)phenyl]methanesulfonamide. Example 277 was prepared according to the procedure used for the preparation of Example 18C, substituting Example 269D for Example 18B, and substituting ethanol for methanol, respectively. Purification by flash chromatography (SiO_2, 0-2% methanol/dichloromethane gradient) afforded 25 mg (49 %) of the title compound. ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.69 (s, 1H), 7.61 (s, 1H), 7.43-7.31 (m, 1H), 7.21-7.11 (m, 2H), 7.08-6.96 (m, 2H), 6.90 (d, J = 8.6 Hz, 1H), 5.79 (s, 1H), 3.92 (q, J = 7.0 Hz, 2H), 3.35 (s, 3H), 3.00 (s, 3H), 1.14 (t, J = 6.9 Hz, 3H). MS (ESI+) m/z 451.1 $(M+H)^+$

278. N-[4-(2,4-difluorophenoxy)-3-{4-[4-(hydroxymethyl)phenyl]-1-methyl-6-oxo-1,6-dihydropyridin-3-yl}phenyl]ethanesulfonamide.

278A. N-(3-(4-chloro-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-4-(2,4-difluorophenoxy)phenyl)ethanesulfonamide. Example 278A was prepared according to the procedure used for the preparation of Example 22, substituting ethanesulfonyl chloride for methanesulfonyl chloride, and Example 269C for Example 20C, respectively to provide the title compound.

278B. N-[4-(2,4-difluorophenoxy)-3-{4-[4-(hydroxymethyl)phenyl]-1-methyl-6-oxo-1,6-dihydropyridin-3-yl}phenyl]ethanesulfonamide. Example 278B was prepared according

to the procedure used for the preparation of Example 1B, substituting 4-(hydroxymethyl)phenylboronic acid for 2-phenoxyphenylboronic acid, and substituting Example 278A for Example 1A, respectively. The reaction mixture was heated at 140 °C instead of 120 °C, to provide the title compound. ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.72-9.65 (m, 1H), 7.82-7.76 (m, 1H), 7.43-7.29 (m, 1H), 7.21-7.11 (m, 2H), 7.12-6.82 (m, 5H), 6.59 (d, J = 8.6 Hz, 1H), 6.44-6.34 (m, 1H), 6.25 (td, J = 9.3,-5.6 Hz, 1H), 4.49-4.42 (m, 2H), 3.49 (s, 3H), 2.88 (q, J = 7.3 Hz, 2H), 1.13 (t, J = 7.3 Hz, 3H). MS (ESI+) m/z 527.1 $(M+H)^+$.

279. N-[4-(2,4-difluorophenoxy)-3-(1-methyl-4-{4-[(4-methylpiperazin-1-yl)methyl]phenyl}-6-oxo-1,6-dihydropyridin-3-yl)phenyl]ethanesulfonamide. Example 279 was prepared according to the procedure used for the preparation of Example 1B, substituting 1-methyl-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl)piperazine for 2-phenoxyphenylboronic acid, and substituting Example 278A for Example 1A, respectively. The reaction mixture was heated at 140°C instead of 120°C, to provide the title compound. ^{1}H NMR (400 MHz, pyridine-d_5) δ 7.51 (d, J = 1.6 Hz, 1H) 7.43 (dd, J = 8.7, 2.7 Hz, 1H), 7.33-7.25 (m, 4H), 7.05 (ddd, J = 11.0, 8.3, 2.8 Hz, 1H), 6.90-6.81 (m, 1H), 6.73 (t, J = 4.4 Hz, 2H), 6.68 (td, J= 5.5 Hz, 2H), 3.51 (s, 3H), 3.47 (s, 2H), 3.18 (q, J = 7.3 Hz, 2H), 2.72 (m, 4H), 2.59 (m, 4H), 2.42 (s, 3H), 1.35 (t, J = 7.3 Hz, 3H). MS (ESI+) m/z 609.1 $(M+H)^+$.

280. N-[4-(2,4-difluorophenoxy)-3-(4-{4-[(dimethylamino)methyl]phenyl}-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)phenyl]ethanesulfonamide. Example 280 was prepared according to the procedure used for the preparation of Example 1B, substituting 4-((dimethylamino)methyl)phenylboronic acid for 2-phenoxyphenylboronic acid, and substituting Example 278A for Example 1A, respectively. The reaction mixture was heated at 140 °C instead of 120 °C, to provide the title compound. ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.68 (s, 1H), 9.54 (bs, 1H), 7.81 (s, 1H), 7.40-7.26 (m, 3H), 7.21-7.14 (m, 2H), 7.12 (d, J = 2.6 Hz, 1H), 7.04 (dd, J = 8.7, 2.7 Hz, 1H), 6.97-6.86 (m, 1H), 6.55 (d, J = 8.7 Hz, 1H), 6.48-6.31 (m, 2H), 4.25-4.18 (m, 2H), 3.47 (s, 3H), 2.96 (q, J = 7.3 Hz, 2H), 2.69 (d, J = 4.3 Hz, 6H), 1.14 (t, J = 7.3 Hz, 3H). MS (ESI+) m/z 554.0 $(M+H)^+$.

281. 3-chloro-1-methyl-5-(2-phenoxyphenyl)pyridin-2(1H)-one.

281A. 5-bromo-3-chloro-1-methylpyridin-2(1H)-one. Example 281A was prepared according to the procedure used for the preparation of Example 1A, substituting 5-bromo-3-chloropyridin-2(1H)-one for 6-chloropyridazin-3(2H)-one, to provide the title compound.

281B. 3-chloro-5-(2-phenoxyphenyl)pyridin-2(1H)-one. Example 281B was prepared according to the procedure used for the preparation of Example 1B, substituting Example

281A for Example 1A to provide the title compound. ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.98 (d, J = 2.4 Hz, 1H), 7.93 (d, J = 2.4 Hz, 1H), 7.51 (dd, J = 7.6, 1.8 Hz, 1H), 7.43-7.29 (m, 3H), 7.25 (td, J = 7.5, 1.3 Hz, 1H), 7.15-7.05 (m, 1H), 7.01-6.91 (m, 3H), 3.54 (s, 3H). MS (ESI+) m/z 312.3 $(M+H)^+$.

282. N-[3-(5-chloro-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-4-(2,4-difluorophenoxy)phenyl]methanesulfonamide.

282A. 5-(5-amino-2-(2,4-difluorophenoxy)phenyl)-3-chloro-1-methylpyridin-2(1H)-one. Example 282A was prepared according to the procedure used for the preparation of Example 1B, substituting Example 5D for 2-phenoxyphenylboronic acid, and substituting Example 281A for Example 1A, respectively, to provide the title compound.

282B. N-(3-(5-chloro-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-4-(2,4-difluorophenoxy)phenyl)methanesulfonamide. Example 282B was prepared according to the procedure used for the preparation of Example 22, substituting Example 282A for Example 20C, to provide the title compound. ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.70 (s, 1H), 7.97 (d, J = 2.4 Hz, 1H), 7.92 (d, J = 2.4 Hz, 1H), 7.50-7.39 (m, 1H), 7.31-7.12 (m, 3H), 7.13-7.02 (m, 1H), 6.88 (d, J = 8.7 Hz, 1H), 3.56 (s, 3H),3.02 (s, 3H). MS (ESI+) m/z 441.1 $(M+H)^+$.

283. N-[3-(5-chloro-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-4-(2,4-difluorophenoxy)phenyl]ethanesulfonamide. Example 283 was prepared according to the procedure used for the preparation of Example 22, substituting Example 282A for Example 20C and substituting ethanesulfonyl chloride for methanesulfonyl chloride, respectively, to provide the title compound. ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.78 (s, 1H), 7.98-7.88 (m, 2H), 7.50-7.39 (m, 1H), 7.28-7.12 (m, 3H), 7.13-7.02 (m, 1H), 6.87 (d, J = 8.7 Hz, 1H), 3.56 (s, 3H), 3.12 (q, J = 7.3 Hz, 2H), 1.22 (t, J = 7.3 Hz, 3H). MS (ESI+) m/z 455.1 $(M+H)^+$.

284. N-[4-(2,4-difluorophenoxy)-3-{1-methyl-4-[4-(morpholin-4-yl)phenyl]-6-oxo-1,6-dihydropyridin-3-yl}phenyl]ethanesulfonamide. Example 284 was prepared according to the procedure used for the preparation of Example 1B, substituting 4-morpholinophenyl boronic acid for 2-phenoxyphenylboronic acid, and substituting Example 278A for Example 1A, respectively. The reaction mixture was heated at 140 °C instead of 120 °C, to provide the title compound. ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.67 (s, 1H), 7.75 (s, 1H), 7.40-7.28 (m, 1H), 7.13 (d, J = 2.7 Hz, 1H), 7.07 (dd, J = 8.7, 2.7 Hz, 1H), 6.97 (s, 1H), 6.96-6.86 (m, 2H), 6.88-6.74 (m, 2H), 6.62 (d, J = 8.7 Hz, 1H), 6.34-6.24 (m, 2H), 3.75-3.66 (m, 4H), 3.46 (s, 3H), 3.13-3.06 (m, 4H), 2.88 (q, J = 7.46 Hz, 2H), 1.12 (t, J = 7.46 Hz, 3H). MS (ESI+) m/z 582.2 $(M+H)^+$.

Example 285. N-[4-(2,4-difluorophenoxy)-3-(4-ethoxy-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)phenyl]ethanesulfonamide. A mixture of Example 278a (0.050 g, 0.110 mmol) and sodium ethoxide (0.187 g, 2.75 mmol) in ethanol (2 mL) was heated at 65 °C for 72 hours. The reaction mixture was cooled to ambient temperature and quenched with water. The mixture was extracted with ethyl acetate, and the organic layer was washed with saturated aqueous sodium chloride, dried over anhydrous magnesium sulfate, filtered, and evaporated. The residue was purifed by flash chromatography (silica gel, 0-2% methanol/dichloromethan gradient) to provide the title compound (0.025 g, 49% yield). ^{1}H NMR (300 MHz, DMSO- d_6) δ 9.75 (s, 1H), 7.60 (s, 1H), 7.36 (ddd, J = 11.2, 8.7, 2.7 Hz, 1H), 7.17 (dd, J = 8.7, 2.7 Hz, 1H), 7.12 (d, J = 2.7 Hz, 1H), 7.05-6.94 (m, 2H), 6.88 (d, J = 8.7 Hz, 1H), 5.78 (s, 1H), 3.90 (q, J = 7.0 Hz, 2H), 3.34 (s, 1H), 3.10 (q, J = 7.0 Hz, 2H), 1.21 (t, J = 7.3 Hz, 3H), 1.13 (t, J = 6.9 Hz, 3H).. MS (ESI+) m/z 465.1 $(M+H)^+$.

Example 286. *N*-[4-(2,4-difluorophenoxy)-3-{1-methyl-4-[2-(morpholin-4-yl)ethoxy]-6-oxo-1,6-dihydropyridin-3-yl}phenyl]ethanesulfonamide. To a slurry of sodium hydride (16.23 mg, 0.440 mmol) in anhydrous dioxane (2 mL) was added portion-wise 2-morpholinoethanol (0.040 mL, 0.327 mmol), and the suspension was stirred for 30 minutes. Example 278a (50 mg, 0.110 mmol) was added and the mixture waa stirred for 2 hours at 75 °C. The mixture was cooled to ambient temperature, cold water (10 mL) was added and the reaction mixture was extracted with ethyl acetate. The combined organic phase was washed with brine, dried (anhydrous $MgSO_4$), filtered, and concentrated under reduced pressure. Purification by reverse phase HPLC (C18, CH_3CN/water (0.1%TFA), 0-100%) afforded the title compound (17 mg, 28% yield). ^{1}H NMR (300 MHz, DMSO- d_6) δ 9.81 (s, 1H), 7.65 (s, 1H), 7.39-7.31 (m, 1H), 7.21 7.10 (m, 2H), 7.04-6.91 (m, 3H), 5.93 (s, 1H), 4.26 (t, J = 4.6 Hz, 2H), 4.21-3.55 (m, 6H), 3.34 (s, 3H), 3.28 2.85 (m, 6H), 1.22 (t, J = 7.3 Hz, 3H). MS (ESI+) m/z 550.1 $(M+H)^+$.

Example 287. N-(3-(4-(cyclopropylmethoxy)-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-4-(2,4-difluorophenoxy)phenyl)ethanesulfonamide. Example 287 was prepared according to the procedure used for the preparation of Example 286, substituting cyclopropylmethanol for 2-morpholinoethanol. ^{1}H NMR (300 MHz, DMSO- d_6) δ 9.78 (s, 1H), 7.60 (s, 1H), 7.41-7.32 (m, 1H), 7.19 (dd, J = 8.7, 2.7 Hz, 1H), 7.15 (d, J = 2.7 Hz, 1H), 7.12-6.94 (m, 2H), 6.91 (d, J = 8.7 Hz, 1H), 5.77 (s, 1H), 3.73 (d, J = 6.8 Hz, 2H), 3.34 (s, 3H), 3.11 (q, J = 7.3 Hz, 2H), 1.22 (t, J = 7.3 Hz, 3H), 1.17-1.00 (m, 1H), 0.50-0.39 (m, 2H), 0.27-0.15 (m, 2H). MS (ESI+) m/z 491.0 $(M+H)^+$.

