

COMPOUNDS AND COMPOSITIONS AS MODULATORS OF TLR SIGNALINGCross-Reference to Related Applications

[0001] This application claims priority to U.S. Provisional Application No. 62/824,170, filed March 26, 2019, entitled “COMPOUNDS AS MODULATORS OF TLR2 SIGNALING” and U.S. Provisional Application No. 62/824,189, filed March 26, 2019, entitled “COMPOUNDS AS MODULATORS OF TLR2 SIGNALING” the contents of which are hereby incorporated by reference in their entirety for all purposes.

Technical Field

[0002] The present disclosure relates to compounds, pharmaceutical compositions comprising such compounds, and use of such compounds in methods of treatment or in medicaments for treatment of inflammatory diseases and certain neurological disorders that are related to inflammatory signaling processes, including but not limited to misfolded proteins.

Background

[0003] Toll-like receptors (TLRs) are sentinel receptors of the immune system. When these receptors are activated on cell surfaces, they initiate recruitment of a family of TIR-domain containing adapter proteins, which induce a signaling cascade that ultimately results in cell-type specific inflammatory responses, resulting in the elevation of pro-inflammatory mediators such as IL1, IL6, IL8 and TNF α . Of the different TLR receptors expressed on mammalian cells, TLR2 forms heterodimers with either TLR1 or TLR6 to initiate inflammatory responses with various microbial derived ligands. Among the various bacterial ligands are lipopolysaccharides (LPS), acylated lipopeptides, lipoglycans, peptidoglycans, porins, glycosylphosphatidyl-inosol anchors, and other bacterial cell wall components such as lipoteichoic acid (LTA) from streptococcus pneumonia. In addition to the microbial activation of TLR2, it has also been found that abnormal aggregation of neuron released oligomeric proteins such as alpha-synuclein (aSyn) can induce similar inflammatory responses in animal models of neurodegenerative diseases, including Parkinson's disease (PD), dementia with Lewy bodies, multiple system atrophy (MSA) and Alzheimer's disease (AD). *See, e.g., Kim et al., Nat. Commun.* 2013, 4, 1562.

[0004] The ability of TLR2 to induce signaling via heterodimers allows discrimination between various recognition patterns, which allows for the design of ligands with specific inhibition patterns. Kajava *et al.*, *J. Biol. Chem.* 2010, 285, 6227. Inhibitors that compete primarily with a specific pathological agonist, such as oligomeric pathogenic alpha-synuclein, but do not affect other ligands involved in pro-inflammatory signaling of bacterial or viral infections or non-competitive TIR-Myd88 inhibitors, such as compounds that function indirectly as non-competitive inhibitors of TLR2 through intracellular TIR-Myd88 inhibition, would therefore be useful as potential therapeutic agents.

[0005] The function of Toll-like receptors has been linked to various protein folding, protein dimerization, and inflammatory processes and to related diseases such as Alzheimer's disease (Gambuzza, M. *et al.*, "Toll-like receptors in Alzheimer's disease: a therapeutic perspective," *CNS Neurol. Disord. Drug Targets* 2014, 13(9), 1542-58), Parkinson's disease and Parkinson's disease with dementia (Beraud, D. *et al.*, "Misfolded α -synuclein and Toll-like receptors: therapeutic targets for Parkinson's disease," *Parkinsonism Relat. Disord.* 2012, 18 (Suppl. 1), S17-20), fronto-temporal dementia, dementia with Lewy bodies (Lewy body disease), multiple system atrophy (Vieira, B. *et al.*, "Neuroinflammation in multiple system atrophy: Response to and cause of α -synuclein aggregation," *Front. Cell Neurosci.* 2015, 9, 437), amyotrophic lateral sclerosis (Casula, M. *et al.*, "Toll-like receptor signaling in amyotrophic lateral sclerosis spinal cord tissue," *Neuroscience* 2011, 179, 233-43), Huntington's disease (Kalathur, R.K.R. *et al.*, "Huntington's disease and its therapeutic target genes: a global functional profile based on the HD Research Crossroads database," *BMC Neurology* 2012, 12, 47), inflammatory diseases, asthma and chronic obstructive pulmonary disease (COPD) (Zuo, L. *et al.*, "Molecular regulation of Toll-like receptors in asthma and COPD," *Front. Physiol.* 2016, 6, 312), chronic peptic ulcers (Smith, S., "Role of Toll-like receptors in *Helicobacter pylori* infection and immunity," *World J. Gastrointest. Pathophysiol.* 2014, 5(3), 133-146), tuberculosis (Harding, C.V. *et al.*, "Regulation of antigen presentation by *Mycobacterium tuberculosis*: a role for Toll-like receptors," *Nat. Rev. Microbiol.* 2010, 8(4), 296-307), rheumatoid arthritis (Huang, Q.-Q. *et al.*, "Role of Toll like receptors in rheumatoid arthritis," *Curr. Rheumatol. Rep.* 2009, 11(5), 357-364), chronic sinusitis (Zhang, Q. *et al.*, "Differential expression of Toll-like receptor pathway genes in chronic rhinosinusitis with or without nasal polyps," *Acta Otolaryngol.* 2013, 133(2), 165-173), hepatitis (including hepatitis B and C) (Zhang, E. *et al.*, "Toll-like receptor

(TLR)-mediated innate immune responses in control of hepatitis B virus (HBV) infection,” *Med. Microbiol. Immunol.* 2015, 204(1), 11-20; Howell, J. *et al.*, “Toll-like receptors in hepatitis C infection: implications for pathogenesis and treatment,” *J. Gastroenterol. Hepatol.* 2013, 28(5), 766-776), gout, lupus, psoriasis, psoriatic arthritis (Santegoets, K.C.M. *et al.*, “Toll-like receptors in rheumatic diseases: are we paying a high price for our defense against bugs?” *FEBS Letters* 2011, 585(23), 3660-3666), vasculitis, laryngitis, pleurisy (Chen, X. *et al.*, “Engagement of Toll-like receptor 2 on CD4(+) T cells facilitates local immune responses in patients with tuberculous pleurisy,” *J. Infect. Dis.* 2009, 200(3), 399-408), eczema (Miller, L.S., “Toll-like receptors in skin,” *Adv. Dermatol.* 2008, 24, 71-87), gastritis (Schmausser, B. *et al.*, “Toll-like receptors TLR4, TLR5 and TLR9 on gastric carcinoma cells: an implication for interaction with *Helicobacter pylori*,” *Int. J. Med. Microbiol.* 2005, 295(3), 179-85), vasculitis (Song, G.G. *et al.*, “Toll-like receptor polymorphisms and vasculitis susceptibility: meta-analysis and systematic review,” *Mol. Biol. Rep.* 2013, 40(2), 1315-23), laryngitis (King, S. N. *et al.*, “Characterization of the Leukocyte Response in Acute Vocal Fold Injury,” *PLoS One*, 2015; 10(10): e0139260), allergic reactions (Gangloff, S.C. *et al.*, “Toll-like receptors and immune response in allergic disease,” *Clin. Rev. Allergy Immunol.* 2004, 26(2), 115-25), multiple sclerosis (Miranda-Hernandez, S. *et al.*, “Role of toll-like receptors in multiple sclerosis,” *Am. J. Clin. Exp. Immunol.* 2013, 2(1), 75-93), Crohn’s disease (Cario, E., “Toll-like receptors in inflammatory bowel diseases: A decade later,” *Inflamm. Bowel Dis.* 2010, 16(9), 1583-1597), and traumatic brain injury (Hua, F. *et al.*, “Genomic profile of Toll-like receptor pathways in traumatically brain-injured mice: effect of exogenous progesterone,” *J. Neuroinflammation* 2011, 8, 42).

[0006] The signal transduction path of TLR2 can be activated either through the external domain (agonist pocket) or by mechanisms involving the cytoplasmic TIR domain that mediates homotypic and heterotypic interactions during signaling. The proteins MyD88 and TIRAP (Mal) are involved in this type of signaling.

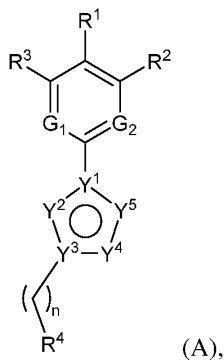
[0007] Importantly, a conserved proline P681 in TLR2 within the BB loop is (Brown V.*et al.* (2006) *European Journal of immunology* 36, 742-753) is involved in the dimerization mechanism. A mutation in this loop from P681H abolishes recruitment of MyD88 and signaling. Thus compounds that bind in the vicinity of this loop and restrict its movement during the dimerization process would be useful as inhibitors of the activation of TLR2.

[0008] TLR9 is a pattern recognition receptor involved in host defense mechanisms. The persistent or inappropriate activation of TLR9 has been implicated in a number of different central nervous system (CNS) and peripheral disorders. Thus inhibition of TLR9, either alone or in combination with TLR2 blockade may provide therapeutic benefit. CNS disorders where TLR9 has been implicated include Parkinson's disease (Maatouk *et al.*, *Nat Commun.* 2018, Jun 22;9(1):2450); Amyotrophic lateral sclerosis (O'Rourke *et al.*, *Science.* 2016, Mar 18;351(6279):1324-9); Guillain-Barre syndrome (Wang *et al.*, *Immunol Invest.* 2011, 2012;41(2):171-82); spinal cord injury (Li *et al.*, *Brain Behav Immun.* 2019 Aug;80:328-343; Li *et al.*, *J. Neuroinflammation.* 2020 Feb 25;17(1):73; David *et al.*, *Neurobiol Dis.* 2013 Jun;54:194-205; Pallottie *et al.*, *Sci Rep.* 2018 Jun 7;8(1):8723) and; multiple sclerosis (Prinz *et al.*, *J Clin Invest.* 2006 Feb;116(2):456-64). Peripheral disorders where TLR9 has been implicated are wide ranging and include multiple forms of tissue injury (mcAlpine *et al.*, *Proc Natl Acad Sci U S A.* 2018 Dec 4;115(49):E11523-E11531), chronic pain (David *et al.*, *Neurobiol Dis.* 2013 Jun;54:194-205), and psoriasis (Balak *et al.*, *Clin Immunol.* 2017 Jan;174:63-72).

[0009] Described herein are compounds that serve as antagonists of TLR2 and/or inhibitors of TLR9 with high potency and selectivity.

Summary

[0010] In one aspect, provided herein is a compound of Formula (A):



or a tautomer, or a pharmaceutically acceptable salt of any of the foregoing, wherein

one of R¹ and R² is -OH and the other is selected from the group consisting of -CN, halogen, -C(O)R^a, -CH=NR^j, -S(O)R^b, -S(O)₂R^c, -NHC(O)R^d, -NHS(O)₂R^e, -C₁-C₆alkyl-R^f, -C₂-C₆alkenyl-R^g, unsubstituted or substituted C₃-C₈ cycloalkyl, unsubstituted or substituted C₃-C₈ cycloalkenyl, and unsubstituted or substituted heterocycloalkyl;

R^a, R^b, R^c, and R^e are each independently H, C₁-C₆alkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, C₁-C₆haloalkyl, unsubstituted or substituted heterocyclyl, unsubstituted or substituted heteroaryl, benzoyl, or styryl;

R^d is H, C₁-C₆alkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, C₁-C₆haloalkyl, unsubstituted or substituted heterocyclyl, unsubstituted or substituted heteroaryl, or benzoyl;

R^f and R^g are each independently -OH, unsubstituted heteroaryl, -NR^mRⁿ, benzoyl, or styryl;

R^m and Rⁿ are each independently H, C₁-C₆alkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, or unsubstituted or substituted cycloalkyl;

R^j is unsubstituted or substituted heterocyclyl, unsubstituted or substituted heteroaryl, unsubstituted or substituted aryl, -OR^k, -NHR^k, -NHC(O)R^k, -NHS(O)₂R^k, or -NHC(NH)NHR^{aa};

R^{aa} is unsubstituted or substituted C₁-C₆alkyl, unsubstituted or substituted C₃-C₈cycloalkyl, unsubstituted or substituted aryl, unsubstituted or substituted heterocycloalkyl, or unsubstituted or substituted heteroaryl;

R^k is C₁-C₆alkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, C₃-C₈cycloalkyl, or aryl, wherein the C₁-C₆alkyl of R^k is unsubstituted or substituted with heterocyclyl or heteroaryl;

R³ is H, C₁-C₆alkyl, C₁-C₆alkoxy, or halogen, wherein the C₁-C₆alkyl and C₁-C₆alkoxy of R³ are each independently unsubstituted or substituted with one or more halogen;

wherein when R² is Br, R³ is H, C₁-C₆alkyl, C₁-C₆alkoxy, Cl, F, or I;

G₁ and G₂ are each independently CH or N, wherein when G₁ is N, G₂ is CH, and when G₂ is N, G₁ is CH;

○ indicates that the ring is aromatic;

Y¹ is C or N;

Y² is CH, N, NH, S, or O;

Y³ is C or N;

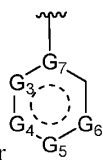
Y⁴ is CH, N, NH, S, or O;

Y^5 is CR^7 , N, NH, S, or O;

wherein no more than one of Y^1 , Y^2 , Y^3 , Y^4 , and Y^5 is S or O and no more than four of Y^1 , Y^2 , Y^3 , Y^4 , and Y^5 are N or NH;

R^7 is H or C_1 - C_6 alkyl;

n is 0, 1, 2, or 3;



R^4 is alkoxy or



indicates that the ring is saturated, partially unsaturated, or fully unsaturated;

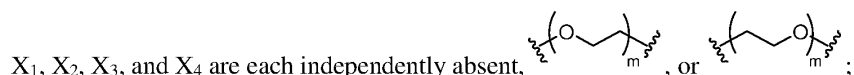
G_3 is $CH(X_1-R^{6a})$, $C(X_1-R^{6a})$, N, $N(X_1-R^{6a})$, S, or O;

G_4 is $CH(X_2-R^{6b})$, $C(X_2-R^{6b})$, N, $N(X_2-R^{6b})$, S, or O;

G_5 is $CH(X_3-R^{6c})$, $C(X_3-R^{6c})$, N, $N(X_3-R^{6c})$, S, or O;

G_6 is $CH(X_4-R^{6d})$, $C(X_4-R^{6d})$, N, $N(X_4-R^{6d})$, S, or O; and

G_7 is N, C, or CH;



m is 1-6;

R^{6a} , R^{6b} , R^{6c} , and R^{6d} are each independently hydrogen, C_1 - C_6 alkyl, C_1 - C_6 alkoxy, halo, -OH, - NR^pR^q , aryl, heterocyclyl, heteroaryl, - C_1 - C_6 alkyl-heterocyclyl, -OC(O)-heterocyclyl, -C(O) R^h , -S(O) $_2NR^{w1}R^{w2}$, -S(O) $_2R^y$, or - $NR^{z1}S(O)_2R^{z2}$, wherein the C_1 - C_6 alkyl and C_1 - C_6 alkoxy of R^{6a} , R^{6b} , R^{6c} , and R^{6d} are each independently unsubstituted or substituted with one or more groups selected from the group consisting of cycloalkyl and halogen; the aryl and heteroaryl of R^{6a} , R^{6b} , R^{6c} , and R^{6d} are each independently unsubstituted or substituted with one or more groups selected from the group consisting of C_1 - C_6 alkyl, C_1 - C_6 alkoxy, C_3 - C_8 cycloalkyl, -OH, and C_1 - C_6 alkyl-OH; and the heterocyclyl, - C_1 - C_6 alkyl-heterocyclyl, and -OC(O)-heterocyclyl of R^{6a} , R^{6b} , R^{6c} , and R^{6d} are each independently unsubstituted or substituted with one or more groups selected from the group consisting of C_1 - C_6 alkyl, C_1 - C_6 alkoxy, halo, -OH, C_1 - C_6 alkyl-OH, =O, and =S; each R^h is independently selected from the group consisting of H, C_1 - C_6 alkyl, C_1 - C_6 alkoxy, and C_3 - C_8 cycloalkyl, and - NR^rR^s ;

each R^p is independently H or C₁-C₆alkyl;

each R^q is independently C₂-C₃alkyl, -C(O)R^t, -C(O)OR^u, -C(O)NR^v;

each R^r, R^s, R^{w1}, and R^{z1} is independently selected from H and C₁-C₆alkyl; and

each R^t, R^u, R^v, R^{w2}, R^y, and R^{z2} is independently selected from H, C₁-C₆alkyl, unsubstituted or substituted C₃-C₈cycloalkyl, and unsubstituted or substituted heterocyclyl;

or

G₅ is CH(X₃-R^{6c}) or C(X₃-R^{6c}), G₆ is CH(X₄-R^{6d}) or C(X₄-R^{6d}), and R^{6c} and R^{6d} are taken together with the carbon atoms to which they are attached to form a 6-membered aryl, a 6-membered heterocyclyl, or a 6-membered heteroaryl ring; wherein the 6-membered aryl, 6-membered heterocyclyl, and 6-membered heteroaryl rings are each independently unsubstituted or substituted.

[0011] In some embodiments of Formula (A),

Y¹ is C or N;

Y² is CH, N, NH, S, or O;

Y³ is C or N;

Y⁴ is CH, N, NH, S, or O;

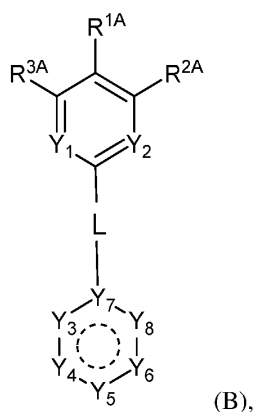
Y⁵ is CH, N, NH, S, or O;

wherein no more than one of Y¹, Y², Y³, Y⁴, and Y⁵ is S or O and no more than three of Y¹, Y², Y³, Y⁴, and Y⁵ are N or NH.

[0012] In some embodiments of Formula (A), one of R¹ and R² is -OH and the other is selected from the group consisting of -CN, halogen, -C(O)R^a, -CH=NR^j, -S(O)R^b, -S(O)₂R^c, -NHC(O)R^d, -NHS(O)₂R^e, -C₁-C₆alkyl-R^f, -C₂-C₆alkenyl-R^g, unsubstituted or substituted C₃-C₈cycloalkyl, unsubstituted or substituted C₃-C₈cycloalkenyl, and unsubstituted or substituted heterocycloalkyl; R^a, R^b, R^c, and R^e are each independently H, C₁-C₆alkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, C₁-C₆haloalkyl, unsubstituted or substituted heterocyclyl, unsubstituted or substituted heteroaryl, benzoyl, or styryl; R^d is H, C₁-C₆alkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, C₁-C₆haloalkyl, unsubstituted or substituted heterocyclyl, unsubstituted or substituted heteroaryl, or benzoyl; R^f and R^g are each independently -OH, unsubstituted heteroaryl, -NR^mRⁿ, benzoyl, or styryl; R^m and Rⁿ are each independently H, C₁-C₆alkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, or unsubstituted or substituted cycloalkyl; R^j is unsubstituted or substituted heterocyclyl, unsubstituted or substituted heteroaryl, unsubstituted or substituted aryl, -OR^k, -NHR^k, -NHC(O)R^k, -

NHS(O)₂R^k, or -NHC(NH)NH₂; R^k is C₁-C₆alkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, C₃-C₈cycloalkyl, or aryl, wherein the C₁-C₆alkyl of R^k is unsubstituted or substituted with heterocyclyl or heteroaryl.

[0013] In one aspect, provided herein is a compound of Formula (B):



or a tautomer, or a pharmaceutically acceptable salt of any of the foregoing,
wherein

L is selected from the group consisting of -C≡C-, *-NHC(O)-, *-C(O)NH-, -NHC(O)NH-, *-NHS(O)₂-, *-NHS(O)(=NH)-, *-S(O)(=NH)NH-, *-S(O)₂NH-, *-S(O)NHNH-, *-NHNHS(O)-, *-C(O)NHNH-, *-NHNHC(O)-, *-NHC(O)O-, and *-OC(O)NH-, wherein * represents the point of attachment to Y₇;

Y₁ and Y₂ are each independently CR^x, or N;

R^x is hydrogen or halogen;

when L is -C≡C-, one of R^{1A} and R^{2A} is -OH and the other is selected from the group consisting of -C(O)R^{a1}, -CH=NR^{j1}, -S(O)R^{b1}, -S(O)₂R^{c1}, -NHC(O)R^{d1}, -NHS(O)₂R^{e1}, -C₁-C₆alkyl-R^{f1}, -C₂-C₆alkenyl-R^{g1}, C₃-C₈cycloalkyl, C₃-C₈cycloalkenyl, and 5- or 6-membered heterocycloalkyl, wherein the C₃-C₈cycloalkyl and C₃-C₈cycloalkenyl are each independently unsubstituted or substituted with one or more =O, and the 5- or 6-membered heterocycloalkyl is unsubstituted or substituted with one or more substituents independently selected from the group consisting of C₁-C₆alkyl, C₃-C₈cycloalkyl, =O, and -C(O)O-C₁-C₆alkyl;

when L is *-NHC(O)-, *-C(O)NH-, -NHC(O)NH-, *-NHS(O)₂-, *-S(O)₂NH-, *-S(O)NHNH-, *-C(O)NHNH-, or *-NHC(O)O-, one of R^{1A} and R^{2A} is -OH and the other is selected from the

group consisting of -C(O)H, -CH=NR^{j1}, and  ;

R^{a1} is H, C₁-C₆alkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, C₁-C₆haloalkyl, 3- to 6-membered heterocyclyl, or 5- to 10-membered heteroaryl, or benzoyl, wherein the 3- to 10-membered heterocyclyl of R^{a1} is unsubstituted or substituted with one or more groups independently selected from the group consisting of C₁-C₆alkyl, C₃-C₈ cycloalkyl, =O, and -C(O)O-C₁-C₆alkyl, and the 5- to 10-membered heteroaryl of R^{a1} is unsubstituted or substituted with one or more groups independently selected from the group consisting of C₁-C₆alkyl, C₃-C₈cycloalkyl, and -C(O)O-C₁-C₆alkyl;

R^{b1}, R^{c1}, R^{d1}, and R^{e1} are each independently H, C₁-C₆alkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, C₁-C₆haloalkyl, 3- to 10-membered heterocyclyl, 5- to 10-membered heteroaryl, benzoyl, or styryl, wherein the 3- to 10-membered heterocyclyl and 5- to 10-membered heteroaryl of R^{b1}, R^{c1}, R^{d1}, and R^{e1} are each independently selected from the group consisting of C₁-C₆alkyl, C₃-C₈cycloalkyl, and -C(O)O-C₁-C₆alkyl;

R^{f1} and R^{g1} are each independently -OH, unsubstituted 5- to 6-membered heteroaryl, -NR^{m1}Rⁿ¹, benzoyl, or styryl;

R^{m1} is C₃-C₈ cycloalkyl, unsubstituted or substituted with one or more groups selected from C₁-C₆alkyl and halo;

Rⁿ¹ is H, C₁-C₆alkyl, C₂-C₆alkenyl, or C₂-C₆alkynyl;

R^{j1} is C₁-C₆alkyl, 5- to 6-membered heterocyclyl, 5- to 6-membered heteroaryl, 6- to 12-membered aryl, -OR^{k1}, -NHR^{k1}, -N(C₁-C₆alkyl)R^{k1}, -NHC(O)R^{k1}, -NHS(O)₂R^{k1}, or -NHC(NH)NHR^{bb}, wherein the 5- to 6-membered heterocyclyl of R^{j1} is unsubstituted or substituted with one or more substituents selected from the group consisting of C₁-C₆alkyl, C₃-C₈cycloalkyl, =O, -C(O)NH-C₁-C₆alkyl, and -C(O)O-C₁-C₆alkyl, and the 5- to 6-membered heteroaryl and 6- to 12-membered aryl of R^{j1} are each independently unsubstituted or substituted with one or more substituents selected from the group consisting of C₁-C₆alkyl, C₃-C₈cycloalkyl, and -C(O)O-C₁-C₆alkyl;

R^{bb} is unsubstituted or substituted C_1 - C_6 alkyl, unsubstituted or substituted C_3 - C_8 cycloalkyl, unsubstituted or substituted aryl, unsubstituted or substituted heterocycloalkyl, or unsubstituted or substituted heteroaryl;

each R^{k1} is independently C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, C_3 - C_8 cycloalkyl, or 6- to 12-membered aryl, wherein the C_1 - C_6 alkyl of R^{k1} is unsubstituted or substituted with a 5- to 6-membered heterocyclyl or a 5- to 6-membered heteroaryl;

R^{3A} is H, C_1 - C_6 alkyl, C_1 - C_6 alkoxy, or halogen, wherein the C_1 - C_6 alkyl and C_1 - C_6 alkoxy of R^{3A} are each independently unsubstituted or substituted with one or more halogen;

 indicates that the ring is saturated, partially unsaturated, or fully unsaturated;

Y_3 is $CH(X_{1A}-R^{6a1})$, $C(X_{1A}-R^{6a1})$, N, $N(X_{1A}-R^{6a1})$, S, or O;

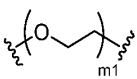
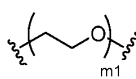
Y_4 is $CH(X_{2A}-R^{6b1})$, $C(X_{2A}-R^{6b1})$, N, $N(X_{2A}-R^{6b1})$, S, or O;

Y_5 is $CH(X_{3A}-R^{6c1})$, $C(X_{3A}-R^{6c1})$, N, $N(X_{3A}-R^{6c1})$, S, or O;

Y_6 is $CH(X_{4A}-R^{6d1})$, $C(X_{4A}-R^{6d1})$, N, $N(X_{4A}-R^{6d1})$, S, or O;

Y_7 is N, C, or CH; and

Y_8 is N, NH, C, or CH;

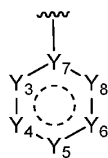
X_{1A} , X_{2A} , X_{3A} , and X_{4A} are each independently absent, , or ; m_1 is 1-6;

R^{6a1} , R^{6b1} , R^{6c1} , and R^{6d1} are each independently hydrogen, C_1 - C_6 alkyl, C_1 - C_6 alkoxy, halo, -OH, $-NR^{p1}R^{q1}$, C_6 - C_{12} aryl, 3- to 10-membered heterocyclyl, 5- to 10-membered heteroaryl, $-C_1$ - C_6 alkyl-5- to 6-membered heterocyclyl, $-OC(O)$ -5- to 6-membered heterocyclyl, $-C(O)R^{h1}$, $-S(O)_2NR^{w1a}R^{w2a}$, $-S(O)_2R^{y1}$, $-NR^{z1a}S(O)_2R^{z2a}$, or $-N(CH_3)CH_2C(CH_3)_3$, wherein the C_1 - C_6 alkyl and C_1 - C_6 alkoxy of R^{6a1} , R^{6b1} , R^{6c1} , and R^{6d1} are each independently unsubstituted or substituted with one or more groups selected from the group consisting of C_3 - C_8 cycloalkyl and halogen; the C_6 - C_{12} aryl and 5- to 10-membered heteroaryl of R^{6a1} , R^{6b1} , R^{6c1} , and R^{6d1} are each independently unsubstituted or substituted with one or more groups selected from the group consisting of C_1 - C_6 alkyl, C_1 - C_6 alkoxy, -OH, and C_1 - C_6 alkyl-OH; and the 3- to 10-membered heterocyclyl, $-C_1$ - C_6 alkyl-5- to 6-membered heterocyclyl, and $-OC(O)$ -5- to 6-membered heterocyclyl of R^{6a1} , R^{6b1} , R^{6c1} , and R^{6d1} are each independently unsubstituted or substituted with one or more groups selected from the group consisting of C_1 - C_6 alkyl,

C₁-C₆alkoxy, -OH, C₁-C₆alkyl-OH, =O, =S, halo, C₃-C₈cycloalkyl, -C(O)NH-C₃-C₈cycloalkyl, C₆-C₁₂ aryl, and 5- to 6-membered heterocyclyl;
 each R^{h1} is independently selected from the group consisting of H, C₁-C₆alkyl, C₁-C₆alkoxy, C₃-C₈cycloalkyl, and -NR^{r1}R^{s1};
 each R^{p1} is independently H or C₁-C₆alkyl;
 each R^{q1} is independently C₂-C₃alkyl, -C(O)R^{t1}, -C(O)OR^{u1}, or -C(O)NR^{v1};
 each R^{r1}, R^{s1}, R^{w1a}, and R^{z1a} is independently selected from H and C₁-C₆alkyl; and
 each R^{t1}, R^{u1}, R^{v1}, R^{w2a}, R^{y1}, and R^{z2a} is independently selected from H, C₁-C₆alkyl, unsubstituted or substituted C₃-C₈cycloalkyl, and unsubstituted or substituted heterocyclyl;

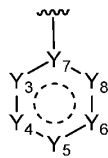
or

Y₅ is CH(X_{3A}-R^{6c1}) or C(X_{3A}-R^{6c1}), Y₆ is CH(X_{4A}-R^{6d1}) or C(X_{4A}-R^{6d1}), and R^{6c1} and R^{6d1} are taken together with the carbon atoms to which they are attached to form a 6-membered aryl, a 6-membered heterocyclyl, or a 6-membered heteroaryl ring;
 wherein the 6-membered aryl, 6-membered heterocyclyl, and 6-membered heteroaryl rings are each independently unsubstituted or substituted with one or more groups selected from the group consisting of C₁-C₆alkyl and -C(O)O-C₁-C₆alkyl;
 wherein no more than one of R^{6a1}, R^{6b1}, R^{6c1}, and R^{6d1} is C₁-C₆alkoxy or -OH; and
 (1) when L is -C≡C-, Y₁ and Y₂ are each CH, one of R^{1A} and R^{2A} is -C(O)H, -CH₂OH, -

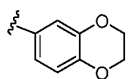


C(O)CH₃ or -NHC(O)CH₃, and R^{3A} is H, is other than cyclohexyl, phenyl, pyridyl, or naphthyl, and R^{6c1} is hydrogen, C₂-C₃alkyl, C₂-C₅alkoxy, Br, Cl, I, -NR^{p1}R^{q1}, C₆-C₁₂ aryl, 3- to 10-membered heterocyclyl, 5- to 10-membered heteroaryl, -C₁-C₆alkyl-5- to 6-membered heterocyclyl, -OC(O)-5- to 6-membered heterocyclyl, -C(O)R^{h1}, -S(O)₂NR^{w1a}R^{w2a}, -S(O)₂R^{y1}, or -NR^{z1a}S(O)₂R^{z2a}, and each R^{h1} is independently selected from the group consisting of C₁-C₆alkyl, C₁-C₆alkoxy, C₃-C₈cycloalkyl, and -NR^{r1}R^{s1};

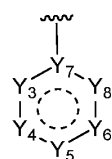
(2) when L is $-C\equiv C-$, Y_1 and Y_2 are each CH, one of R^{1A} and R^{2A} is $-C(O)H$, and R^{3A} is –



CH_3 , t-Bu, or C_2 - C_3 alkoxy, is other than phenyl and pyridyl, R^{b1} and R^{d1} are other

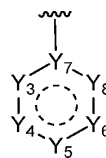
than , and R^{6c1} is other than $-OH$;

(3) when L is $-C\equiv C-$, Y_1 and Y_2 are each CH, one of R^{1A} and R^{2A} is piperidinyl, pyrrolidinyl, pyrrolidinone, piperazinyl, morpholinyl, or thiadiazolidinone 1,1-dioxide, and R^{3A}



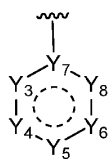
is H, is other than naphthyl, and R^{6c1} is other than fluoro;

(4) when L is $^*-NHS(O)_2-$ or $^*-S(O)_2NH-$, Y_1 and Y_2 are each CH, one of R^{1A} and R^{2A} is



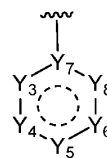
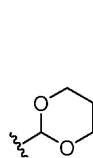
$-C(O)H$, $-CH=NR^{j1}$, or , and R^{3A} is H or Br, is other than phenyl, and R^{6a1} , R^{6b1} , R^{6c1} , and R^{6d1} are each independently hydrogen, C_2 - C_6 alkyl, C_1 - C_6 alkoxy, $-OH$, $-NR^{p1}R^{q1}$, C_6 - C_{12} aryl, 3- to 10-membered heterocyclyl, 5- to 10-membered heteroaryl, $-C_1$ - C_6 alkyl-5- to 6-membered heterocyclyl, $-OC(O)$ -5- to 6-membered heterocyclyl, $-C(O)R^{h1}$, $-S(O)_2NR^{w1a}R^{w2a}$, $-S(O)_2R^{y1}$, or $-NR^{z1a}S(O)_2R^{z2a}$,

(5) when L is $^*-C(O)NH-$ or $^*-NHC(O)-$, Y_1 and Y_2 are each CH, one of R^{1A} and R^{2A} is –



$C(O)H$, and R^{3A} is H or Cl, is other than phenyl, and R^{6a1} is other than $-CF_3$; and

(6) when L is $-NHC(O)NH-$, Y_1 and Y_2 are each CH, one of R^{1A} and R^{2A} is $-C(O)H$ or



, and R^{3A} is H or Cl, is other than cyclohexyl, and R^{6c1} is other than chloro.