Example 288. N-(4-(2,4-difluorophenoxy)-3-(4-(2-(dimethylamino)ethoxy)-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)phenyl)ethanesulfonamide. Example 288 was prepared according to the procedure used for the preparation of Example 286, substituting 2-(dimethylamino)ethanol for 2-morpholinoethanol. ^{1}H NMR (300 MHz, DMSO- d_6) δ 9.78 (s, 1H), 7.66 (s, 1H), 7.22 7.12 (m, 2H), 7.07-6.92 (m, 3H), 6.92 (s, 1H), 5.95 (s, 1H), 4.25 (t, J = 4.8 Hz, 2H), 3.35 (s, 3H), 3.11 (q, J = 7.3 Hz, 2H), 2.71-2.65 (m, 6H), 1.23 (t, J = 7.3 Hz, 3H). MS (ESI+) m/z 508.0 $(M+H)^+$.

Example 289. *N*-{4-(2,4-difluorophenoxy)-3-[1-methyl-6-oxo-4-(propan-2-yloxy)-1,6-dihydropyridin-3-yl]phenyl}ethanesulfonamide. Example 289 was prepared according to the procedure used for the preparation of Example 286, substituting propan-2-ol for 2-morpholinoethanol. ^{1}H NMR (300 MHz, DMSO- d_6) δ 9.76 (s, 1H), 7.59 (s, 1H), 7.37 (ddd, J = 11.4, 8.7, 2.7 Hz, 1H), 7.20 7.11 (m, 2H), 7.07-6.93 (m, 2H), 6.91 (d, J = 8.5 Hz, 1H), 5.80 (s, 1H), 4.59 4.51 (m, J = 6 Hz, 1H), 3.34 (s, 3H), 3.11 (q, J = 7.3 Hz, 2H), 1.21 (d, J = 7.3 Hz, 3H), 1.18-1.05 (d, J = 6 Hz, 6H). MS (ESI+) m/z 479.0 $(M+H)^+$.

Example 290. *N*-{4-(2,4-difluorophenoxy)-3-[1-methyl-4-(2-methylpropoxy)-6-oxo-1,6-dihydropyridin-3-yl]phenyl}ethanesulfonamide. Example 290 was prepared according to the procedure used for the preparation of Example 286, substituting 2-methylpropan-1-ol for 2-morpholinoethanol. ^{1}H NMR (300 MHz, DMSO- d_6) δ 9.77 (s, 1H), 7.58 (s, 1H), 7.38-7.17 (m, 2H), 7.13 (d, J = 2.7 Hz, 1H), 7.03-6.92 (m, 2H), 6.87 (td, J = 9.1, 5.6 Hz, 1H), 5.76 (s, 1H), 3.62 (d, J = 6.4 Hz, 2H), 3.33 (s, 3H), 3.07 (q, J = 7.3 Hz, 2H), 1.93-1.76 (m, 1H), 1.20 (t, J = 7.3 Hz, 3H), 0.81 (d, J = 6.7 Hz, 6H). MS (ESI+) m/z 493.0 $(M+H)^+$.

Example 291. *N*-{4-(2,4-difluorophenoxy)-3-[1-methyl-6-oxo-4-(tetrahydrofuran-3-ylmethoxy)-1,6-dihydropyridin-3-yl]phenyl}ethanesulfonamide. Example 291 was prepared according to the procedure used for the preparation of Example 286, substituting (tetrahydrofuran-3-yl)methanol for 2-morpholinoethanol. ^{1}H NMR (300 MHz, DMSO- d_6) δ 9.78 (s, 1H), 7.59 (s, 1H), 7.39-7.28 (m, 1H), 7.21 (dd, J = 8.7, 2.7 Hz, 1H), 7.12 (d, J = 2.7 Hz, 1H), 7.03-6.84 (m, 3H), 5.82 (s, 1H), 3.89-3.74 (m, 2H), 3.65 3.53 (m, 4H), 3.33 (s, 3H), 3.09 (q, J = 7.3 Hz, 2H), 2.50 (m, 1H), 1.93 1.78 (m, 1H), 1.61 1.47 (m, 1H), 1.21 (t, J = 7.3 Hz, 3H). MS (ESI+) m/z 521.0 $(M+H)^+$.

Example 292. *N*-[4-(2,4-difluorophenoxy)-3-(1-methyl-6-oxo-4-propoxy-1,6-dihydropyridin-3-yl)phenyl]ethanesulfonamide. Example 292 was prepared according to the procedure used for the preparation of Example 286, substituting propan-1-ol for 2-morpholinoethanol. ^{1}H NMR (300 MHz, DMSO- d_6) δ 9.76 (s, 1H), 7.59 (s, 1H), 7.40-7.26 (m, 1H), 7.19 (dd, J = 8.7, 2.7 Hz, 1H), 7.13 (d, J = 2.7 Hz, 1H), 7.04-6.83 (m, 3H), 5.78 (s,

1H), 3.89-3.72 (t, J = 7.3 Hz, 2H), 3.46 (s, 3H), 3.24-2.97 (q, J = 7.3 Hz, 2H), 1.69-1.41 (sextet, J = 7.3 Hz, 2H), 1.30-1.12 (t,J = 7.3 Hz, 3H), 0.90-0.72 (t, J = 7.3 Hz, 3H). MS (ESI+) m/z 479.0 $(M+H)^+$.

Example 293. *N*-{4-(2,4-difluorophenoxy)-3-[1-methyl-6-oxo-4-(2,2,2-trifluoroethoxy)-1,6-dihydropyridin-3-yl]phenyl}ethanesulfonamide. Example 293 was prepared according to the procedure used for the preparation of Example 286, substituting 2,2,2-trifluoroethanol for 2-morpholinoethanol. ^{1}H NMR (300 MHz, DMSO- d_6) δ 9.77 (s, 1H), 7.69 (s, 1H), 7.41-7.30 (m, 1H), 7.20 (dd, J = 8.7, 2.7 Hz, 1H), 7.13 (d, J = 2.7 Hz, 1H), 7.05-6.86 (m, 3H), 6.03 (s, 1H), 4.70 (q, J = 8.8 Hz, 2H), 3.37 (s, 3H), 3.07 (q, J = 7.3 Hz, 2H), 1.20 (t, J = 7.3 Hz, 3H). MS (ESI+) m/z 519.0 $(M+H)^+$.

Biological Examples

Bromodomain domain binding assay

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.

Synthesis of Alexa647-labeled bromodomain inhibitor compound 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._Methyl 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)acetate (see e.g., WO 2006129623)(100.95 mg, 0.243 mmol was suspended in 1 mL methanol to which was added 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 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 purified product were lyophilized to afford 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) (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 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-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 1X 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 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 equation to obtain IC_{50}s. Inhibition constants (K_i) were calculated from the IC_{50}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 < 3. The K_i 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^{o} and an atmosphere of 5% CO_2. For compound testing, MX-1 cells were plated in 96-well black bottom plates at a density of 5000 cells/well in 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 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 cells and analyzed using the GraphPad Prism software with sigmoidal curve fitting to

obtain EC_{50}s. 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. The EC_{50} values are reported in Table 1 for the indicated compounds.

Table 1

Example #	TR-FRET Binding K_i: BRD4 (BDI_K57-E168) (μM)	TR-FRET Binding K_i: BRD4 (BDII_E352-M457) (μM)	Cellular proliferation: EC_{50} (μM)
1	3.16	2.48	20.0
2	11.70	2.86	13.5
3	0.988	4.83	N/A
4	2.99	8.53	N/A
5	0.922	0.688	>3
6	5.24	4.54	N/A
7	1.97	10.40	N/A
8	8.59	17.80	N/A
9	10.50	9.26	N/A
10	2.44	1.50	3.7
11	4.04	4.37	9.46
12	0.721	0.895	2.66
13	13.10	10.20	N/A
14	2.55	1.22	11.5
15	17.80	16.30	N/A
16	1.110	8.42	5.9
17	0.513	4.52	2.63
18	3.51	0.555	4.3
19	8.85	8.58	N/A
20	2.70	0.524	7.16
21	0.346	0.116	1.34
22	0.258	0.052	0.73
23	0.536	0.315	3.8
24	0.326	0.108	1.01
25	0.097	0.013	0.45
26	0.569	0.104	0.80
27	0.296	0.079	0.72
28	1.11	0.364	7.62

29	3.49	0.950	4.53
30	4.85	1.33	12.9
31	0.238	0.047	0.42
32	5.320	12.20	N/A
33	3.000	2.29	4.1
34	8.62	6.34	N/A
35	4.38	1.67	N/A
36	5.97	4.73	N/A
37	1.73	1.790	10.0
38	6.350	6.83	N/A
39	3.67	15.47	N/A
40	10.71	20.59	N/A
41	12.90	20.30	N/A
42	12.60	>22.2	N/A
43	5.82	>22.2	N/A
44	2.71	5.110	N/A
45	5.67	11.10	N/A
46	4.39	18.00	N/A
47	5.28	>22.2	N/A
48	9.44	1.08	N/A
49	6.68	0.748	7.11
50	2.91	2.94	9.52
51	11.60	6.60	N/A
52	9.00	10.50	N/A
53	11.50	14.30	N/A
54	4.12	0.356	4.24
55	6.89	0.778	13.7
56	3.09	0.739	10.4
57	0.598	0.250	1.86
58	0.264	0.064	0.444
59	9.79	2.11	30.0
60	0.170	0.413	3.0
61	0.048	0.050	0.911
62	0.007	0.005	0.281
63	0.085	0.024	0.739
64	0.448	0.507	N/A
65	0.797	0.140	N/A
66	0.141	0.159	2.48
67	0.071	0.093	1.73

68	0.063	0.072	1.11
69	0.098	0.225	3.0
70	0.089	0.062	0.815
71	0.062	0.133	0.398
72	0.225	0.128	3.75
73	0.462	0.307	1.13
74	0.632	1.050	N/A
75	0.264	0.195	1.39
76	0.755	1.280	N/A
77	0.511	0.380	N/A
78	0.435	0.211	>3
79	0.126	0.088	1.87
80	0.708	0.439	N/A
81	1.12	0.733	>3
82	4.07	2.48	N/A
83	3.61	6.83	N/A
84	1.02	1.01	N/A
85	1.61	0.791	N/A
86	>13	2.74	N/A
87	2.01	3.09	N/A
88	6.79	4.44	N/A
89	8.10	3.89	N/A
90	4.55	2.33	N/A
91	1.62	0.714	N/A
92	0.770	0.455	1.13
93	>13	3.24	N/A
94	0.402	0.154	N/A
95	0.172	0.145	>3
96	8.33	13.40	N/A
97	0.561	0.176	N/A
98	0.216	0.071	0.639
99	0.142	0.059	0.558
100	0.143	0.072	>3
101	0.233	0.150	1.13
102	2.60	0.960	N/A
103	0.253	0.109	>3
104	1.60	0.562	N/A
105	0.516	0.115	3.0
106	0.176	0.925	N/A

107	1.76	2.580	N/A
108	0.410	0.327	N/A
109	1.26	1.530	N/A
110	>13	13.50	N/A
111	2.47	1.970	N/A
112	0.138	0.181	1.28
113	0.407	0.317	N/A
114	0.328	0.184	N/A
115	11.10	6.940	N/A
116	1.05	0.553	N/A
117	1.49	0.619	N/A
118	>13	17.20	N/A
119	0.135	0.064	0.615
120	0.611	1.19	N/A
121	1.120	2.96	N/A
122	8.560	4.52	N/A
123	7.260	1.17	N/A
124	8.120	17.70	N/A
125	>13	16.00	N/A
126	9.34	>22.2	N/A
127	0.256	0.164	3.0
128	1.640	0.376	N/A
129	0.520	0.264	N/A
130	>13	17.10	N/A
131	6.39	0.410	N/A
132	>13	8.05	N/A
133	0.782	0.159	N/A
134	4.32	4.06	N/A
135	0.604	0.411	N/A
136	4.33	6.70	N/A
137	3.26	1.17	N/A
138	9.04	3.44	N/A
139	1.52	1.24	N/A
140	>13	8.21	N/A
141	0.526	0.297	N/A
142	2.40	1.730	N/A
143	3.20	5.470	N/A
144	9.24	3.370	N/A
145	>13	10.20	N/A

146	>13	12.20	N/A
147	0.281	0.205	N/A
148	>13	19.70	N/A
149	0.213	0.259	0.384
150	0.471	0.411	N/A
151	0.400	0.258	N/A
152	6.62	7.270	N/A
153	5.96	3.090	N/A
154	11.90	5.940	N/A
155	5.52	6.900	N/A
156	>13	13.100	N/A
157	5.51	4.750	N/A
158	0.800	0.627	N/A
159	5.45	8.420	N/A
160	8.54	10.200	N/A
161	0.026	0.025	0.244
162	0.109	0.075	N/A
163	1.99	0.366	N/A
164	8.65	0.990	N/A
165	0.567	0.492	N/A
166	0.705	1.010	N/A
167	5.43	7.370	N/A
168	1.07	0.993	N/A
169	0.599	0.562	N/A
170	1.67	1.620	N/A
171	0.253	0.215	N/A
172	0.572	0.593	N/A
173	0.805	0.545	N/A
174	0.854	0.764	N/A
175	2.95	2.490	N/A
176	3.66	2.080	N/A
177	4.17	1.070	N/A
178	3.34	4.540	N/A
179	0.923	0.488	N/A
180	0.045	0.068	0.372
181	3.95	6.160	N/A
182	0.691	0.358	N/A
183	0.256	0.166	N/A
184	2.14	1.960	N/A

185	1.04	0.438	N/A
186	1.32	0.854	N/A
187	4.95	2.250	N/A
188	0.670	1.130	N/A
189	3.14	1.480	N/A
190	6.56	2.420	N/A
191	0.386	0.239	1.43
192	1.04	0.395	N/A
193	0.167	1.010	1.29
194	1.52	1.430	N/A
195	0.664	0.317	N/A
196	1.08	0.670	N/A
197	1.06	0.725	N/A
198	0.282	0.092	N/A
199	>13	5.660	N/A
200	0.344	0.971	N/A
201	2.41	1.710	N/A
202	0.227	0.251	N/A
203	3.51	1.520	N/A
204	1.02	1.960	N/A
205	2.83	2.970	N/A
206	0.412	0.672	N/A
207	7.02	11.800	N/A
208	0.901	1.510	N/A
209	5.49	11.680	N/A
210	9.87	15.200	N/A
211	2.15	1.520	N/A
212	0.090	0.117	N/A
213	>13	15.200	N/A
214	>13	10.400	N/A
215	11.50	11.800	N/A
216	0.719	0.462	N/A
217	9.81	2.40	N/A
218	1.58	1.25	9.7
219	7.25	0.308	5.5
220	24.30	1.91	16.4
221	1.30	0.539	7.2
222	7.41	2.80	N/A
223	0.635	0.623	4.81

224	0.048	0.113	0.208
225	0.152	0.107	10.0
226	0.271	1.13	10.0
227	0.157	0.420	3.0
228	0.142	0.154	3.0
229	0.032	0.022	0.507
230	0.056	0.048	0.395
231	0.045	0.539	0.911
232	0.028	0.101	0.357
233	0.019	0.110	0.423
234	0.021	0.216	1.29
235	0.048	0.017	0.238
236	0.014	0.082	0.501
237	0.016	0.227	1.38
238	0.029	0.050	0.643
239	0.033	0.040	0.138
240	0.037	0.136	0.285
241	0.035	0.027	0.181
242	0.045	0.338	0.556
243	0.115	0.257	0.279
244	0.116	0.282	0.481
245	0.079	0.439	1.01
246	0.043	0.132	0.238
247	0.022	0.194	0.425
248	0.156	4.570	0.488
249	0.086	0.701	>3
250	0.143	12.50	3.0
251	0.197	0.260	1.1
252	0.297	0.695	3.0
253	0.942	3.29	3.0
254	0.324	3.27	N/A
255	0.635	0.142	3.0
256	0.219	0.094	1.06
257	0.018	0.032	0.173
258	0.730	0.382	1.51
259	0.029	0.009	0.13
260	0.243	0.425	2.35
261	0.026	0.066	0.387
262	0.078	0.290	0.783

263	0.049	0.121	0.304
264	0.034	0.055	0.176
265	0.132	0.172	1.72
266	0.058	0.341	>3
267	0.048	0.101	>3
268	0.483	0.095	0.579
269	0.246	0.204	N/A
270	0.027	0.018	0.138
271	0.011	0.0033	0.047
272	0.017	0.0046	0.167
273	0.005	0.0025	0.107
274	0.025	0.006	0.077
275	0.056	0.119	0.223
276	0.916	0.570	N/A
277	0.011	0.005	0.048
278	0.008	0.0014	0.063
279	0.003	0.0013	0.045
280	0.004	0.0017	0.038
281	0.150	0.509	1.65
282	0.020	0.100	N/A
283	0.017	0.039	0.194
284	0.006	0.0018	N/A
285	0.005	0.0012	0.024
286	0.083	0.076	>3
287	0.007	0.0022	0.060
288	0.190	0.551	N/A
289	0.015	0.0024	0.077
290	0.012	0.0032	0.138
291	0.016	0.0063	0.112
292	0.005	0.0017	0.045
293	0.037	0.0060	0.106

N/A means not determined.

Proliferation panel assay.

The compounds of Examples 224 and 261 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 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 EC_{50} for the compounds of Examples 224 and 261 and reported in Table 2.

Table 2

Cell line Type	Cell Line	Compound of Example 224	Compound of Example 261
		Cellular Proliferation EC_{50} (μM)	Cellular Proliferation EC_{50} (μM)
AML	Raji	0.129	0.134
AML	SKM1	0.116	0.135
Bladder	EJ-1	1.593	1.159
Breast	MDAMB231	0.72	0.46
Breast	MDAMB453	0.32	0.34
Colon	DLD-1	0.85	0.62
Colon	GEO	0.55	0.67
Glioblastoma	D54MG	0.423	0.338
Head & Neck	FaDu	0.28	0.27
Hepatocellular	HepG2	0.486	0.51
Melanoma	A-375	0.430	0.498
Multiple Myeloma	NCI-H929	0.109	0.098
Multiple Myeloma	OPM2	0.050	0.055
Multiple Myeloma	RPMI-8226	0.279	0.305
NHL	Ly18	0.52	0.51
NHL	Ramos	0.37	0.39
NSCLC	H1299	0.75	0.74
NSCLC	H1975	0.38	0.47
NSCLC	H460	0.11	0.31
Pancreas	BxPC3FP5	0.23	0.23
Pancreas	HPAC	0.38	0.50
Prostate	PC3M	1.45	1.40
RCC	786-0	0.273	0.250
Sarcoma	SK-LMS-1	0.448	0.348

LPS (lipopolysaccharide) induced IL-6 production mouse assay

Compounds of the Examples listed in Table 3 were assayed for their ability to inhibit LPS (lipopolysaccharide) induced IL-6 production in mice. Severe combined immunodeficient female mice (8 per group) received an intraperitoneal challenge of lipopolysaccharide (2.5 mg/kg, L2630 E.coli 0111:B4) one hour after oral administration of

compounds. Mice were euthanized 2 hours after lipopolysaccharide 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 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 (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 3 all exhibited a p value less than 0.05.

Table 3

Inhibition of LPS induced IL-6 production

Compound of Example #	% inhibition
22	53.9 at 50 mg/kg
233	75.9 at 30 mg/kg
235	58.7 at 30 mg/kg
240	72.6 at 30 mg/kg
241	73.9 at 3 mg/kg
257	49.7 at 30 mg/kg
261	42.2 at 30 mg/kg
270	68.8 at 3 mg/kg
271	76.9 at 3 mg/kg
285	84.0 at 3 mg/kg
292	58.0 at 3 mg/kg

Xenograft tumor growth inhibition assay

The effect of example compounds to inhibit growth of human tumor xenografts implanted in mice was evaluated. Briefly, cells obtained from culture (MV4-11 and OPM-2) or tumor brie (MX-1) were suspended in cell culture medium (MEM, Suspension, no Calcium, no Glutamine, Life Technologies Corporation) containing Matrigel (phenol red free, Becton Dickinson Biosciences Discovery Labware) and inoculated subcutaneously (approximately 5 million per site) into the right hind flank of SCID-beige (MV4-11 and OPM-2) or SCID (MX-1) female mice (Charles Rivers Labs) on study day 0. Administration of compound formulated in 2% EtOH, 5% Tween-80, 20% PEG-400, 73% HPMC (Example

240, OPM-2 and MX-1) or 5% DMSO, 5% ETOH, 30% PEG400,60% Phosal 53 (Example 240, MV4-11 and Examples 290 and 271, OPM-2) was initiated at the time of size match.

Tumors were measured with 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, mm^3; L: length, mm. W: width, mm). Tumor volume was measured throughout the treatment period or until the mean tumor volume in each group reached an endpoint of >1000 mm^3. Results are shown in Tables 4, 5, and 6.

Table 4 - MX-1 human breast cancer xenograft model

Treatment	Dose route, regimen	%TGI[a]	% TGD[b]
Compound of Example 240	30 mg/kg/day PO, QDx14	61***	51***
Compound of Example 240	10 mg/kg/day PO, QDx14	55***	35**
Compound of Example 240	3 mg/kg/day PO, QDx14	40*	20

a. Tumor growth inhibition, %TGI = 100 - mean tumor volume of treatment group / mean tumor volume of control group x 100. Dosing began on study day 12. The p values (as indicated by asterisks) are derived from Student's T test comparison of treatment group vs. control group based on tumor volumes on study day 27. *$p<0.05$, ** $p<0.01$, *** $p<0.001$.

b. Tumor growth delay, %TGD = (T – C) / C x 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 mm^3. *$p<0.05$, ** $p<0.01$, *** $p<0.001$.

Table 5 - MV4-11 human AML xenograft model

Treatment	Dose route, regimen	% TGI[a]
Compound of Example 240	3 mg/kg/day PO, QDx14	0
Compound of Example 240	10 mg/kg/day PO, QDx14	23
Compound of Example 240	30 mg/kg/day PO, QDx14	65[b]**

a. Tumor growth inhibition, %TGI = 100 - mean tumor volume of treatment group / mean tumor volume of control group x 100. Dosing began on study day 18. The p values (as indicated by asterisks) are derived from Student's T test comparison of treatment group vs. control group based on tumor volumes on study day 31. ** p<0.01.

b. 23% loss in body weight.

Table 6 - OPM-2 human multiple myeloma cancer xenograft model

Treatment	Dose route, regimen	% TGI [a]	% TGD [b]
Compound of Example 240	30 mg/kg/day PO, QDx14	36**	113**
Compound of Example 270	10 mg/kg/day PO, QDx21	60	59**
Compound of Example 270	3 mg/kg/day PO, QDx21	42*	17
Compound of Example 271	3 mg/kg/day PO, QDx21	73*	93***
Compound of Example 271	1 mg/kg/day PO, QDx21	66*	51***

a. Tumor growth inhibition, %TGI = 100 - mean tumor volume of treatment group / mean tumor volume of control group x 100. Dosing began on study day 17 (Example 240) or 18 (Example 270 and 271). The p values (as indicated by asterisks) are derived from Student's T test comparison of treatment group vs. control group based on tumor volumes on study day 38 (Example 270) or 35 (Examples 270 and 271). *p<0.05, ** p<0.01, *** <0.001.

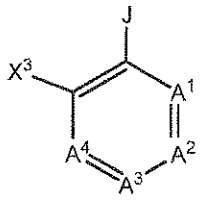
b. Tumor growth delay, %TGD = (T – C) / C x 100, where T = median time to endpoint of treatment group and C = median time to endpoint of control group. The p values (as indicated by asterisks) derived from Kaplan Meier log-rank comparison of treatment group vs. treatment control group based on an endpoint of 1000 mm^3. *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.

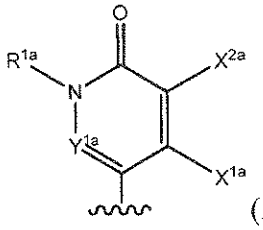
CLAIMS:

1. A compound of formula (I), or a pharmaceutically acceptable salt thereof:

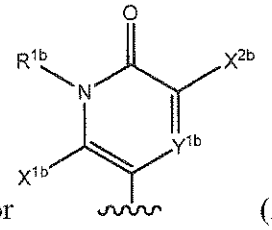


I

Wherein J is a group of formula IIa or IIb:



(IIa) or



(IIb);

wherein

R^{1a} is C_1-C_3 alkyl, C_2-C_3 alkylene-OH, or C_1-C_3 haloalkyl;

Y^{1a} is N or CR^{xa}, wherein R^{xa} is H, halo, C_1-C_3 alkyl, -O-C_1-C_3 alkyl, C_1-C_3 haloalkyl, -O-C_1-C_3 haloalkyl, aryl, aryl-C_1-C_3alkylene-OH, aryl-C_1-C_3alkylene-heterocycloalkyl, $C(O)NR^{10}R^{12}$, wherein heterocycloalkyl of aryl-C_1-C_3alkylene-heterocycloalkyl may be substituted with one to three C_1-C_3alkyl,

R^{1b} is H, C_1-C_3 alkyl, C_2-C_3 alkylene-OH, or C_1-C_3 haloalkyl;

Y^{1b} is N or CR^{xb}, wherein R^{xb} is heteroaryl, H, halo, C_1-C_3 alkyl, -O-C_1-C_3 alkyl, C_1-C_3 haloalkyl, -O-C_1-C_3 haloalkyl, aryl, aryl-C_1-C_3alkylene-OH, aryl-C_1-C_3alkylene-heterocycloalkyl, $C(O)NR^{10}R^{12}$, wherein heterocycloalkyl of aryl-C_1-C_3alkylene-heterocycloalkyl may be substituted with one to three C_1-C_3alkyl; wherein said heteroaryl may be substituted with one to three groups selected from the group consisting of: C_1-C_6 alkyl, C_1-C_3alkylene-aryl, C_1-C_3alkylene-heteroaryl, C_1-C_3alkylene-heterocycloalkyl, COOH, and COO-C_1-C_4alkyl,

X^{2a} is selected from the group consisting of: H, $-NR^{10}R^{12}$, halo, OH, -O-C_1-C_4 alkyl, aryl, heteroaryl, and $-NR^{10}C(O)$-C_1-C_4 alkyl;

X^{2b} is C_1-C_3 alkyl, C_2-C_3 alkylene-OH, or C_1-C_3 haloalkyl;