[0014] In some embodiments of Formula (B), R^{j1} is C_1 - C_6 alkyl, 5- to 6-membered heterocyclyl, 5- to 6-membered heteroaryl, 6- to 12-membered aryl, $-OR^{k1}$, $-NHR^{k1}$, $-N(C_1-C_6alkyl)R^{k1}$, $-NHC(O)R^{k1}$, $-NHS(O)_2R^{k1}$, or $-NHC(NH)NH_2$, wherein the 5- to 6-membered heterocyclyl of R^{j1} is unsubstituted or substituted with one or more substituents selected from the group consisting of C_1 - C_6 alkyl, C_3 - C_8 cycloalkyl, $=O$, $-C(O)NH-C_1-C_6alkyl$, and $-C(O)O-C_1-C_6alkyl$, and the 5- to 6-membered heteroaryl and 6- to 12-membered aryl of R^{j1} are each independently unsubstituted or substituted with one or more substituents selected from the group consisting of C_1 - C_6 alkyl, C_3 - C_8 cycloalkyl, and $-C(O)O-C_1-C_6alkyl$; and R^{6a1} , R^{6b1} , R^{6c1} , and R^{6d1} are each independently hydrogen, C_1 - C_6 alkyl, C_1 - C_6 alkoxy, halo, $-OH$, $-NR^{p1}R^{q1}$, C_6 - C_{12} aryl, 3- to 10-membered heterocyclyl, 5- to 10-membered heteroaryl, $-C_1-C_6alkyl$ -5- to 6-membered heterocyclyl, $-OC(O)$ -5- to 6-membered heterocyclyl, $-C(O)R^{h1}$, $-S(O)_2NR^{w1a}R^{w2a}$, $-S(O)_2R^{y1}$, or $-NR^{z1a}S(O)_2R^{z2a}$, wherein the C_1 - C_6 alkyl and C_1 - C_6 alkoxy of R^{6a1} , R^{6b1} , R^{6c1} , and R^{6d1} are each independently unsubstituted or substituted with one or more groups selected from the group consisting of C_3 - C_8 cycloalkyl and halogen; the C_6 - C_{12} aryl and 5- to 10-membered heteroaryl of R^{6a1} , R^{6b1} , R^{6c1} , and R^{6d1} are each independently unsubstituted or substituted with one or more groups selected from the group consisting of C_1 - C_6 alkyl, C_1 - C_6 alkoxy, $-OH$, and C_1 - C_6alkyl - $-OH$; and the 3- to 10-membered heterocyclyl, $-C_1-C_6alkyl$ -5- to 6-membered heterocyclyl, and $-OC(O)$ -5- to 6-membered heterocyclyl of R^{6a1} , R^{6b1} , R^{6c1} , and R^{6d1} are each independently unsubstituted or substituted with one or more groups selected from the group consisting of C_1 - C_6 alkyl, C_1 - C_6 alkoxy, $-OH$, C_1 - C_6alkyl - $-OH$, $=O$, and $=S$.

[0015] In a further aspect, provided herein are pharmaceutical compositions comprising at least one compound of Formula (A) or Formula (B), such as a compound of Table 1A or Table 1B, or a tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, optionally further comprising a pharmaceutically acceptable excipient.

[0016] In another aspect, provided herein is a method of treating a disease or condition associated with TLR2 heterodimerization, comprising administering to a subject in need of such treatment an effective amount of at least one compound of Formula (A) or Formula (B), such as a compound of Table 1A or Table 1B, or a tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, and/or a pharmaceutical composition comprising at least one compound of Formula (A) or Formula (B), such as a compound of Table 1A or Table 1B. In some embodiments of any of the methods described herein, the disease or condition is selected from

the group consisting of: Alzheimer's disease, Parkinson's disease, fronto-temporal dementia, dementia with Lewy bodies (Lewy body disease), Parkinson's disease with dementia, multiple system atrophy, amyotrophic lateral sclerosis, Huntington's disease, Progressive Supranuclear Palsy (PSP), Niemann-Pick disease type C, inflammatory diseases, asthma, chronic obstructive pulmonary disease (COPD), chronic peptic ulcers, irritable bowel disease, tuberculosis, rheumatoid arthritis, osteoarthritis, chronic sinusitis, hepatitis, hepatitis B, hepatitis C, gout, lupus, pleurisy, eczema, gastritis, psoriasis, psoriatic arthritis, vasculitis, laryngitis, allergic reactions, multiple sclerosis, Crohn's disease, traumatic brain injury, CIDP (chronic inflammatory demyelinating polyneuropathy), stroke, ischemic heart disease, atopic dermatitis, acne vulgaris, rosacea, non-alcoholic fatty liver disease, non-alcoholic steatohepatitis, corneal wounds, corneal disorders, corneal HSV, Stargardt disease (Juvenile macular degeneration), age-related macular degeneration, sepsis, diabetic wounds, herpes simplex virus, and anti-fungal, anti-bacterial, antiviral and antitumor diseases or conditions.

[0017] In yet another aspect, provided herein is a method of interfering with the heterodimerization of TLR2 in a cell, or modulating, preventing, slowing, reversing, or inhibiting TLR2 heterodimerization in a cell, comprising contacting the cell with an effective amount of at least one compound of Formula (A) or Formula (B), such as a compound of Table 1A or Table 1B, or a tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, and/or with at least one pharmaceutical composition comprising at least one compound of Formula (A) or Formula (B), such as a compound of Table 1A or Table 1B, wherein the contacting is *in vitro*, *ex vivo*, or *in vivo*.

[0018] In another aspect, provided herein is a method of treating a disease or condition associated with inhibition of TLR9, comprising administering to a subject in need of such treatment an effective amount of at least one compound of Formula (A) or Formula (B), such as a compound of Table 1A or Table 1B, or a tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, and/or a pharmaceutical composition comprising at least one compound of Formula (A) or Formula (B), such as a compound of Table 1A or Table 1B. In some embodiments of any of the methods described herein, the disease or condition is a central nervous system (CNS) or peripheral disorder. In some embodiments, the CNS disorder is Parkinson's disease, Amyotrophic lateral sclerosis, Guillain-Barre syndrome, spinal cord injury,

or multiple sclerosis. In some embodiments, the peripheral disorders include multiple forms of tissue injury, chronic pain, and psoriasis.

[0019] Additional embodiments, features, and advantages of the present disclosure will be apparent from the following detailed description and through practice of the present disclosure.

[0020] For the sake of brevity, the disclosures of publications cited in this specification, including patents, are herein incorporated by reference.

Detailed Description

[0021] The present disclosure relates to compounds, pharmaceutical compositions comprising such compounds, and use of such compounds in methods of treatment or in medicaments for treatment of inflammatory diseases and certain neurological disorders that are related to inflammatory signaling processes, including but not limited to misfolded proteins.

[0022] It is to be understood that this disclosure is not limited to particular embodiments described, as such may, of course, vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to be limiting.

[0023] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as is commonly understood by one of ordinary skill in the art to which this disclosure belongs. All patents, applications, published applications and other publications referred to herein are incorporated by reference in their entireties. If a definition set forth in this section is contrary to or otherwise inconsistent with a definition set forth in a patent, application, or other publication that is herein incorporated by reference, the definition set forth in this section prevails over the definition incorporated herein by reference.

[0024] As used herein and in the appended claims, the singular forms “a,” “an,” and “the” include plural referents unless the context clearly dictates otherwise. It is further noted that the claims may be drafted to exclude any optional element. As such, this statement is intended to serve as antecedent basis for use of such exclusive terminology as “solely,” “only” and the like in connection with the recitation of claim elements, or use of a “negative” limitation.

[0025] As used herein, the terms “including,” “containing,” and “comprising” are used in their open, non-limiting sense.

[0026] To provide a more concise description, some of the quantitative expressions given herein are not qualified with the term “about”. It is understood that, whether the term “about” is used explicitly or not, every quantity given herein is meant to refer to the actual given value, and it is also meant to refer to the approximation to such given value that would reasonably be inferred based on the ordinary skill in the art, including equivalents and approximations due to the experimental and/or measurement conditions for such given value. Whenever a yield is given as a percentage, such yield refers to a mass of the entity for which the yield is given with respect to the maximum amount of the same entity that could be obtained under the particular stoichiometric conditions. Concentrations that are given as percentages refer to mass ratios, unless indicated differently.

[0027] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this disclosure belongs. Although any methods and materials similar or equivalent to those described herein can also be used in the practice or testing of the present disclosure. All publications mentioned herein are incorporated herein by reference to disclose and describe the methods and/or materials in connection with which the publications are cited.

[0028] Except as otherwise noted, the methods and techniques of the present embodiments are generally performed according to conventional methods well known in the art and as described in various general and more specific references that are cited and discussed throughout the present specification. See, e.g., Loudon, *Organic Chemistry*, Fourth Edition, New York: Oxford University Press, 2002, pp. 360-361, 1084-1085; Smith and March, *March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure*, Fifth Edition, Wiley-Interscience, 2001.

[0029] The nomenclature used herein to name the subject compounds is illustrated in the Examples herein. This nomenclature has generally been derived using the commercially-available ChemBioDraw Ultra software, Version 14.0.

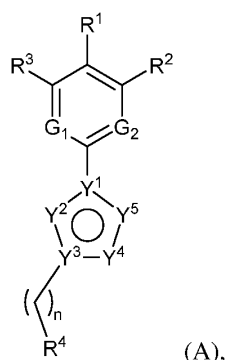
[0030] It is appreciated that certain features of the disclosure, which are, for clarity, described in the context of separate embodiments, may also be provided in combination in a single embodiment. Conversely, various features of the disclosure, which are, for brevity, described in the context of a single embodiment, may also be provided separately or in any

suitable subcombination. All combinations of the embodiments pertaining to the chemical groups represented by the variables are specifically embraced by the present disclosure and are disclosed herein just as if each and every combination was individually and explicitly disclosed, to the extent that such combinations embrace compounds that are stable compounds (i.e., compounds that can be isolated, characterized, and tested for biological activity). In addition, all subcombinations of the chemical groups listed in the embodiments describing such variables are also specifically embraced by the present disclosure and are disclosed herein just as if each and every such sub-combination of chemical groups was individually and explicitly disclosed herein.

Compounds

[0031] Compounds and salts thereof (such as pharmaceutically acceptable salts) are detailed herein, including in the Summary and in the appended claims. Also provided are the use of all of the compounds described herein, including any and all stereoisomers, including geometric isomers (e.g., cis/trans isomers or E/Z isomers), enantiomers, diastereomers, and mixtures thereof in any ratio including racemic mixtures, salts and solvates of the compounds described herein, as well as methods of making such compounds. Any compound described herein may also be referred to as a drug.

[0032] In one aspect, provided are compounds of Formula (A):



or a tautomer, or a pharmaceutically acceptable salt of any of the foregoing,
wherein

one of R^1 and R^2 is $-OH$ and the other is selected from the group consisting of $-CN$, halogen, $-C(O)R^a$, $-CH=NR^j$, $-S(O)R^b$, $-S(O)_2R^c$, $-NHC(O)R^d$, $-NHS(O)_2R^e$, $-C_1-C_6alkyl-R^f$, $-C_2-$

C₆alkenyl-R^g, unsubstituted or substituted C₃-C₈ cycloalkyl, unsubstituted or substituted C₃-C₈ cycloalkenyl, and unsubstituted or substituted heterocycloalkyl;

R^a, R^b, R^c, and R^e are each independently H, C₁-C₆alkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, C₁-C₆haloalkyl, unsubstituted or substituted heterocyclyl, unsubstituted or substituted heteroaryl, benzoyl, or styryl;

R^d is H, C₁-C₆alkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, C₁-C₆haloalkyl, unsubstituted or substituted heterocyclyl, unsubstituted or substituted heteroaryl, or benzoyl;

R^f and R^g are each independently -OH, unsubstituted heteroaryl, -NR^mRⁿ, benzoyl, or styryl;

R^m and Rⁿ are each independently H, C₁-C₆alkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, or unsubstituted or substituted cycloalkyl;

R^j is unsubstituted or substituted heterocyclyl, unsubstituted or substituted heteroaryl, unsubstituted or substituted aryl, -OR^k, -NHR^k, -NHC(O)R^k, -NHS(O)₂R^k, or -NHC(NH)NHR^{aa};

R^{aa} is unsubstituted or substituted C₁-C₆alkyl, unsubstituted or substituted C₃-C₈cycloalkyl, unsubstituted or substituted aryl, unsubstituted or substituted heterocycloalkyl, or unsubstituted or substituted heteroaryl;

R^k is C₁-C₆alkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, C₃-C₈cycloalkyl, or aryl, wherein the C₁-C₆alkyl of R^k is unsubstituted or substituted with heterocyclyl or heteroaryl;

R³ is H, C₁-C₆alkyl, C₁-C₆alkoxy, or halogen, wherein the C₁-C₆alkyl and C₁-C₆alkoxy of R³ are each independently unsubstituted or substituted with one or more halogen;

wherein when R² is Br, R³ is H, C₁-C₆alkyl, C₁-C₆alkoxy, Cl, F, or I;

G₁ and G₂ are each independently CH or N, wherein when G₁ is N, G₂ is CH, and when G₂ is N, G₁ is CH;

○ indicates that the ring is aromatic;

Y¹ is C or N;

Y² is CH, N, NH, S, or O;

Y³ is C or N;

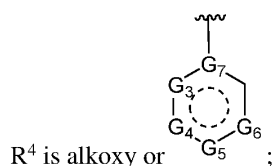
Y⁴ is CH, N, NH, S, or O;

Y⁵ is CR⁷, N, NH, S, or O;

wherein no more than one of Y^1 , Y^2 , Y^3 , Y^4 , and Y^5 is S or O and no more than four of Y^1 , Y^2 , Y^3 , Y^4 , and Y^5 are N or NH;

R^7 is H or C_1 - C_6 alkyl;

n is 0, 1, 2, or 3;



R^4 is alkoxy or



indicates that the ring is saturated, partially unsaturated, or fully unsaturated;

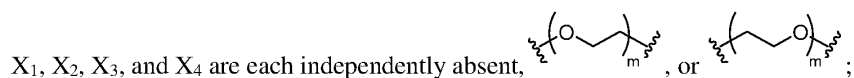
G_3 is $CH(X_1-R^{6a})$, $C(X_1-R^{6a})$, N, $N(X_1-R^{6a})$, S, or O;

G_4 is $CH(X_2-R^{6b})$, $C(X_2-R^{6b})$, N, $N(X_2-R^{6b})$, S, or O;

G_5 is $CH(X_3-R^{6c})$, $C(X_3-R^{6c})$, N, $N(X_3-R^{6c})$, S, or O;

G_6 is $CH(X_4-R^{6d})$, $C(X_4-R^{6d})$, N, $N(X_4-R^{6d})$, S, or O; and

G_7 is N, C, or CH;



X_1 , X_2 , X_3 , and X_4 are each independently absent,

m is 1-6;

R^{6a} , R^{6b} , R^{6c} , and R^{6d} are each independently hydrogen, C_1 - C_6 alkyl, C_1 - C_6 alkoxy, halo, -OH, - NR^pR^q , aryl, heterocyclyl, heteroaryl, - C_1 - C_6 alkyl-heterocyclyl, -OC(O)-heterocyclyl, -C(O) R^h , -S(O) $_2NR^{w1}R^{w2}$, -S(O) $_2R^y$, or - $NR^{z1}S(O)_2R^{z2}$, wherein the C_1 - C_6 alkyl and C_1 - C_6 alkoxy of R^{6a} , R^{6b} , R^{6c} , and R^{6d} are each independently unsubstituted or substituted with one or more groups selected from the group consisting of cycloalkyl and halogen; the aryl and heteroaryl of R^{6a} , R^{6b} , R^{6c} , and R^{6d} are each independently unsubstituted or substituted with one or more groups selected from the group consisting of C_1 - C_6 alkyl, C_1 - C_6 alkoxy, C_3 - C_8 cycloalkyl, -OH, and C_1 - C_6 alkyl-OH; and the heterocyclyl, - C_1 - C_6 alkyl-heterocyclyl, and -OC(O)-heterocyclyl of R^{6a} , R^{6b} , R^{6c} , and R^{6d} are each independently unsubstituted or substituted with one or more groups selected from the group consisting of C_1 - C_6 alkyl, C_1 - C_6 alkoxy, halo, -OH, C_1 - C_6 alkyl-OH, =O, and =S; each R^h is independently selected from the group consisting of H, C_1 - C_6 alkyl, C_1 -

C_6 alkoxy, and C_3 - C_8 cycloalkyl, and - NR^pR^s ;

each R^p is independently H or C_1 - C_6 alkyl;

each R^q is independently C_2 - C_3 alkyl, $-C(O)R^t$, $-C(O)OR^u$, $-C(O)NR^v$;

each R^r , R^s , R^{w1} , and R^{z1} is independently selected from H and C_1 - C_6 alkyl; and

each R^t , R^u , R^v , R^{w2} , R^y , and R^{z2} is independently selected from H, C_1 - C_6 alkyl, unsubstituted or substituted C_3 - C_8 cycloalkyl, and unsubstituted or substituted heterocyclyl;

or

G_5 is $CH(X_3-R^{6c})$ or $C(X_3-R^{6c})$, G_6 is $CH(X_4-R^{6d})$ or $C(X_4-R^{6d})$, and R^{6c} and R^{6d} are taken

together with the carbon atoms to which they are attached to form a 6-membered aryl, a 6-membered heterocyclyl, or a 6-membered heteroaryl ring; wherein the 6-membered aryl, 6-membered heterocyclyl, and 6-membered heteroaryl rings are each independently unsubstituted or substituted.

[0033] In some embodiments of Formula (A),

Y^1 is C or N;

Y^2 is CH, N, NH, S, or O;

Y^3 is C or N;

Y^4 is CH, N, NH, S, or O;

Y^5 is CH, N, NH, S, or O;

wherein no more than one of Y^1 , Y^2 , Y^3 , Y^4 , and Y^5 is S or O and no more than three of Y^1 , Y^2 , Y^3 , Y^4 , and Y^5 are N or NH; and

one of R^1 and R^2 is $-OH$ and the other is selected from the group consisting of $-CN$, halogen, $-C(O)R^a$, $-CH=NR^j$, $-S(O)R^b$, $-S(O)_2R^c$, $-NHC(O)R^d$, $-NHS(O)_2R^e$, $-C_1$ - C_6 alkyl- R^f , $-C_2$ - C_6 alkenyl- R^g , unsubstituted or substituted C_3 - C_8 cycloalkyl, unsubstituted or substituted C_3 - C_8 cycloalkenyl, and unsubstituted or substituted heterocycloalkyl; R^a , R^b , R^c , and R^e are each independently H, C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, C_1 - C_6 haloalkyl, unsubstituted or substituted heterocyclyl, unsubstituted or substituted heteroaryl, benzoyl, or styryl; R^d is H, C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, C_1 - C_6 haloalkyl, unsubstituted or substituted heterocyclyl, unsubstituted or substituted heteroaryl, or benzoyl; R^f and R^g are each independently $-OH$, unsubstituted heteroaryl, $-NR^mR^n$, benzoyl, or styryl; R^m and R^n are each independently H, C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, or unsubstituted or substituted cycloalkyl; R^j is unsubstituted or substituted heterocyclyl, unsubstituted or substituted heteroaryl, unsubstituted or substituted aryl, $-OR^k$, $-NHR^k$, $-NHC(O)R^k$, $-NHS(O)_2R^k$, or $-NHC(NH)NH_2$; R^k is C_1 -

C₆alkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, C₃-C₈cycloalkyl, or aryl, wherein the C₁-C₆alkyl of R^k is unsubstituted or substituted with heterocyclyl or heteroaryl.

[0034] In some embodiments, when any particular group is substituted, the indicated group is substituted by one or more substituents selected from the group consisting of oxo, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, halogen, -CN, -OR^{A1}, -SR^{A1}, -NR^{A2}R^{A3}, -NO₂, -C=NH(OR^{A1}), -C(O)R^{A1}, -OC(O)R^{A1}, -C(O)OR^{A1}, -C(O)NR^{A2}R^{A3}, -OC(O)NR^{A2}R^{A3}, -NR^{A1}C(O)R^{A2}, -NR^{A1}C(O)OR^{A2}, -NR^{A1}C(O)NR^{A2}R^{A3}, -S(O)R^{A1}, -S(O)₂R^{A1}, -NR^{A1}S(O)R^{A2}, -C(O)NR^{A1}S(O)R^{A2}, -NR^{A1}S(O)₂R^{A2}, -C(O)NR^{A1}S(O)₂R^{A2}, -S(O)NR^{A2}R^{A3}, -S(O)₂NR^{A2}R^{A3}, -P(O)(OR^{A2})(OR^{A3}), C₃-C₈ cycloalkyl, 3-12-membered heterocyclyl, 5- to 10-membered heteroaryl, C₆-C₁₄ aryl, -(C₁-C₃ alkylene)CN, -(C₁-C₃ alkylene)OR^{A1}, -(C₁-C₃ alkylene)SR^{A1}, -(C₁-C₃ alkylene)NR^{A2}R^{A3}, -(C₁-C₃ alkylene)CF₃, -(C₁-C₃ alkylene)NO₂, -C=NH(OR^{A1}), -(C₁-C₃ alkylene)C(O)R^{A1}, -(C₁-C₃ alkylene)OC(O)R^{A1}, -(C₁-C₃ alkylene)C(O)OR^{A1}, -(C₁-C₃ alkylene)C(O)NR^{A2}R^{A3}, -(C₁-C₃ alkylene)OC(O)NR^{A2}R^{A3}, -(C₁-C₃ alkylene)NR^{A1}C(O)R^{A2}, -(C₁-C₃ alkylene)NR^{A1}C(O)OR^{A2}, -(C₁-C₃ alkylene)NR^{A1}C(O)NR^{A2}R^{A3}, -(C₁-C₃ alkylene)S(O)R^{A1}, -(C₁-C₃ alkylene)S(O)₂R^{A1}, -(C₁-C₃ alkylene)NR^{A1}S(O)R^{A2}, -C(O)(C₁-C₃ alkylene)NR^{A1}S(O)R^{A2}, -(C₁-C₃ alkylene)NR^{A1}S(O)₂R^{A2}, -(C₁-C₃ alkylene)C(O)NR^{A1}S(O)₂R^{A2}, -(C₁-C₃ alkylene)S(O)NR^{A2}R^{A3}, -(C₁-C₃ alkylene)S(O)₂NR^{A2}R^{A3}, -(C₁-C₃ alkylene)P(O)(OR^{A2})(OR^{A3}), -(C₁-C₃ alkylene)(C₃-C₈ cycloalkyl), -(C₁-C₃ alkylene)(3-12-membered heterocyclyl), -(C₁-C₃ alkylene)(5-10-membered heteroaryl) and -(C₁-C₃ alkylene)(C₆-C₁₄ aryl), wherein the one or more substituents are each independently unsubstituted or substituted with one or more further substituents selected from the group consisting of halogen, oxo, -OR^{A4}, -NR^{A4}R^{A5}, -C(O)R^{A4}, -CN, -S(O)R^{A4}, -S(O)₂R^{A4}, -P(O)(OR^{A4})(OR^{A5}), -(C₁-C₃ alkylene)OR^{A4}, -(C₁-C₃ alkylene)NR^{A4}R^{A5}, -(C₁-C₃ alkylene)C(O)R^{A4}, -(C₁-C₃ alkylene)S(O)R^{A4}, -(C₁-C₃ alkylene)S(O)₂R^{A4}, -(C₁-C₃ alkylene)P(O)(OR^{A4})(OR^{A5}), C₃-C₈ cycloalkyl, C₁-C₆ alkyl, and C₁-C₆ alkyl substituted by oxo, -OH or halogen; wherein each R^{A1} is independently hydrogen, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₈ cycloalkyl, C₆-C₁₄ aryl, 5-6-membered heteroaryl or 3-6-membered heterocyclyl, wherein the C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₈ cycloalkyl, C₆-C₁₄ aryl, 5-6-membered heteroaryl and 3-6-membered heterocyclyl are independently unsubstituted or substituted by halogen, oxo, -CN, -OR^{A6}, -NR^{A6}R^{A7}, -P(O)(OR^{A6})(OR^{A6}), phenyl, phenyl substituted by halogen, C₁-C₆ alkyl, or C₁-C₆ alkyl substituted by halogen, -OH or oxo; R^{A2} and

R^{A3} are each independently hydrogen, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₈ cycloalkyl, C₆-C₁₄ aryl, 5-6-membered heteroaryl or 3-6 membered heterocyclyl, wherein the C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₈ cycloalkyl, C₆-C₁₄ aryl, 5-6-membered heteroaryl and 3-6 membered heterocyclyl are each independently unsubstituted or substituted by halogen, oxo, -CN, -OR^{A6}, -NR^{A6}R^{A7}, C₁-C₆ alkyl, or C₁-C₆ alkyl substituted by halogen, -OH or oxo; and R^{A4}, R^{A5}, R^{A6} and R^{A7} are each independently hydrogen, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ alkyl substituted by one or more halogen, C₂-C₆ alkenyl substituted by one or more halogen, or C₂-C₆ alkynyl substituted by one or more halogen.

[0035] In some embodiments, one of R¹ and R² is -OH and the other is selected from the group consisting of -CN, halogen, -C(O)R^a, -CH=NR^j, -S(O)R^b, -S(O)₂R^c, -NHC(O)R^d, -NHS(O)₂R^e, -C₁-C₆alkyl-R^f, -C₂-C₆alkenyl-R^g, C₃-C₈ cycloalkyl, C₃-C₈ cycloalkenyl, and 5- or 6-membered heterocycloalkyl, wherein the C₃-C₈ cycloalkyl and C₃-C₈ cycloalkenyl are each independently unsubstituted or substituted with one or more =O, and the 5- or 6-membered heterocycloalkyl is unsubstituted or substituted with one or more substituents selected from the group consisting of C₁-C₆alkyl, C₃-C₈cycloalkyl, =O, and -C(O)O-C₁-C₆alkyl;

R^a, R^b, R^c, and R^e are each independently H, C₁-C₆alkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, C₁-C₆haloalkyl, 3- to 10-membered heterocyclyl, 5- to 10-membered heteroaryl, benzoyl, or styryl, wherein the 3- to 10-membered heterocyclyl of R^a, R^b, R^c, and R^e are each independently selected from the group consisting of C₁-C₆alkyl, C₃-C₈cycloalkyl, =O, and -C(O)O-C₁-C₆alkyl, and the 5- to 10-membered heteroaryl of R^a, R^b, R^c, and R^e are each independently selected from the group consisting of C₁-C₆alkyl, C₃-C₈cycloalkyl, and -C(O)O-C₁-C₆alkyl;

R^d is H, C₁-C₆alkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, C₁-C₆haloalkyl, 3- to 10-membered heterocyclyl, 5- to 10-membered heteroaryl, or benzoyl, wherein the 3- to 10-membered heterocyclyl of R^d is selected from the group consisting of C₁-C₆alkyl, C₃-C₈cycloalkyl, =O, and -C(O)O-C₁-C₆alkyl, and the 5- to 10-membered heteroaryl of R^d is selected from the group consisting of C₁-C₆alkyl, C₃-C₈cycloalkyl, and -C(O)O-C₁-C₆alkyl;

R^f and R^g are each independently -OH, unsubstituted 5- to 6-membered heteroaryl, -NR^mRⁿ, benzoyl, or styryl;

R^m and Rⁿ are each independently H, C₁-C₆alkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, or C₃-C₈ cycloalkyl, wherein the C₃-C₈ cycloalkyl is unsubstituted or substituted with one or more groups selected from C₁-C₆alkyl and halo;

R^j is 5- to 6-membered heterocyclyl, 5- to 6-membered heteroaryl, 6- to 12-membered aryl, -OR^k, -NHR^k, -NHC(O)R^k, -NHS(O)₂R^k, or -NHC(NH)NH₂, wherein the 5- to 6-membered heterocyclyl of R^j is unsubstituted or substituted with one or more substituents selected from the group consisting of C₁-C₆alkyl, C₃-C₈cycloalkyl, =O, and -C(O)O-C₁-C₆alkyl, and the 5- to 6-membered heteroaryl and 6- to 12-membered aryl of R^j are each independently unsubstituted or substituted with one or more substituents selected from the group consisting of C₁-C₆alkyl, C₃-C₈cycloalkyl, and -C(O)O-C₁-C₆alkyl; and

R^k is C₁-C₆alkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, C₃-C₈cycloalkyl, or 6- to 12-membered aryl, wherein the C₁-C₆alkyl is unsubstituted or substituted with 5- to 6-membered heterocyclyl or 5- to 6-membered heteroaryl.

[0036] In some embodiments, R^{6a} , R^{6b} , R^{6c} , and R^{6d} are each independently hydrogen, C₁-C₆alkyl, C₁-C₆alkoxy, halo, -OH, -NR^pR^q, C₆-C₁₂ aryl, 3- to 10-membered heterocyclyl, 5- to 10-membered heteroaryl, -C₁-C₆alkyl-5- to 6-membered heterocyclyl, -OC(O)-5- to 6-membered heterocyclyl, -C(O)R^h, -S(O)₂NR^{w1}R^{w2}, -S(O)₂R^y, or -NR^{z1}S(O)₂R^{z2}, wherein the C₁-C₆alkyl and C₁-C₆alkoxy of R^{6a} , R^{6b} , R^{6c} , and R^{6d} are each independently unsubstituted or substituted with one or more groups selected from the group consisting of C₃-C₈ cycloalkyl and halogen; the C₆-C₁₂ aryl and 5- to 10-membered heteroaryl of R^{6a} , R^{6b} , R^{6c} , and R^{6d} are each independently unsubstituted or substituted with one or more groups selected from the group consisting of C₁-C₆alkyl, C₁-C₆alkoxy, C₃-C₈cycloalkyl, -OH, and C₁-C₆alkyl-OH; and the 3- to 10-membered heterocyclyl, -C₁-C₆alkyl-5- to 6-membered heterocyclyl, and -OC(O)-5- to 6-membered heterocyclyl of R^{6a} , R^{6b} , R^{6c} , and R^{6d} are each independently unsubstituted or substituted with one or more groups selected from the group consisting of C₁-C₆alkyl, C₁-C₆alkoxy, halo, -OH, C₁-C₆alkyl-OH, =O, and =S;

R^h is selected from the group consisting of H, C₁-C₆alkyl, C₁-C₆alkoxy, C₃-C₈cycloalkyl, and -NR^rR^s;

R^p is H or C₁-C₆alkyl;

R^q is C₂-C₃alkyl, -C(O)R^t, -C(O)OR^u, -C(O)NR^v;

R^r , R^s , R^{w1} , and R^{z1} each independently selected from H and C₁-C₆alkyl; and

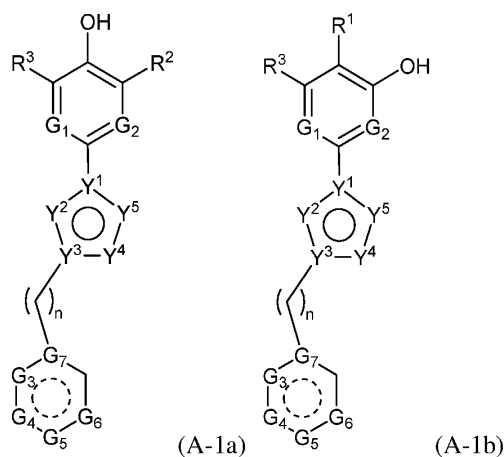
R^t , R^u , R^v , R^{w2} , R^y , and R^{z2} are each independently selected from H, C₁-C₆alkyl, unsubstituted or substituted C₃-C₈cycloalkyl, and unsubstituted or substituted heterocyclyl;

or

G_5 is $CH(X_3-R^{6c})$ or $C(X_3-R^{6c})$, G_6 is $CH(X_4-R^{6d})$ or $C(X_4-R^{6d})$, and R^{6c} and R^{6d} are taken together with the carbon atoms to which they are attached to form a 6-membered aryl, a 6-membered heterocyclyl, or a 6-membered heteroaryl ring; wherein the 6-membered aryl, 6-membered heterocyclyl, and 6-membered heteroaryl rings are each independently unsubstituted or substituted with one or more groups selected from the group consisting of C_1 - C_6 alkyl and $-C(O)O-C_1$ - C_6 alkyl; and

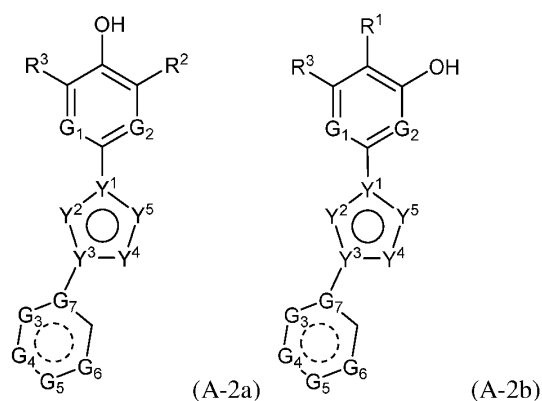
wherein no more than one of R^{6a} , R^{6b} , R^{6c} , and R^{6d} is C_1 - C_6 alkoxy or $-OH$.

[0037] In some embodiments, the compound of Formula (A) is a compound of Formula (A-1a) or (A-1b):



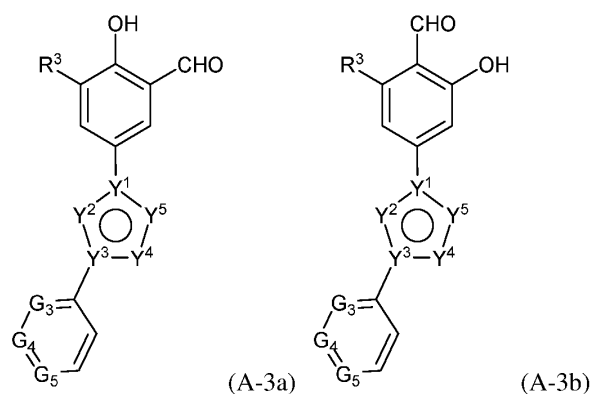
wherein R^1 , R^2 , R^3 , G^1 , G^2 , G^3 , G^4 , G^5 , G^6 , G^7 , Y^1 , Y^2 , Y^3 , Y^4 , Y^5 , and n are as defined for Formula (A).

[0038] In some embodiments, the compound of Formula (A) is a compound of Formula (A-2a) or (A-2b):



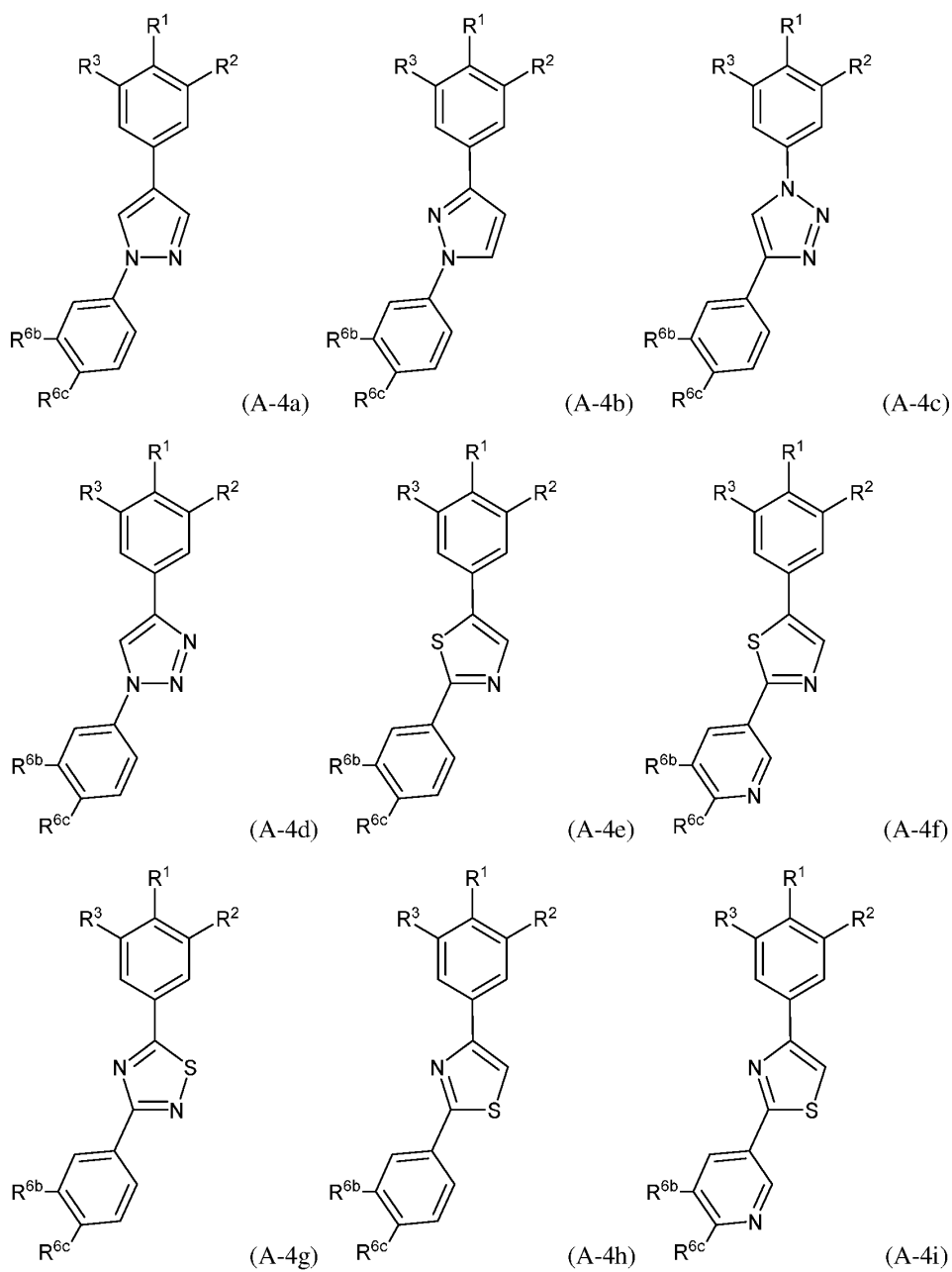
wherein R^1 , R^2 , R^3 , G^1 , G^2 , G^3 , G^4 , G^5 , G^6 , G^7 , Y^1 , Y^2 , Y^3 , Y^4 , and Y^5 are as defined for Formula (A).

[0039] In some embodiments, the compound of Formula (A) is a compound of Formula (A-3a) or (A-3b),



wherein R^3 , G^3 , G^4 , G^5 , Y^1 , Y^2 , Y^3 , Y^4 , and Y^5 are as defined for Formula (A).

[0040] In some embodiments, the compound of Formula (A) is a compound of Formula (A-4a), (A-4b), (A-4c), (A-4d), (A-4e), (A-4f), (A-4g), (A-4h), or (A-4i):

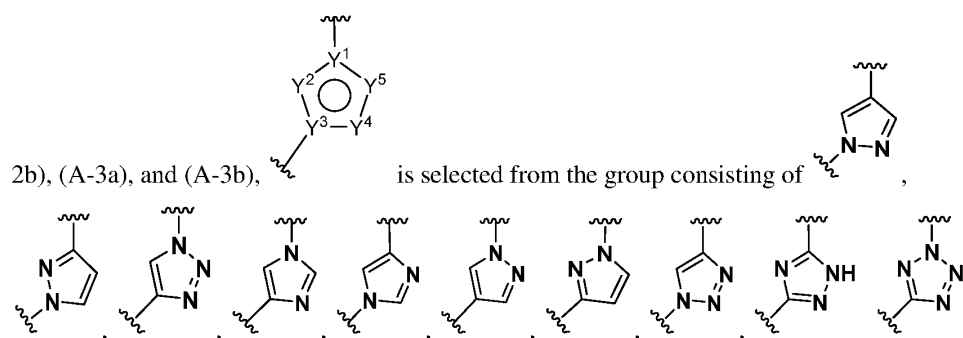


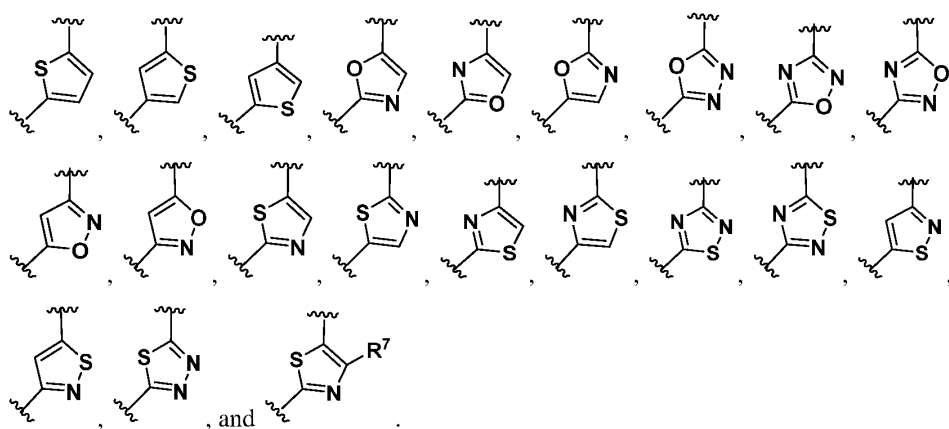
wherein R^1 , R^2 , R^3 , R^{6b} , and R^{6c} are as defined for Formula (A).

[0041] In some embodiments of Formula (A), including Formula (A-1a), (A-1b), (A-2a), (A-2b), (A-3a), and (A-3b), Y^1 is C. In other embodiments, Y^1 is N. In some embodiments, Y^2 is CH. In some embodiments, Y^2 is N. In some embodiments Y^2 is NH. In some embodiments, Y^2 is S. In other embodiments, Y^2 is O. In some embodiments, Y^3 is C. In other embodiments, Y^3 is N. In some embodiments, Y^4 is CH. In some embodiments, Y^4 is N. In some embodiments, Y^4 is NH. In some embodiments, Y^4 is S. In other embodiments, Y^4 is O. In some embodiments, Y^5 is CR^7 , wherein R^7 is H or C_1 - C_6 alkyl. In some embodiments, Y^5 is CH. In some embodiments, Y^5 is CR^7 , wherein R^7 is C_1 - C_6 alkyl. In some embodiments, Y^5 is $C(CH_3)$. In some embodiments, Y^5 is N. In some embodiments, Y^5 is NH. In some embodiments, Y^5 is S. In other embodiments, Y^5 is O.

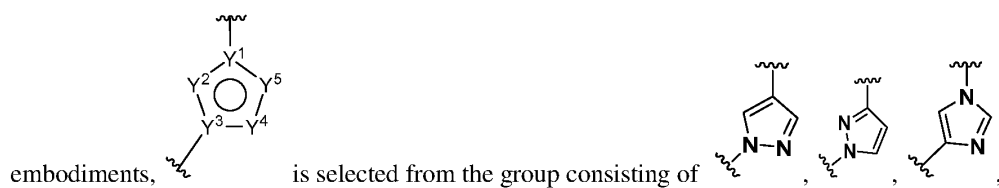
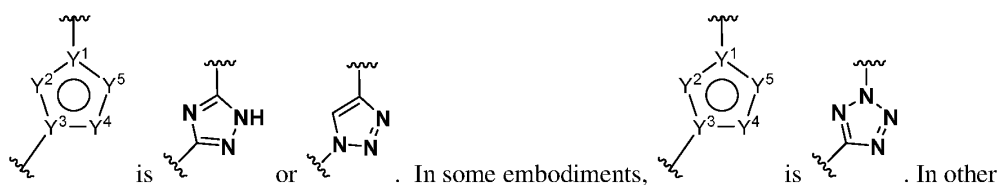
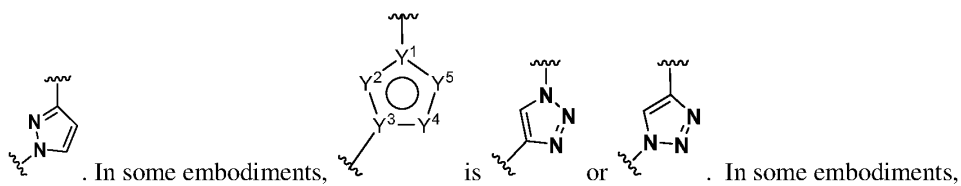
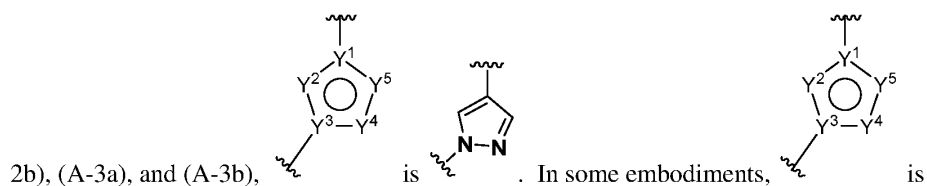
[0042] In some embodiments of Formula (A), including Formula (A-1a), (A-1b), (A-2a), (A-2b), (A-3a), and (A-3b), one of Y^1 , Y^2 , Y^3 , Y^4 , and Y^5 is N, and the rest are other than N. In some embodiments, two of Y^1 , Y^2 , Y^3 , Y^4 , and Y^5 are N, and the rest are other than N. In other embodiments, three of Y^1 , Y^2 , Y^3 , Y^4 , and Y^5 are N, and the rest are other than N. In other embodiments, four of Y^1 , Y^2 , Y^3 , Y^4 , and Y^5 are N. In some embodiments of Formula (A), one of Y^1 , Y^2 , Y^3 , Y^4 , and Y^5 is S, and the rest are other than S. In some embodiments of Formula (A), one of Y^1 , Y^2 , Y^3 , Y^4 , and Y^5 is O, and the rest are other than O. In some embodiments, no more than one of Y^1 , Y^2 , Y^3 , Y^4 , and Y^5 is S or O. In some embodiments, no more than three of Y^1 , Y^2 , Y^3 , Y^4 , and Y^5 are N or NH. In some embodiments, no more than four of Y^1 , Y^2 , Y^3 , Y^4 , and Y^5 are N or NH.

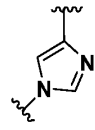
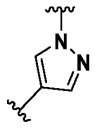
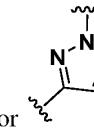
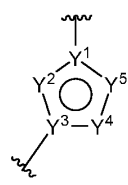
[0043] In some embodiments of Formula (A), including Formula (A-1a), (A-1b), (A-2a), (A-

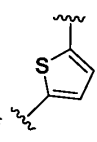
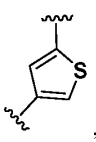
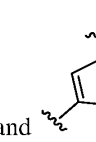


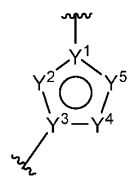
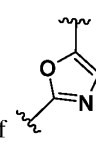
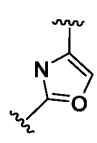
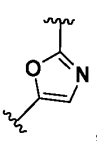
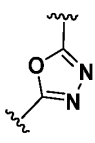


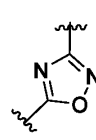
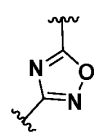
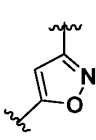
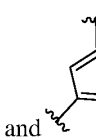
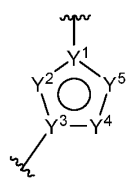
[0044] In some embodiments of Formula (A), including Formula (A-1a), (A-1b), (A-2a), (A-

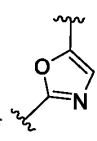
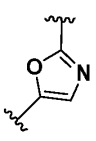
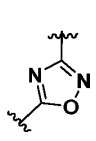
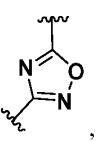
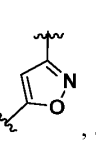
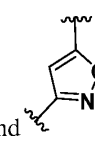


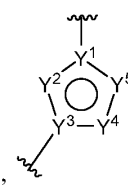
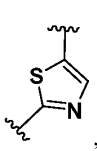
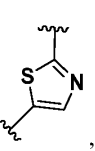
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 In some embodiments of Formula (A),
 
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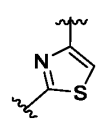
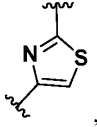
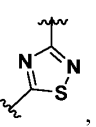
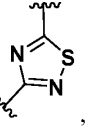
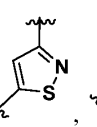
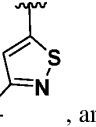
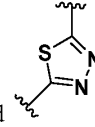
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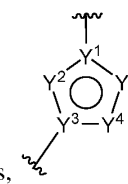
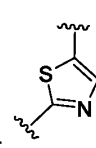
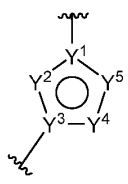
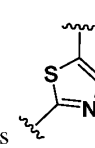

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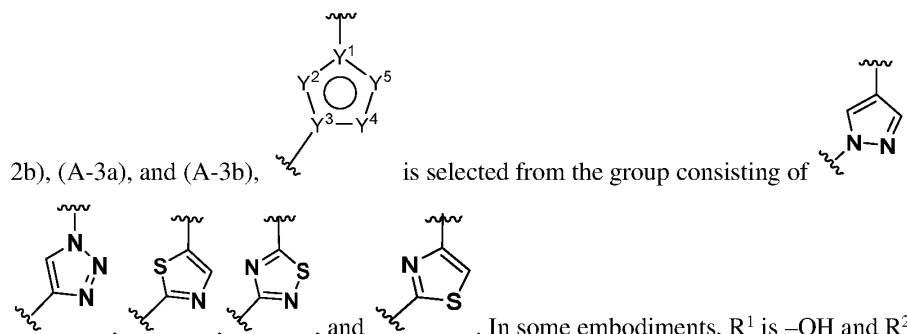
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 In some embodiments,
 
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[0045] In some embodiments of Formula (A), including Formula (A-1a), (A-1b), (A-2a), (A-



C(O)H. In other embodiments, R² is -OH and R¹ is -C(O)H. In some embodiments, R¹ is -OH, R² is -C(O)H, and R³ is halo. In other embodiments, R² is -OH, R¹ is -C(O)H, and R³ is halo. In some embodiments, R¹ is -OH, R² is -C(O)H, and R³ is fluoro. In other embodiments, R² is -OH, R¹ is -C(O)H, and R³ is fluoro.

[0046] In some embodiments of Formula (A), including Formula (A-1a), (A-2a), (A-3a), (A-4a), (A-4b), (A-4c), (A-4d), (A-4e), (A-4f), (A-4g), (A-4h), and (A-4i), R¹ is -OH and R² is selected from the group consisting of -CN, halogen, -C(O)R^a, -CH=NRⁱ, -S(O)R^b, -S(O)₂R^c, -NHC(O)R^d, -NHS(O)₂R^e, -C₁-C₆alkyl-R^f, -C₂-C₆alkenyl-R^g, unsubstituted or substituted C₃-C₈ cycloalkyl, unsubstituted or substituted C₃-C₈ cycloalkenyl, and unsubstituted or substituted heterocycloalkyl. In some embodiments, R¹ is -OH and R² is selected from the group consisting of -CN, halogen, -C(O)R^a, -CH=NRⁱ, -S(O)R^b, -S(O)₂R^c, -NHC(O)R^d, -NHS(O)₂R^e, -C₁-C₆alkyl-R^f, -C₂-C₆alkenyl-R^g, C₃-C₈ cycloalkyl, C₃-C₈ cycloalkenyl, and heterocycloalkyl, wherein the C₃-C₈ cycloalkyl, C₃-C₈ cycloalkenyl, and heterocycloalkyl are optionally substituted with one or more substituents selected from the group consisting of C₁-C₆ alkyl, C₁-C₆ haloalkyl, halo, -OH, -C(O)H, -C(O)OH, -C(O)OC₁-C₆ alkyl, -OC₁-C₆ alkyl, and C₃-C₈ cycloalkyl. In some embodiments, R^a, R^b, R^c, and R^e are each independently H, C₁-C₆alkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, C₁-C₆haloalkyl, unsubstituted or substituted heterocyclyl, unsubstituted or substituted heteroaryl, benzoyl, or styryl. In some embodiments R^a, R^b, R^c, and R^e are each independently H, C₁-C₆alkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, C₁-C₆haloalkyl, heterocyclyl, heteroaryl, benzoyl, or styryl, wherein the heterocyclyl and heteroaryl are optionally substituted with one or more substituents selected from the group consisting of C₁-C₆ alkyl, C₁-C₆ haloalkyl, halo, -OH, -C(O)H, -C(O)OH, -C(O)OC₁-C₆ alkyl, -OC₁-C₆ alkyl, and

C₃-C₈ cycloalkyl. In some embodiments, R^d is H, C₁-C₆alkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, C₁-C₆haloalkyl, unsubstituted or substituted heterocyclyl, unsubstituted or substituted heteroaryl, or benzoyl. In some embodiments, R^d is H, C₁-C₆alkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, C₁-C₆haloalkyl, heterocyclyl, heteroaryl, or benzoyl, wherein the heterocyclyl and heteroaryl are optionally substituted with one or more substituents selected from the group consisting of C₁-C₆alkyl, C₁-C₆haloalkyl, halo, -OH, -C(O)H, -C(O)OH, -C(O)OC₁-C₆alkyl, -OC₁-C₆alkyl, and C₃-C₈cycloalkyl. In some embodiments, R^f and R^g are each independently -OH, unsubstituted heteroaryl, -NR^mRⁿ, benzoyl, or styryl, wherein R^m and Rⁿ are each independently H, C₁-C₆alkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, or C₃-C₈cycloalkyl, wherein the C₃-C₈cycloalkyl is optionally substituted with one or more substituents selected from the group consisting of C₁-C₆alkyl, C₁-C₆haloalkyl, halo, -OH, -C(O)H, -C(O)OH, -C(O)OC₁-C₆alkyl, -OC₁-C₆alkyl, and C₃-C₈cycloalkyl. In some embodiments, R^j is heterocyclyl, aryl, -OR^k, -NHR^k, -NHC(O)R^k, -NHS(O)₂R^k, or -NHC(NH)NH₂, wherein the heterocyclyl and aryl are optionally substituted with one or more substituents selected from the group consisting of C₁-C₆alkyl, C₁-C₆haloalkyl, halo, -OH, -C(O)H, -C(O)OH, -C(O)OC₁-C₆alkyl, -OC₁-C₆alkyl, and C₃-C₈cycloalkyl. In some embodiments, R¹ is -OH and R² is selected from the group consisting of -CN, halogen, -C(O)H, -CH=NR^j, unsubstituted or substituted C₃-C₈cycloalkyl, unsubstituted or substituted C₃-C₈cycloalkenyl, and unsubstituted or substituted heterocycloalkyl.

[0047] In some embodiments of Formula (A), including Formula (A-1b), (A-2b), (A-3b), (A-4a), (A-4b), (A-4c), (A-4d), (A-4e), (A-4f), (A-4g), (A-4h), and (A-4i), R² is -OH and R¹ is selected from the group consisting of -CN, halogen, -C(O)R^a, -CH=NRⁱ, -S(O)R^b, -S(O)₂R^c, -NHC(O)R^d, -NHS(O)₂R^e, -C₁-C₆alkyl-R^f, -C₂-C₆alkenyl-R^g, unsubstituted or substituted C₃-C₈cycloalkyl, unsubstituted or substituted C₃-C₈cycloalkenyl, and unsubstituted or substituted heterocycloalkyl. In some embodiments, R² is -OH and R¹ is selected from the group consisting of -CN, halogen, -C(O)R^a, -CH=NRⁱ, -S(O)R^b, -S(O)₂R^c, -NHC(O)R^d, -NHS(O)₂R^e, -C₁-C₆alkyl-R^f, -C₂-C₆alkenyl-R^g, C₃-C₈cycloalkyl, C₃-C₈cycloalkenyl, and heterocycloalkyl, wherein the C₃-C₈cycloalkyl, C₃-C₈cycloalkenyl, and heterocycloalkyl are optionally substituted with one or more substituents selected from the group consisting of C₁-C₆alkyl, C₁-C₆haloalkyl, halo, -OH, -C(O)H, -C(O)OH, -C(O)OC₁-C₆alkyl, -OC₁-C₆alkyl, and C₃-C₈cycloalkyl. In some embodiments, R^a, R^b, R^c, and R^e are each independently H, C₁-C₆alkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, C₁-C₆haloalkyl, unsubstituted or substituted heterocyclyl,

unsubstituted or substituted heteroaryl, benzoyl, or styryl. In some embodiments R^a , R^b , R^c , and R^e are each independently H, C₁-C₆alkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, C₁-C₆haloalkyl, heterocyclyl, heteroaryl, benzoyl, or styryl, wherein the heterocyclyl and heteroaryl are optionally substituted with one or more substituents selected from the group consisting of C₁-C₆alkyl, C₁-C₆haloalkyl, halo, -OH, -C(O)H, -C(O)OH, -C(O)OC₁-C₆alkyl, -OC₁-C₆alkyl, and C₃-C₈cycloalkyl. In some embodiments, R^d is H, C₁-C₆alkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, C₁-C₆haloalkyl, unsubstituted or substituted heterocyclyl, unsubstituted or substituted heteroaryl, or benzoyl. In some embodiments, R^d is H, C₁-C₆alkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, C₁-C₆haloalkyl, heterocyclyl, heteroaryl, or benzoyl, wherein the heterocyclyl and heteroaryl are optionally substituted with one or more substituents selected from the group consisting of C₁-C₆alkyl, C₁-C₆haloalkyl, halo, -OH, -C(O)H, -C(O)OH, -C(O)OC₁-C₆alkyl, -OC₁-C₆alkyl, and C₃-C₈cycloalkyl. In some embodiments, R^f and R^g are each independently -OH, unsubstituted heteroaryl, -NR^mRⁿ, benzoyl, or styryl, wherein R^m and Rⁿ are each independently H, C₁-C₆alkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, or C₃-C₈cycloalkyl, wherein the C₃-C₈cycloalkyl is optionally substituted with one or more substituents selected from the group consisting of C₁-C₆alkyl, C₁-C₆haloalkyl, halo, -OH, -C(O)H, -C(O)OH, -C(O)OC₁-C₆alkyl, -OC₁-C₆alkyl, and C₃-C₈cycloalkyl. In some embodiments, R^j is heterocyclyl, aryl, -OR^k, -NHR^k, -NHC(O)R^k, -NHS(O)₂R^k, or -NHC(NH)NH₂, wherein the heterocyclyl and aryl are optionally substituted with one or more substituents selected from the group consisting of C₁-C₆alkyl, C₁-C₆haloalkyl, halo, -OH, -C(O)H, -C(O)OH, -C(O)OC₁-C₆alkyl, -OC₁-C₆alkyl, and C₃-C₈cycloalkyl. In some embodiments, R² is -OH and R¹ is selected from the group consisting of -CN, halogen, -C(O)H, -CH=NR^j, unsubstituted or substituted C₃-C₈cycloalkyl, unsubstituted or substituted C₃-C₈cycloalkenyl, and unsubstituted or substituted heterocycloalkyl.

[0048] In some embodiments of Formula (A), including Formula (A-1a), (A-1b), (A-2a), (A-2b), (A-3a), (A-3b), (A-4a), (A-4b), (A-4c), (A-4d), (A-4e), (A-4f), (A-4g), (A-4h), and (A-4i), one of R¹ and R² is -OH and the other is -CH=NR^j, wherein R^j is unsubstituted or substituted heterocyclyl, unsubstituted or substituted aryl, -OR^k, -NHR^k, -NHC(O)R^k, -NHS(O)₂R^k, or -NHC(NH)NH₂. In some embodiments, one of R¹ and R² is -OH and the other is -CH=NR^j, wherein R^j is unsubstituted or substituted heterocyclyl, unsubstituted or substituted aryl, -OR^k, -NHR^k, -NHC(O)R^k, -NHS(O)₂R^k, or -NHC(NH)NHR^{aa}, where R^{aa} is unsubstituted or substituted C₁-C₆alkyl, unsubstituted or substituted C₃-C₈cycloalkyl, unsubstituted or substituted aryl,

unsubstituted or substituted heterocycloalkyl, or unsubstituted or substituted heteroaryl. In some embodiments, R^{aa} is unsubstituted or substituted C_1 - C_6 alkyl. In certain embodiments, R^{aa} is C_1 - C_6 alkyl substituted with $-OH$ or $-(OCH_2CH_2)_vOH$, where v is 1, 2, or 3. In some embodiments, R^{aa} is unsubstituted or substituted C_3 - C_8 cycloalkyl. In some embodiments, R^{aa} is unsubstituted or substituted aryl. In some embodiments, R^{aa} is unsubstituted or substituted C_6 - C_{14} aryl. In some embodiments, R^{aa} is unsubstituted or substituted heterocycloalkyl. In some embodiments, R^{aa} is unsubstituted or substituted 3- to 18-membered heterocycloalkyl. In some embodiments, R^{aa} is unsubstituted or substituted 3- to 6-membered heterocycloalkyl. In some embodiments, R^{aa} is unsubstituted or substituted heteroaryl. In some embodiments, R^{aa} is unsubstituted or substituted 5- to 18-membered heteroaryl. In some embodiments, R^{aa} is unsubstituted or substituted 5- to 10-membered heteroaryl. In some embodiments, R^{aa} is C_3 - C_8 cycloalkyl, C_6 - C_{14} aryl, 3- to 18-membered heterocycloalkyl, or 5- to 18-membered heteroaryl, each optionally substituted with C_1 - C_6 alkyl. In some embodiments, one of R^1 and R^2 is $-OH$ and the other is $-CH=NR^j$, wherein R^j is unsubstituted or substituted 4- to 12-membered heterocyclyl. In some embodiments, one of R^1 and R^2 is $-OH$ and the other is $-CH=NR^j$, wherein R^j is unsubstituted or substituted 5- to 6-membered heterocyclyl. In certain embodiments, one of R^1 and R^2 is $-OH$ and the other is $-CH=NR^j$, wherein R^j is an unsubstituted heterocyclyl. In some embodiments, one of R^1 and R^2 is $-OH$ and the other is $-CH=NR^j$, wherein R^j is pyrrolidinyl, pyrazolidinyl, imidazolidinyl, tetrahydrofuranyl, 1,3-dioxolanyl, tetrahydrothiophenyl, oxathiolanyl, sulfolanyl, piperidinyl, piperazinyl, tetrahydropyranyl, dioxanyl, thianyl, dithianyl, trithianyl, morpholinyl, or thiomorpholinyl. In other embodiments, one of R^1 and R^2 is $-OH$ and the other is $-CH=NR^j$, wherein R^j is a heterocyclyl substituted with one or more substituents selected from the group consisting of C_1 - C_6 alkyl, C_3 - C_8 cycloalkyl, and oxo. In some embodiments, R^j is a heterocyclyl, wherein the nitrogen and/or sulfur atom(s) of the heterocyclyl are optionally oxidized to provide for N-oxide, $-S(O)-$, or $-SO_2-$ moieties.