X^{1a} and X^{1b} are each selected from the group consisting of: hydrogen, halo, C_1-C_6 alkyl, C_1-C_4 haloalkyl, -O-C_1-C_4 alkyl, -O-C_1-C_6 cycloalkyl, -O-C_1-C_3

alkylene-C_3-C_7 cycloalkyl, -O-C_1-C_4 haloalkyl, -O-C_1-C_3 alkylene-heterocycloalkyl, -O-C_1-C_6 alkylene-OH , -O-C_1-C_6 alkylene-$N(R^{10})_2$ -O-C_1-C_3 alkylene-C(O)O-C_1-C_4 alkyl, -NR^{10}-C_1-C_6 alkyl, -NR^{10}-C_1-C_6 haloalkyl, -NR^{10}-C(O)OC_1-C_6 alkyl, -NR^{10}-C(O)OC_1-C_6 haloalkyl, -NR^{10}-C(O)$NR^{10}R^{12}$, -NR^{10}-SO_2R^{12}, -NR^{10}-C_3-C_7 cycloalkyl, -O-C_1-C_3 alkylene-C(O)O-C_1-C_4 alkyl, -NR^{10}-C_1-C_6 alkyl, -NR^{10}-C_1-C_6 haloalkyl, -NR^{10}-C_1-C_3 alkylene-C_3-C_7 cycloalkyl, C_1-C_4 alkylene-OH, -C_1-C_3 alkylene-C(O)O C_1-C_4 alkyl, C_1-C_3 alkylene-NR^{10}C(O)-C_1-C_4 alkyl, -C_1-C_3 alkylene-C(O)$NR^{10}R^{12}$, -C_2-C_4 alkenylene-C(O)-O-C_1-C_4 alkyl, -C(O)-C_1-C_4 alkyl, C(O)O-C_1-C_4 alkyl, C(O)$NR^{10}R^{12}$, -NR^{10}C(O)-C_1-C_4 alkyl, -$NR^{10}SO_2$-C_1-C_4 alkyl, -NR^{10}-C_1-C_3 alkylene-C(O)-C_1-C_4 alkyl, -NR^{10}-C_1-C_3 alkylene-C(O)O-C_1-C_4 alkyl, -$SO_2NR^{10}R^{12}$, and any of groups i-v:

i) C_3-C_{14} cycloalkyl, which may be substituted with 1 to 3 of R^2, where R^2 is selected from the group consisting of: halo, oxo, CN, -O-C_1-C_4 alkyl, -O-C_1-C_4 haloalkyl, -$NR^{10}R^{12}$, C(O)$NR^{10}R^{12}$, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C(O)-C_1-C_4 alkyl, -C(O)O-C_1-C_4 alkyl, $SO_2NR^{10}R^{12}$, SO_2-C_1-C_4 alkyl, and aryl, wherein said aryl may be substituted with 1 to 3 substituents independently selected from group consisting of: halo, C_1-C_3 alkyl, C(O)-C_1-C_3alkyl, C(O)OH, C(O)$NR^{10}R^{12}$, and heteroaryl;

ii) heterocycloalkenyl, which may be substituted with 1 to 3 of R^2, where R^2 is selected from the group consisting of: halo, oxo, CN, -O-C_1-C_4 alkyl, -O-C_1-C_4 haloalkyl, -$NR^{10}R^{12}$, C(O)$NR^{10}R^{12}$, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C(O)-C_1-C_4 alkyl, -C(O)O-C_1-C_4 alkyl, $SO_2NR^{10}R^{12}$, SO_2-C_1-C_4 alkyl, and aryl, wherein said aryl may be substituted with 1 to 3 substituents independently selected from group consisting of: halo, C_1-C_3 alkyl, C(O)-C_1-C_3alkyl, C(O)OH, C(O)$NR^{10}R^{12}$, and heteroaryl;

iii) heterocycloalkyl, which may be substituted with 1 to 3 of R^3, where R^3 is selected from the group consisting of: halo, oxo, CN, -O-C_1-C_4 alkyl, -O-C_1-C_4 haloalkyl, -$NR^{10}R^{12}$, C(O)$NR^{10}R^{12}$, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C(O)-C_1-C_4 alkyl, -C(O)O-C_1-C_4 alkyl, $SO_2NR^{10}R^{12}$, SO_2-C_1-C_4 alkyl, and aryl, wherein said aryl may be substituted with 1 to 3 substituents independently selected from group consisting of: halo, C_1-C_3 alkyl, C(O)-C_1-C_3alkyl, C(O)OH, C(O)$NR^{10}R^{12}$, and heteroaryl;

iv) heteroaryl, which may be substituted with 1 to 3 of R^4, where R^4 is selected from the group consisting of: , halo, oxo, CN, -O-C_1-C_4 alkyl, -O-C_1-C_4 haloalkyl, -$NR^{10}R^{12}$, C(O)$NR^{10}R^{12}$, C_1-C_6 alkyl, C_1-C_4 haloalkyl, C_1-C_6 alkylene-heterocycloalkyl, C_1-C_6alkylene-aryl, C_1-C_6alkylene-heteroaryl, C(O)-C_1-C_4 alkyl, -C(O)O-C_1-C_4 alkyl, $SO_2NR^{10}R^{12}$, SO_2-C_1-C_4 alkyl, -NR^{14}C(O)C_1-C_4-alkyl, NH-C_1-C_4 alkylene-aryl, heterocycloalkyl, and aryl, wherein said aryl may be substituted with 1 to 3 substituents independently selected from group consisting of: halo, C_1-C_3 alkyl, C(O)-C_1-C_3alkyl, C(O)OH, C(O)$NR^{10}R^{12}$, and heteroaryl,

wherein said heterocycloalkyl or heterocycloalkyl group of C_1-C_6 alkylene-heterocycloalkyl may be substituted with 1 to 3 independently selected C_1-C_3 alkyl groups, and wherein said heteroaryl group of C_1-C_6 alkylene-heteroaryl and said aryl groups of C_1-C_6 alkylene-aryl and NH-C_1-C_4 alkylene-aryl may be substituted with substituents 1 to 3 groups independently selected from C_1-C_3 alkyl and $NR^{14}R^{16}$;

v) aryl, which may be substituted with 1 to 3 of R^6, where R^6 is selected from the group consisting of: halo, CN, -$NR^{14}R^{16}$, -$NR^{14}SO_2$-C_1-C_4 alkyl, C(O)H, -C_1-C_4 alkylene-$NR^{14}R^{16}$, $SO_2NR^{14}R^{16}$, C(O)OC_1-C_4 alkyl, -SO_2-heterocycloalkyl, -SO_2-C_1-C_6 alkyl, -C_1-C_6 alkyl, -O-C_1-C_6 alkyl, -C_1-C_6 haloalkyl, -O-C_1-C_6 haloalkyl, -C_1-C_6 alkylene-heterocycloalkyl, C_1-C_6alkylene-aryl, and C_1-C_6alkylene-heteroaryl,

wherein said heterocycloalkyl of said C_1-C_6 alkylene-heterocycloalkyl may be substituted with 1 to 3 groups independently selected from the group consisting of C_1-C_6 alkyl and -CH_2-phenyl, and C_1-C_4 alkylene-aryl,

wherein the heteroaryl of said C_1-C_6 alkylene-heteroaryl and the aryl of said C_1-C_6 alkylene-aryl may be substituted with 1 to 3 groups independently selected from the group consisting of C_1-C_4 alkyl, C_1-C_4 haloalkyl, and halo-C_1-C_3 alkylene-CN, -C_1-C_3 alkylene-OH, -C_1-C_3 alkylene-C(O)O-C_1-C_3 alkyl, -C_1-C_3 alkylene-O-C_1-C_3 alkyl, -C_1-C_3 alkylene-OC(O)-C_1-C_3 alkyl, -C_1-C_3 alkylene-NR^{14}-aryl, C_1-C_3 alkylene-NR^{14}-C(O)-C_1-C_4alkyl, -C_1-C_3 alkylene-$NR^{14}SO_2$-C_1-C_4 alkyl, -C(O)-C_1-C_3 alkylene, and -C(O)-heterocycloalkyl,

wherein said heterocycloalkyl of C(O)-heterocycloalkyl may be substituted with 1 to 3 groups independently selected from the

group consisting of: C_1-C_6 alkyl, -C(O)-$NHCH_2$-aryl, -CH-(OH)-C_1-C_6 alkyl, -CH(OH)-C_2-C_6 alkenyl, -CH(OH)-C_3-C_7 cycloalkyl, -CH(OH)-phenyl, -C(O)$NR^{14}R^{16}$-C_3-C_{14}cycloalkyl, -C(O)NR^{14}-C_1-C_3 alkylene-$NR^{14}R^{16}$, -C(O)NR^{14}-C_1-C_3 alkylene-CN, -C(O)NR^{14}-C_1-C_3 alkylene-$NR^{14}R^{16}$, -C(O)$NR^{14}R^{16}$, -C(O)NH-C_3-C_{14} cycloalkyl, -C(O)NH-C_1-C_3 alkylene-O-C_1-C_3 alkyl, C(O)NH-C_1-C_3 alkylene-OH, -NR^{14}-C_3-C_{14} cycloalkyl, -NR^{14}-C_1-C_3 alkylene-heterocycloalkyl, -NR^{14}C(O)-C_1-C_4 alkyl, heterocycloalkyl, and heteroaryl, wherein said heterocycloalkyl or heteroaryl may be substituted with 1-3 substituents independently selected from the group consisting of: halo, C_1-C_4 alkyl, C_1-C_4 haloalkyl and aryl;

where R^{14} and R^{16} are independently selected from the group consisting of: C_1-C_4 alkyl, C_3-C_7-cycloalkyl, -C_1-C_3-alkylene-$NR^{10}R^{12}$, aryl, and H,

where $R^{10}$and R^{12} are at each occurrence independently selected from the group consisting of H, C_1-C_4 alkyl, C_1-C_3-alkylene-aryl, C_1-C_3-alkylene-heteroarylaryl, C_1-C_3-alkylene-C_3-C_7-cycloalkyl, and cyclopropyl;

where X^3 is absent or is L-G, where L is absent or is selected from the group consisting of:

-O-, -O-C_1-C_3 alkylene-, -NR^{30}-, -C(O)-, -C_1-C_3 alkylene-, wherein said C_1-C_3 alkylene may be substituted with one to two substituents independently selected from the group consisting of: OH, -$NR^{20}R^{22}$, -NH-heterocycloalkyl, and -O-C_1-C_3 alkyl, and wherein R^{30} is H or C_1-C_4 alkyl, or C_1-C_4 haloalkyl; and

G is selected from the group consisting of:

aryl, heteroaryl, C_1-C_6 alkyl, C_3-C_7 cycloalkyl, heterocycloalkyl, wherein G may be substituted with 1 to 3 groups independently selected from the group consisting of halo, CN, OH, -C_1-C_4 alkyl, -C_1-C_4 haloalkyl, -SO_2-R^{32}, -O-R^{32}, -C(O)-R^{32}, -C(O)O-R^{32}, -$NR^{20}R^{22}$, -NR^{20}C(O)OR^{32}, -NR^{20}C(O)R^{32}, -$NR^{20}SO_2OR^{34}$, -NR^{20}C(O)$NR^{36}R^{38}$, aryl, and aryl substituted with one to three groups independently selected from the group consisting of halo, CN, OH, -C_1-C_4 alkyl, and -C_1-C_4 haloalkyl,

wherein R^{32} is selected from -C_1-C_4 alkyl and -C_1-C_4 haloalkyl,

wherein R^{34} is selected from -C_1-C_4 alkyl and -C_1-C_4 haloalkyl,

wherein R^{36} and R^{38} are independently selected from the group consisting of hydrogen, -C_1-C_4 alkyl, and -C_1-C_3 haloalkyl;

where one of A^1, A^2, A^3, and A^4 is CR^{18}, one of A^1, A^2, A^3, and A^4 is N or CR^{19}, and two of A^1, A^2, A^3, and A^4 are CR^{19}, where R^{19} is independently selected from the group consisting of: H, -OR^{20}, CN, -$NR^{20}R^{22}$, halo, C_1-C_4 alkyl, C_1-C_4 haloalkyl, and SO_2R^{20},