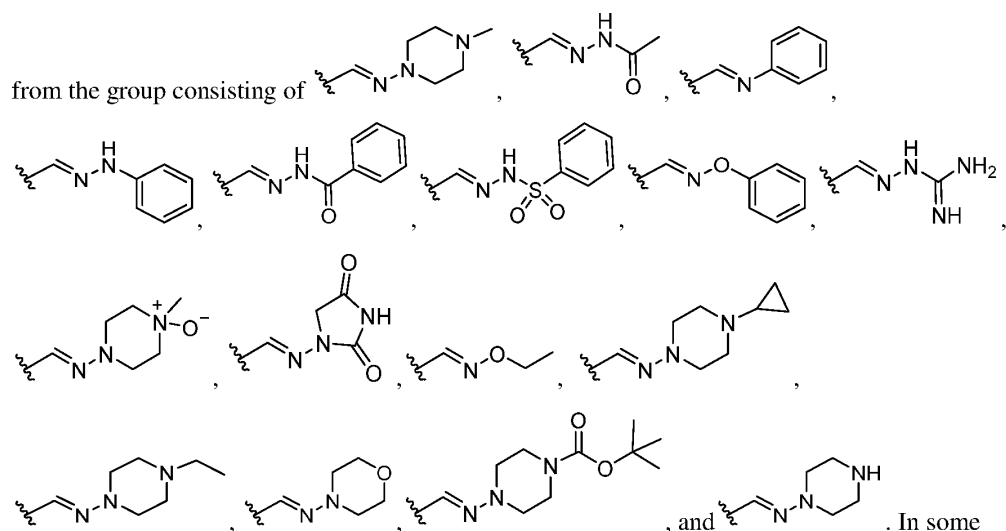
[0049] In some embodiments of Formula (A), including Formula (A-1a), (A-1b), (A-2a), (A-2b), (A-3a), (A-3b), (A-4a), (A-4b), (A-4c), (A-4d), (A-4e), (A-4f), (A-4g), (A-4h), and (A-4i), one of R^1 and R^2 is $-OH$ and the other is $-CH=NR^j$, wherein R^j is unsubstituted or substituted aryl. In some embodiments, one of R^1 and R^2 is $-OH$ and the other is $-CH=NR^j$, wherein R^j is unsubstituted or substituted 6- to 14-membered aryl. In some embodiments, one of R^1 and R^2 is $-OH$ and the other is $-CH=NR^j$, wherein R^j is unsubstituted phenyl or naphthyl. In other

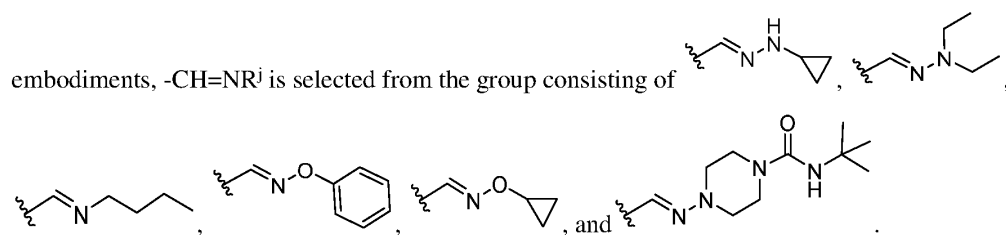
embodiments, one of R^1 and R^2 is $-OH$ and the other is $-CH=NR^j$, wherein R^j is a phenyl or naphthyl substituted with one or more substituents selected from the group consisting of C_1 - C_6 alkyl, C_3 - C_8 cycloalkyl, and oxo.

[0050] In some embodiments of Formula (A), including Formula (A-1a), (A-1b), (A-2a), (A-2b), (A-3a), (A-3b), (A-4a), (A-4b), (A-4c), (A-4d), (A-4e), (A-4f), (A-4g), (A-4h), and (A-4i), one of R^1 and R^2 is $-OH$ and the other is $-CH=NR^j$, wherein R^j is $-OR^k$. In some embodiments, one of R^1 and R^2 is $-OH$ and the other is $-CH=NR^j$, wherein R^j is $-OC_1$ - C_6 alkyl. In some embodiments, one of R^1 and R^2 is $-OH$ and the other is $-CH=NR^j$, wherein R^j is $-OC_1$ - C_6 alkenyl or $-OC_1$ - C_6 alkynyl. In some embodiments, one of R^1 and R^2 is $-OH$ and the other is $-CH=NR^j$, wherein R^j is $-OC_3$ - C_8 cycloalkyl. In other embodiments, one of R^1 and R^2 is $-OH$ and the other is $-CH=NR^j$, wherein R^j is $-O$ -aryl. In some embodiments, one of R^1 and R^2 is $-OH$ and the other is $-CH=NR^j$, wherein R^j is $-NHR^k$. In some embodiments, one of R^1 and R^2 is $-OH$ and the other is $-CH=NR^j$, wherein R^j is $-NHC_1$ - C_6 alkyl. In some embodiments, one of R^1 and R^2 is $-OH$ and the other is $-CH=NR^j$, wherein R^j is $-NHC_1$ - C_6 alkenyl or $-NHC_1$ - C_6 alkynyl. In some embodiments, one of R^1 and R^2 is $-OH$ and the other is $-CH=NR^j$, wherein R^j is $-NHC_3$ - C_8 cycloalkyl. In other embodiments, one of R^1 and R^2 is $-OH$ and the other is $-CH=NR^j$, wherein R^j is $-NH$ -aryl. In some embodiments, one of R^1 and R^2 is $-OH$ and the other is $-CH=NR^j$, wherein R^j is $-NHC(O)R^k$. In some embodiments, one of R^1 and R^2 is $-OH$ and the other is $-CH=NR^j$, wherein R^j is $-NHC(O)C_1$ - C_6 alkyl. In some embodiments, one of R^1 and R^2 is $-OH$ and the other is $-CH=NR^j$, wherein R^j is $-NHC(O)C_1$ - C_6 alkenyl or $-NHC(O)C_1$ - C_6 alkynyl. In some embodiments, one of R^1 and R^2 is $-OH$ and the other is $-CH=NR^j$, wherein R^j is $-NHC(O)C_3$ - C_8 cycloalkyl. In other embodiments, one of R^1 and R^2 is $-OH$ and the other is $-CH=NR^j$, wherein R^j is $-NHC(O)$ -aryl. In some embodiments, one of R^1 and R^2 is $-OH$ and the other is $-CH=NR^j$, wherein R^j is $-NHS(O)_2R^k$. In some embodiments, one of R^1 and R^2 is $-OH$ and the other is $-CH=NR^j$, wherein R^j is $-NHS(O)_2C_1$ - C_6 alkyl. In some embodiments, one of R^1 and R^2 is $-OH$ and the other is $-CH=NR^j$, wherein R^j is $-NHS(O)_2C_1$ - C_6 alkenyl or $-NHS(O)_2C_1$ - C_6 alkynyl. In some embodiments, one of R^1 and R^2 is $-OH$ and the other is $-CH=NR^j$, wherein R^j is $-NHS(O)_2C_3$ - C_8 cycloalkyl. In other embodiments, one of R^1 and R^2 is $-OH$ and the other is $-CH=NR^j$, wherein R^j is $-NHS(O)_2$ -aryl. In some embodiments, one of R^1 and R^2 is $-OH$ and the other is $-CH=NR^j$, wherein R^j is $-NHC(NH)NHR^{aa}$. In some embodiments, R^{aa} is unsubstituted or substituted C_1 - C_6 alkyl. In certain embodiments, R^{aa} is C_1 - C_6 alkyl substituted

with $-\text{OH}$ or $-(\text{OCH}_2\text{CH}_2)_v\text{OH}$, where v is 1, 2, or 3. In some embodiments, R^{aa} is unsubstituted or substituted C_3 - C_8 cycloalkyl. In some embodiments, R^{aa} is unsubstituted or substituted aryl. In some embodiments, R^{aa} is unsubstituted or substituted C_6 - C_{14} aryl. In some embodiments, R^{aa} is unsubstituted or substituted heterocycloalkyl. In some embodiments, R^{aa} is unsubstituted or substituted 3- to 18-membered heterocycloalkyl. In some embodiments, R^{aa} is unsubstituted or substituted 3- to 6-membered heterocycloalkyl. In some embodiments, R^{aa} is unsubstituted or substituted heteroaryl. In some embodiments, R^{aa} is unsubstituted or substituted 5- to 18-membered heteroaryl. In some embodiments, R^{aa} is unsubstituted or substituted 5- to 10-membered heteroaryl. In some embodiments, R^{aa} is C_3 - C_8 cycloalkyl, C_6 - C_{14} aryl, 3- to 18-membered heterocycloalkyl, or 5- to 18-membered heteroaryl, each optionally substituted with C_1 - C_6 alkyl.

[0051] In some embodiments of Formula (A), including Formula (A-1a), (A-1b), (A-2a), (A-2b), (A-3a), (A-3b), (A-4a), (A-4b), (A-4c), (A-4d), (A-4e), (A-4f), (A-4g), (A-4h), and (A-4i), one of R^1 and R^2 is $-\text{OH}$ and the other is $-\text{CH}=\text{NR}^j$, wherein R^j is $-\text{NHC}(\text{NH})\text{NH}_2$. In some embodiments, one of R^1 and R^2 is $-\text{OH}$ and the other is $-\text{CH}=\text{NR}^j$, wherein $-\text{CH}=\text{NR}^j$ is selected





[0052] In some embodiments of Formula (A), including Formula (A-1a), (A-1b), (A-2a), (A-2b), (A-3a), (A-3b), (A-4a), (A-4b), (A-4c), (A-4d), (A-4e), (A-4f), (A-4g), (A-4h), and (A-4i), one of R^1 and R^2 is $-\text{OH}$ and the other is $-\text{C}_1\text{-C}_6\text{alkyl-R}^f$, wherein R^f is selected from the group consisting of $-\text{OH}$, unsubstituted heteroaryl, $-\text{NR}^m\text{R}^n$, benzoyl, or styryl, and R^m and R^n are each independently H, $\text{C}_1\text{-C}_6\text{alkyl}$, $\text{C}_2\text{-C}_6\text{alkenyl}$, $\text{C}_2\text{-C}_6\text{alkynyl}$, or unsubstituted or substituted $\text{C}_3\text{-C}_8$ cycloalkyl. In some embodiments, one of R^1 and R^2 is $-\text{OH}$ and the other is $-\text{C}_2\text{-C}_6\text{alkenyl-R}^g$, wherein R^g is selected from the group consisting of $-\text{OH}$, unsubstituted heteroaryl, $-\text{NR}^m\text{R}^n$, benzoyl, or styryl, and R^m and R^n are each independently H, $\text{C}_1\text{-C}_6\text{alkyl}$, $\text{C}_2\text{-C}_6\text{alkenyl}$, $\text{C}_2\text{-C}_6\text{alkynyl}$, or unsubstituted or substituted $\text{C}_3\text{-C}_8$ cycloalkyl. In some embodiments, R^m and R^n are each independently H, $\text{C}_1\text{-C}_6\text{alkyl}$, $\text{C}_2\text{-C}_6\text{alkenyl}$, $\text{C}_2\text{-C}_6\text{alkynyl}$, or unsubstituted $\text{C}_3\text{-C}_8$ cycloalkyl, or $\text{C}_3\text{-C}_8$ cycloalkyl substituted with one or more substituents selected from the group consisting of $\text{C}_1\text{-C}_6\text{alkyl}$, $\text{C}_2\text{-C}_6\text{alkenyl}$, $\text{C}_2\text{-C}_6\text{alkynyl}$, $\text{C}_1\text{-C}_6\text{alkoxy}$, $\text{C}_1\text{-C}_6\text{haloalkyl}$, $-\text{OH}$, and halo. In some embodiments, R^m is unsubstituted or substituted $\text{C}_3\text{-C}_8$ cycloalkyl, and R^n is H, $\text{C}_1\text{-C}_6\text{alkyl}$, $\text{C}_2\text{-C}_6\text{alkenyl}$, or $\text{C}_2\text{-C}_6\text{alkynyl}$. In some embodiments, R^m is $\text{C}_3\text{-C}_8$ cycloalkyl, and R^n is H.

[0053] In some embodiments of Formula (A), including Formula (A-1a), (A-1b), (A-2a), (A-2b), (A-3a), (A-3b), (A-4a), (A-4b), (A-4c), (A-4d), (A-4e), (A-4f), (A-4g), (A-4h), and (A-4i), one of R^1 and R^2 is $-\text{OH}$ and the other is unsubstituted $\text{C}_3\text{-C}_8$ cycloalkyl. In other embodiments, one of R^1 and R^2 is $-\text{OH}$ and the other is substituted $\text{C}_3\text{-C}_8$ cycloalkyl. In some embodiments, one of R^1 and R^2 is $-\text{OH}$ and the other is unsubstituted $\text{C}_3\text{-C}_8$ cycloalkenyl. In other embodiments, one of R^1 and R^2 is $-\text{OH}$ and the other is substituted $\text{C}_3\text{-C}_8$ cycloalkenyl.

[0054] In some embodiments of Formula (A), including Formula (A-1a), (A-1b), (A-2a), (A-2b), (A-3a), (A-3b), (A-4a), (A-4b), (A-4c), (A-4d), (A-4e), (A-4f), (A-4g), (A-4h), and (A-4i), R^3 is selected from the group consisting of $\text{C}_1\text{-C}_6\text{alkyl}$, $\text{C}_1\text{-C}_6\text{alkoxy}$, and halogen. In some embodiments, R^3 is methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, secbutyl, or tertbutyl. In

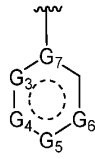
some embodiments, R³ is methyl, ethyl, isopropyl, or tertbutyl. In some embodiments, R³ is methoxy, ethoxy, propoxy, isopropoxy, butoxy, or tertbutoxy. In some embodiments, R³ is F, Cl, Br, or I. In some embodiments, R³ is -OCH₃. In some embodiments, R³ is F. In other embodiments, R³ is H.

[0055] In some embodiments of Formula (A), including Formula (A-1a), (A-1b), (A-2a), (A-2b), (A-3a), (A-3b), (A-4a), (A-4b), (A-4c), (A-4d), (A-4e), (A-4f), (A-4g), (A-4h), and (A-4i), one of R¹ and R² is -OH and the other is -C(O)H. In some embodiments, R¹ is -OH, R² is -C(O)H, and R³ is H. In some embodiments, R¹ is -OH, R² is -C(O)H, and R³ is unsubstituted C₁-C₆alkyl. In some embodiments, R¹ is -OH, R² is -C(O)H, and R³ is C₁-C₆haloalkyl. In some embodiments, R¹ is -OH, R² is -C(O)H, and R³ is unsubstituted C₁-C₆alkoxy. In some embodiments, R¹ is -OH, R² is -C(O)H, and R³ is C₁-C₆alkoxy substituted with one or more halogen. In other embodiments, R¹ is -OH, R² is -C(O)H, and R³ is halogen. In certain embodiments, R¹ is -OH, R² is -C(O)H, and R³ is fluoro. In certain embodiments, R¹ is -OH, R² is -C(O)H, and R³ is methyl. In some embodiments, R¹ is -OH, R² is -C(O)H, and R³ is methoxy. In some embodiments, R² is -OH, R¹ is -C(O)H, and R³ is H. In some embodiments, R² is -OH, R¹ is -C(O)H, and R³ is unsubstituted C₁-C₆alkyl. In some embodiments, R² is -OH, R¹ is -C(O)H, and R³ is C₁-C₆haloalkyl. In some embodiments, R² is -OH, R¹ is -C(O)H, and R³ is unsubstituted C₁-C₆alkoxy. In some embodiments, R² is -OH, R¹ is -C(O)H, and R³ is C₁-C₆alkoxy substituted with one or more halogen. In other embodiments, R² is -OH, R¹ is -C(O)H, and R³ is halogen. In certain embodiments, R² is -OH, R¹ is -C(O)H, and R³ is fluoro. In certain embodiments, R² is -OH, R¹ is -C(O)H, and R³ is methyl. In some embodiments, R² is -OH, R¹ is -C(O)H, and R³ is methoxy.

[0056] In some embodiments of Formula (A), including Formula (A-1a), (A-1b), (A-2a), and (A-2b), G₁ and G₂ are each CH. In some embodiments, G₁ is CH and G₂ is N. In other embodiments, G₁ is N and G₂ is CH.

[0057] In some embodiments of Formula (A), including Formula (A-1a) and (A-1b), n is 0. In some embodiments, n is 1. In some embodiments, n is 2. In other embodiments, n is 3. In some embodiments, R⁴ is C₁-C₆alkoxy. In some embodiments, R⁴ is methoxy, ethoxy, propoxy,

isopropoxy, butoxy, isobutoxy, secbutoxy, or tertbutoxy. In other embodiments, R^4 is



In some embodiments, n is 0 and R^4 is alkoxy. In some embodiments, n is 0 and R^4 is



In some embodiments, n is 1 and R^4 is alkoxy. In some embodiments, n is 1 and R^4 is



In some embodiments, n is 2 and R^4 is alkoxy. In some embodiments, n is 2 and R^4 is



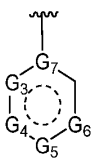
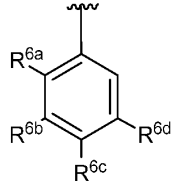
In some embodiments, n is 3 and R^4 is alkoxy. In some embodiments, n is 3 and R^4 is



[0058] In some embodiments of Formula (A), including Formula (A-1a), (A-1b), (A-2a), and (A-2b), G_3 is $CH(X_1-R^{6a})$, $C(X_1-R^{6a})$, N, $N(X_1-R^{6a})$, S, or O; G_4 is $CH(X_2-R^{6b})$, $C(X_2-R^{6b})$, N, $N(X_2-R^{6b})$, S, or O; G_5 is $CH(X_3-R^{6c})$, $C(X_3-R^{6c})$, N, $N(X_3-R^{6c})$, S, or O; G_6 is $CH(X_4-R^{6d})$, $C(X_4-R^{6d})$, N, $N(X_4-R^{6d})$, S, O, or absent; and G_7 is N, C, or CH, wherein G_1 , G_2 , G_3 , G_4 , G_5 , G_6 , and G_7 each have a charge of zero (e.g., the nitrogen of G_1 , G_2 , G_3 , G_4 , G_5 , G_6 , and G_7 is not cationic).

[0059] In some embodiments of Formula (A), including Formula (A-1a), (A-1b), (A-2a),

and (A-2b),

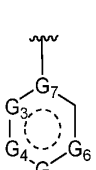
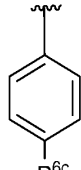



is

, wherein one or more of R^{6a} , R^{6b} , R^{6c} , and R^{6d} is

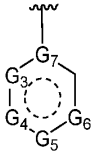
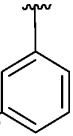
selected from the group consisting of C₁-C₆alkyl, C₁-C₆alkoxy, halo, -OH, -NR^pR^q, C₆-C₁₂ aryl, 3- to 10-membered heterocyclyl, 5- to 10-membered heteroaryl, -C₁-C₆alkyl-5- to 6-membered heterocyclyl, -OC(O)-5- to 6-membered heterocyclyl, -C(O)R^h, -S(O)₂NR^{w1}R^{w2}, -S(O)₂R^y, and -NR^{z1}S(O)₂R^{z2}.

[0060] In some embodiments of Formula (A), including Formula (A-1a), (A-1b), (A-2a),

and (A-2b),  is , wherein R^{6c} is selected from the group consisting of C₁-C₆alkyl, C₁-C₆alkoxy, halo, -OH, -NR^pR^q, C₆-C₁₂ aryl, 3- to 10-membered heterocyclyl, 5- to 10-membered heteroaryl, -C₁-C₆alkyl-5- to 6-membered heterocyclyl, -OC(O)-5- to 6-membered heterocyclyl, -C(O)R^h, -S(O)₂NR^{w1}R^{w2}, -S(O)₂R^y, or -NR^{z1}S(O)₂R^{z2}. In some embodiments, R^{6c} is unsubstituted C₁-C₆alkyl. For instance, in some embodiments, R^{6c} is methyl, ethyl, propyl, isopropyl, butyl, isobutyl, secbutyl, and tertbutyl. In some embodiments, R^{6c} is C₁-C₆alkyl substituted with one or more groups selected from the group consisting of C₃-C₈ cycloalkyl and halogen. In some embodiments, R^{6c} is C₁-C₆alkoxy. For instance, in some embodiments, R^{6c} is methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, secbutoxy, and tertbutoxy. In some embodiments, R^{6c} is C₁-C₆alkoxy substituted with one or more groups selected from the group consisting of C₃-C₈ cycloalkyl and halogen. In some embodiments, R^{6c} is halo. For instance, in some embodiments, R^{6c} is fluoro, chloro, or bromo. In other embodiments, R^{6c} is C₁-C₆haloalkyl. For instance, in some embodiments, R^{6c} is fluoroethyl, trifluoromethyl, difluoromethyl, trifluoroethyl, and trichloromethyl. In some embodiments, R^{6c} is -C(O)R^h, wherein R^h is H, C₁-C₆alkyl, C₁-C₆alkoxy, C₃-C₈cycloalkyl, or -NR^rR^s. For instance, in some embodiments, R^{6c} is -C(O)H, -C(O)CH₃, -C(O)OC(CH₃)₃, or -C(O)-cyclopropyl. In some embodiments, R^{6c} is an unsubstituted 5- to 6-membered heterocycle. In some embodiments, R^{6c} is a 5- to 6-membered heterocycle, substituted with one or more groups selected from the group consisting of C₁-C₆alkyl, C₁-C₆alkoxy, halo, -OH, C₁-C₆alkyl-OH, =O, and =S. In some embodiments, R^{6c} is pyrrolidinyl, pyrazolidinyl, imidazolidinyl, tetrahydrofuranyl, 1,3-dioxolanyl, tetrahydrothiophenyl, oxathiolanyl, sulfolanyl, piperidinyl, piperazinyl, tetrahydropyranyl, dioxanyl, thianyl, dithianyl, trithianyl, morpholinyl, or thiomorpholinyl, each optionally substituted with one or more substituents selected from the

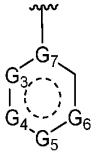
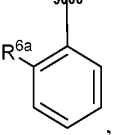
group consisting of C₁-C₆alkyl, C₁-C₆alkoxy, halo, -OH, C₁-C₆alkyl-OH, =O, and =S. In some embodiments, R^{6c} is pyrrolidinyl, pyrazolidinyl, imidazolidinyl, tetrahydrofuranyl, 1,3-dioxolanyl, tetrahydrothiophenyl, oxathiolanyl, sulfolanyl, piperidinyl, piperazinyl, tetrahydropyranyl, dioxanyl, thianyl, dithianyl, trithianyl, morpholinyl, or thiomorpholinyl. In some embodiments, R^{6c} is pyrrolidinyl. In certain embodiments, R^{6c} is 4-pyrrolidin-1-yl. In some embodiments, R^{6c} is an unsubstituted 5- to 10-membered heteroaryl. In some embodiments, R^{6c} is a 5- to 10-membered heteroaryl, substituted with one or more groups selected from the group consisting of C₁-C₆alkyl, C₁-C₆alkoxy, -OH, and C₁-C₆alkyl-OH. In some embodiments, R^{6c} is pyrrolyl, pyrazolyl, imidazolyl, triazolyl, tetrazolyl, furanyl, isoxazolyl, oxazolyl, oxadiazolyl, thiophenyl, isothiazolyl, thiazolyl, thiadiazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl, or tetrazinyl, each substituted with one or more substituents selected from the group consisting of C₁-C₆alkyl, C₁-C₆alkoxy, -OH, and C₁-C₆alkyl-OH. In some embodiments, R^{6c} is pyrrolyl, pyrazolyl, imidazolyl, triazolyl, tetrazolyl, furanyl, isoxazolyl, oxazolyl, oxadiazolyl, thiophenyl, isothiazolyl, thiazolyl, thiadiazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl, or tetrazinyl.

[0061] In some embodiments of Formula (A), including Formula (A-1a), (A-1b), (A-2a),

and (A-2b),  is  R^{6b}, wherein R^{6b} is selected from the group consisting of C₁-C₆alkyl, C₁-C₆alkoxy, halo, -OH, -NR^pR^q, C₆-C₁₂ aryl, 3- to 10-membered heterocyclyl, 5- to 10-membered heteroaryl, -C₁-C₆alkyl-5- to 6-membered heterocyclyl, -OC(O)-5- to 6-membered heterocyclyl, -C(O)R^h, -S(O)₂NR^{w1}R^{w2}, -S(O)₂R^y, or -NR^{z1}S(O)₂R^{z2}. In some embodiments, R^{6b} is unsubstituted C₁-C₆alkyl. For instance, in some embodiments, R^{6b} is methyl, ethyl, propyl, isopropyl, butyl, isobutyl, secbutyl, and tertbutyl. In some embodiments, R^{6b} is C₁-C₆alkyl substituted with one or more groups selected from the group consisting of C₃-C₈ cycloalkyl and halogen. In some embodiments, R^{6b} is C₁-C₆alkoxy. For instance, in some embodiments, R^{6b} is methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, secbutoxy, and tertbutoxy. In some embodiments, R^{6b} is C₁-C₆alkoxy substituted with one or more groups selected from the group consisting of C₃-C₈ cycloalkyl and halogen. In some embodiments, R^{6b} is halo. For instance, in some embodiments, R^{6b} is fluoro, chloro, or bromo. In other

embodiments, R^{6b} is C_1 - C_6 haloalkyl. For instance, in some embodiments, R^{6b} is fluoroethyl, trifluoromethyl, difluoromethyl, trifluoroethyl, and trichloromethyl. In some embodiments, R^{6b} is $-C(O)R^h$, wherein R^h is H, C_1 - C_6 alkyl, C_1 - C_6 alkoxy, C_3 - C_8 cycloalkyl, or $-NR^iR^j$. For instance, in some embodiments, R^{6b} is $-C(O)H$, $-C(O)CH_3$, $-C(O)OC(CH_3)_3$, or $-C(O)$ -cyclopropyl. In some embodiments, R^{6b} is an unsubstituted 5- to 6-membered heterocycle. In some embodiments, R^{6b} is a 5- to 6-membered heterocycle, substituted with one or more groups selected from the group consisting of C_1 - C_6 alkyl, C_1 - C_6 alkoxy, halo, $-OH$, C_1 - C_6 alkyl- $-OH$, $=O$, and $=S$. In some embodiments, R^{6b} is pyrrolidinyl, pyrazolidinyl, imidazolidinyl, tetrahydrofuranyl, 1,3-dioxolanyl, tetrahydrothiophenyl, oxathiolanyl, sulfolanyl, piperidinyl, piperazinyl, tetrahydropyranyl, dioxanyl, thianyl, dithianyl, trithianyl, morpholinyl, or thiomorpholinyl, each substituted with one or more substituents selected from the group consisting of C_1 - C_6 alkyl, C_1 - C_6 alkoxy, halo, $-OH$, C_1 - C_6 alkyl- $-OH$, $=O$, and $=S$. In some embodiments, R^{6b} is pyrrolidinyl, pyrazolidinyl, imidazolidinyl, tetrahydrofuranyl, 1,3-dioxolanyl, tetrahydrothiophenyl, oxathiolanyl, sulfolanyl, piperidinyl, piperazinyl, tetrahydropyranyl, dioxanyl, thianyl, dithianyl, trithianyl, morpholinyl, or thiomorpholinyl. In some embodiments, R^{6b} is an unsubstituted 5- to 10-membered heteroaryl. In some embodiments, R^{6b} is a 5- to 10-membered heteroaryl, substituted with one or more groups selected from the group consisting of C_1 - C_6 alkyl, C_1 - C_6 alkoxy, $-OH$, and C_1 - C_6 alkyl- $-OH$. In some embodiments, R^{6b} is pyrrolyl, pyrazolyl, imidazolyl, triazolyl, tetrazolyl, furanyl, isoxazolyl, oxazolyl, oxadiazolyl, thiophenyl, isothiazolyl, thiazolyl, thiadiazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl, or tetrazinyl, each substituted with one or more groups selected from the group consisting of C_1 - C_6 alkyl, C_1 - C_6 alkoxy, $-OH$, and C_1 - C_6 alkyl- $-OH$. In some embodiments, R^{6b} is pyrrolyl, pyrazolyl, imidazolyl, triazolyl, tetrazolyl, furanyl, isoxazolyl, oxazolyl, oxadiazolyl, thiophenyl, isothiazolyl, thiazolyl, thiadiazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl, or tetrazinyl.

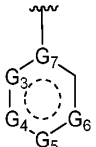
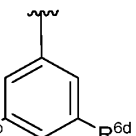
[0062] In some embodiments of Formula (A), including Formula (A-1a), (A-1b), (A-2a),

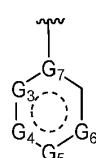
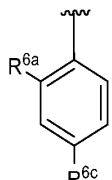
and (A-2b),  is , wherein R^{6a} is selected from the group consisting of C_1 - C_6 alkyl, C_1 - C_6 alkoxy, halo, $-OH$, $-NR^pR^q$, C_6 - C_{12} aryl, 3- to 10-membered heterocyclyl, 5- to

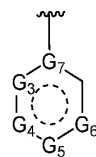
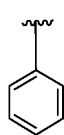
10-membered heteroaryl, -C₁-C₆alkyl-5- to 6-membered heterocyclyl, -OC(O)-5- to 6-membered heterocyclyl, -C(O)R^h, -S(O)₂NR^{w1}R^{w2}, -S(O)₂R^y, or -NR^{z1}S(O)₂R^{z2}. In some embodiments, R^{6a} is unsubstituted C₁-C₆alkyl. For instance, in some embodiments, R^{6a} is methyl, ethyl, propyl, isopropyl, butyl, isobutyl, secbutyl, and tertbutyl. In some embodiments, R^{6a} is C₁-C₆alkyl substituted with one or more groups selected from the group consisting of C₃-C₈cycloalkyl and halogen. In some embodiments, R^{6a} is C₁-C₆alkoxy. For instance, in some embodiments, R^{6a} is methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, secbutoxy, and tertbutoxy. In some embodiments, R^{6a} is C₁-C₆alkoxy substituted with one or more groups selected from the group consisting of C₃-C₈cycloalkyl and halogen. In some embodiments, R^{6a} is halo. For instance, in some embodiments, R^{6a} is fluoro, chloro, or bromo. In other embodiments, R^{6a} is C₁-C₆haloalkyl. For instance, in some embodiments, R^{6a} is fluoroethyl, trifluoromethyl, difluoromethyl, trifluoroethyl, and trichloromethyl. In some embodiments, R^{6a} is -C(O)R^h, wherein R^h is H, C₁-C₆alkyl, C₁-C₆alkoxy, C₃-C₈cycloalkyl, or -NR^rR^s. For instance, in some embodiments, R^{6a} is -C(O)H, -C(O)CH₃, -C(O)OC(CH₃)₃, or -C(O)-cyclopropyl. In some embodiments, R^{6a} is an unsubstituted 5- to 6-membered heterocycle. In some embodiments, R^{6a} is a 5- to 6-membered heterocycle, substituted with one or more groups selected from the group consisting of C₁-C₆alkyl, C₁-C₆alkoxy, halo, -OH, C₁-C₆alkyl-OH, =O, and =S. In some embodiments, R^{6a} is pyrrolidinyl, pyrazolidinyl, imidazolidinyl, tetrahydrofuranyl, 1,3-dioxolanyl, tetrahydrothiophenyl, oxathiolanyl, sulfolanyl, piperidinyl, piperazinyl, tetrahydropyranyl, dioxanyl, thianyl, dithianyl, trithianyl, morpholinyl, or thiomorpholinyl, each substituted with one or more substituents selected from the group consisting of C₁-C₆alkyl, C₁-C₆alkoxy, halo, -OH, C₁-C₆alkyl-OH, =O, and =S. In some embodiments, R^{6a} is pyrrolidinyl, pyrazolidinyl, imidazolidinyl, tetrahydrofuranyl, 1,3-dioxolanyl, tetrahydrothiophenyl, oxathiolanyl, sulfolanyl, piperidinyl, piperazinyl, tetrahydropyranyl, dioxanyl, thianyl, dithianyl, trithianyl, morpholinyl, or thiomorpholinyl. In some embodiments, R^{6a} is an unsubstituted 5- to 10-membered heteroaryl. In some embodiments, R^{6a} is a 5- to 10-membered heteroaryl, substituted with one or more groups selected from the group consisting of C₁-C₆alkyl, C₁-C₆alkoxy, -OH, and C₁-C₆alkyl-OH. In some embodiments, R^{6a} is pyrrolyl, pyrazolyl, imidazolyl, triazolyl, tetrazolyl, furanyl, isoxazolyl, oxazolyl, oxadiazolyl, thiophenyl, isothiazolyl, thiazolyl, thiadiazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl, or tetrazinyl, each substituted with one or more substituents selected from the group consisting of C₁-C₆alkyl, C₁-C₆alkoxy, -OH, and C₁-

C₆alkyl-OH. In some embodiments, R^{6a} is pyrrolyl, pyrazolyl, imidazolyl, triazolyl, tetrazolyl, furanyl, isoxazolyl, oxazolyl, oxadiazolyl, thiophenyl, isothiazolyl, thiazolyl, thiadiazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl, or tetrazinyl.

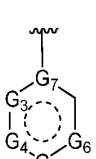
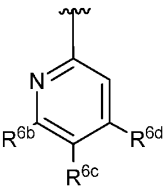
[0063] In some embodiments of Formula (A), including Formula (A-1a), (A-1b), (A-2a),

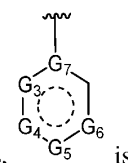
and (A-2b),  is , wherein R^{6b} and R^{6d} are each independently selected from the group consisting of C₁-C₆alkyl, C₁-C₆alkoxy, halo, -OH, -NR^pR^q, C₆-C₁₂ aryl, 3- to 10-membered heterocyclyl, 5- to 10-membered heteroaryl, -C₁-C₆alkyl-5- to 6-membered heterocyclyl, -OC(O)-5- to 6-membered heterocyclyl, -C(O)R^h, -S(O)₂NR^{w1}R^{w2}, -S(O)₂R^y, or -

NR^{z1}S(O)₂R^{z2}. In some embodiments,  is , wherein R^{6a} and R^{6c} are each independently selected from the group consisting of C₁-C₆alkyl, C₁-C₆alkoxy, halo, -OH, -NR^pR^q, C₆-C₁₂ aryl, 3- to 10-membered heterocyclyl, 5- to 10-membered heteroaryl, -C₁-C₆alkyl-5- to 6-membered heterocyclyl, -OC(O)-5- to 6-membered heterocyclyl, -C(O)R^h, -

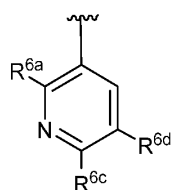
S(O)₂NR^{w1}R^{w2}, -S(O)₂R^y, or -NR^{z1}S(O)₂R^{z2}. In some embodiments,  is .

[0064] In some embodiments of Formula (A), including Formula (A-1a), (A-1b), (A-2a),

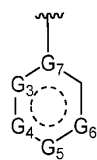
and (A-2b),  is , wherein one or more of R^{6b}, R^{6c}, and R^{6d} is selected from the group consisting of C₁-C₆alkyl, C₁-C₆haloalkyl, halo, C₆-C₁₂ aryl, 3- to 10-membered



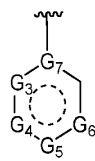
heterocyclyl, and 5- to 10-membered heteroaryl. In some embodiments,



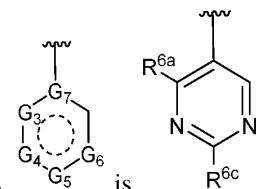
, wherein one or more of R^{6a}, R^{6c}, and R^{6d} is selected from the group consisting of C₁-C₆alkyl, C₁-C₆haloalkyl, halo, C₆-C₁₂ aryl, 3- to 10-membered heterocyclyl, and 5- to 10-



membered heteroaryl. In some embodiments, is R^{6b}, wherein one or more of R^{6a}, R^{6b}, and R^{6d} is selected from the group consisting of C₁-C₆alkyl, C₁-C₆haloalkyl, halo, C₆-C₁₂ aryl, 3- to 10-membered heterocyclyl, and 5- to 10-membered heteroaryl. In some

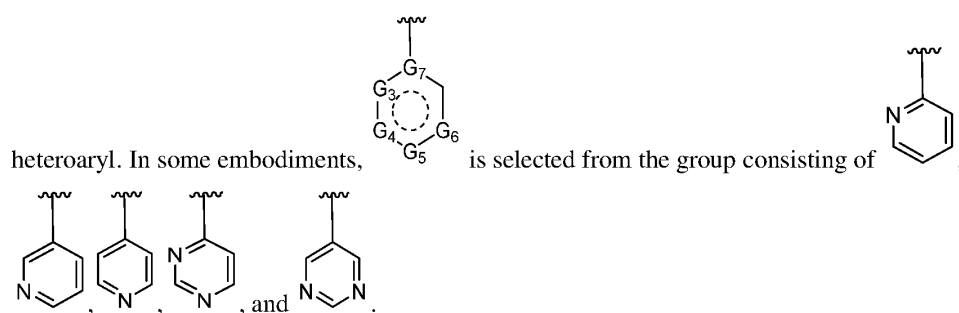


embodiments, is R^{6b}, wherein one or both of R^{6b} and R^{6d} is selected from the group consisting of C₁-C₆alkyl, C₁-C₆haloalkyl, halo, C₆-C₁₂ aryl, 3- to 10-membered

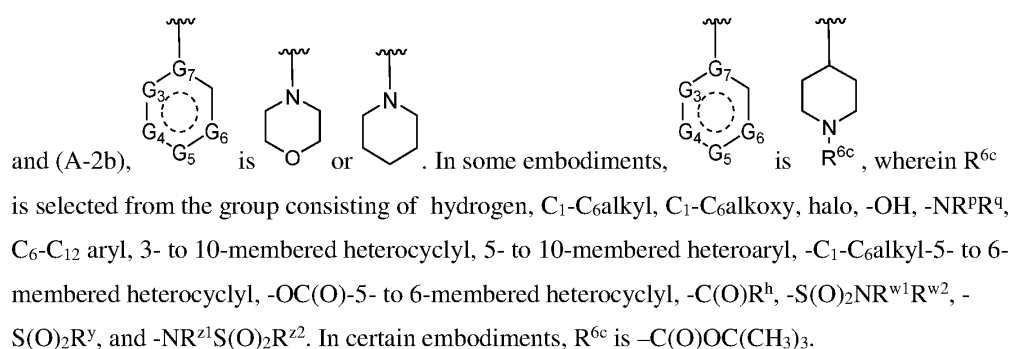


heterocyclyl, and 5- to 10-membered heteroaryl. In some embodiments,

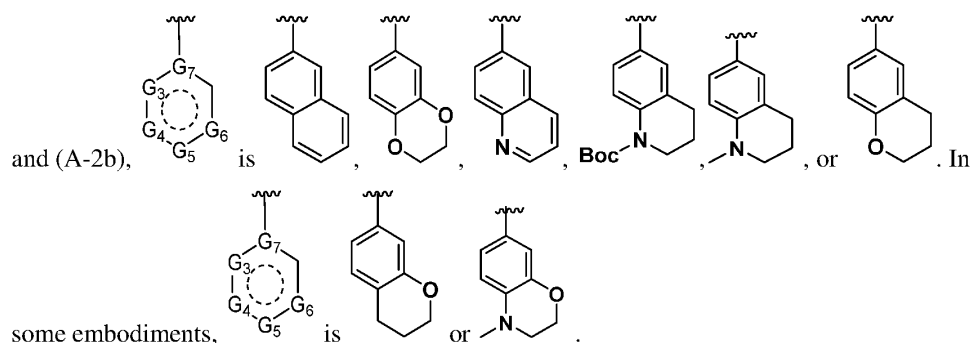
wherein one or both of R^{6a} and R^{6c} is selected from the group consisting of C₁-C₆alkyl, C₁-C₆haloalkyl, halo, C₆-C₁₂ aryl, 3- to 10-membered heterocyclyl, and 5- to 10-membered



[0065] In some embodiments of Formula (A), including Formula (A-1a), (A-1b), (A-2a),



[0066] In some embodiments of Formula (A), including Formula (A-1a), (A-1b), (A-2a),

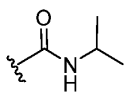
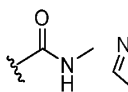


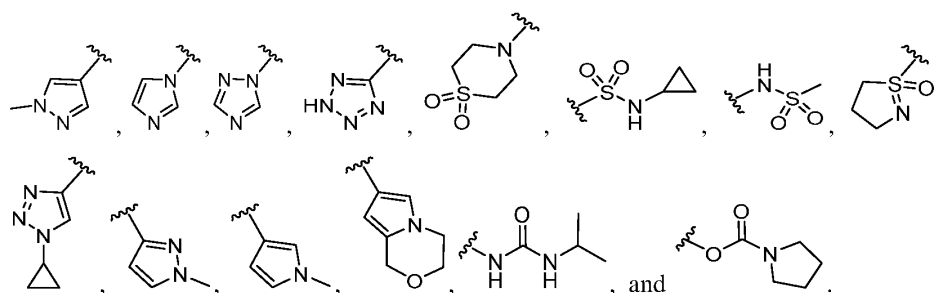
[0067] In any of the foregoing embodiments of Formula (A), including Formula (A-1a), (A-1b), (A-2a), and (A-2b), one or more of R^{6a}, R^{6b}, R^{6c}, and R^{6d} is selected from the group consisting of C₁-C₆alkyl, C₁-C₆haloalkyl, halo, C₆-C₁₂ aryl, 3- to 10-membered heterocyclyl, and 5- to 10-membered heteroaryl. In some embodiments, one or more of R^{6a}, R^{6b}, R^{6c}, and R^{6d} is C₆-C₁₂ aryl, unsubstituted or substituted with one or more groups selected from the group consisting of C₁-C₆alkyl, C₁-C₆alkoxy, -OH, and C₁-C₆alkyl-OH. For instance, in some

embodiments, one of R^{6a} , R^{6b} , R^{6c} , and R^{6d} is phenyl or naphthyl. In some embodiments, one or more of R^{6a} , R^{6b} , R^{6c} , and R^{6d} is 3- to 10-membered heterocyclyl, unsubstituted or substituted with one or more groups selected from the group consisting of C_1 - C_6 alkyl, C_1 - C_6 alkoxy, halo, -OH, C_1 - C_6 alkyl-OH, =O, and =S. For instance, in some embodiments, one of R^{6a} , R^{6b} , R^{6c} , and R^{6d} is pyrrolidinyl, pyrazolidinyl, imidazolidinyl, tetrahydrofuranyl, 1,3-dioxolanyl, tetrahydrothiophenyl, oxathiolanyl, sulfolanyl, piperidinyl, piperazinyl, tetrahydropyranyl, dioxanyl, thianyl, dithianyl, trithianyl, morpholinyl, thiomorpholinyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, decahydroquinolinyl, decahydroisoquinolinyl, indolinyl, isoindolinyl, tetrahydronaphthylridinyl or hexahydrobenzoimidazolyl, each independently unsubstituted or substituted with one or more groups selected from the group consisting of C_1 - C_6 alkyl, C_1 - C_6 alkoxy, halo, -OH, C_1 - C_6 alkyl-OH, =O, and =S.

[0068] In some embodiments of Formula (A), including Formula (A-1a), (A-1b), (A-2a), and (A-2b), one of R^{6a} , R^{6b} , R^{6c} , and R^{6d} is selected from the group consisting of C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, halo, C_6 - C_{12} aryl, 3- to 10-membered heterocyclyl, and 5- to 10-membered heteroaryl. In certain embodiments, one of R^{6a} , R^{6b} , R^{6c} , and R^{6d} is selected from the group consisting of methyl, ethyl, F, Cl, $-CF_3$, pyrrolidinyl, piperidinyl, morpholinyl, piperazinyl, pyrazolyl, and triazolyl. In certain embodiments, one of R^{6a} , R^{6b} , R^{6c} , and R^{6d} is selected from the group consisting of pyrrolidinyl, piperidinyl, morpholinyl, piperazinyl, pyrazolyl, and triazolyl, each optionally substituted with one or more groups selected from the group consisting of C_1 - C_6 alkyl, C_1 - C_6 alkoxy, halo, -OH, C_1 - C_6 alkyl-OH, =O, and =S. In some embodiments, two or three of R^{6a} , R^{6b} , R^{6c} , and R^{6d} is selected from the group consisting of methyl, ethyl, F, Cl, $-CF_3$, pyrrolidinyl, piperidinyl, morpholinyl, piperazinyl, pyrazolyl, and triazolyl. In some embodiments, one of R^{6a} , R^{6b} , R^{6c} , and R^{6d} is selected from the group consisting of methyl,

ethyl, methoxy, F, Cl, $-CF_3$, , , and . In some embodiments, one of

R^{6a} , R^{6b} , R^{6c} , and R^{6d} is selected from the group consisting of , , and .



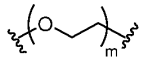
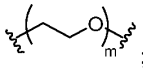
[0069] In other embodiments of Formula (A), including Formula (A-1a), (A-1b), (A-2a), and (A-2b), R^{6a} , R^{6b} , R^{6c} , and R^{6d} are each H.

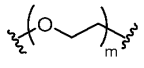
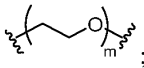
[0070] In some embodiments of Formula (A), including Formula (A-1a), (A-1b), (A-2a), (A-2b), (A-3a), and (A-3b), G_3 is $CH(X_1-R^{6a})$, $C(X_1-R^{6a})$, or $N(X_1-R^{6a})$, X_1 is absent,

; and R^{6a} is hydrogen, C_1 - C_6 alkyl, C_1 - C_6 alkoxy, halo, -OH, - NR^pR^q , aryl, heterocyclyl, heteroaryl, - C_1 - C_6 alkyl-heterocyclyl, -OC(O)-heterocyclyl, -C(O) R^h , -S(O) $_2NR^{w1}R^{w2}$, -S(O) $_2R^y$, or - $NR^{z1}S(O)_2R^{z2}$, wherein the C_1 - C_6 alkyl and C_1 - C_6 alkoxy of R^{6a} are each independently unsubstituted or substituted with one or more groups selected from the group consisting of cycloalkyl and halogen; the aryl and heteroaryl of R^{6a} are each independently unsubstituted or substituted with one or more groups selected from the group consisting of C_1 - C_6 alkyl, C_1 - C_6 alkoxy, C_3 - C_8 cycloalkyl, -OH, and C_1 - C_6 alkyl-OH; and the heterocyclyl, - C_1 - C_6 alkyl-heterocyclyl, and -OC(O)-heterocyclyl of R^{6a} are each independently unsubstituted or substituted with one or more groups selected from the group consisting of C_1 - C_6 alkyl, C_1 - C_6 alkoxy, halo, -OH, C_1 - C_6 alkyl-OH, =O, and =S; R^h is selected from the group consisting of H, C_1 - C_6 alkyl, C_1 - C_6 alkoxy, and C_3 - C_8 cycloalkyl, and - NR^pR^q ; R^p is H or C_1 - C_6 alkyl; R^q is C_2 - C_3 alkyl, -C(O) R^t , -C(O) OR^u , -C(O) NR^v ; R^t , R^s , R^{w1} , and R^{z1} each independently selected from H and C_1 - C_6 alkyl; and R^t , R^u , R^v , R^{w2} , R^y , and R^{z2} are each independently selected from H, C_1 - C_6 alkyl, unsubstituted or substituted C_3 - C_8 cycloalkyl, and unsubstituted or substituted heterocyclyl.

[0071] In some embodiments of Formula (A), including Formula (A-1a), (A-1b), (A-2a), (A-2b), (A-3a), and (A-3b), G_3 is $CH(X_1-R^{6a})$ or $C(X_1-R^{6a})$, wherein X_1 is absent; R^{6a} is hydrogen, C_1 - C_6 alkyl, C_1 - C_6 alkoxy, halo, -OH, - NR^pR^q , aryl, heterocyclyl, heteroaryl, or -C(O) R^h , wherein C_1 - C_6 alkyl and C_1 - C_6 alkoxy are unsubstituted or substituted with C_3 - C_8 cycloalkyl or halogen;

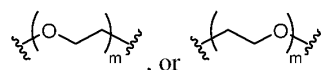
R^p is H or C₁-C₆alkyl; R^q is C₂-C₃alkyl; and R^h is selected from the group consisting of H, C₁-C₆alkyl, C₁-C₆alkoxy, or C₃-C₈ cycloalkyl. In some embodiments, G_3 is CH(X_1 - R^{6a}) or C(X_1 -

R^{6a}), wherein X_1 is  or ; m is 1-6; R^{6a} is hydrogen, C₁-C₆alkyl, C₁-C₆alkoxy, halo, -OH, -NR^pR^q, aryl, heterocyclyl, heteroaryl, or -C(O)R^h, wherein C₁-C₆alkyl and C₁-C₆alkoxy are unsubstituted or substituted with C₃-C₈ cycloalkyl or halogen; R^p is H or C₁-C₆alkyl; R^q is C₂-C₃alkyl; and R^h is selected from the group consisting of H, C₁-C₆alkyl, C₁-C₆alkoxy, or C₃-C₈ cycloalkyl. In some embodiments, G_3 is N or N(X_1 - R^{6a}), wherein X_1 is absent; R^{6a} is hydrogen, C₁-C₆alkyl, C₁-C₆alkoxy, halo, -OH, -NR^pR^q, aryl, heterocyclyl, heteroaryl, or -C(O)R^h, wherein C₁-C₆alkyl and C₁-C₆alkoxy are unsubstituted or substituted with C₃-C₈ cycloalkyl or halogen; R^p is H or C₁-C₆alkyl; R^q is C₂-C₃alkyl; and R^h is selected from the group consisting of H, C₁-C₆alkyl, C₁-C₆alkoxy, or C₃-C₈ cycloalkyl. In some

embodiments, G_3 is N or N(X_1 - R^{6a}), wherein X_1 is  or ; m is 1-6; R^{6a} is hydrogen, C₁-C₆alkyl, C₁-C₆alkoxy, halo, -OH, -NR^pR^q, aryl, heterocyclyl, heteroaryl, or -C(O)R^h, wherein C₁-C₆alkyl and C₁-C₆alkoxy are unsubstituted or substituted with C₃-C₈ cycloalkyl or halogen; R^p is H or C₁-C₆alkyl; R^q is C₂-C₃alkyl; and R^h is selected from the group consisting of H, C₁-C₆alkyl, C₁-C₆alkoxy, or C₃-C₈ cycloalkyl. In some of any of the preceding embodiments, R^{6a} is methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, secbutyl, or tertbutyl. In some of any of the preceding embodiments, R^{6a} is C₁-C₆ alkyl substituted with C₃-C₈ cycloalkyl or halogen. In some of any of the preceding embodiments, R^{6a} is methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, secbutoxy, or tertbutoxy. In some of any of the preceding embodiments, R^{6a} is C₁-C₆alkoxy substituted with C₃-C₈ cycloalkyl or halogen. In some of any of the preceding embodiments, R^{6a} is fluoro, chloro, bromo, or iodo. In some of any of the preceding embodiments, R^{6a} is -N(CH₂CH₃)₂, -N(CH₂CH₂CH₃)₂, or -N(CH₂CH₃)(CH₂CH₂CH₃). In some of any of the preceding embodiments, R^{6a} is phenyl or naphthyl. In some of any of the preceding embodiments, R^{6a} is a 5- to 14-membered heterocyclyl. In some embodiments, R^{6a} is a 5- to 6-membered heterocyclyl. In some of any of the preceding embodiments, R^{6a} is pyrrolidinyl, pyrazolidinyl, imidazolidinyl, tetrahydrofuranyl, 1,3-dioxolanyl, tetrahydrothiophenyl, oxathiolanyl, sulfolanyl, piperidinyl, piperazinyl, tetrahydropyranyl, dioxanyl, thianyl, dithianyl, trithianyl, morpholinyl, or thiomorpholinyl. In some of any of the preceding embodiments, R^{6a} is a 5- to 14-membered heteroaryl. In some

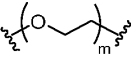
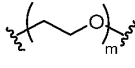
embodiments, R^{6a} is a 5- to 6-membered heteroaryl. In some of any of the preceding embodiments, R^{6a} is pyrrolyl, pyrazolyl, imidazolyl, triazolyl, tetrazolyl, furanyl, isoxazolyl, oxazolyl, oxadiazolyl, thiophenyl, isothiazolyl, thiazolyl, thiadiazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl, or tetrazinyl. In some of any of the preceding embodiments, R^{6a} is aryl, heterocyclyl, or heteroaryl, each substituted with C_1 - C_6 alkyl. In some of any of the preceding embodiments, R^{6a} is $-C(O)H$, $-C(O)C_1$ - C_6 alkyl, $-C(O)C_1$ - C_6 alkoxy, or $-C(O)C_3$ - C_8 cycloalkyl. In some of any of the preceding embodiments, R^{6a} is $-OH$, $-NR^pR^q$, aryl, heterocyclyl, heteroaryl, unsubstituted C_1 - C_6 alkoxy, or C_1 - C_6 alkoxy substituted with C_3 - C_8 cycloalkyl or halogen. In some of any of the preceding embodiments, R^{6a} is hydrogen, $-CH_3$, $-OH$, $-OCH_3$, $-C(O)OC(CH_3)_3$, $-N(CH_2CH_3)_2$, phenyl, morpholinyl, piperidinyl, piperazinyl, 4-ethylpiperazinyl, pyrrolidinyl, pyrazolyl, cyclopropylmethoxy, or cyclopropanecarbonyl. In some embodiments, G_3 is S. In other embodiments, G_3 is O.

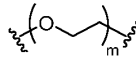
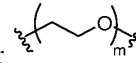
[0072] In some embodiments of Formula (A), including Formula (A-1a), (A-1b), (A-2a), (A-2b), (A-3a), and (A-3b), G_4 is $CH(X_2-R^{6b})$, $C(X_2-R^{6b})$, or $N(X_2-R^{6b})$, wherein X_2 is absent,



; R^{6b} is hydrogen, C_1 - C_6 alkyl, C_1 - C_6 alkoxy, halo, $-OH$, $-NR^pR^q$, aryl, heterocyclyl, heteroaryl, $-C_1$ - C_6 alkyl-heterocyclyl, $-OC(O)$ -heterocyclyl, $-C(O)R^h$, $-S(O)_2NR^{w1}R^{w2}$, $-S(O)_2R^y$, or $-NR^{z1}S(O)_2R^{z2}$, wherein the C_1 - C_6 alkyl and C_1 - C_6 alkoxy of R^{6b} are each independently unsubstituted or substituted with one or more groups selected from the group consisting of cycloalkyl and halogen; the aryl and heteroaryl of R^{6b} are each independently unsubstituted or substituted with one or more groups selected from the group consisting of C_1 - C_6 alkyl, C_1 - C_6 alkoxy, C_3 - C_8 cycloalkyl, $-OH$, and C_1 - C_6 alkyl- $-OH$; and the heterocyclyl, $-C_1$ - C_6 alkyl-heterocyclyl, and $-OC(O)$ -heterocyclyl of R^{6b} are each independently unsubstituted or substituted with one or more groups selected from the group consisting of C_1 - C_6 alkyl, C_1 - C_6 alkoxy, halo, $-OH$, C_1 - C_6 alkyl- $-OH$, $=O$, and $=S$; R^h is selected from the group consisting of H, C_1 - C_6 alkyl, C_1 - C_6 alkoxy, and C_3 - C_8 cycloalkyl, and $-NR^pR^q$; R^p is H or C_1 - C_6 alkyl; R^q is C_2 - C_3 alkyl, $-C(O)R^t$, $-C(O)OR^u$, $-C(O)NR^v$; R^t , R^s , R^{w1} , and R^{z1} each independently selected from H and C_1 - C_6 alkyl; and R^t , R^u , R^v , R^{w2} , R^y , and R^{z2} are each independently selected from H, C_1 - C_6 alkyl, unsubstituted or substituted C_3 - C_8 cycloalkyl, and unsubstituted or substituted heterocyclyl.

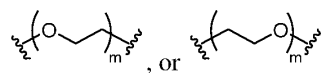
[0073] In some embodiments of Formula (A), including Formula (A-1a), (A-1b), (A-2a), (A-2b), (A-3a), and (A-3b), G_4 is $CH(X_2-R^{6b})$ or $C(X_2-R^{6b})$, wherein X_2 is absent; R^{6b} is hydrogen, C_1 - C_6 alkyl, C_1 - C_6 alkoxy, halo, $-OH$, $-NR^pR^q$, aryl, heterocyclyl, heteroaryl, or $-C(O)R^h$, wherein C_1 - C_6 alkyl and C_1 - C_6 alkoxy are unsubstituted or substituted with C_3 - C_8 cycloalkyl or halogen; R^p is H or C_1 - C_6 alkyl; R^q is C_2 - C_3 alkyl; and R^h is selected from the group consisting of H, C_1 - C_6 alkyl, C_1 - C_6 alkoxy, or C_3 - C_8 cycloalkyl. In some embodiments, G_4 is $CH(X_2-R^{6b})$ or $C(X_2-$

$R^{6b})$, wherein X_2 is  or ; m is 1-6; R^{6b} is hydrogen, C_1 - C_6 alkyl, C_1 - C_6 alkoxy, halo, $-OH$, $-NR^pR^q$, aryl, heterocyclyl, heteroaryl, or $-C(O)R^h$, wherein C_1 - C_6 alkyl and C_1 - C_6 alkoxy are unsubstituted or substituted with C_3 - C_8 cycloalkyl or halogen; R^p is H or C_1 - C_6 alkyl; R^q is C_2 - C_3 alkyl; and R^h is selected from the group consisting of H, C_1 - C_6 alkyl, C_1 - C_6 alkoxy, or C_3 - C_8 cycloalkyl. In some embodiments, G_4 is N or $N(X_2-R^{6b})$, wherein X_2 is absent; R^{6b} is hydrogen, C_1 - C_6 alkyl, C_1 - C_6 alkoxy, halo, $-OH$, $-NR^pR^q$, aryl, heterocyclyl, heteroaryl, or $-C(O)R^h$, wherein C_1 - C_6 alkyl and C_1 - C_6 alkoxy are unsubstituted or substituted with C_3 - C_8 cycloalkyl or halogen; R^p is H or C_1 - C_6 alkyl; R^q is C_2 - C_3 alkyl; and R^h is selected from the group consisting of H, C_1 - C_6 alkyl, C_1 - C_6 alkoxy, or C_3 - C_8 cycloalkyl. In some

embodiments, G_4 is N or $N(X_2-R^{6b})$, wherein X_2 is  or ; m is 1-6; R^{6b} is hydrogen, C_1 - C_6 alkyl, C_1 - C_6 alkoxy, halo, $-OH$, $-NR^pR^q$, aryl, heterocyclyl, heteroaryl, or $-C(O)R^h$, wherein C_1 - C_6 alkyl and C_1 - C_6 alkoxy are unsubstituted or substituted with C_3 - C_8 cycloalkyl or halogen; R^p is H or C_1 - C_6 alkyl; R^q is C_2 - C_3 alkyl; and R^h is selected from the group consisting of H, C_1 - C_6 alkyl, C_1 - C_6 alkoxy, or C_3 - C_8 cycloalkyl. In some of any of the preceding embodiments, R^{6b} is methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, secbutyl, or tertbutyl. In some of any of the preceding embodiments, R^{6b} is C_1 - C_6 alkyl substituted with C_3 - C_8 cycloalkyl or halogen. In some of any of the preceding embodiments, R^{6b} is methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, secbutoxy, or tertbutoxy. In some of any of the preceding embodiments, R^{6b} is C_1 - C_6 alkoxy substituted with C_3 - C_8 cycloalkyl or halogen. In some of any of the preceding embodiments, R^{6b} is fluoro, chloro, bromo, or iodo. In some of any of the preceding embodiments, R^{6b} is $-N(CH_2CH_3)_2$, $-N(CH_2CH_2CH_3)_2$, or $-N(CH_2CH_3)(CH_2CH_2CH_3)$. In some of any of the preceding embodiments, R^{6b} is phenyl or naphthyl. In some of any of the preceding embodiments, R^{6b} is a 5- to 14-membered heterocyclyl. In some embodiments, R^{6b} is a 5- to 6-membered heterocyclyl. In some of any of

the preceding embodiments, R^{6b} is pyrrolidinyl, pyrazolidinyl, imidazolidinyl, tetrahydrofuranyl, 1,3-dioxolanyl, tetrahydrothiophenyl, oxathiolanyl, sulfolanyl, piperidinyl, piperazinyl, tetrahydropyranyl, dioxanyl, thianyl, dithianyl, trithianyl, morpholinyl, or thiomorpholinyl. In some of any of the preceding embodiments, R^{6b} is a 5- to 14-membered heteroaryl. In some embodiments, R^{6b} is a 5- to 6-membered heteroaryl. In some of any of the preceding embodiments, R^{6b} is pyrrolyl, pyrazolyl, imidazolyl, triazolyl, tetrazolyl, furanyl, isoxazolyl, oxazolyl, oxadiazolyl, thiophenyl, isothiazolyl, thiazolyl, thiadiazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl, or tetrazinyl. In some of any of the preceding embodiments, R^{6b} is aryl, heterocyclyl, or heteroaryl, each substituted with C_1 - C_6 alkyl. In some of any of the preceding embodiments, R^{6b} is $-C(O)H$, $-C(O)C_1$ - C_6 alkyl, $-C(O)C_1$ - C_6 alkoxy, or $-C(O)C_3$ - C_8 cycloalkyl. In some of any of the preceding embodiments, R^{6b} is $-OH$, $-NR^pR^q$, aryl, heterocyclyl, heteroaryl, unsubstituted C_1 - C_6 alkoxy, or C_1 - C_6 alkoxy substituted with C_3 - C_8 cycloalkyl or halogen. In some of any of the preceding embodiments, R^{6b} is hydrogen, $-CH_3$, $-OH$, $-OCH_3$, $-C(O)OC(CH_3)_3$, $-N(CH_2CH_3)_2$, phenyl, morpholinyl, piperidinyl, piperazinyl, 4-ethylpiperazinyl, pyrrolidinyl, pyrazolyl, cyclopropylmethoxy, or cyclopropanecarbonyl. In some embodiments, G_4 is S. In other embodiments, G_4 is O.