wherein R^{18} is selected from the group consisting of: H, NO_2, C_1-C_3 alkyene-SO_2-C_1-C_6 alkyl, C_1-C_3 alkyene-SO_2-C_1-C_6 haloalkyl, C_1-C_3 alkyene-SO_2-$NR^{20}R^{22}$, -$NR^{20}R^{22}$, -$NHSO_2$-NH_2, -$NR^{40}SO_2$-C_1-C_4 alkyl, -$NR^{40}SO_2$-C_1-C_4 haloalkyl, -$NR^{40}SO_2$-CH_2-C(O)OH, -$NR^{40}SO_2$-CH_2-C(O)OC_1-C_4, -$NR^{40}SO_2$-C_1-C_4 alkyl, -$NR^{40}SO_2$-C_1-C_4 haloalkyl, -$NR^{40}SO_2$-C_3-C_7 cycloalkyl, -$NR^{40}SO_2$-aryl, -$NR^{40}SO_2$-heteroaryl, -$NR^{40}SO_2$-C_1-C_4 alkyl, -$NR^{40}SO_2$-C_1-C_4 haloalkyl, -$NR^{40}SO_2$-C_1-C_3 alkylene-C_3-C_{14} cycloalkyl, -$NR^{40}SO_2$-C_1-C_3 alkylene-heterocycloalkyl, -$NR^{40}SO_2$-C_1-C_3 alkylene-heteroaryl, -$NR^{40}SO_2$-C_1-C_3 alkylene-aryl, -SO_2-$NR^{40}R^{42}$, -SO_2-NR^{40}-C_1-C_4 alkyl, -SO_2-NR^{40}-C_1-C_4 haloalkyl, -SO_2-NR^{40}-C_3-C_{14} cycloalkyl, -SO_2-NR^{40}-C(O)$NR^{20}R^{22}$, -SO_2-NR^{40}-heterocycloalkyl, -SO_2-NR^{40}-heteroaryl, -SO_2-NR^{40}-aryl, -SO_2-C_1-C_6 alkyl, -SO_2-C_1-C_6 haloalkyl, -SO_2-C_3-C_{14} cycloalkyl, -SO_2-heterocycloalkyl, -SO_2-heteroaryl, -SO_2-aryl, -$NR^{40}SO_2$-$NR^{20}R^{22}$, -NR^{40}C(O)-C_1-C_4 alkyl, -NR^{40}C(O)NH-C_1-C_4 alkyl, -NR^{40}C(O)-heteroaryl, -NR^{40}C(O)-aryl, -NR^{40}C(O)O-C_1-C_4 alkyl, -NR^{40}C(O)O-heteroaryl, -NR^{40}C(O)-aryl, -NR^{40}C(O)-CH_2NH-C(O)O-C_1-C_4 alkyl, -C(O)CH_2-$NR^{20}R^{22}$, -C(O)$NR^{20}R^{22}$, C(O)OH, C_1-C_3 alkylene-NR^{40}-C(O)-C_1-C_4 alkyl, C_1-C_3 alkylene-NR^{40}-C(O)-C_1-C_3 haloalkyl, -NR^{40}-heteroaryl, C_3-C_{14} cycloalkyl, heterocycloalkyl, heterocycloalkyl-aryl, heteroaryl, aryl, C_1-C_3 alkylene-cycloalkyl, C_1-C_3 alkylene-heterocycloalkyl, C_1-C_3 alkylene-heteroaryl, and C_1-C_3 alkylene-aryl,

wherein any of the cycloalkyl, heterocycloalkyl, heteroaryl, or aryl groups of R^{18} may be substituted with 1 to 3 of C_1-C_4 alkyl, C_1-C_4 haloalkyl or halo,

wherein R^{40} and R^{42} are independently selected from the group consisting of: H and C_1-C_4 alkyl, and

wherein R^{20} and R^{22} are at each occurrence independently selected from the group consisting of: H and C_1-C_4 alkyl.

2. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein A^1 is CR^{19}, A^2 is CR^{18}, A^3 is CR^{19}, and A^4 is CR^{19}.

3. The compound of claim 2, or a pharmaceutically acceptable salt thereof, wherein A^1 is CH, A^2 is CR^{18}, A^3 is CH, and A^4 is CH.

4. The compound of claim 3, or a pharmaceutically acceptable salt thereof, wherein R^{18} is selected from the group consisting of:

NO_2, C_1-C_3 alkyene-SO_2-C_1-C_6 alkyl, C_1-C_3 alkyene-SO_2-C_1-C_6 haloalkyl, C_1-C_3 alkyene-SO_2-$NR^{20}R^{22}$, -$NR^{20}R^{22}$, -$NHSO_2$-NH_2, -$NR^{40}SO_2$-C_1-C_4 alkyl, -$NR^{40}SO_2$-C_1-C_4 haloalkyl, -$NR^{40}SO_2$-CH_2-C(O)OH, -$NR^{40}SO_2$-CH_2-C(O)OC_1-C_4, -$NR^{40}SO_2$-C_1-C_4 alkyl, -$NR^{40}SO_2$-C_1-C_4 haloalkyl, -$NR^{40}SO_2$-C_3-C_7 cycloalkyl, -$NR^{40}SO_2$-aryl, -$NR^{40}SO_2$-heteroaryl, -$NR^{40}SO_2$-C_1-C_4 alkyl, -$NR^{40}SO_2$-C_1-C_4 haloalkyl, -$NR^{40}SO_2$-C_1-C_3 alkylene-C_3-C_{14} cycloalkyl, -$NR^{40}SO_2$-C_1-C_3 alkylene-heterocycloalkyl, -$NR^{40}SO_2$-C_1-C_3 alkylene-heteroaryl, -$NR^{40}SO_2$-C_1-C_3 alkylene-aryl, -SO_2-$NR^{40}R^{42}$, -SO_2-NR^{40}-C_1-C_4 alkyl, -SO_2-NR^{40}-C_1-C_4 haloalkyl, -SO_2-NR^{40}-C_3-C_{14} cycloalkyl, -SO_2-NR^{40}-C(O)$NR^{20}R^{22}$, -SO_2-NR^{40}-heterocycloalkyl, -SO_2-NR^{40}-heteroaryl, -SO_2-NR^{40}-aryl, -SO_2-C_1-C_6 alkyl, -SO_2-C_1-C_6 haloalkyl, -SO_2-C_3-C_{14} cycloalkyl, -SO_2-heterocycloalkyl, -SO_2-heteroaryl, -SO_2-aryl, -$NR^{40}SO_2$-$NR^{20}R^{22}$, -NR^{40}C(O)-C_1-C_4 alkyl, -NR^{40}C(O)NH-C_1-C_4 alkyl, -NR^{40}C(O)-heteroaryl, -NR^{40}C(O)-aryl, -NR^{40}C(O)O-C_1-C_4 alkyl, -NR^{40}C(O)O-heteroaryl, -NR^{40}C(O)-aryl, -NR^{40}C(O)-CH_2NH-C(O)O-C_1-C_4 alkyl, -C(O)CH_2-$NR^{20}R^{22}$, -C(O)$NR^{20}R^{22}$, C(O)OH, C_1-C_3 alkylene-NR^{40}-C(O)-C_1-C_4 alkyl, C_1-C_3 alkylene-NR^{40}-C(O)-C_1-C_3 haloalkyl, -NR^{40}-heteroaryl, C_3-C_{14} cycloalkyl, heterocycloalkyl, heterocycloalkyl-aryl, heteroaryl, aryl, C_1-C_3 alkylene-cycloalkyl, C_1-C_3 alkylene-heterocycloalkyl, C_1-C_3 alkylene-heteroaryl, and C_1-C_3 alkylene-aryl,

5. The compound of claim 4, or a pharmaceutically acceptable salt thereof, wherein R^{18} is selected from the group consisting of:

$NR^{40}SO_2$-C_1-C_4 alkyl, -$NR^{40}SO_2$-C_1-C_4 haloalkyl, -SO_2-NR^{40}-C_1-C_4 alkyl, -SO_2-NR^{40}-C_1-C_4 haloalkyl, -SO_2-C_1-C_6 alkyl, and -SO_2-C_1-C_6 haloalkyl.

6. The compound of claim 5, or a pharmaceutically acceptable salt thereof, wherein R^{40} is H.

7. The compound of claim 6, or a pharmaceutically acceptable salt thereof, wherein X^3 is L-G and L is -O-, or -O-C_1-C_3 alkylene-.

8. The compound of claim 6, or a pharmaceutically acceptable salt thereof, wherein G is aryl or C_3-C_7 cycloalkyl, wherein G may be substituted with 1 to 3 groups independently selected from the group consisting of CN, OH, -$NR^{20}R^{22}$, -C_1-C_4 haloalkyl, -SO_2-C_1-C_4 alkyl, halo, C(O)-C_1-C_4-alkyl, -C(O)-C_1-C_4-alkyl, -O-C_1-C_4 alkyl, -O-C_1-C_4 haloalkyl, -C_1-C_4 alkyl, -$NR^{20}C(O)R^{32}$, -$NR^{20}SO_2OR^{34}$, -$NR^{20}C(O)NR^{36}R^{38}$,

wherein R^{32} is selected from -C_1-C_4 alkyl and -C_1-C_4 haloalkyl,

wherein R^{34} is selected from -C_1-C_4 alkyl and -C_1-C_4 haloalkyl,

wherein R^{36} and R^{38} are independently selected from the group consisting of hydrogen, -C_1-C_4 alkyl, and -C_1-C_3 haloalkyl.

9. The compound of claim 8, or a pharmaceutically acceptable salt thereof, wherein is L is –O-, and –G is phenyl substituted with 1 to 3 halo.

10. The compound of claim 9, or a pharmaceutically acceptable salt thereof, wherein L is –O-, and –G is phenyl substituted with 1 to 3 fluoro.

11. The compound of claim 10, or a pharmaceutically acceptable salt thereof, wherein said phenyl is 2,4-difluoro-phenyl.

12. The compound of claim 8, or a pharmaceutically acceptable salt thereof, wherein is L is –O-C_1-C_3 alkyene, and –G is C_3-C_7 cycloalkyl.

13. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein J is IIa, Y^{1a} is N, R^{1a} is methyl, and X^{2a} is hydrogen.

14. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein J is IIa, Y^{1a} is CR^{xa}, wherein R^{xa} is H, R^{1a} is methyl, and X^{2a} is hydrogen.

15. The compound of claim 13 or 14, or a pharmaceutically acceptable salt thereof, wherein X^{1a} is hydrogen.

16. The compound of claim 13 or 14, a pharmaceutically acceptable salt thereof, wherein X^{1a} is selected from the group consisting of:

halo, -O-C_1-C_4 alkyl, and aryl, wherein said aryl may be substituted with 1 to 3 of R^6, where R^6 is selected from the group consisting of: $NR^{14}SO_2$-C_1-C_4 alkyl, -C_1-C_3 alkylene-$NR^{14}R^{16}$, -C_1-C_6 alkylene-heterocycloalkyl, wherein said heterocycloalkyl of said C_1-C_6 alkylene-heterocycloalkyl may be substituted with 1 to 3 groups independently selected from the group consisting of C_1-C_6 alkyl and -CH_2-phenyl, wherein said aryl of said C_1-C_6 alkylene-aryl may be substituted with 1 to 3 groups independently selected from the group consisting of: -C_1-C_3 alkylene-OH, and heterocycloalkyl, wherein said heterocycloalkyl may be substituted with 1-3 substituents independently selected from the group consisting of: C_1-C_4 alkyl, C_1-C_4 haloalkyl and aryl.

17. The compound of claim 8, or a pharmaceutically acceptable salt thereof, wherein J is IIb, R^{1b} is hydrogen, X^{2b} is methyl, Y^{1b} is CR^{xb}, and R^{xb} is H.

18. The compound of claim 17, or a pharmaceutically acceptable salt thereof, wherein X^{1b} is hydrogen.

19. The compound of claim 18, or a pharmaceutically acceptable salt thereof, wherein is L is –O-, and –G is phenyl substituted with 1 to 3 halo.

20. The compound of claim 19, or a pharmaceutically acceptable salt thereof, wherein is –G is phenyl substituted with 1 to 3 halo.

21. The compound of claim 20, or a pharmaceutically acceptable salt thereof, wherein said phenyl is 2,4-difluoro-phenyl.

22. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein said compound is selected from the group consisting of:

1-methyl-5-(2-phenoxyphenyl)pyridin-2(1H)-one;

N-[3-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-4-phenoxyphenyl]methanesulfonamide;

methyl {[3-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-4-phenoxyphenyl]sulfamoyl}acetate;

{[3-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-4-phenoxyphenyl]sulfamoyl}acetic acid;

1-methyl-N-[3-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-4-phenoxyphenyl]-1H-imidazole-4-sulfonamide;

N-[3-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-4-phenoxyphenyl]-1H-imidazole-4-sulfonamide;

2,2,2-trifluoro-N-[3-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-4-phenoxyphenyl]ethanesulfonamide;

N-methyl-N'-[3-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-4-phenoxyphenyl]sulfuric diamide;

N-{3-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-4-[4-(trifluoromethyl)phenoxy]phenyl}methanesulfonamide;

N-[4-(4-fluorophenoxy)-3-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)phenyl]methanesulfonamide;

N-[4-(4-chlorophenoxy)-3-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)phenyl]methanesulfonamide;

N-[3-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-4-(pyridin-3-yloxy)phenyl]methanesulfonamide;

N-[4-(2-chlorophenoxy)-3-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)phenyl]methanesulfonamide;

N-{3-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-4-[2-(trifluoromethyl)phenoxy]phenyl}methanesulfonamide;

N-[4-(2-cyanophenoxy)-3-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)phenyl]methanesulfonamide;

N-[4-(2-methoxyphenoxy)-3-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)phenyl]methanesulfonamide;

N-[4-(2-fluorophenoxy)-3-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)phenyl]methanesulfonamide;

N-[4-(2,4-difluorophenoxy)-3-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)phenyl]methanesulfonamide;

N-[4-(2,4-difluorophenoxy)-3-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)phenyl]ethanesulfonamide;

N-[4-(3,5-difluorophenoxy)-3-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)phenyl]methanesulfonamide;

N-[4-(3-chlorophenoxy)-3-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)phenyl]methanesulfonamide;

N-{3-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-4-[3-(trifluoromethyl)phenoxy]phenyl}methanesulfonamide;

N-[4-(3-cyanophenoxy)-3-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)phenyl]methanesulfonamide;

N-[4-(3-fluorophenoxy)-3-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)phenyl]methanesulfonamide;

N-[4-(cyclohexyloxy)-3-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)phenyl]methanesulfonamide;

N-[4-(cyclopentyloxy)-3-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)phenyl]methanesulfonamide;

N-[3-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-4-(tetrahydrofuran-3-yloxy)phenyl]methanesulfonamide;