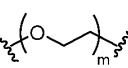
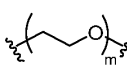
[0074] In some embodiments of Formula (A), including Formula (A-1a), (A-1b), (A-2a), (A-2b), (A-3a), and (A-3b), G_5 is $CH(X_3-R^{6c})$, $C(X_3-R^{6c})$, or $N(X_3-R^{6c})$, wherein X_3 is absent,

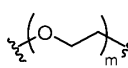
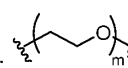


; R^{6c} is hydrogen, C_1 - C_6 alkyl, C_1 - C_6 alkoxy, halo, $-OH$, $-NR^pR^q$, aryl, heterocyclyl, heteroaryl, $-C_1$ - C_6 alkyl-heterocyclyl, $-OC(O)$ -heterocyclyl, $-C(O)R^h$, $-S(O)_2NR^{w1}R^{w2}$, $-S(O)_2R^y$, or $-NR^{z1}S(O)_2R^{z2}$, wherein the C_1 - C_6 alkyl and C_1 - C_6 alkoxy of R^{6c} are each independently unsubstituted or substituted with one or more groups selected from the group consisting of cycloalkyl and halogen; the aryl and heteroaryl of R^{6c} are each independently unsubstituted or substituted with one or more groups selected from the group consisting of C_1 - C_6 alkyl, C_1 - C_6 alkoxy, C_3 - C_8 cycloalkyl, $-OH$, and C_1 - C_6 alkyl- $-OH$; and the heterocyclyl, $-C_1$ - C_6 alkyl-heterocyclyl, and $-OC(O)$ -heterocyclyl of R^{6c} are each independently unsubstituted or substituted with one or more groups selected from the group consisting of C_1 - C_6 alkyl, C_1 - C_6 alkoxy, halo, $-OH$, C_1 - C_6 alkyl- $-OH$, $=O$, and $=S$; R^h is selected from the group consisting of H, C_1 - C_6 alkyl, C_1 - C_6 alkoxy, and C_3 - C_8 cycloalkyl, and $-NR^pR^q$; R^p is H or C_1 - C_6 alkyl; R^q is C_2 - C_3 alkyl, $-C(O)R^t$, $-C(O)OR^u$, $-C(O)NR^v$; R^t , R^s , R^{w1} , and R^{z1} each independently selected from

H and C₁-C₆alkyl; and R^t, R^u, R^v, R^{w2}, R^y, and R^{z2} are each independently selected from H, C₁-C₆alkyl, unsubstituted or substituted C₃-C₈cycloalkyl, and unsubstituted or substituted heterocyclyl.

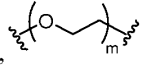
[0075] In some embodiments of Formula (A), including Formula (A-1a), (A-1b), (A-2a), (A-2b), (A-3a), and (A-3b), G₅ is CH(X₃-R^{6c}) or C(X₃-R^{6c}), wherein X₃ is absent; R^{6c} is hydrogen, C₁-C₆alkyl, C₁-C₆alkoxy, halo, -OH, -NR^pR^q, aryl, heterocyclyl, heteroaryl, or -C(O)R^h, wherein C₁-C₆alkyl and C₁-C₆alkoxy are unsubstituted or substituted with C₃-C₈ cycloalkyl or halogen; R^p is H or C₁-C₆alkyl; R^q is C₂-C₃alkyl; and R^h is selected from the group consisting of H, C₁-C₆alkyl, C₁-C₆alkoxy, or C₃-C₈ cycloalkyl. In some embodiments, G₅ is CH(X₃-R^{6c}) or C(X₃-

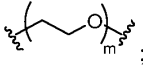
R^{6c}), wherein X₃ is  or ; m is 1-6; R^{6c} is hydrogen, C₁-C₆alkyl, C₁-C₆alkoxy, halo, -OH, -NR^pR^q, aryl, heterocyclyl, heteroaryl, or -C(O)R^h, wherein C₁-C₆alkyl and C₁-C₆alkoxy are unsubstituted or substituted with C₃-C₈ cycloalkyl or halogen; R^p is H or C₁-C₆alkyl; R^q is C₂-C₃alkyl; and R^h is selected from the group consisting of H, C₁-C₆alkyl, C₁-C₆alkoxy, or C₃-C₈cycloalkyl. In some embodiments, G₅ is N or N(X₃-R^{6c}), wherein X₃ is absent; R^{6c} is hydrogen, C₁-C₆alkyl, C₁-C₆alkoxy, halo, -OH, -NR^pR^q, aryl, heterocyclyl, heteroaryl, or -C(O)R^h, wherein C₁-C₆alkyl and C₁-C₆alkoxy are unsubstituted or substituted with C₃-C₈ cycloalkyl or halogen; R^p is H or C₁-C₆alkyl; R^q is C₂-C₃alkyl; and R^h is selected from the group consisting of H, C₁-C₆alkyl, C₁-C₆alkoxy, or C₃-C₈cycloalkyl. In some

embodiments, G₅ is N or N(X₃-R^{6c}), wherein X₃ is  or ; m is 1-6; R^{6c} is hydrogen, C₁-C₆alkyl, C₁-C₆alkoxy, halo, -OH, -NR^pR^q, aryl, heterocyclyl, heteroaryl, or -C(O)R^h, wherein C₁-C₆alkyl and C₁-C₆alkoxy are unsubstituted or substituted with C₃-C₈ cycloalkyl or halogen; R^p is H or C₁-C₆alkyl; R^q is C₂-C₃alkyl; and R^h is selected from the group consisting of H, C₁-C₆alkyl, C₁-C₆alkoxy, or C₃-C₈cycloalkyl. In some of any of the preceding embodiments, R^{6c} is methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, secbutyl, or tertbutyl. In some of any of the preceding embodiments, R^{6c} is C₁-C₆alkyl substituted with C₃-C₈ cycloalkyl or halogen. In some of any of the preceding embodiments, R^{6c} is methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, secbutoxy, or tertbutoxy. In some of any of the preceding embodiments, R^{6c} is C₁-C₆alkoxy substituted with C₃-C₈ cycloalkyl or halogen. In some of any of the preceding embodiments, R^{6c} is fluoro, chloro, bromo, or iodo. In some of any of the preceding embodiments, R^{6c} is -N(CH₂CH₃)₂, -N(CH₂CH₂CH₃)₂, or -

$N(CH_2CH_3)(CH_2CH_2CH_3)$. In some of any of the preceding embodiments, R^{6c} is phenyl or naphthyl. In some of any of the preceding embodiments, R^{6c} is a 5- to 14-membered heterocyclyl. In some embodiments, R^{6c} is a 5- to 6-membered heterocyclyl. In some of any of the preceding embodiments, R^{6c} is pyrrolidinyl, pyrazolidinyl, imidazolidinyl, tetrahydrofuranyl, 1,3-dioxolanyl, tetrahydrothiophenyl, oxathiolanyl, sulfolanyl, piperidinyl, piperazinyl, tetrahydropyranyl, dioxanyl, thianyl, dithianyl, trithianyl, morpholinyl, or thiomorpholinyl. In some of any of the preceding embodiments, R^{6c} is a 5- to 14-membered heteroaryl. In some embodiments, R^{6c} is a 5- to 6-membered heteroaryl. In some of any of the preceding embodiments, R^{6c} is pyrrolyl, pyrazolyl, imidazolyl, triazolyl, tetrazolyl, furanyl, isoxazolyl, oxazolyl, oxadiazolyl, thiophenyl, isothiazolyl, thiazolyl, thiadiazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl, or tetrazinyl. In some of any of the preceding embodiments, R^{6c} is aryl, heterocyclyl, or heteroaryl, each substituted with C_1 - C_6 alkyl. In some of any of the preceding embodiments, R^{6c} is $-C(O)H$, $-C(O)C_1$ - C_6 alkyl, $-C(O)C_1$ - C_6 alkoxy, or $-C(O)C_3$ - C_8 cycloalkyl. In some of any of the preceding embodiments, R^{6c} is $-OH$, $-NR^pR^q$, aryl, heterocyclyl, heteroaryl, unsubstituted C_1 - C_6 alkoxy, or C_1 - C_6 alkoxy substituted with C_3 - C_8 C_3 - C_8 cycloalkyl or halogen. In some of any of the preceding embodiments, R^{6c} is hydrogen, $-CH_3$, $-OH$, $-OCH_3$, $-C(O)OC(CH_3)_3$, $-N(CH_2CH_3)_2$, phenyl, morpholinyl, piperidinyl, piperazinyl, 4-ethylpiperazinyl, pyrrolidinyl, pyrazolyl, cyclopropylmethoxy, or cyclopropanecarbonyl. In some embodiments, G_5 is S. In other embodiments, G_5 is O.

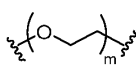
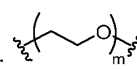
[0076] In some embodiments of Formula (A), including Formula (A-1a), (A-1b), (A-2a),

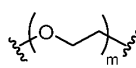
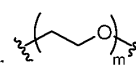
and (A-2b), G_6 is $CH(X_4-R^{6d})$, $C(X_4-R^{6d})$, or $N(X_4-R^{6d})$, wherein X_4 is absent, , or

; R^{6d} is hydrogen, C_1 - C_6 alkyl, C_1 - C_6 alkoxy, halo, $-OH$, $-NR^pR^q$, aryl, heterocyclyl, heteroaryl, $-C_1$ - C_6 alkyl-heterocyclyl, $-OC(O)$ -heterocyclyl, $-C(O)R^h$, $-S(O)_2NR^{w1}R^{w2}$, $-S(O)_2R^y$, or $-NR^{z1}S(O)_2R^{z2}$, wherein the C_1 - C_6 alkyl and C_1 - C_6 alkoxy of R^{6d} are each independently unsubstituted or substituted with one or more groups selected from the group consisting of cycloalkyl and halogen; the aryl and heteroaryl of R^{6d} are each independently unsubstituted or substituted with one or more groups selected from the group consisting of C_1 - C_6 alkyl, C_1 - C_6 alkoxy, C_3 - C_8 cycloalkyl, $-OH$, and C_1 - C_6 alkyl- $-OH$; and the heterocyclyl, $-C_1$ - C_6 alkyl-heterocyclyl, and $-OC(O)$ -heterocyclyl of R^{6d} are each independently unsubstituted or substituted with one or more groups selected from the group consisting of C_1 - C_6 alkyl, C_1 -

C₆alkoxy, halo, -OH, C₁-C₆alkyl-OH, =O, and =S; R^h is selected from the group consisting of H, C₁-C₆alkyl, C₁-C₆alkoxy, and C₃-C₈cycloalkyl, and -NR^pR^s; R^p is H or C₁-C₆alkyl; R^q is C₂-C₃alkyl, -C(O)R^t, -C(O)OR^u, -C(O)NR^v; R^t, R^s, R^{w1}, and R^{z1} each independently selected from H and C₁-C₆alkyl; and R^t, R^u, R^v, R^{w2}, R^y, and R^{z2} are each independently selected from H, C₁-C₆alkyl, unsubstituted or substituted C₃-C₈cycloalkyl, and unsubstituted or substituted heterocyclyl.

[0077] In some embodiments of Formula (A), including Formula (A-1a), (A-1b), (A-2a), and (A-2b), G₆ is CH(X₄-R^{6d}) or C(X₄-R^{6d}), wherein X₄ is absent; R^{6d} is hydrogen, C₁-C₆alkyl, C₁-C₆alkoxy, halo, -OH, -NR^pR^q, aryl, heterocyclyl, heteroaryl, or -C(O)R^h, wherein C₁-C₆alkyl and C₁-C₆alkoxy are unsubstituted or substituted with C₃-C₈ cycloalkyl or halogen; R^p is H or C₁-C₆alkyl; R^q is C₂-C₃alkyl; and R^h is selected from the group consisting of H, C₁-C₆alkyl, C₁-C₆alkoxy, or C₃-C₈cycloalkyl. In some embodiments, G₆ is CH(X₄-R^{6d}) or C(X₄-R^{6d}), wherein

X₄ is  or ; m is 1-6; R^{6d} is hydrogen, C₁-C₆alkyl, C₁-C₆alkoxy, halo, -OH, -NR^pR^q, aryl, heterocyclyl, heteroaryl, or -C(O)R^h, wherein C₁-C₆alkyl and C₁-C₆alkoxy are unsubstituted or substituted with C₃-C₈ cycloalkyl or halogen; R^p is H or C₁-C₆alkyl; R^q is C₂-C₃alkyl; and R^h is selected from the group consisting of H, C₁-C₆alkyl, C₁-C₆alkoxy, or C₃-C₈cycloalkyl. In some embodiments, G₆ is N or N(X₄-R^{6d}), wherein X₄ is absent; R^{6d} is hydrogen, C₁-C₆alkyl, C₁-C₆alkoxy, halo, -OH, -NR^pR^q, aryl, heterocyclyl, heteroaryl, or -C(O)R^h, wherein C₁-C₆alkyl and C₁-C₆alkoxy are unsubstituted or substituted with C₃-C₈ cycloalkyl or halogen; R^p is H or C₁-C₆alkyl; R^q is C₂-C₃alkyl; and R^h is selected from the group consisting of H, C₁-C₆alkyl, C₁-C₆alkoxy, or C₃-C₈cycloalkyl. In some embodiments, G₆ is N or

N(X₄-R^{6d}), wherein X₄ is  or ; m is 1-6; R^{6d} is hydrogen, C₁-C₆alkyl, C₁-C₆alkoxy, halo, -OH, -NR^pR^q, aryl, heterocyclyl, heteroaryl, or -C(O)R^h, wherein C₁-C₆alkyl and C₁-C₆alkoxy are unsubstituted or substituted with C₃-C₈ cycloalkyl or halogen; R^p is H or C₁-C₆alkyl; R^q is C₂-C₃alkyl; and R^h is selected from the group consisting of H, C₁-C₆alkyl, C₁-C₆alkoxy, or C₃-C₈cycloalkyl. In some of any of the preceding embodiments, R^{6d} is methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, secbutyl, or tertbutyl. In some of any of the preceding embodiments, R^{6d} is C₁-C₆alkyl substituted with C₃-C₈ cycloalkyl or halogen. In some of any of the preceding embodiments, R^{6d} is methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, secbutoxy, or tertbutoxy. In some of any of the preceding embodiments, R^{6d} is C₁-

C₆alkoxy substituted with C₃-C₈ cycloalkyl or halogen. In some of any of the preceding embodiments, R^{6d} is fluoro, chloro, bromo, or iodo. In some of any of the preceding embodiments, R^{6d} is -N(CH₂CH₃)₂, -N(CH₂CH₂CH₃)₂, or -N(CH₂CH₃)(CH₂CH₂CH₃). In some of any of the preceding embodiments, R^{6d} is phenyl or naphthyl. In some of any of the preceding embodiments, R^{6d} is a 5- to 14-membered heterocyclyl. In some embodiments, R^{6d} is a 5- to 6-membered heterocyclyl. In some of any of the preceding embodiments, R^{6d} is pyrrolidinyl, pyrazolidinyl, imidazolidinyl, tetrahydrofuranyl, 1,3-dioxolanyl, tetrahydrothiophenyl, oxathiolanyl, sulfolanyl, piperidinyl, piperazinyl, tetrahydropyranyl, dioxanyl, thianyl, dithianyl, trithianyl, morpholinyl, or thiomorpholinyl. In some of any of the preceding embodiments, R^{6d} is a 5- to 14-membered heteroaryl. In some embodiments, R^{6d} is a 5- to 6-membered heteroaryl. In some of any of the preceding embodiments, R^{6d} is pyrrolyl, pyrazolyl, imidazolyl, triazolyl, tetrazolyl, furanyl, isoxazolyl, oxazolyl, oxadiazolyl, thiophenyl, isothiazolyl, thiazolyl, thiadiazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl, or tetrazinyl. In some of any of the preceding embodiments, R^{6d} is aryl, heterocyclyl, or heteroaryl, each substituted with C₁-C₆alkyl. In some of any of the preceding embodiments, R^{6d} is -C(O)H, -C(O)C₁-C₆alkyl, -C(O)C₁-C₆alkoxy, or -C(O)C₃-C₈cycloalkyl. In some of any of the preceding embodiments, R^{6d} is -OH, -NR^pR^q, aryl, heterocyclyl, heteroaryl, unsubstituted C₁-C₆alkoxy, or C₁-C₆alkoxy substituted with C₃-C₈ cycloalkyl or halogen. In some of any of the preceding embodiments, R^{6d} is hydrogen, -CH₃, -OH, -OCH₃, -C(O)OC(CH₃)₃, -N(CH₂CH₃)₂, phenyl, morpholinyl, piperidinyl, piperazinyl, 4-ethylpiperazinyl, pyrrolidinyl, pyrazolyl, cyclopropylmethoxy, or cyclopropanecarbonyl. In some embodiments, G₆ is S. In other embodiments, G₆ is O. In some embodiments, G₆ is absent.

[0078] In some embodiments of Formula (A), including Formula (A-1a), (A-1b), (A-2a), and (A-2b), G₅ is CH(X₃-R^{6c}), G₆ is CH(X₄-R^{6d}), ring  is saturated, and R^{6c} and R^{6d} are taken together with the carbon atoms to which they are attached to form a 6-membered heterocyclyl ring; wherein the heterocyclyl ring is unsubstituted or substituted. In some embodiments, G₅ is C(X₃-R^{6c}), G₆ is C(X₄-R^{6d}), ring  is partially unsaturated or fully unsaturated, and R^{6c} and R^{6d} are taken together with the carbon atoms to which they are attached to form a 6-membered aryl, heterocyclyl, or heteroaryl ring; wherein each 6-membered aryl, heterocyclyl, and heteroaryl ring is unsubstituted or substituted. In some embodiments, G₅ is

$C(X_3-R^{6c})$, G_6 is $C(X_4-R^{6d})$,  is fully unsaturated, and R^{6c} and R^{6d} are taken together with the carbon atoms to which they are attached to form a 6-membered aryl, heterocyclyl, or heteroaryl ring; wherein each 6-membered aryl, heterocyclyl, and heteroaryl ring is unsubstituted or substituted. In some embodiments, R^{6c} and R^{6d} come together with the carbon atoms to which they are attached to form a phenyl ring. In some embodiments, R^{6c} and R^{6d} are taken together with the carbon atoms to which they are attached to form a 6-membered heterocyclyl or heteroaryl ring, wherein the 6-membered heterocyclyl or heteroaryl ring contains one, two, or three heteroatoms selected from the group consisting of N, S, and O. In some embodiments, R^{6c} and R^{6d} are taken together with the carbon atoms to which they are attached to form an unsubstituted 6-membered aryl, heterocyclyl, or heteroaryl ring. In some embodiments, R^{6c} and R^{6d} are taken together with the carbon atoms to which they are attached to form a 6-membered aryl, heterocyclyl, or heteroaryl ring, wherein the 6-membered aryl, heterocyclyl, or heteroaryl ring is substituted with one or more substituents selected from the group consisting of C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, halo, -OH, -C(O)H, -C(O)OH, -C(O)OC $_1$ - C_6 alkyl, -OC $_1$ - C_6 alkyl, and C_3 - C_8 cycloalkyl.

[0079] In some embodiments of Formula (A), including Formula (A-1a), (A-1b), (A-2a), and (A-2b), G_7 is N. In some embodiments, G_7 is C. In other embodiments, G_7 is CH.

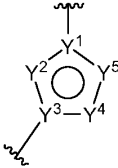
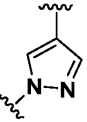
[0080] In some embodiments of Formula (A), including Formula (A-1a), (A-1b), (A-2a), and (A-2b), one of R^{6a} , R^{6b} , R^{6c} , and R^{6d} is selected from the group consisting of C_1 - C_6 alkyl, C_1 - C_6 alkoxy, halo, -OH, -NR^pR^q, aryl, heterocyclyl, heteroaryl, and -C(O)R^h, wherein the C_1 - C_6 alkyl and C_1 - C_6 alkoxy of R^{6a} , R^{6b} , R^{6c} , and R^{6d} are each independently unsubstituted or substituted with C_3 - C_8 cycloalkyl or halogen; and the rest of R^{6a} , R^{6b} , R^{6c} , and R^{6d} are each H. In some embodiments, one of R^{6a} , R^{6b} , R^{6c} , and R^{6d} is selected from the group consisting of C_1 - C_6 alkyl, C_1 - C_6 alkoxy, halo, -OH, -NR^pR^q, 6- to 12-membered aryl, 3- to 12-membered heterocyclyl, 5- to 12-membered heteroaryl, and -C(O)R^h, wherein the C_1 - C_6 alkyl and C_1 - C_6 alkoxy of R^{6a} , R^{6b} , R^{6c} , and R^{6d} are each independently unsubstituted or substituted with C_3 - C_8 cycloalkyl or halogen; and the rest of R^{6a} , R^{6b} , R^{6c} , and R^{6d} are each H. In some embodiments, two of R^{6a} , R^{6b} , R^{6c} , and R^{6d} are selected from the group consisting of C_1 - C_6 alkyl, C_1 - C_6 alkoxy, halo, -OH, -NR^pR^q, aryl, heterocyclyl, heteroaryl, and -C(O)R^h, wherein the C_1 - C_6 alkyl and C_1 - C_6 alkoxy of R^{6a} , R^{6b} , R^{6c} , and R^{6d} are each independently unsubstituted or

substituted with C₃-C₈ cycloalkyl or halogen; and the rest of R^{6a}, R^{6b}, R^{6c}, and R^{6d} are each H. In some embodiments, two of R^{6a}, R^{6b}, R^{6c}, and R^{6d} is selected from the group consisting of C₁-C₆alkyl, C₁-C₆alkoxy, halo, -OH, -NR^pR^q, 6- to 12-membered aryl, 3- to 12-membered heterocyclyl, 5- to 12-membered heteroaryl, and -C(O)R^h, wherein the C₁-C₆alkyl and C₁-C₆alkoxy of R^{6a}, R^{6b}, R^{6c}, and R^{6d} are each independently unsubstituted or substituted with C₃-C₈ cycloalkyl or halogen; and the rest of R^{6a}, R^{6b}, R^{6c}, and R^{6d} are each H.

[0081] In some embodiments of Formula (A), including Formula (A-1a), (A-1b), (A-2a), and (A-2b), one of R^{6a}, R^{6b}, R^{6c}, and R^{6d} is selected from the group consisting of C₁-C₆alkyl, C₁-C₆alkoxy, halo, -OH, -NR^pR^q, aryl, heterocyclyl, heteroaryl, and -C(O)R^h, wherein the C₁-C₆alkyl and C₁-C₆alkoxy of R^{6a}, R^{6b}, R^{6c}, and R^{6d} are each independently unsubstituted or substituted with C₃-C₈ cycloalkyl or halogen; and the rest of R^{6a}, R^{6b}, R^{6c}, and R^{6d} are each H. In some embodiments, one of R^{6a}, R^{6b}, R^{6c}, and R^{6d} is selected from the group consisting of -C₁-C₆alkyl-heterocyclyl, -OC(O)-heterocyclyl, -S(O)₂NR^{w1}R^{w2}, -S(O)₂R^y, and -NR^{z1}S(O)₂R^{z2}; wherein R^{w1} and R^{z1} each independently selected from H and C₁-C₆alkyl, and R^{w2}, R^y, and R^{z2} are each independently selected from H, C₁-C₆alkyl, unsubstituted or substituted C₃-C₈cycloalkyl, and unsubstituted or substituted 3- to 12-membered heterocyclyl.

[0082] In some embodiments of Formula (A), including Formula (A-1a), (A-1b), (A-2a), and (A-2b), two of R^{6a}, R^{6b}, R^{6c}, and R^{6d} is selected from the group consisting of C₁-C₆alkyl, C₁-C₆alkoxy, halo, -OH, -NR^pR^q, aryl, heterocyclyl, heteroaryl, and -C(O)R^h, wherein the C₁-C₆alkyl and C₁-C₆alkoxy of R^{6a}, R^{6b}, R^{6c}, and R^{6d} are each independently unsubstituted or substituted with C₃-C₈ cycloalkyl or halogen; and the rest of R^{6a}, R^{6b}, R^{6c}, and R^{6d} are each H.

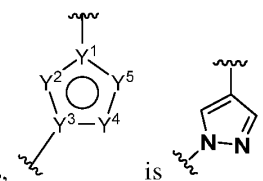
[0083] In some embodiments of Formula (A), R³ is H, C₁-C₃alkyl, C₁-C₆alkoxy, or halogen, wherein the C₁-C₆alkyl and C₁-C₆alkoxy of R³ are each independently unsubstituted or substituted with one or more halogen. In some embodiments, when R² is -C(O)H, R³ is

methoxy, and  is , at least one of R^{6a}, R^{6b}, R^{6c}, and R^{6d} are selected from C₁-C₆alkyl, C₁-C₆alkoxy, halo, -OH, -NR^pR^q, aryl, heterocyclyl, heteroaryl, -C₁-C₆alkyl-heterocyclyl, -OC(O)-heterocyclyl, -C(O)R^h, -S(O)₂NR^{w1}R^{w2}, -S(O)₂R^y, and -NR^{z1}S(O)₂R^{z2}. In

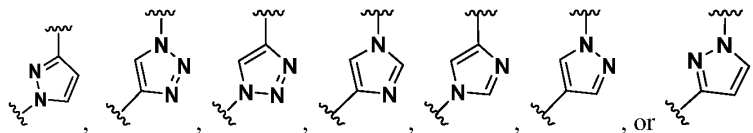
some embodiments, one of R^1 and R^2 is $-\text{OH}$ and the other is $-\text{CH}=\text{NR}^j$, wherein R^j is a phenyl or naphthyl substituted with one or more substituents selected from the group consisting of C_1 -



C_6 alkyl, C_3 - C_8 cycloalkyl, and oxo. In some embodiments, n is 0 and R^4 is . In some embodiments, one of R^1 and R^2 is $-\text{OH}$ and the other is $-\text{CH}=\text{NR}^j$, wherein NR^j is unsubstituted



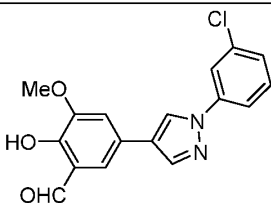
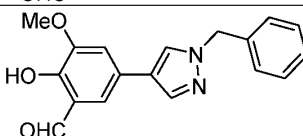
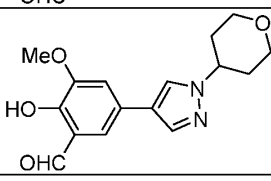
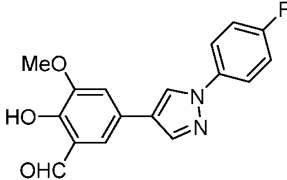
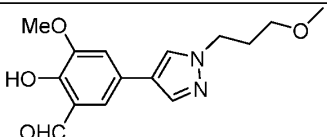
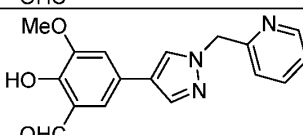
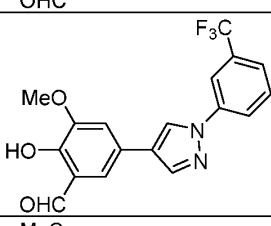
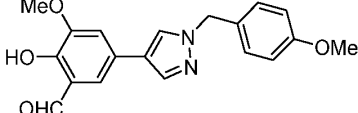
or substituted 4- to 12-membered heterocyclyl. In some embodiments,

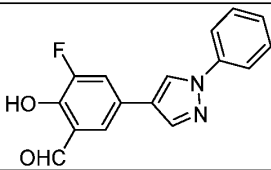
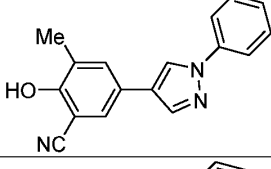
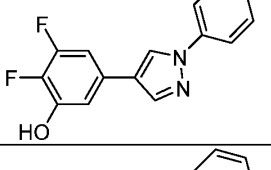
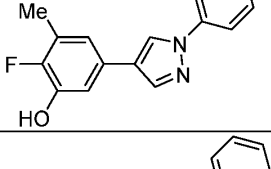
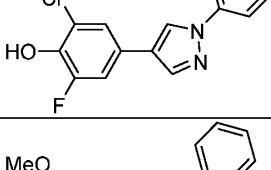
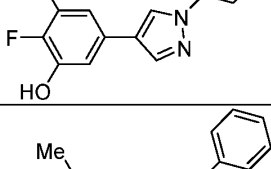
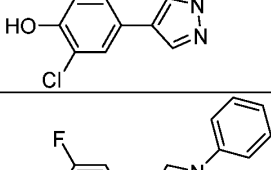
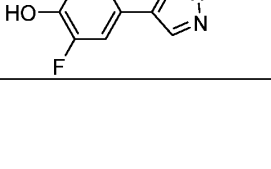


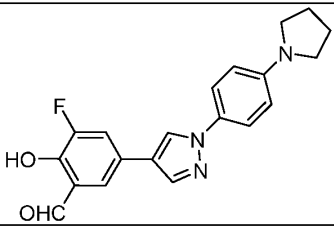
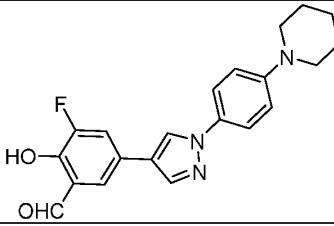
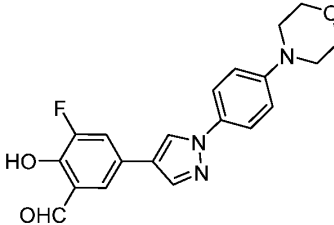
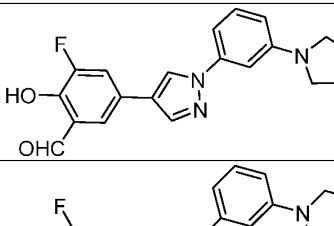
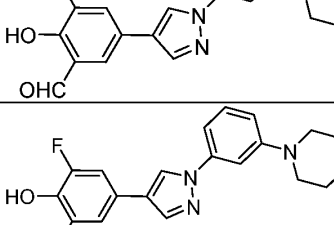
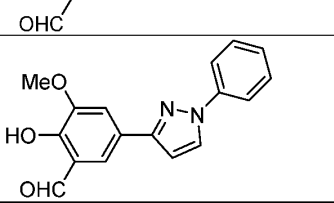
[0084] In some embodiments, provided herein are compounds and salts thereof described in Table 1A.

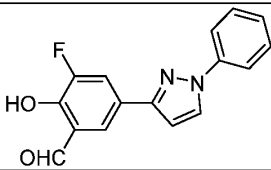
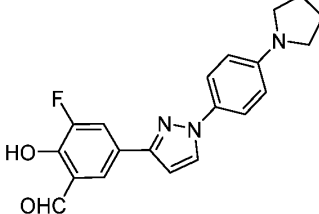
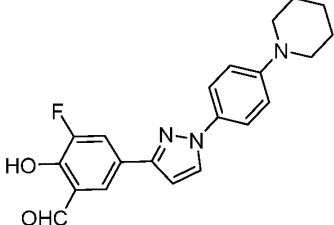
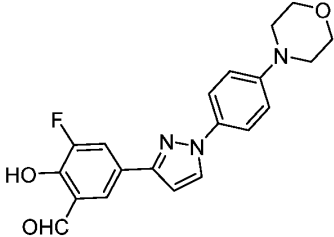
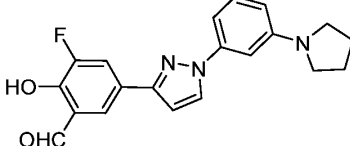
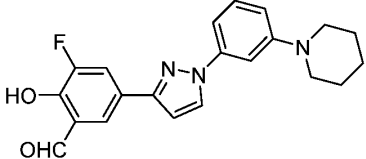
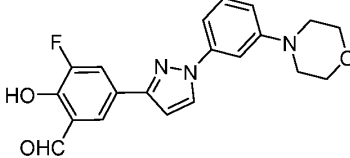
Table 1A.

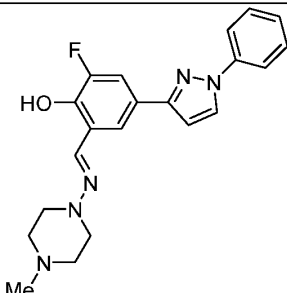
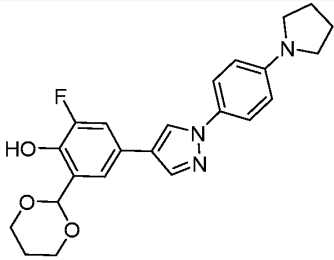
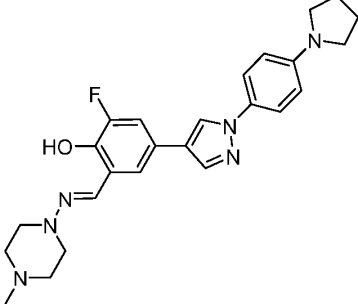
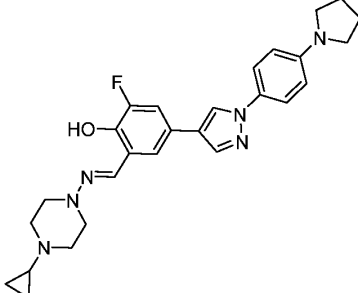
Compound No.	Chemical Structure	Chemical Name
A1		2-hydroxy-3-methoxy-5-(1-phenyl-1H-pyrazol-4-yl)benzaldehyde
A2		2-hydroxy-3-methoxy-5-(1-(2-morpholinoethyl)-1H-pyrazol-4-yl)benzaldehyde

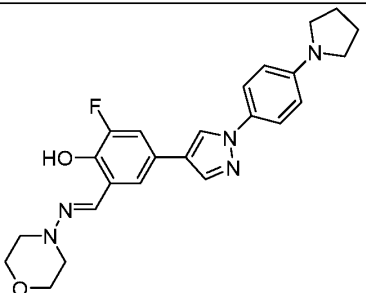
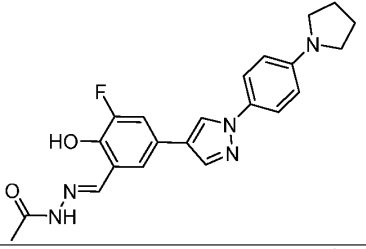
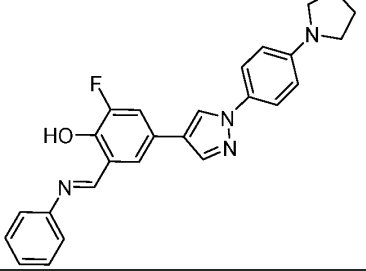
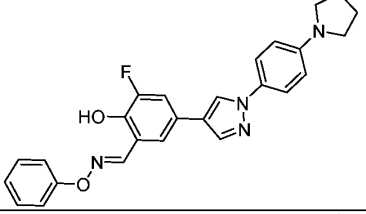
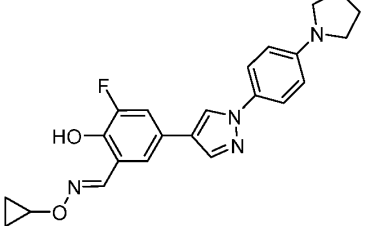
A3		5-(1-(3-chlorophenyl)-1H-pyrazol-4-yl)-2-hydroxy-3-methoxybenzaldehyde
A4		5-(1-benzyl-1H-pyrazol-4-yl)-2-hydroxy-3-methoxybenzaldehyde
A5		2-hydroxy-3-methoxy-5-(1-(tetrahydro-2H-pyran-4-yl)-1H-pyrazol-4-yl)benzaldehyde
A6		5-(1-(4-fluorophenyl)-1H-pyrazol-4-yl)-2-hydroxy-3-methoxybenzaldehyde
A7		2-hydroxy-3-methoxy-5-(1-(3-methoxypropyl)-1H-pyrazol-4-yl)benzaldehyde
A8		2-hydroxy-3-methoxy-5-(1-(pyridin-2-ylmethyl)-1H-pyrazol-4-yl)benzaldehyde
A9		2-hydroxy-3-methoxy-5-(1-(3-(trifluoromethyl)phenyl)-1H-pyrazol-4-yl)benzaldehyde
A10		2-hydroxy-3-methoxy-5-(1-(4-methoxybenzyl)-1H-pyrazol-4-yl)benzaldehyde

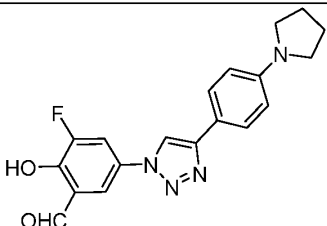
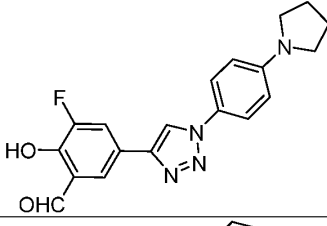
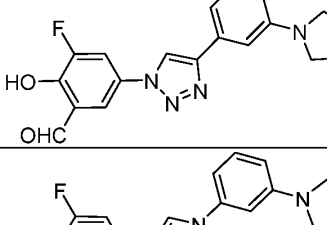
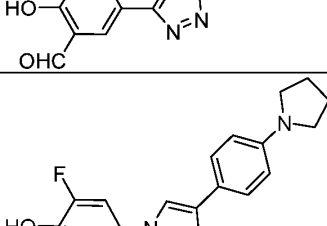
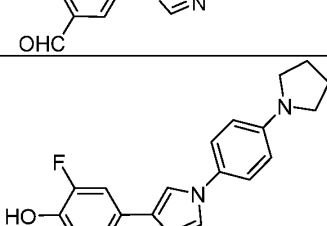
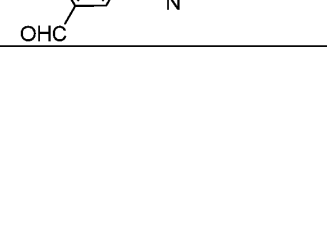
A11		3-fluoro-2-hydroxy-5-(1-phenyl-1H-pyrazol-4-yl)benzaldehyde
A12		2-hydroxy-3-methyl-5-(1-phenyl-1H-pyrazol-4-yl)benzonitrile
A13		2,3-difluoro-5-(1-phenyl-1H-pyrazol-4-yl)phenol
A14		2-fluoro-3-methyl-5-(1-phenyl-1H-pyrazol-4-yl)phenol
A15		2-chloro-6-fluoro-4-(1-phenyl-1H-pyrazol-4-yl)phenol
A16		2-fluoro-3-methoxy-5-(1-phenyl-1H-pyrazol-4-yl)phenol
A17		2-chloro-6-methyl-4-(1-phenyl-1H-pyrazol-4-yl)phenol
A18		2,6-difluoro-4-(1-phenyl-1H-pyrazol-4-yl)phenol

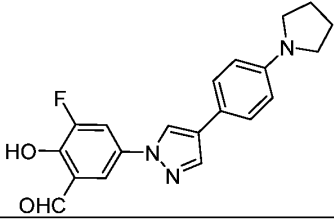
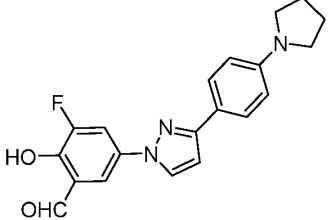
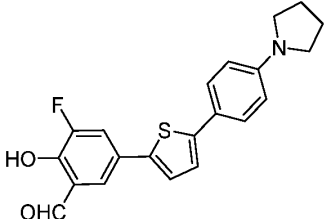
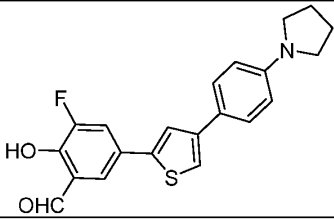
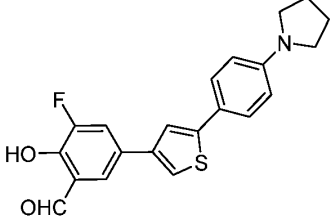
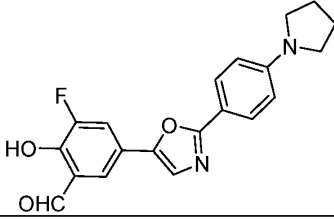
A19		3-fluoro-2-hydroxy-5-(1-(4-(pyrrolidin-1-yl)phenyl)-1H-pyrazol-4-yl)benzaldehyde
A20		3-fluoro-2-hydroxy-5-(1-(4-(piperidin-1-yl)phenyl)-1H-pyrazol-4-yl)benzaldehyde
A21		3-fluoro-2-hydroxy-5-(1-(4-morpholinophenyl)-1H-pyrazol-4-yl)benzaldehyde
A22		3-fluoro-2-hydroxy-5-(1-(3-(pyrrolidin-1-yl)phenyl)-1H-pyrazol-4-yl)benzaldehyde
A23		3-fluoro-2-hydroxy-5-(1-(3-(piperidin-1-yl)phenyl)-1H-pyrazol-4-yl)benzaldehyde
A24		3-fluoro-2-hydroxy-5-(1-(3-morpholinophenyl)-1H-pyrazol-4-yl)benzaldehyde
A25		2-hydroxy-3-methoxy-5-(1-phenyl-1H-pyrazol-3-yl)benzaldehyde

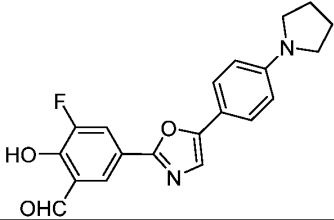
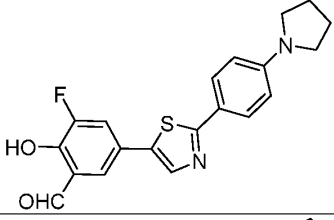
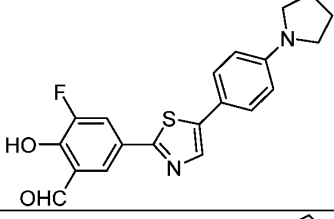
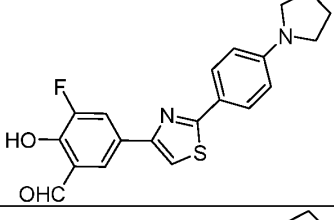
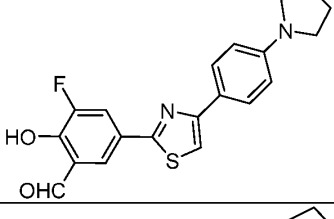
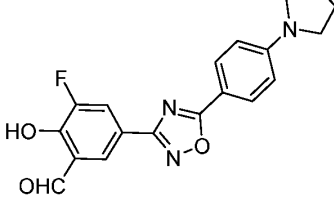
A26		3-fluoro-2-hydroxy-5-(1-phenyl-1H-pyrazol-3-yl)benzaldehyde
A27		3-fluoro-2-hydroxy-5-(1-(4-(pyrrolidin-1-yl)phenyl)-1H-pyrazol-3-yl)benzaldehyde
A28		3-fluoro-2-hydroxy-5-(1-(4-(piperidin-1-yl)phenyl)-1H-pyrazol-3-yl)benzaldehyde
A29		3-fluoro-2-hydroxy-5-(1-(4-morpholinophenyl)-1H-pyrazol-3-yl)benzaldehyde
A30		3-fluoro-2-hydroxy-5-(1-(3-(pyrrolidin-1-yl)phenyl)-1H-pyrazol-3-yl)benzaldehyde
A31		3-fluoro-2-hydroxy-5-(1-(3-(piperidin-1-yl)phenyl)-1H-pyrazol-3-yl)benzaldehyde
A32		3-fluoro-2-hydroxy-5-(1-(3-morpholinophenyl)-1H-pyrazol-3-yl)benzaldehyde

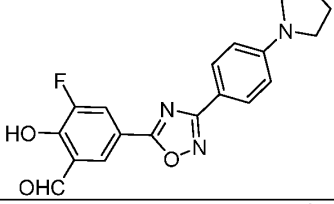
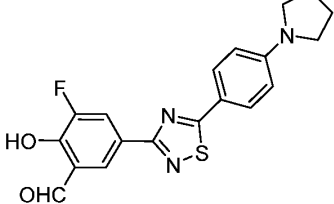
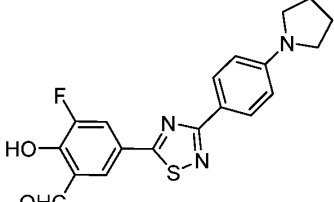
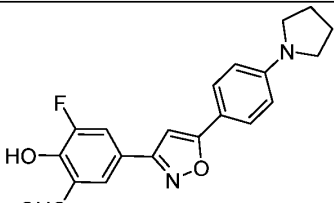
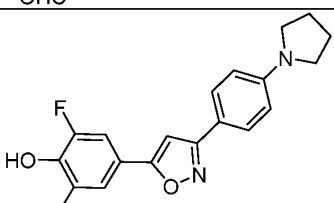
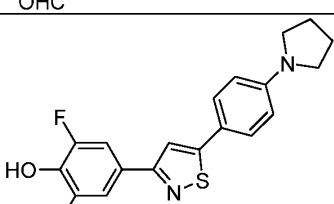
A33		(E)-2-fluoro-6-(((4-methylpiperazin-1-yl)imino)methyl)-4-(1-phenyl-1H-pyrazol-3-yl)phenol
A34		2-(1,3-dioxan-2-yl)-6-fluoro-4-(1-(4-(pyrrolidin-1-yl)phenyl)-1H-pyrazol-4-yl)phenol
A35		(E)-2-fluoro-6-(((4-methylpiperazin-1-yl)imino)methyl)-4-(1-(4-(pyrrolidin-1-yl)phenyl)-1H-pyrazol-4-yl)phenol
A36		(E)-2-(((4-cyclopropylpiperazin-1-yl)imino)methyl)-6-fluoro-4-(1-(4-(pyrrolidin-1-yl)phenyl)-1H-pyrazol-4-yl)phenol

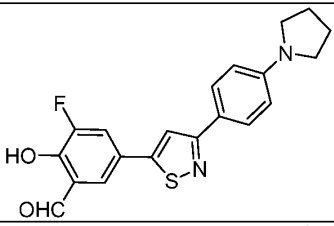
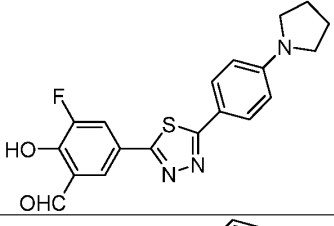
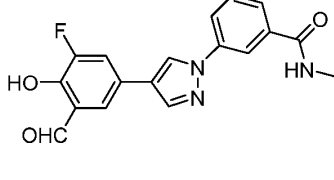
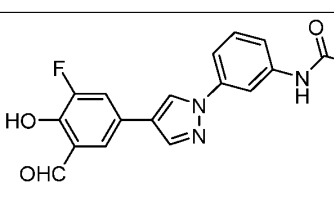
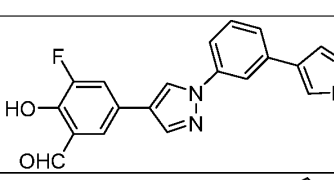
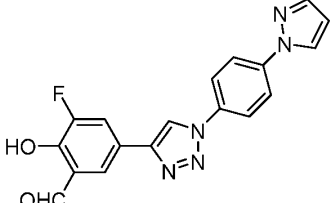
A37		(E)-2-fluoro-6-((morpholinoimino)methyl)-4-(1-(4-(pyrrolidin-1-yl)phenyl)-1H-pyrazol-4-yl)phenol
A38		(E)-N'-(3-fluoro-2-hydroxy-5-(1-(4-(pyrrolidin-1-yl)phenyl)-1H-pyrazol-4-yl)benzylidene)acetohydrazide
A39		(E)-2-fluoro-6-((phenylimino)methyl)-4-(1-(4-(pyrrolidin-1-yl)phenyl)-1H-pyrazol-4-yl)phenol
A40		(E)-3-fluoro-2-hydroxy-5-(1-(4-(pyrrolidin-1-yl)phenyl)-1H-pyrazol-4-yl)benzaldehyde O-phenyl oxime
A41		(E)-3-fluoro-2-hydroxy-5-(1-(4-(pyrrolidin-1-yl)phenyl)-1H-pyrazol-4-yl)benzaldehyde O-cyclopropyl oxime

A42		3-fluoro-2-hydroxy-5-(4-(4-(pyrrolidin-1-yl)phenyl)-1H-1,2,3-triazol-1-yl)benzaldehyde
A43		3-fluoro-2-hydroxy-5-(1-(4-(pyrrolidin-1-yl)phenyl)-1H-1,2,3-triazol-4-yl)benzaldehyde
A44		3-fluoro-2-hydroxy-5-(4-(3-(pyrrolidin-1-yl)phenyl)-1H-1,2,3-triazol-1-yl)benzaldehyde
A45		3-fluoro-2-hydroxy-5-(1-(3-(pyrrolidin-1-yl)phenyl)-1H-1,2,3-triazol-4-yl)benzaldehyde
A46		3-fluoro-2-hydroxy-5-(4-(4-(pyrrolidin-1-yl)phenyl)-1H-imidazol-1-yl)benzaldehyde
A47		3-fluoro-2-hydroxy-5-(1-(4-(pyrrolidin-1-yl)phenyl)-1H-imidazol-4-yl)benzaldehyde

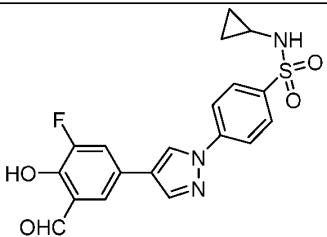
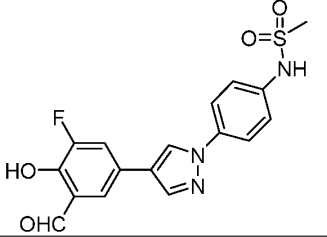
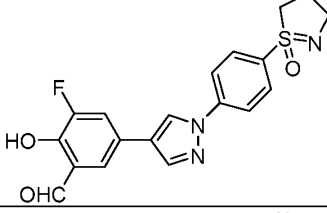
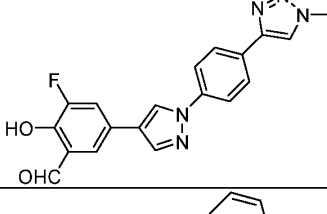
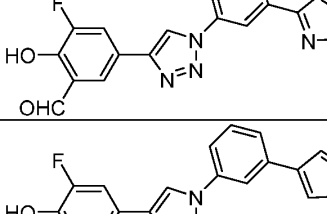
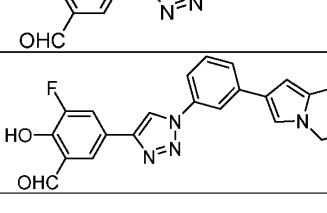
A48		3-fluoro-2-hydroxy-5-(4-(4-(pyrrolidin-1-yl)phenyl)-1H-pyrazol-1-yl)benzaldehyde
A49		3-fluoro-2-hydroxy-5-(3-(4-(pyrrolidin-1-yl)phenyl)-1H-pyrazol-1-yl)benzaldehyde
A50		3-fluoro-2-hydroxy-5-(5-(4-(pyrrolidin-1-yl)phenyl)thiophen-2-yl)benzaldehyde
A51		3-fluoro-2-hydroxy-5-(4-(4-(pyrrolidin-1-yl)phenyl)thiophen-2-yl)benzaldehyde
A52		3-fluoro-2-hydroxy-5-(5-(4-(pyrrolidin-1-yl)phenyl)thiophen-3-yl)benzaldehyde
A53		3-fluoro-2-hydroxy-5-(2-(4-(pyrrolidin-1-yl)phenyl)oxazol-5-yl)benzaldehyde

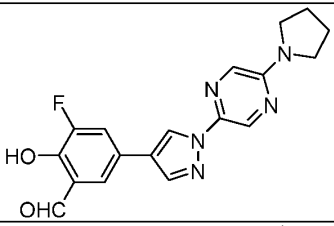
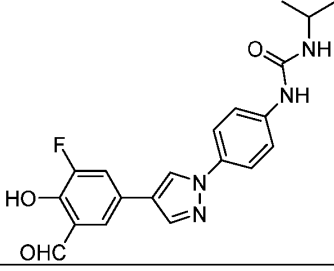
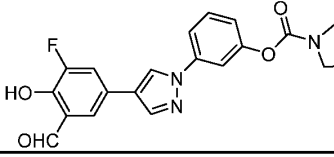
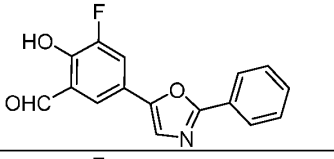
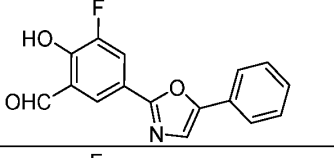
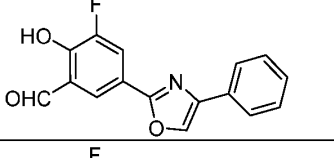
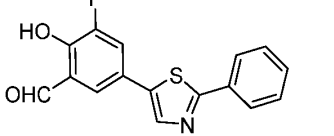
A54		3-fluoro-2-hydroxy-5-(5-(4-(pyrrolidin-1-yl)phenyl)oxazol-2-yl)benzaldehyde
A55		3-fluoro-2-hydroxy-5-(2-(4-(pyrrolidin-1-yl)phenyl)thiazol-5-yl)benzaldehyde
A56		3-fluoro-2-hydroxy-5-(5-(4-(pyrrolidin-1-yl)phenyl)thiazol-2-yl)benzaldehyde
A57		3-fluoro-2-hydroxy-5-(2-(4-(pyrrolidin-1-yl)phenyl)thiazol-4-yl)benzaldehyde
A58		3-fluoro-2-hydroxy-5-(4-(4-(pyrrolidin-1-yl)phenyl)thiazol-2-yl)benzaldehyde
A59		3-fluoro-2-hydroxy-5-(5-(4-(pyrrolidin-1-yl)phenyl)-1,2,4-oxadiazol-3-yl)benzaldehyde

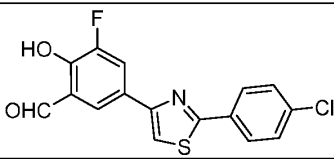
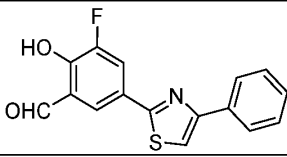
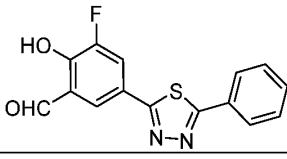
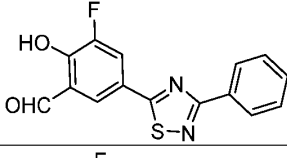
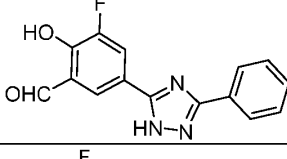
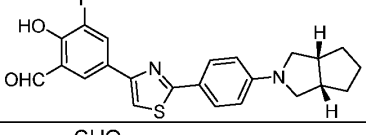
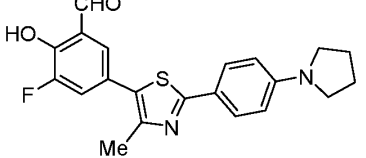
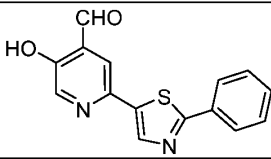
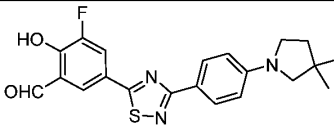
A60		3-fluoro-2-hydroxy-5-(3-(4-(pyrrolidin-1-yl)phenyl)-1,2,4-oxadiazol-5-yl)benzaldehyde
A61		3-fluoro-2-hydroxy-5-(5-(4-(pyrrolidin-1-yl)phenyl)-1,2,4-thiadiazol-3-yl)benzaldehyde
A62		3-fluoro-2-hydroxy-5-(3-(4-(pyrrolidin-1-yl)phenyl)-1,2,4-thiadiazol-5-yl)benzaldehyde
A63		3-fluoro-2-hydroxy-5-(5-(4-(pyrrolidin-1-yl)phenyl)isoxazol-3-yl)benzaldehyde
A64		3-fluoro-2-hydroxy-5-(3-(4-(pyrrolidin-1-yl)phenyl)isoxazol-5-yl)benzaldehyde
A65		3-fluoro-2-hydroxy-5-(5-(4-(pyrrolidin-1-yl)phenyl)isothiazol-3-yl)benzaldehyde

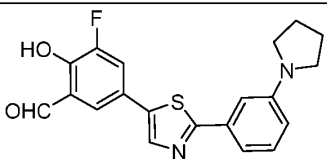
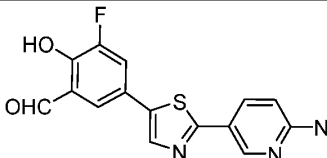
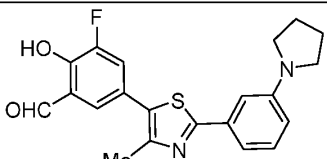
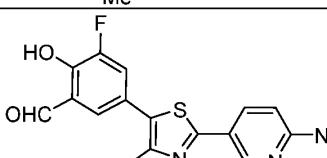
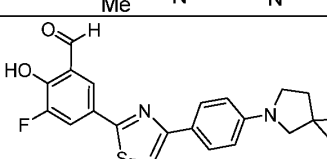
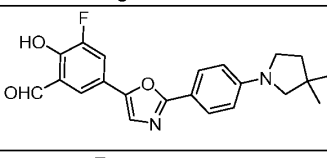
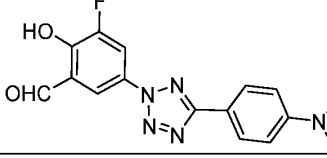
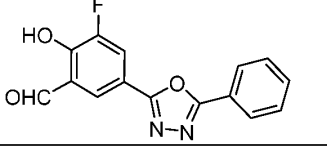
A66		3-fluoro-2-hydroxy-5-(3-(4-(pyrrolidin-1-yl)phenyl)isothiazol-5-yl)benzaldehyde
A67		3-fluoro-2-hydroxy-5-(5-(4-(pyrrolidin-1-yl)phenyl)-1,3,4-thiadiazol-2-yl)benzaldehyde
A68		3-(4-(3-fluoro-5-formyl-4-hydroxyphenyl)-1H-pyrazol-1-yl)-N-isopropylbenzamide
A69		N-(3-(4-(3-fluoro-5-formyl-4-hydroxyphenyl)-1H-pyrazol-1-yl)phenyl)acetamide
A70		3-fluoro-2-hydroxy-5-(1-(3-(1-methyl-1H-pyrazol-4-yl)phenyl)-1H-pyrazol-4-yl)benzaldehyde
A71		5-(1-(4-(1H-pyrazol-1-yl)phenyl)-1H-1,2,3-triazol-4-yl)-3-fluoro-2-hydroxybenzaldehyde

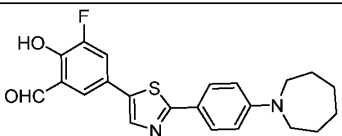
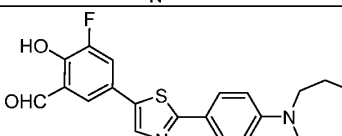
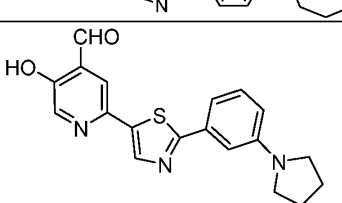
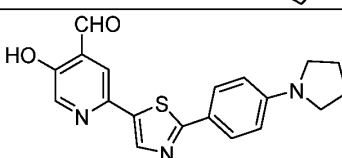
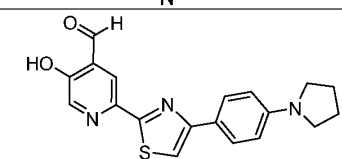
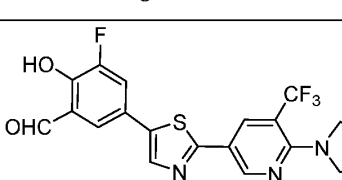
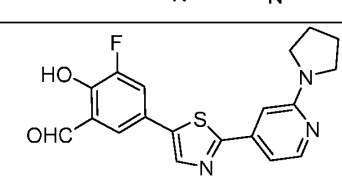
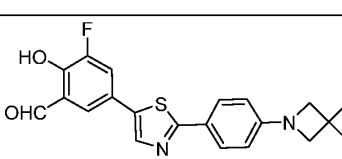
A72		5-(1-(4-(1H-imidazol-1-yl)phenyl)-1H-pyrazol-4-yl)-3-fluoro-2-hydroxybenzaldehyde
A73		5-(1-(4-(1H-1,2,4-triazol-1-yl)phenyl)-1H-pyrazol-4-yl)-3-fluoro-2-hydroxybenzaldehyde
A74		5-(1-(4-(2H-tetrazol-5-yl)phenyl)-1H-pyrazol-4-yl)-3-fluoro-2-hydroxybenzaldehyde
A75		5-(1-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1H-pyrazol-4-yl)-3-fluoro-2-hydroxybenzaldehyde
A76		5-(1-(4-(1,1-dioxidothiomorpholino)phenyl)-1H-pyrazol-4-yl)-3-fluoro-2-hydroxybenzaldehyde
A77		5-(1-(4-(4,4-difluoropiperidin-1-yl)phenyl)-1H-pyrazol-4-yl)-3-fluoro-2-hydroxybenzaldehyde

A78		N-cyclopropyl-4-(4-(3-fluoro-5-formyl-4-hydroxyphenyl)-1H-pyrazol-1-yl)benzenesulfonamide
A79		N-(4-(4-(3-fluoro-5-formyl-4-hydroxyphenyl)-1H-pyrazol-1-yl)phenyl)methanesulfonamide
A80		3-fluoro-2-hydroxy-5-(1-(4-(1-oxido-4,5-dihydro-3H-11b-isothiazol-1-yl)phenyl)-1H-pyrazol-4-yl)benzaldehyde
A81		5-(1-(4-(1-cyclopropyl-1H-1,2,3-triazol-4-yl)phenyl)-1H-pyrazol-4-yl)-3-fluoro-2-hydroxybenzaldehyde
A82		3-fluoro-2-hydroxy-5-(1-(3-(1-methyl-1H-pyrazol-3-yl)phenyl)-1H-1,2,3-triazol-4-yl)benzaldehyde
A83		3-fluoro-2-hydroxy-5-(1-(3-(1-methyl-1H-pyrrol-3-yl)phenyl)-1H-1,2,3-triazol-4-yl)benzaldehyde
A84		5-(1-(3-(3,4-dihydro-1H-pyrrolo[2,1-c][1,4]oxazin-7-yl)phenyl)-1H-1,2,3-triazol-4-yl)-3-fluoro-2-hydroxybenzaldehyde

A85		3-fluoro-2-hydroxy-5-(1-(5-(pyrrolidin-1-yl)pyrazin-2-yl)-1H-pyrazol-4-yl)benzaldehyde
A86		1-(4-(4-(3-fluoro-5-formyl-4-hydroxyphenyl)-1H-pyrazol-1-yl)phenyl)-3-isopropylurea
A87		3-(4-(3-fluoro-5-formyl-4-hydroxyphenyl)-1H-pyrazol-1-yl)phenyl pyrrolidine-1-carboxylate
A88		3-fluoro-2-hydroxy-5-(2-phenyloxazol-5-yl)benzaldehyde
A89		3-fluoro-2-hydroxy-5-(5-phenyloxazol-2-yl)benzaldehyde
A90		3-fluoro-2-hydroxy-5-(4-phenyloxazol-2-yl)benzaldehyde
A91		3-fluoro-2-hydroxy-5-(2-phenylthiazol-5-yl)benzaldehyde

A92		5-(2-(4-chlorophenyl)thiazol-4-yl)-3-fluoro-2-hydroxybenzaldehyde
A93		3-fluoro-2-hydroxy-5-(4-phenylthiazol-2-yl)benzaldehyde
A94		3-fluoro-2-hydroxy-5-(5-phenyl-1,3,4-thiadiazol-2-yl)benzaldehyde
A95		3-fluoro-2-hydroxy-5-(3-phenyl-1,2,4-thiadiazol-5-yl)benzaldehyde
A96		3-fluoro-2-hydroxy-5-(3-phenyl-1H-1,2,4-triazol-5-yl)benzaldehyde
A97		3-fluoro-5-(2-(4-((3aR,6aS)-hexahydrocyclopenta[c]pyrrol-2(1H)-yl)phenyl)thiazol-4-yl)-2-hydroxybenzaldehyde
A98		3-fluoro-2-hydroxy-5-(4-methyl-2-(4-(pyrrolidin-1-yl)phenyl)thiazol-5-yl)benzaldehyde
A99		5-hydroxy-2-(2-phenylthiazol-5-yl)isonicotinaldehyde
A100		5-(3-(4-(3,3-dimethylpyrrolidin-1-yl)phenyl)-1,2,4-thiadiazol-5-yl)-3-fluoro-2-hydroxybenzaldehyde