N-[3-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-4-(tetrahydro-2H-pyran-4-ylmethoxy)phenyl]methanesulfonamide;

N-[3-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-4-phenoxyphenyl]-1H-pyrrole-2-carboxamide;

tert-butyl (2-{[3-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-4-phenoxyphenyl]amino}-2-oxoethyl)carbamate;

N-[3-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-4-phenoxyphenyl]glycinamide;

1-methyl-5-[2-phenoxy-5-(pyridin-2-ylamino)phenyl]pyridin-2(1H)-one;

N-ethyl-3-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-4-phenoxybenzenesulfonamide;

3-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-4-phenoxybenzenesulfonamide;

N-[2-methyl-5-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-4-phenoxyphenyl]methanesulfonamide;

4-methoxy-1-methyl-5-(2-phenoxyphenyl)pyridin-2(1H)-one;

N-[3-(4-methoxy-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-4-phenoxyphenyl]methanesulfonamide;

N-{4-(2,4-difluorophenoxy)-3-[1-methyl-6-oxo-4-(trifluoromethyl)-1,6-dihydropyridin-3-yl]phenyl}ethanesulfonamide;

N-[3-(4-chloro-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-4-(2,4-difluorophenoxy)phenyl]methanesulfonamide;

N-[4-(2,4-difluorophenoxy)-3-(4-methoxy-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)phenyl]methanesulfonamide;

N-[4-(2,4-difluorophenoxy)-3-(4-methoxy-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)phenyl]ethanesulfonamide;

N-[4-(2,4-difluorophenoxy)-3-{4-[4-(hydroxymethyl)phenyl]-1-methyl-6-oxo-1,6-dihydropyridin-3-yl}phenyl]methanesulfonamide;

N-[4-(2,4-difluorophenoxy)-3-(1-methyl-4-{4-[(4-methylpiperazin-1-yl)methyl]phenyl}-6-oxo-1,6-dihydropyridin-3-yl)phenyl]methanesulfonamide;

N-[4-(2,4-difluorophenoxy)-3-{1-methyl-4-[4-(morpholin-4-yl)phenyl]-6-oxo-1,6-dihydropyridin-3-yl}phenyl]methanesulfonamide;

5-[2-(cyclopropylmethoxy)-5-(ethylsulfonyl)phenyl]-4-methoxy-1-methylpyridin-2(1H)-one;

5-{2-(2,4-difluorophenoxy)-5-[(methylsulfonyl)amino]phenyl}-N,1-dimethyl-2-oxo-1,2-dihydropyridine-4-carboxamide;

N-[4-(2,4-difluorophenoxy)-3-(4-ethoxy-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)phenyl]methanesulfonamide;

N-[4-(2,4-difluorophenoxy)-3-{4-[4-(hydroxymethyl)phenyl]-1-methyl-6-oxo-1,6-dihydropyridin-3-yl}phenyl]ethanesulfonamide;

N-[4-(2,4-difluorophenoxy)-3-(1-methyl-4-{4-[(4-methylpiperazin-1-yl)methyl]phenyl}-6-oxo-1,6-dihydropyridin-3-yl)phenyl]ethanesulfonamide;

N-[4-(2,4-difluorophenoxy)-3-(4-{4-[(dimethylamino)methyl]phenyl}-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)phenyl]ethanesulfonamide;

3-chloro-1-methyl-5-(2-phenoxyphenyl)pyridin-2(1H)-one;

N-[3-(5-chloro-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-4-(2,4-difluorophenoxy)phenyl]methanesulfonamide;

N-[3-(5-chloro-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-4-(2,4-difluorophenoxy)phenyl]ethanesulfonamide; and

N-[4-(2,4-difluorophenoxy)-3-{1-methyl-4-[4-(morpholin-4-yl)phenyl]-6-oxo-1,6-dihydropyridin-3-yl}phenyl]ethanesulfonamide.

23. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein said compound is selected from the group consisting of:

2-methyl-6-(2-phenoxyphenyl)pyridazin-3(2H)-one;

6-[2-(benzyloxy)phenyl]-2-methylpyridazin-3(2H)-one;

-[2-(1-methyl-6-oxo-1,6-dihydropyridazin-3-yl)phenoxy]benzonitrile;

6-[2-(cyclopentyloxy)phenyl]-2-methylpyridazin-3(2H)-one;

6-[2-(4-hydroxybutoxy)phenyl]-2-methylpyridazin-3(2H)-one;

2-methyl-6-[2-(pyridin-2-yloxy)phenyl]pyridazin-3(2H)-one;

2-methyl-6-{2-[4-(trifluoromethyl)phenoxy]phenyl}pyridazin-3(2H)-one;

2-methyl-6-{2-[4-(methylsulfonyl)phenoxy]phenyl}pyridazin-3(2H)-one;

2-methyl-6-(5-nitro-2-phenoxyphenyl)pyridazin-3(2H)-one;

6-(5-amino-2-phenoxyphenyl)-2-methylpyridazin-3(2H)-one;

4-methyl-N-[3-(1-methyl-6-oxo-1,6-dihydropyridazin-3-yl)-4-phenoxyphenyl]benzenesulfonamide;

N-[3-(1-methyl-6-oxo-1,6-dihydropyridazin-3-yl)-4-phenoxyphenyl]acetamide;

3-(1-methyl-6-oxo-1,6-dihydropyridazin-3-yl)-4-phenoxybenzonitrile;

3-(1-methyl-6-oxo-1,6-dihydropyridazin-3-yl)-4-phenoxybenzamide;

3-(1-methyl-6-oxo-1,6-dihydropyridazin-3-yl)-4-phenoxybenzoic acid;

N-[3-(1-methyl-6-oxo-1,6-dihydropyridazin-3-yl)-4-phenoxybenzyl]acetamide;

2,2,2-trifluoro-N-[3-(1-methyl-6-oxo-1,6-dihydropyridazin-3-yl)-4-phenoxybenzyl]acetamide;

5-methoxy-2-methyl-6-(2-phenoxyphenyl)pyridazin-3(2H)-one;

N-[3-(4-methoxy-1-methyl-6-oxo-1,6-dihydropyridazin-3-yl)phenyl]methanesulfonamide;

6-(5-amino-2-phenoxyphenyl)-5-methoxy-2-methylpyridazin-3(2H)-one;

N-[3-(4-methoxy-1-methyl-6-oxo-1,6-dihydropyridazin-3-yl)-4-phenoxyphenyl]acetamide;

N-[3-(4-methoxy-1-methyl-6-oxo-1,6-dihydropyridazin-3-yl)-4-phenoxyphenyl]methanesulfonamide;

N-[3-(4-methoxy-1-methyl-6-oxo-1,6-dihydropyridazin-3-yl)-4-phenoxyphenyl]-N-methylmethanesulfonamide;

N-[3-(4-methoxy-1-methyl-6-oxo-1,6-dihydropyridazin-3-yl)-4-phenoxyphenyl]propane-1-sulfonamide;

2,2,2-trifluoro-N-[3-(4-methoxy-1-methyl-6-oxo-1,6-dihydropyridazin-3-yl)-4-phenoxyphenyl]ethanesulfonamide;

N-[3-(4-methoxy-1-methyl-6-oxo-1,6-dihydropyridazin-3-yl)-4-phenoxyphenyl]cyclopentanesulfonamide;

N-[3-(4-methoxy-1-methyl-6-oxo-1,6-dihydropyridazin-3-yl)-4-phenoxyphenyl]-1-phenylmethanesulfonamide;

3,3,3-trifluoro-N-[3-(4-methoxy-1-methyl-6-oxo-1,6-dihydropyridazin-3-yl)-4-phenoxyphenyl]propane-1-sulfonamide;

Ethyl [3-(4-methoxy-1-methyl-6-oxo-1,6-dihydropyridazin-3-yl)-4-phenoxyphenyl]carbamate;

1-ethyl-3-[3-(4-methoxy-1-methyl-6-oxo-1,6-dihydropyridazin-3-yl)-4-phenoxyphenyl]urea;

N'-[3-(4-methoxy-1-methyl-6-oxo-1,6-dihydropyridazin-3-yl)-4-phenoxyphenyl]-N,N-dimethylsulfuric diamide;

4-[2-(4-methoxy-1-methyl-6-oxo-1,6-dihydropyridazin-3-yl)phenoxy]benzonitrile;

6-[2-(4-fluorophenoxy)phenyl]-5-methoxy-2-methylpyridazin-3(2H)-one;

6-[2-(3-chloro-4-fluorophenoxy)phenyl]-5-methoxy-2-methylpyridazin-3(2H)-one;

5-methoxy-6-[2-(4-methoxyphenoxy)phenyl]-2-methylpyridazin-3(2H)-one;

6-[2-(3-fluorophenoxy)phenyl]-5-methoxy-2-methylpyridazin-3(2H)-one;

6-[2-(4-chlorophenoxy)phenyl]-5-methoxy-2-methylpyridazin-3(2H)-one;

methyl {[1-methyl-6-oxo-3-(2-phenoxyphenyl)-1,6-dihydropyridazin-4-yl]oxy}acetate;

6-[2-(cyclohexyloxy)phenyl]-5-methoxy-2-methylpyridazin-3(2H)-one;

5-methoxy-2-methyl-6-[2-(pyridin-2-ylmethoxy)phenyl]pyridazin-3(2H)-one;

6-[2-(1H-indazol-5-ylmethoxy)phenyl]-5-methoxy-2-methylpyridazin-3(2H)-one;

6-[2-(2-cyclohexylethoxy)phenyl]-5-methoxy-2-methylpyridazin-3(2H)-one;

tert-butyl 4-{[2-(4-methoxy-1-methyl-6-oxo-1,6-dihydropyridazin-3-yl)phenoxy]methyl}piperidine-1-carboxylate;

5-methoxy-2-methyl-6-[2-(piperidin-4-ylmethoxy)phenyl]pyridazin-3(2H)-one;

5-methoxy-2-methyl-6-[2-(pyridin-4-ylmethoxy)phenyl]pyridazin-3(2H)-one;

6-[2-(cyclopentylmethoxy)phenyl]-5-methoxy-2-methylpyridazin-3(2H)-one;

5-methoxy-2-methyl-6-[2-(tetrahydro-2H-pyran-4-ylmethoxy)phenyl]pyridazin-3(2H)-one;

methyl 1-[1-methyl-6-oxo-3-(2-phenoxyphenyl)-1,6-dihydropyridazin-4-yl]pyrrolidine-3-carboxylate;

Ethyl 1-[1-methyl-6-oxo-3-(2-phenoxyphenyl)-1,6-dihydropyridazin-4-yl]pyrrolidine-3-carboxylate;

methyl N-[1-methyl-6-oxo-3-(2-phenoxyphenyl)-1,6-dihydropyridazin-4-yl]glycinate;

2-methyl-5-(4-methyl-3-oxopiperazin-1-yl)-6-(2-phenoxyphenyl)pyridazin-3(2H)-one;

6-(biphenyl-2-yl)-2-methylpyridazin-3(2H)-one;

2'-(1-methyl-6-oxo-1,6-dihydropyridazin-3-yl)biphenyl-3-carbonitrile;

5-(2-fluoropyridin-4-yl)-2-methyl-6-(2-phenoxyphenyl)pyridazin-3(2H)-one;

2-methyl-5-(2-oxo-1,2-dihydropyridin-4-yl)-6-(2-phenoxyphenyl)pyridazin-3(2H)-one;

2-methyl-5-(1-methyl-2-oxo-1,2-dihydropyridin-4-yl)-6-(2-phenoxyphenyl)pyridazin-3(2H)-one;

5-(2-methoxypyridin-4-yl)-2-methyl-6-(2-phenoxyphenyl)pyridazin-3(2H)-one;

N-{3-[4-(2-methoxypyridin-4-yl)-1-methyl-6-oxo-1,6-dihydropyridazin-3-yl]-4-phenoxyphenyl}methanesulfonamide;

Ethyl 3-[1-methyl-6-oxo-3-(2-phenoxyphenyl)-1,6-dihydropyridazin-4-yl]benzoate;

2-methyl-5-{3-[(4-methylpiperazin-1-yl)methyl]phenyl}-6-(2-phenoxyphenyl)pyridazin-3(2H)-one;

2-methyl-5-{4-[(4-methylpiperazin-1-yl)methyl]phenyl}-6-(2-phenoxyphenyl)pyridazin-3(2H)-one;

N-[3-(1-methyl-4-{4-[(4-methylpiperazin-1-yl)methyl]phenyl}-6-oxo-1,6-dihydropyridazin-3-yl)-4-phenoxyphenyl]methanesulfonamide;

N-{3-[1-methyl-4-(4-methylphenyl)-6-oxo-1,6-dihydropyridazin-3-yl]-4-phenoxyphenyl}methanesulfonamide;

5-(3-amino-4-methylphenyl)-2-methyl-6-(2-phenoxyphenyl)pyridazin-3(2H)-one;

4-[1-methyl-6-oxo-3-(2-phenoxyphenyl)-1,6-dihydropyridazin-4-yl]benzaldehyde;

2-methyl-5-[4-(morpholin-4-ylmethyl)phenyl]-6-(2-phenoxyphenyl)pyridazin-3(2H)-one;

2-methyl-6-(2-phenoxyphenyl)-5-[4-(piperidin-1-ylmethyl)phenyl]pyridazin-3(2H)-one;

2-methyl-5-{4-[(4-methylpiperidin-1-yl)methyl]phenyl}-6-(2-phenoxyphenyl)pyridazin-3(2H)-one;

5-{4-[(diethylamino)methyl]phenyl}-2-methyl-6-(2-phenoxyphenyl)pyridazin-3(2H)-one;

2-methyl-6-(2-phenoxyphenyl)-5-[4-(piperazin-1-ylmethyl)phenyl]pyridazin-3(2H)-one;

2-methyl-6-(2-phenoxyphenyl)-5-[4-(pyrrolidin-1-ylmethyl)phenyl]pyridazin-3(2H)-one;

5-[4-(1-hydroxypropyl)phenyl]-2-methyl-6-(2-phenoxyphenyl)pyridazin-3(2H)-one;

5-[4-(1-hydroxy-2-methylpropyl)phenyl]-2-methyl-6-(2-phenoxyphenyl)pyridazin-3(2H)-one;

5-{4-[cyclopentyl(hydroxy)methyl]phenyl}-2-methyl-6-(2-phenoxyphenyl)pyridazin-3(2H)-one;

5-[4-(1-hydroxyethyl)phenyl]-2-methyl-6-(2-phenoxyphenyl)pyridazin-3(2H)-one;

5-{4-[hydroxy(phenyl)methyl]phenyl}-2-methyl-6-(2-phenoxyphenyl)pyridazin-3(2H)-one;

5-[4-(1-hydroxybut-3-en-1-yl)phenyl]-2-methyl-6-(2-phenoxyphenyl)pyridazin-3(2H)-one;

5-[4-(hydroxymethyl)phenyl]-2-methyl-6-(2-phenoxyphenyl)pyridazin-3(2H)-one;

5-[4-(methoxymethyl)phenyl]-2-methyl-6-(2-phenoxyphenyl)pyridazin-3(2H)-one;

4-[1-methyl-6-oxo-3-(2-phenoxyphenyl)-1,6-dihydropyridazin-4-yl]benzyl acetate;

tert-butyl 4-[1-methyl-6-oxo-3-(2-phenoxyphenyl)-1,6-dihydropyridazin-4-yl]-3,6-dihydropyridine-1(2H)-carboxylate;

2-methyl-6-(2-phenoxyphenyl)-5-(1,2,3,6-tetrahydropyridin-4-yl)pyridazin-3(2H)-one;

2-methyl-5-(1-methyl-1,2,3,6-tetrahydropyridin-4-yl)-6-(2-phenoxyphenyl)pyridazin-3(2H)-one;

5-(1-acetyl-1,2,3,6-tetrahydropyridin-4-yl)-2-methyl-6-(2-phenoxyphenyl)pyridazin-3(2H)-one;

2-methyl-5-[1-(methylsulfonyl)-1,2,3,6-tetrahydropyridin-4-yl]-6-(2-phenoxyphenyl)pyridazin-3(2H)-one;

tert-butyl 4-[1-methyl-6-oxo-3-(2-phenoxyphenyl)-1,6-dihydropyridazin-4-yl]piperidine-1-carboxylate;

2-methyl-6-(2-phenoxyphenyl)-5-(piperidin-4-yl)pyridazin-3(2H)-one;

2-methyl-5-(1-methylpiperidin-4-yl)-6-(2-phenoxyphenyl)pyridazin-3(2H)-one;

5-(1-acetylpiperidin-4-yl)-2-methyl-6-(2-phenoxyphenyl)pyridazin-3(2H)-one;

2-methyl-5-[1-(methylsulfonyl)piperidin-4-yl]-6-(2-phenoxyphenyl)pyridazin-3(2H)-one;

2-methyl-5-[4-(5-methyl-1,3,4-oxadiazol-2-yl)phenyl]-6-(2-phenoxyphenyl)pyridazin-3(2H)-one;

methyl 3-{4-[1-methyl-6-oxo-3-(2-phenoxyphenyl)-1,6-dihydropyridazin-4-yl]phenyl}propanoate;

5-(4-benzylphenyl)-2-methyl-6-(2-phenoxyphenyl)pyridazin-3(2H)-one;

{4-[1-methyl-6-oxo-3-(2-phenoxyphenyl)-1,6-dihydropyridazin-4-yl]phenyl}acetonitrile;

5-[4-(5,6-dihydro-4H-1,3-oxazin-2-yl)phenyl]-2-methyl-6-(2-phenoxyphenyl)pyridazin-3(2H)-one;

2-methyl-5-[4-(2-methylpropyl)phenyl]-6-(2-phenoxyphenyl)pyridazin-3(2H)-one;

Ethyl {4-[1-methyl-6-oxo-3-(2-phenoxyphenyl)-1,6-dihydropyridazin-4-yl]phenyl}acetate;

N-{4-[1-methyl-6-oxo-3-(2-phenoxyphenyl)-1,6-dihydropyridazin-4-yl]benzyl}methanesulfonamide;

N-{4-[1-methyl-6-oxo-3-(2-phenoxyphenyl)-1,6-dihydropyridazin-4-yl]benzyl}acetamide;

N-(2-{4-[1-methyl-6-oxo-3-(2-phenoxyphenyl)-1,6-dihydropyridazin-4-yl]phenyl}ethyl)acetamide;

5-[4-(3-hydroxypropyl)phenyl]-2-methyl-6-(2-phenoxyphenyl)pyridazin-3(2H)-one;

methyl 4-[1-methyl-6-oxo-3-(2-phenoxyphenyl)-1,6-dihydropyridazin-4-yl]benzoate;

2-methyl-5-(1-methyl-1H-pyrazol-4-yl)-6-(2-phenoxyphenyl)pyridazin-3(2H)-one;

2-methyl-6-(2-phenoxyphenyl)-5-(pyridin-4-yl)pyridazin-3(2H)-one;

N-{4-[1-methyl-6-oxo-3-(2-phenoxyphenyl)-1,6-dihydropyridazin-4-yl]phenyl}acetamide;

N-{3-[1-methyl-6-oxo-3-(2-phenoxyphenyl)-1,6-dihydropyridazin-4-yl]phenyl}acetamide;

5-(4-ethoxy-3-fluorophenyl)-2-methyl-6-(2-phenoxyphenyl)pyridazin-3(2H)-one;

N,N-dimethyl-4-[1-methyl-6-oxo-3-(2-phenoxyphenyl)-1,6-dihydropyridazin-4-yl]benzamide;

N,N-dimethyl-3-[1-methyl-6-oxo-3-(2-phenoxyphenyl)-1,6-dihydropyridazin-4-yl]benzamide;

2-methyl-5-[3-(2-methylpropoxy)phenyl]-6-(2-phenoxyphenyl)pyridazin-3(2H)-one;

5-[3-fluoro-4-(propan-2-yloxy)phenyl]-2-methyl-6-(2-phenoxyphenyl)pyridazin-3(2H)-one;

4-[1-methyl-6-oxo-3-(2-phenoxyphenyl)-1,6-dihydropyridazin-4-yl]benzenesulfonamide;

5-(1-benzyl-1H-pyrazol-4-yl)-2-methyl-6-(2-phenoxyphenyl)pyridazin-3(2H)-one;

N-cyclopropyl-4-[1-methyl-6-oxo-3-(2-phenoxyphenyl)-1,6-dihydropyridazin-4-yl]benzamide;

5-(3,5-dimethyl-1H-pyrazol-4-yl)-2-methyl-6-(2-phenoxyphenyl)pyridazin-3(2H)-one;

5-(6-methoxypyridin-3-yl)-2-methyl-6-(2-phenoxyphenyl)pyridazin-3(2H)-one;

5-(4-ethoxyphenyl)-2-methyl-6-(2-phenoxyphenyl)pyridazin-3(2H)-one;

5-(isoquinolin-4-yl)-2-methyl-6-(2-phenoxyphenyl)pyridazin-3(2H)-one;

N-{4-[1-methyl-6-oxo-3-(2-phenoxyphenyl)-1,6-dihydropyridazin-4-yl]phenyl}methanesulfonamide;

N-{3-[1-methyl-6-oxo-3-(2-phenoxyphenyl)-1,6-dihydropyridazin-4-yl]phenyl}methanesulfonamide;

N-{5-[1-methyl-6-oxo-3-(2-phenoxyphenyl)-1,6-dihydropyridazin-4-yl]pyridin-3-yl}acetamide;

N-methyl-5-[1-methyl-6-oxo-3-(2-phenoxyphenyl)-1,6-dihydropyridazin-4-yl]pyridine-3-carboxamide;

2-methyl-6-(2-phenoxyphenyl)-5-[6-(propan-2-yloxy)pyridin-3-yl]pyridazin-3(2H)-one;

5-(3-acetyl-2-fluorophenyl)-2-methyl-6-(2-phenoxyphenyl)pyridazin-3(2H)-one;

5-(2,6-dimethoxypyridin-3-yl)-2-methyl-6-(2-phenoxyphenyl)pyridazin-3(2H)-one;

methyl 2-[1-methyl-6-oxo-3-(2-phenoxyphenyl)-1,6-dihydropyridazin-4-yl]benzoate;

N-methyl-4-[1-methyl-6-oxo-3-(2-phenoxyphenyl)-1,6-dihydropyridazin-4-yl]benzamide;

N-methyl-3-[1-methyl-6-oxo-3-(2-phenoxyphenyl)-1,6-dihydropyridazin-4-yl]benzamide;

2-methyl-5-[1-(3-methylbutyl)-1H-pyrazol-4-yl]-6-(2-phenoxyphenyl)pyridazin-3(2H)-one;

2-methyl-6-(2-phenoxyphenyl)-5-[2-(propan-2-yloxy)pyridin-3-yl]pyridazin-3(2H)-one;

5-(1,3-benzothiazol-5-yl)-2-methyl-6-(2-phenoxyphenyl)pyridazin-3(2H)-one;

5-(5-acetyl-2-fluorophenyl)-2-methyl-6-(2-phenoxyphenyl)pyridazin-3(2H)-one;

5-(2,3-dihydro-1,4-benzodioxin-6-yl)-2-methyl-6-(2-phenoxyphenyl)pyridazin-3(2H)-one;

5-[3-(1-methoxyethyl)phenyl]-2-methyl-6-(2-phenoxyphenyl)pyridazin-3(2H)-one;

5-[4-(1-methoxyethyl)phenyl]-2-methyl-6-(2-phenoxyphenyl)pyridazin-3(2H)-one;

5-(3-ethoxy-2-fluorophenyl)-2-methyl-6-(2-phenoxyphenyl)pyridazin-3(2H)-one;

5-(2,1,3-benzothiadiazol-5-yl)-2-methyl-6-(2-phenoxyphenyl)pyridazin-3(2H)-one;

5-[5-(benzylamino)pyridin-3-yl]-2-methyl-6-(2-phenoxyphenyl)pyridazin-3(2H)-one;

2-methyl-5-[3-(morpholin-4-yl)phenyl]-6-(2-phenoxyphenyl)pyridazin-3(2H)-one;

2-methyl-6-(2-phenoxyphenyl)-5-[6-(2,2,2-trifluoroethoxy)pyridin-3-yl]pyridazin-3(2H)-one;

2-methyl-5-[3-(morpholin-4-ylmethyl)phenyl]-6-(2-phenoxyphenyl)pyridazin-3(2H)-one;

2-methyl-6-(2-phenoxyphenyl)-5-[3-(thiomorpholin-4-ylcarbonyl)phenyl]pyridazin-3(2H)-one;

5-[5-(cyclopentylamino)pyridin-3-yl]-2-methyl-6-(2-phenoxyphenyl)pyridazin-3(2H)-one;

N-cyclopropyl-5-[1-methyl-6-oxo-3-(2-phenoxyphenyl)-1,6-dihydropyridazin-4-yl]pyridine-3-carboxamide;

N-cyclopentyl-5-[1-methyl-6-oxo-3-(2-phenoxyphenyl)-1,6-dihydropyridazin-4-yl]pyridine-3-carboxamide;

N,N-diethyl-3-[1-methyl-6-oxo-3-(2-phenoxyphenyl)-1,6-dihydropyridazin-4-yl]benzenesulfonamide;

2-methyl-5-[4-(morpholin-4-ylcarbonyl)phenyl]-6-(2-phenoxyphenyl)pyridazin-3(2H)-one;

N-cyclohexyl-N-methyl-3-[1-methyl-6-oxo-3-(2-phenoxyphenyl)-1,6-dihydropyridazin-4-yl]benzamide;

2-methyl-5-[4-(morpholin-4-yl)phenyl]-6-(2-phenoxyphenyl)pyridazin-3(2H)-one;

N-[3-(dimethylamino)propyl]-4-[1-methyl-6-oxo-3-(2-phenoxyphenyl)-1,6-dihydropyridazin-4-yl]benzamide;

2-methyl-6-(2-phenoxyphenyl)-5-[6-(piperazin-1-yl)pyridin-3-yl]pyridazin-3(2H)-one;

3-fluoro-N,N-dimethyl-5-[1-methyl-6-oxo-3-(2-phenoxyphenyl)-1,6-dihydropyridazin-4-yl]benzamide;

2-methyl-5-[2-(morpholin-4-yl)pyridin-4-yl]-6-(2-phenoxyphenyl)pyridazin-3(2H)-one;

2-methyl-5-{3-[(4-methylpiperidin-1-yl)carbonyl]phenyl}-6-(2-phenoxyphenyl)pyridazin-3(2H)-one;

2-fluoro-N,N-dimethyl-5-[1-methyl-6-oxo-3-(2-phenoxyphenyl)-1,6-dihydropyridazin-4-yl]benzamide;

2-methyl-6-(2-phenoxyphenyl)-5-[3-(pyrrolidin-1-ylsulfonyl)phenyl]pyridazin-3(2H)-one;

2-methyl-6-(2-phenoxyphenyl)-5-[3-(piperidin-1-ylcarbonyl)phenyl]pyridazin-3(2H)-one;

N,N-diethyl-4-[1-methyl-6-oxo-3-(2-phenoxyphenyl)-1,6-dihydropyridazin-4-yl]benzamide;

N-methyl-4-[1-methyl-6-oxo-3-(2-phenoxyphenyl)-1,6-dihydropyridazin-4-yl]benzenesulfonamide;

N,N-diethyl-3-[1-methyl-6-oxo-3-(2-phenoxyphenyl)-1,6-dihydropyridazin-4-yl]benzamide;

2-methyl-5-[4-(4-methylpiperazin-1-yl)phenyl]-6-(2-phenoxyphenyl)pyridazin-3(2H)-one;

2-methyl-5-(6-{[2-(morpholin-4-yl)ethyl]amino}pyridin-3-yl)-6-(2-phenoxyphenyl)pyridazin-3(2H)-one;

N-[3-(dimethylamino)propyl]-3-[1-methyl-6-oxo-3-(2-phenoxyphenyl)-1,6-dihydropyridazin-4-yl]benzamide;

5-[6-(benzylamino)pyridin-3-yl]-2-methyl-6-(2-phenoxyphenyl)pyridazin-3(2H)-one;

N-(2-cyanoethyl)-4-[1-methyl-6-oxo-3-(2-phenoxyphenyl)-1,6-dihydropyridazin-4-yl]benzamide;

2-methyl-5-[5-methyl-6-(morpholin-4-yl)pyridin-3-yl]-6-(2-phenoxyphenyl)pyridazin-3(2H)-one;

N,N-diethyl-3-fluoro-5-[1-methyl-6-oxo-3-(2-phenoxyphenyl)-1,6-dihydropyridazin-4-yl]benzamide;

N-tert-butyl-4-[1-methyl-6-oxo-3-(2-phenoxyphenyl)-1,6-dihydropyridazin-4-yl]benzamide;

N-cyclopentyl-4-[1-methyl-6-oxo-3-(2-phenoxyphenyl)-1,6-dihydropyridazin-4-yl]benzamide;

4-[1-methyl-6-oxo-3-(2-phenoxyphenyl)-1,6-dihydropyridazin-4-yl]-N-(2-methylpropyl)benzamide;

N-(3-methoxypropyl)-4-[1-methyl-6-oxo-3-(2-phenoxyphenyl)-1,6-dihydropyridazin-4-yl]benzamide;

2-methyl-5-{1-[2-(morpholin-4-yl)ethyl]-1H-pyrazol-4-yl}-6-(2-phenoxyphenyl)pyridazin-3(2H)-one;

N-(2-methoxyethyl)-4-[1-methyl-6-oxo-3-(2-phenoxyphenyl)-1,6-dihydropyridazin-4-yl]benzamide;

2-methyl-5-[2-(4-methylpiperazin-1-yl)pyridin-4-yl]-6-(2-phenoxyphenyl)pyridazin-3(2H)-one;

2-methyl-5-[3-(morpholin-4-ylcarbonyl)phenyl]-6-(2-phenoxyphenyl)pyridazin-3(2H)-one;

2-methyl-5-[3-(5-methyl-1,3,4-oxadiazol-2-yl)phenyl]-6-(2-phenoxyphenyl)pyridazin-3(2H)-one;

N-cyclopropyl-3-[1-methyl-6-oxo-3-(2-phenoxyphenyl)-1,6-dihydropyridazin-4-yl]benzamide;

2-methyl-6-(2-phenoxyphenyl)-5-[4-(pyrrolidin-1-ylsulfonyl)phenyl]pyridazin-3(2H)-one;

2-methyl-5-[6-(morpholin-4-yl)pyridin-3-yl]-6-(2-phenoxyphenyl)pyridazin-3(2H)-one;

2-methyl-6-(2-phenoxyphenyl)-5-{4-[4-(propan-2-yl)piperazin-1-yl]phenyl}pyridazin-3(2H)-one;

N,N-diethyl-2-fluoro-5-[1-methyl-6-oxo-3-(2-phenoxyphenyl)-1,6-dihydropyridazin-4-yl]benzamide;

N-benzyl-4-[1-methyl-6-oxo-3-(2-phenoxyphenyl)-1,6-dihydropyridazin-4-yl]benzamide;

2-methyl-6-(2-phenoxyphenyl)-5-[4-(pyrrolidin-1-ylcarbonyl)phenyl]pyridazin-3(2H)-one;

2-methyl-6-(2-phenoxyphenyl)-5-[6-(piperidin-1-yl)pyridin-3-yl]pyridazin-3(2H)-one;

N-cyclohexyl-4-[1-methyl-6-oxo-3-(2-phenoxyphenyl)-1,6-dihydropyridazin-4-yl]benzamide;

N-[2-(dimethylamino)ethyl]-3-[1-methyl-6-oxo-3-(2-phenoxyphenyl)-1,6-dihydropyridazin-4-yl]benzamide;

2-methyl-6-(2-phenoxyphenyl)-5-{4-[(phenylamino)methyl]phenyl}pyridazin-3(2H)-one;

2-methyl-5-[2-(4-methylpiperazin-1-yl)pyrimidin-5-yl]-6-(2-phenoxyphenyl)pyridazin-3(2H)-one;

methyl {4-[1-methyl-6-oxo-3-(2-phenoxyphenyl)-1,6-dihydropyridazin-4-yl]phenyl}acetate;

5-(5-ethoxypyridin-3-yl)-2-methyl-6-(2-phenoxyphenyl)pyridazin-3(2H)-one;

2-methyl-5-[4-(methylamino)phenyl]-6-(2-phenoxyphenyl)pyridazin-3(2H)-one;

5-[2-(dimethylamino)pyrimidin-5-yl]-2-methyl-6-(2-phenoxyphenyl)pyridazin-3(2H)-one;

{3-[1-methyl-6-oxo-3-(2-phenoxyphenyl)-1,6-dihydropyridazin-4-yl]phenyl}acetonitrile;

2-methyl-5-(1-methyl-1H-pyrrol-2-yl)-6-(2-phenoxyphenyl)pyridazin-3(2H)-one;

2-methyl-6-(2-phenoxyphenyl)-5-(pyridin-3-yl)pyridazin-3(2H)-one;

2-methyl-5-(6-methylpyridin-3-yl)-6-(2-phenoxyphenyl)pyridazin-3(2H)-one;

5-(3-methoxyphenyl)-2-methyl-6-(2-phenoxyphenyl)pyridazin-3(2H)-one;

2-methyl-5-(4-methyl-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazin-7-yl)-6-(2-phenoxyphenyl)pyridazin-3(2H)-one;

5-(4-fluoro-3-methoxyphenyl)-2-methyl-6-(2-phenoxyphenyl)pyridazin-3(2H)-one;

5-(2-aminopyridin-4-yl)-2-methyl-6-(2-phenoxyphenyl)pyridazin-3(2H)-one;

5-(3-acetylphenyl)-2-methyl-6-(2-phenoxyphenyl)pyridazin-3(2H)-one;

N-ethyl-4-[1-methyl-6-oxo-3-(2-phenoxyphenyl)-1,6-dihydropyridazin-4-yl]benzamide;

5-(3-fluoro-4-methoxyphenyl)-2-methyl-6-(2-phenoxyphenyl)pyridazin-3(2H)-one;

5-(1,5-dimethyl-1H-pyrazol-4-yl)-2-methyl-6-(2-phenoxyphenyl)pyridazin-3(2H)-one;

2-methyl-5-(2-methylpyridin-4-yl)-6-(2-phenoxyphenyl)pyridazin-3(2H)-one;

2-methyl-5-[1-(2-methylpropyl)-1H-pyrazol-4-yl]-6-(2-phenoxyphenyl)pyridazin-3(2H)-one;

2-methyl-5-(4-methylpyridin-3-yl)-6-(2-phenoxyphenyl)pyridazin-3(2H)-one;

2-methyl-5-(1-methyl-1H-indol-5-yl)-6-(2-phenoxyphenyl)pyridazin-3(2H)-one;

5-[3-(dimethylamino)phenyl]-2-methyl-6-(2-phenoxyphenyl)pyridazin-3(2H)-one;

5-(2-fluoro-5-methoxyphenyl)-2-methyl-6-(2-phenoxyphenyl)pyridazin-3(2H)-one;

2-methyl-5-(5-methylfuran-2-yl)-6-(2-phenoxyphenyl)pyridazin-3(2H)-one;

5-(1-ethyl-1H-pyrazol-4-yl)-2-methyl-6-(2-phenoxyphenyl)pyridazin-3(2H)-one;

5-(3-methoxypyridin-4-yl)-2-methyl-6-(2-phenoxyphenyl)pyridazin-3(2H)-one;

2-methyl-5-(1-methyl-1H-indol-2-yl)-6-(2-phenoxyphenyl)pyridazin-3(2H)-one;

N,N-dimethyl-5-[1-methyl-6-oxo-3-(2-phenoxyphenyl)-1,6-dihydropyridazin-4-yl]pyridine-3-carboxamide;

5-[5-(dimethylamino)pyridin-3-yl]-2-methyl-6-(2-phenoxyphenyl)pyridazin-3(2H)-one;

5-butyl-2-methyl-6-(2-phenoxyphenyl)pyridazin-3(2H)-one;

methyl 1-methyl-6-oxo-3-(2-phenoxyphenyl)-1,6-dihydropyridazine-4-carboxylate;

methyl (2E)-3-[1-methyl-6-oxo-3-(2-phenoxyphenyl)-1,6-dihydropyridazin-4-yl]prop-2-enoate;

methyl 3-[1-methyl-6-oxo-3-(2-phenoxyphenyl)-1,6-dihydropyridazin-4-yl]propanoate;

5-acetyl-2-methyl-6-(2-phenoxyphenyl)pyridazin-3(2H)-one;

6-(2-benzylphenyl)-2-methylpyridazin-3(2H)-one;

N-[4-(2,4-difluorophenoxy)-3-(4-ethoxy-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)phenyl]ethanesulfonamide;

N-[4-(2,4-difluorophenoxy)-3-{1-methyl-4-[2-(morpholin-4-yl)ethoxy]-6-oxo-1,6-dihydropyridin-3-yl}phenyl]ethanesulfonamide;

N-(3-(4-(cyclopropylmethoxy)-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-4-(2,4-difluorophenoxy)phenyl)ethanesulfonamide;

N-(4-(2,4-difluorophenoxy)-3-(4-(2-(dimethylamino)ethoxy)-1-methyl-6-oxo-1,6-dihydropyridin-3-yl)phenyl)ethanesulfonamide;

N-{4-(2,4-difluorophenoxy)-3-[1-methyl-6-oxo-4-(propan-2-yloxy)-1,6-dihydropyridin-3-yl]phenyl}ethanesulfonamide;

N-{4-(2,4-difluorophenoxy)-3-[1-methyl-4-(2-methylpropoxy)-6-oxo-1,6-dihydropyridin-3-yl]phenyl}ethanesulfonamide;

N-{4-(2,4-difluorophenoxy)-3-[1-methyl-6-oxo-4-(tetrahydrofuran-3-ylmethoxy)-1,6-dihydropyridin-3-yl]phenyl}ethanesulfonamide;

N-[4-(2,4-difluorophenoxy)-3-(1-methyl-6-oxo-4-propoxy-1,6-dihydropyridin-3-yl)phenyl]ethanesulfonamide; and

N-{4-(2,4-difluorophenoxy)-3-[1-methyl-6-oxo-4-(2,2,2-trifluoroethoxy)-1,6-dihydropyridin-3-yl]phenyl}ethanesulfonamide.

24. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein said compound is selected from the group consisting of:

3-methyl-5-(2-phenoxyphenyl)pyridin-2(1H)-one;

N-[3-(5-methyl-6-oxo-1,6-dihydropyridin-3-yl)-4-phenoxyphenyl]methanesulfonamide;

N-[3-(5-methyl-6-oxo-1,6-dihydropyridin-3-yl)-4-phenoxyphenyl]acetamide;

N-[4-(2,4-difluorophenoxy)-3-(5-methyl-6-oxo-1,6-dihydropyridin-3-yl)phenyl]methanesulfonamide;

N-[4-(2,4-difluorophenoxy)-3-(5-methyl-6-oxo-1,6-dihydropyridin-3-yl)phenyl]ethanesulfonamide;

N-[4-(2,4-difluorophenoxy)-3-(5-methyl-6-oxo-1,6-dihydropyridin-3-yl)phenyl]acetamide;

N-{4-[(4,4-difluorocyclohexyl)oxy]-3-(5-methyl-6-oxo-1,6-dihydropyridin-3-yl)phenyl}methanesulfonamide; and

N-{4-[(4,4-difluorocyclohexyl)oxy]-3-(5-methyl-6-oxo-1,6-dihydropyridin-3-yl)phenyl}ethanesulfonamide.

25. A pharmaceutical composition comprising a therapeutically effective amount of a compound of formula (I) according to claim 1, or a pharmaceutically acceptable acceptable salt thereof, in combination with a pharmaceutically acceptable carrier.