A101		3-fluoro-2-hydroxy-5-(2-(3-(pyrrolidin-1-yl)phenyl)thiazol-5-yl)benzaldehyde
A102		3-fluoro-2-hydroxy-5-(2-(6-(pyrrolidin-1-yl)pyridin-3-yl)thiazol-5-yl)benzaldehyde
A103		3-fluoro-2-hydroxy-5-(4-methyl-2-(3-(pyrrolidin-1-yl)phenyl)thiazol-5-yl)benzaldehyde
A104		3-fluoro-2-hydroxy-5-(4-methyl-2-(6-(pyrrolidin-1-yl)pyridin-3-yl)thiazol-5-yl)benzaldehyde
A105		5-(4-(4-(3,3-dimethylpyrrolidin-1-yl)phenyl)thiazol-2-yl)-3-fluoro-2-hydroxybenzaldehyde
A106		5-(2-(4-(3,3-dimethylpyrrolidin-1-yl)phenyl)oxazol-5-yl)-3-fluoro-2-hydroxybenzaldehyde
A107		3-fluoro-2-hydroxy-5-(5-(4-(pyrrolidin-1-yl)phenyl)-2H-tetrazol-2-yl)benzaldehyde
A108		3-fluoro-2-hydroxy-5-(5-phenyl-1,3,4-oxadiazol-2-yl)benzaldehyde

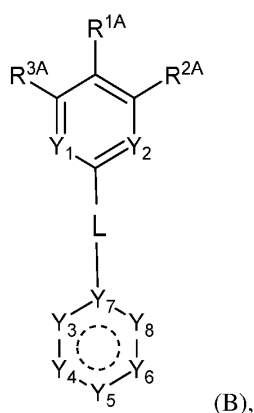
A109		5-(2-(4-(azepan-1-yl)phenyl)thiazol-5-yl)-3-fluoro-2-hydroxybenzaldehyde
A110		5-(2-(4-(azocan-1-yl)phenyl)thiazol-5-yl)-3-fluoro-2-hydroxybenzaldehyde
A111		5-hydroxy-2-(2-(3-(pyrrolidin-1-yl)phenyl)thiazol-5-yl)isonicotinaldehyde
A112		5-hydroxy-2-(2-(4-(pyrrolidin-1-yl)phenyl)thiazol-5-yl)isonicotinaldehyde
A113		5-hydroxy-2-(4-(4-(pyrrolidin-1-yl)phenyl)thiazol-2-yl)isonicotinaldehyde
A114		3-fluoro-2-hydroxy-5-(2-(6-(pyrrolidin-1-yl)-5-(trifluoromethyl)pyridin-3-yl)thiazol-5-yl)benzaldehyde
A115		3-fluoro-2-hydroxy-5-(2-(2-(pyrrolidin-1-yl)pyridin-4-yl)thiazol-5-yl)benzaldehyde
A116		5-(2-(4-(2-azaspiro[3.3]heptan-2-yl)phenyl)thiazol-5-yl)-3-fluoro-2-hydroxybenzaldehyde

A117		3-fluoro-2-hydroxy-5-(2-(4-(piperidin-1-yl)phenyl)thiazol-5-yl)benzaldehyde
A118		<u>5-(2-(4-(3,3-dimethylindolin-1-yl)phenyl)thiazol-5-yl)-3-fluoro-2-hydroxybenzaldehyde</u>
A119		<u>3-fluoro-2-hydroxy-5-(4-(4-(piperidin-1-yl)phenyl)thiazol-2-yl)benzaldehyde</u>
A120		<u>5-(4-(4-(azepan-1-yl)phenyl)thiazol-2-yl)-3-fluoro-2-hydroxybenzaldehyde</u>
A121		<u>5-(4-(4-(2-azaspiro[3.3]heptan-2-yl)phenyl)thiazol-2-yl)-3-fluoro-2-hydroxybenzaldehyde</u>
A122		<u>5-(4-(4-(3,3-dimethylindolin-1-yl)phenyl)thiazol-2-yl)-3-fluoro-2-hydroxybenzaldehyde</u>
A123		<u>3-fluoro-2-hydroxy-5-(2-(6-(pyrrolidin-1-yl)pyridin-3-yl)thiazol-4-yl)benzaldehyde</u>
A124		<u>3-fluoro-2-hydroxy-5-(2-(3-(pyrrolidin-1-yl)phenyl)thiazol-4-yl)benzaldehyde</u>

A125		<u>3-fluoro-2-hydroxy-5-(5-(3-(pyrrolidin-1-yl)phenyl)-1,2,4-thiadiazol-3-yl)benzaldehyde</u>
A126		<u>3-fluoro-2-hydroxy-5-(2-(6-(piperidin-1-yl)pyridin-3-yl)thiazol-4-yl)benzaldehyde</u>
A127		<u>3-fluoro-2-hydroxy-5-(2-(6-(piperidin-1-yl)pyridin-3-yl)thiazol-5-yl)benzaldehyde</u>
A128		<u>5-(2-(4-(2,6-dimethylmorpholino)phenyl)thiazol-5-yl)-3-fluoro-2-hydroxybenzaldehyde</u>
A129		<u>5-(2-(4-(azetidin-1-yl)phenyl)thiazol-5-yl)-3-fluoro-2-hydroxybenzaldehyde</u>
A130		<u>5-(2-(4-chlorophenyl)thiazol-5-yl)-3-fluoro-2-hydroxybenzaldehyde</u>

and pharmaceutically acceptable salts thereof.

[0085] In one aspect, provided are compounds of Formula (B):



or a tautomer, or a pharmaceutically acceptable salt of any of the foregoing,
wherein

L is selected from the group consisting of $-\text{C}\equiv\text{C}-$, $^*\text{-NHC(O)-}$, $^*\text{-C(O)NH-}$, -NHC(O)NH- , $^*\text{-NHS(O)}_2\text{-}$, $^*\text{-NHS(O)(=NH)-}$, $^*\text{-S(O)(=NH)NH-}$, $^*\text{-S(O)}_2\text{NH-}$, $^*\text{-S(O)NHNH-}$, $^*\text{-NHNHS(O)-}$, $^*\text{-C(O)NHNH-}$, $^*\text{-NHNHC(O)-}$, $^*\text{-NHC(O)O-}$, and $^*\text{-OC(O)NH-}$, wherein * represents the point of attachment to Y_7 ;

Y_1 and Y_2 are each independently CR^x or N;

R^x is hydrogen or halogen;

when L is $-\text{C}\equiv\text{C}-$, one of R^{1A} and R^{2A} is $-\text{OH}$ and the other is selected from the group consisting of $-\text{C(O)R}^{a1}$, $-\text{CH=NR}^{j1}$, $-\text{S(O)R}^{b1}$, $-\text{S(O)}_2\text{R}^{c1}$, $-\text{NHC(O)R}^{d1}$, $-\text{NHS(O)}_2\text{R}^{e1}$, $-\text{C}_1\text{-C}_6\text{alkyl-R}^{f1}$, $-\text{C}_2\text{-C}_6\text{alkenyl-R}^{g1}$, $\text{C}_3\text{-C}_8\text{ cycloalkyl}$, $\text{C}_3\text{-C}_8\text{ cycloalkenyl}$, and 5- or 6-membered heterocycloalkyl, wherein the $\text{C}_3\text{-C}_8\text{ cycloalkyl}$ and $\text{C}_3\text{-C}_8\text{ cycloalkenyl}$ are each independently unsubstituted or substituted with one or more $=\text{O}$, and the 5- or 6-membered heterocycloalkyl is unsubstituted or substituted with one or more substituents independently selected from the group consisting of $\text{C}_1\text{-C}_6\text{alkyl}$, $\text{C}_3\text{-C}_8\text{ cycloalkyl}$, $=\text{O}$, and $-\text{C(O)O-C}_1\text{-C}_6\text{alkyl}$;

when L is $^*\text{-NHC(O)-}$, $^*\text{-C(O)NH-}$, -NHC(O)NH- , $^*\text{-NHS(O)}_2\text{-}$, $^*\text{-S(O)}_2\text{NH-}$, $^*\text{-S(O)NHNH-}$, $^*\text{-C(O)NHNH-}$, or $^*\text{-NHC(O)O-}$, one of R^{1A} and R^{2A} is $-\text{OH}$ and the other is selected from

the group consisting of $-\text{C(O)H}$, $-\text{CH=NR}^{j1}$, and ;

R^{a1} is H, $\text{C}_1\text{-C}_6\text{alkyl}$, $\text{C}_2\text{-C}_6\text{alkenyl}$, $\text{C}_2\text{-C}_6\text{alkynyl}$, $\text{C}_1\text{-C}_6\text{haloalkyl}$, 3- to 6-membered heterocyclyl, or 5- to 10-membered heteroaryl, or benzoyl, wherein the 3- to 10-

membered heterocyclyl of R^{a1} is unsubstituted or substituted with one or more groups independently selected from the group consisting of C_1 - C_6 alkyl, C_3 - C_8 cycloalkyl, $=O$, and $-C(O)O-C_1-C_6$ alkyl, and the 5- to 10-membered heteroaryl of R^{a1} is unsubstituted or substituted with one or more groups independently selected from the group consisting of C_1 - C_6 alkyl, C_3 - C_8 cycloalkyl, and $-C(O)O-C_1-C_6$ alkyl;

R^{b1} , R^{c1} , R^{d1} , and R^{e1} are each independently H, C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, C_1 - C_6 haloalkyl, 3- to 10-membered heterocyclyl, 5- to 10-membered heteroaryl, benzoyl, or styryl, wherein the 3- to 10-membered heterocyclyl and 5- to 10-membered heteroaryl of R^{b1} , R^{c1} , R^{d1} , and R^{e1} are each independently selected from the group consisting of C_1 - C_6 alkyl, C_3 - C_8 cycloalkyl, and $-C(O)O-C_1-C_6$ alkyl;

R^{f1} and R^{g1} are each independently $-OH$, unsubstituted 5- to 6-membered heteroaryl, $-NR^{m1}R^{n1}$, benzoyl, or styryl;

R^{m1} is C_3 - C_8 cycloalkyl, unsubstituted or substituted with one or more groups selected from C_1 - C_6 alkyl and halo;

R^{n1} is H, C_1 - C_6 alkyl, C_2 - C_6 alkenyl, or C_2 - C_6 alkynyl;

R^{j1} is C_1 - C_6 alkyl, 5- to 6-membered heterocyclyl, 5- to 6-membered heteroaryl, 6- to 12-membered aryl, $-OR^{k1}$, $-NHR^{k1}$, $-N(C_1-C_6alkyl)R^{k1}$, $-NHC(O)R^{k1}$, $-NHS(O)_2R^{k1}$, or $-NHC(NH)NHR^{bb}$, wherein the 5- to 6-membered heterocyclyl of R^{j1} is unsubstituted or substituted with one or more substituents selected from the group consisting of C_1 - C_6 alkyl, C_3 - C_8 cycloalkyl, $=O$, $-C(O)NH-C_1-C_6$ alkyl, and $-C(O)O-C_1-C_6$ alkyl, and the 5- to 6-membered heteroaryl and 6- to 12-membered aryl of R^{j1} are each independently unsubstituted or substituted with one or more substituents selected from the group consisting of C_1 - C_6 alkyl, C_3 - C_8 cycloalkyl, and $-C(O)O-C_1-C_6$ alkyl;

R^{bb} is unsubstituted or substituted C_1 - C_6 alkyl, unsubstituted or substituted C_3 - C_8 cycloalkyl, unsubstituted or substituted aryl, unsubstituted or substituted heterocycloalkyl, or unsubstituted or substituted heteroaryl;

each R^{k1} is independently C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, C_3 - C_8 cycloalkyl, or 6- to 12-membered aryl, wherein the C_1 - C_6 alkyl of R^{k1} is unsubstituted or substituted with a 5- to 6-membered heterocyclyl or a 5- to 6-membered heteroaryl;

R^{3A} is H, C_1 - C_6 alkyl, C_1 - C_6 alkoxy, or halogen, wherein the C_1 - C_6 alkyl and C_1 - C_6 alkoxy of R^{3A} are each independently unsubstituted or substituted with one or more halogen;

○ indicates that the ring is saturated, partially unsaturated, or fully unsaturated;

Y_3 is $CH(X_{1A}-R^{6a1})$, $C(X_{1A}-R^{6a1})$, N, $N(X_{1A}-R^{6a1})$, S, or O;

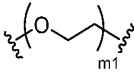
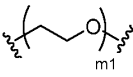
Y_4 is $CH(X_{2A}-R^{6b1})$, $C(X_{2A}-R^{6b1})$, N, $N(X_{2A}-R^{6b1})$, S, or O;

Y_5 is $CH(X_{3A}-R^{6c1})$, $C(X_{3A}-R^{6c1})$, N, $N(X_{3A}-R^{6c1})$, S, or O;

Y_6 is $CH(X_{4A}-R^{6d1})$, $C(X_{4A}-R^{6d1})$, N, $N(X_{4A}-R^{6d1})$, S, or O;

Y_7 is N, C, or CH; and

Y_8 is N, NH, C, or CH;

X_{1A} , X_{2A} , X_{3A} , and X_{4A} are each independently absent, , or ; m_1 is 1-6;

R^{6a1} , R^{6b1} , R^{6c1} , and R^{6d1} are each independently hydrogen, C₁-C₆alkyl, C₁-C₆alkoxy, halo, -OH, -NR^{p1}R^{q1}, C₆-C₁₂ aryl, 3- to 10-membered heterocyclyl, 5- to 10-membered heteroaryl, -C₁-C₆alkyl-5- to 6-membered heterocyclyl, -OC(O)-5- to 6-membered heterocyclyl, -C(O)R^{h1}, -S(O)₂NR^{w1a}R^{w2a}, -S(O)₂R^{y1}, -NR^{z1a}S(O)₂R^{z2a}, or -N(CH₃)CH₂C(CH₃)₃, wherein the C₁-C₆alkyl and C₁-C₆alkoxy of R^{6a1} , R^{6b1} , R^{6c1} , and R^{6d1} are each independently unsubstituted or substituted with one or more groups selected from the group consisting of C₃-C₈cycloalkyl and halogen; the C₆-C₁₂ aryl and 5- to 10-membered heteroaryl of R^{6a1} , R^{6b1} , R^{6c1} , and R^{6d1} are each independently unsubstituted or substituted with one or more groups selected from the group consisting of C₁-C₆alkyl, C₁-C₆alkoxy, -OH, and C₁-C₆alkyl-OH; and the 3- to 10-membered heterocyclyl, -C₁-C₆alkyl-5- to 6-membered heterocyclyl, and -OC(O)-5- to 6-membered heterocyclyl of R^{6a1} , R^{6b1} , R^{6c1} , and R^{6d1} are each independently unsubstituted or substituted with one or more groups selected from the group consisting of C₁-C₆alkyl, C₁-C₆alkoxy, -OH, C₁-C₆alkyl-OH, =O, =S, halo, C₃-C₈cycloalkyl, -C(O)NH-C₃-C₈cycloalkyl, C₆-C₁₂ aryl, and 5- to 6-membered heterocyclyl; each R^{h1} is independently selected from the group consisting of H, C₁-C₆alkyl, C₁-C₆alkoxy, C₃-C₈cycloalkyl, and -NR^{r1}R^{s1}; each R^{p1} is independently H or C₁-C₆alkyl; each R^{q1} is independently C₂-C₃alkyl, -C(O)R^{t1}, -C(O)OR^{u1}, or -C(O)NR^{v1}; each R^{r1} , R^{s1} , R^{w1a} , and R^{z1a} is independently selected from H and C₁-C₆alkyl; and

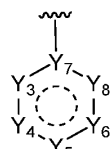
each R^{11} , R^{u1} , R^{v1} , R^{w2a} , R^{y1} , and R^{z2a} is independently selected from H, C_1 - C_6 alkyl, unsubstituted or substituted C_3 - C_8 cycloalkyl, and unsubstituted or substituted heterocyclyl;

or

Y_5 is $CH(X_{3A}-R^{6c1})$ or $C(X_{3A}-R^{6c1})$, Y_6 is $CH(X_{4A}-R^{6d1})$ or $C(X_{4A}-R^{6d1})$, and R^{6c1} and R^{6d1} are taken together with the carbon atoms to which they are attached to form a 6-membered aryl, a 6-membered heterocyclyl, or a 6-membered heteroaryl ring; wherein the 6-membered aryl, 6-membered heterocyclyl, and 6-membered heteroaryl rings are each independently unsubstituted or substituted with one or more groups selected from the group consisting of C_1 - C_6 alkyl and $-C(O)O-C_1$ - C_6 alkyl; and wherein no more than one of R^{6a1} , R^{6b1} , R^{6c1} , and R^{6d1} is C_1 - C_6 alkoxy or $-OH$.

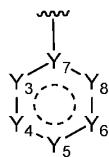
[0086] In some embodiments, of Formula (B), one or more of the following applies:

(1) when L is $-C\equiv C-$, Y_1 and Y_2 are each CH, one of R^{1A} and R^{2A} is $-C(O)H$, $-CH_2OH$, -

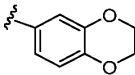


$C(O)CH_3$ or $-NHC(O)CH_3$, and R^{3A} is H, is other than cyclohexyl, phenyl, pyridyl, or naphthyl, and R^{6c1} is hydrogen, C_2 - C_3 alkyl, C_2 - C_5 alkoxy, Br, Cl, I, $-NR^{p1}R^{q1}$, C_6 - C_{12} aryl, 3- to 10-membered heterocyclyl, 5- to 10-membered heteroaryl, $-C_1$ - C_6 alkyl-5- to 6-membered heterocyclyl, $-OC(O)$ -5- to 6-membered heterocyclyl, $-C(O)R^{h1}$, $-S(O)_2NR^{w1a}R^{w2a}$, $-S(O)_2R^{y1}$, or $-NR^{z1a}S(O)_2R^{z2a}$, and each R^{h1} is independently selected from the group consisting of C_1 - C_6 alkyl, C_1 - C_6 alkoxy, C_3 - C_8 cycloalkyl, and $-NR^{r1}R^{s1}$;

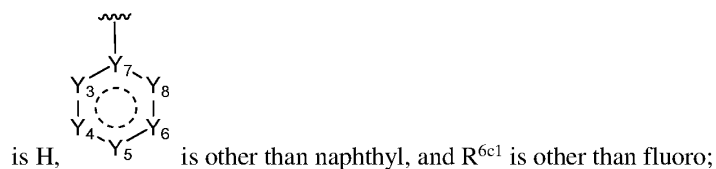
(2) when L is $-C\equiv C-$, Y_1 and Y_2 are each CH, one of R^{1A} and R^{2A} is $-C(O)H$, and R^{3A} is -



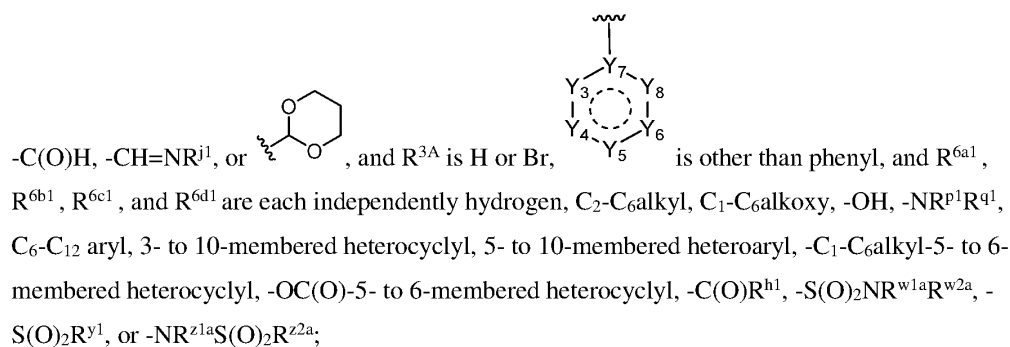
CH_3 , t-Bu, or C_2 - C_3 alkoxy, is other than phenyl and pyridyl, R^{b1} and R^{d1} are other

than , and R^{6c1} is other than $-OH$;

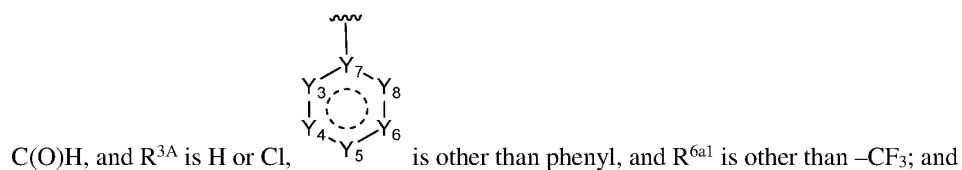
(3) when L is $-C\equiv C-$, Y_1 and Y_2 are each CH, one of R^{1A} and R^{2A} is piperidinyl, pyrrolidinyl, pyrrolidinone, piperazinyl, morpholinyl, or thiadiazolidinone 1,1-dioxide, and R^{3A}



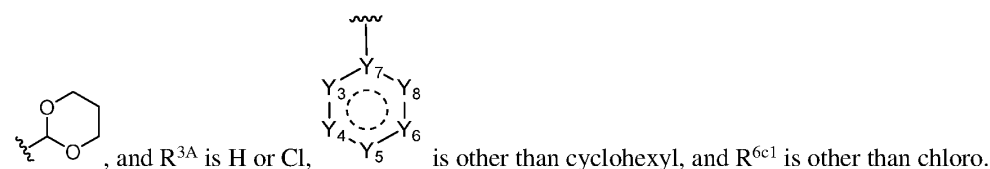
(4) when L is $^*-NHS(O)_2-$ or $^*-S(O)_2NH-$, Y_1 and Y_2 are each CH, one of R^{1A} and R^{2A} is



(5) when L is $^*-C(O)NH-$ or $^*-NHC(O)-$, Y_1 and Y_2 are each CH, one of R^{1A} and R^{2A} is -



(6) when L is $-NHC(O)NH-$, Y_1 and Y_2 are each CH, one of R^{1A} and R^{2A} is $-C(O)H$ or



[0087] In some embodiments of Formula (B), R^{j1} is C_1 - C_6 alkyl, 5- to 6-membered heterocyclyl, 5- to 6-membered heteroaryl, 6- to 12-membered aryl, $-OR^{k1}$, $-NHR^{k1}$, $-N(C_1-C_6alkyl)R^{k1}$, $-NHC(O)R^{k1}$, $-NHS(O)_2R^{k1}$, or $-NHC(NH)NH_2$, wherein the 5- to 6-membered heterocyclyl of R^{j1} is unsubstituted or substituted with one or more substituents selected from the group consisting of C_1 - C_6 alkyl, C_3 - C_8 cycloalkyl, $=O$, $-C(O)NH-C_1-C_6alkyl$, and $-C(O)O-C_1-C_6alkyl$, and the 5- to 6-membered heteroaryl and 6- to 12-membered aryl of R^{j1} are each independently unsubstituted or substituted with one or more substituents selected from the group

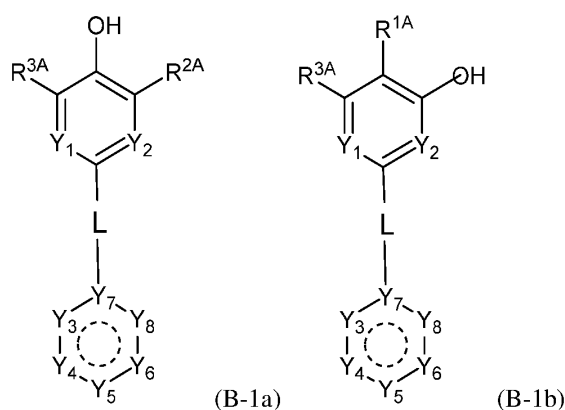
consisting of C₁-C₆alkyl, C₃-C₈cycloalkyl, and -C(O)O-C₁-C₆alkyl; and R^{6a1}, R^{6b1}, R^{6c1}, and R^{6d1} are each independently hydrogen, C₁-C₆alkyl, C₁-C₆alkoxy, halo, -OH, -NR^{p1}R^{q1}, C₆-C₁₂ aryl, 3- to 10-membered heterocyclyl, 5- to 10-membered heteroaryl, -C₁-C₆alkyl-5- to 6-membered heterocyclyl, -OC(O)-5- to 6-membered heterocyclyl, -C(O)R^{h1}, -S(O)₂NR^{w1a}R^{w2a}, -S(O)₂R^{y1}, or -NR^{z1a}S(O)₂R^{z2a}, wherein the C₁-C₆alkyl and C₁-C₆alkoxy of R^{6a1}, R^{6b1}, R^{6c1}, and R^{6d1} are each independently unsubstituted or substituted with one or more groups selected from the group consisting of C₃-C₈cycloalkyl and halogen; the C₆-C₁₂ aryl and 5- to 10-membered heteroaryl of R^{6a1}, R^{6b1}, R^{6c1}, and R^{6d1} are each independently unsubstituted or substituted with one or more groups selected from the group consisting of C₁-C₆alkyl, C₁-C₆alkoxy, -OH, and C₁-C₆alkyl-OH; and the 3- to 10-membered heterocyclyl, -C₁-C₆alkyl-5- to 6-membered heterocyclyl, and -OC(O)-5- to 6-membered heterocyclyl of R^{6a1}, R^{6b1}, R^{6c1}, and R^{6d1} are each independently unsubstituted or substituted with one or more groups selected from the group consisting of C₁-C₆alkyl, C₁-C₆alkoxy, -OH, C₁-C₆alkyl-OH, =O, and =S.

[0088] In some embodiments, R^{3A} is selected from the group consisting of C₁-C₆alkyl, C₁-C₆alkoxy, and halogen, wherein the C₁-C₆alkyl and C₁-C₆alkoxy of R^{3A} are each independently unsubstituted or substituted with one or more halogen, and R^{1A}, R^{2A}, L, Y₁, Y₂, Y₃, Y₄, Y₅, Y₆, and Y₇ are as defined for Formula (B) or any variation or embodiment thereof. In some embodiments, R^{3A} is selected from the group consisting of C₁-C₆alkyl, C₁-C₆alkoxy, and halogen, and R^{1A}, R^{2A}, L, Y₁, Y₂, Y₃, Y₄, Y₅, Y₆, and Y₇ are as defined for Formula (B) or any variation or embodiment thereof. In some embodiments, R^{3A} is selected from the group consisting of C₁-C₃alkyl, methoxy, and F, wherein the C₁-C₃alkyl, methoxy are each independently unsubstituted or substituted with halogen, and R^{1A}, R^{2A}, L, Y₁, Y₂, Y₃, Y₄, Y₅, Y₆, and Y₇ are as defined for Formula (B) or any variation or embodiment thereof.

[0089] In some embodiments of Formula (B), R^{6a1}, R^{6b1}, R^{6c1}, and R^{6d1} are each independently hydrogen, C₁-C₆alkyl, C₁-C₆alkoxy, halo, -OH, -NR^{p1}R^{q1}, C₆-C₁₂ aryl, 3- to 10-membered heterocyclyl, 5- to 10-membered heteroaryl, -C₁-C₆alkyl-5- to 6-membered heterocyclyl, -OC(O)-5- to 6-membered heterocyclyl, -C(O)R^{h1}, -S(O)₂NR^{w1a}R^{w2a}, -S(O)₂R^{y1}, or -NR^{z1a}S(O)₂R^{z2a}, wherein the C₁-C₆alkyl and C₁-C₆alkoxy of R^{6a1}, R^{6b1}, R^{6c1}, and R^{6d1} are each independently unsubstituted or substituted with one or more groups selected from the group consisting of C₃-C₈cycloalkyl and halogen; the C₆-C₁₂ aryl and 5- to 10-membered heteroaryl of R^{6a1}, R^{6b1}, R^{6c1}, and R^{6d1} are each independently unsubstituted or substituted with one or more

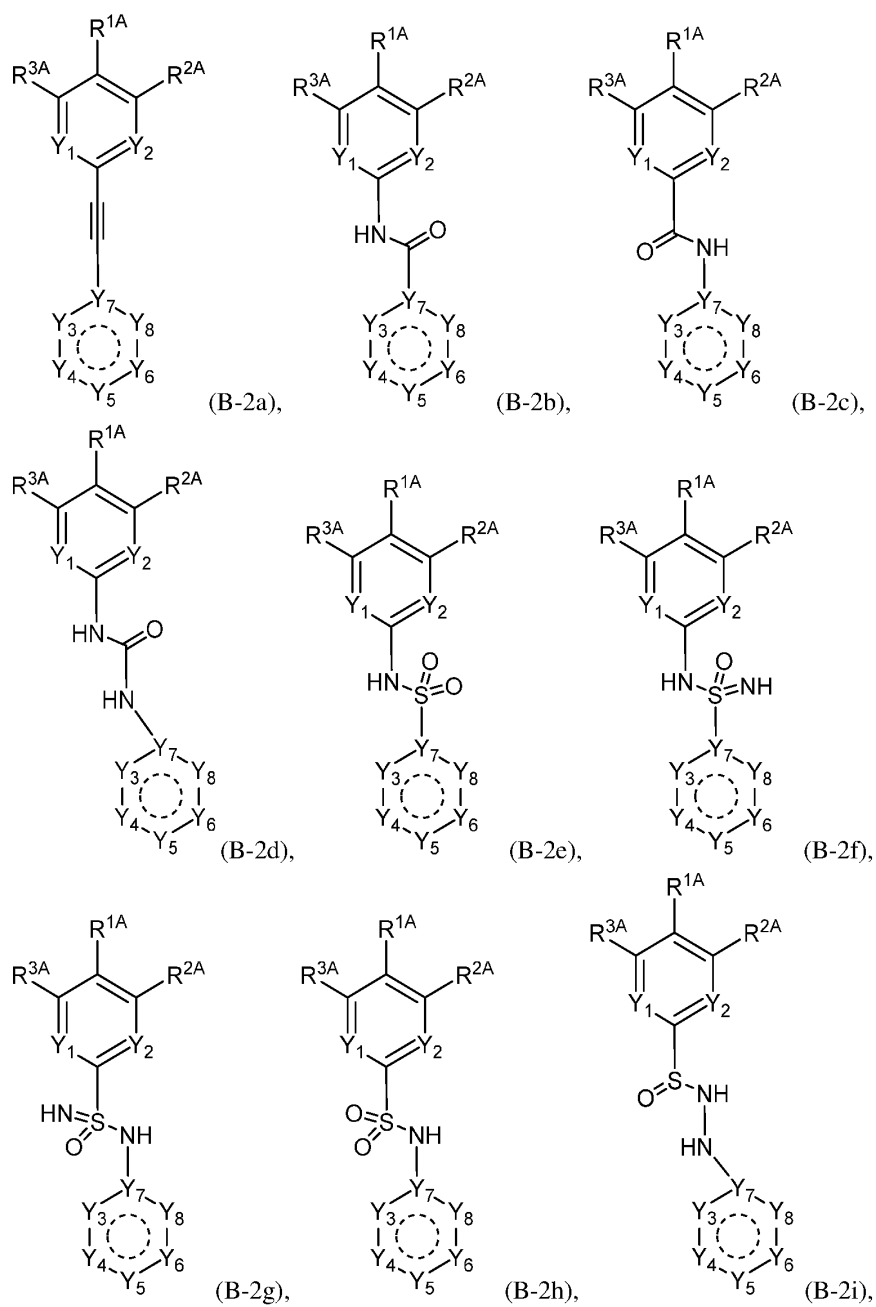
groups selected from the group consisting of C₁-C₆alkyl, C₁-C₆alkoxy, -OH, and C₁-C₆alkyl-OH; and the 3- to 10-membered heterocyclyl, -C₁-C₆alkyl-5- to 6-membered heterocyclyl, and -OC(O)-5- to 6-membered heterocyclyl of R^{6a1}, R^{6b1}, R^{6c1}, and R^{6d1} are each independently unsubstituted or substituted with one or more groups selected from the group consisting of C₁-C₆alkyl, C₁-C₆alkoxy, -OH, C₁-C₆alkyl-OH, =O, and =S.

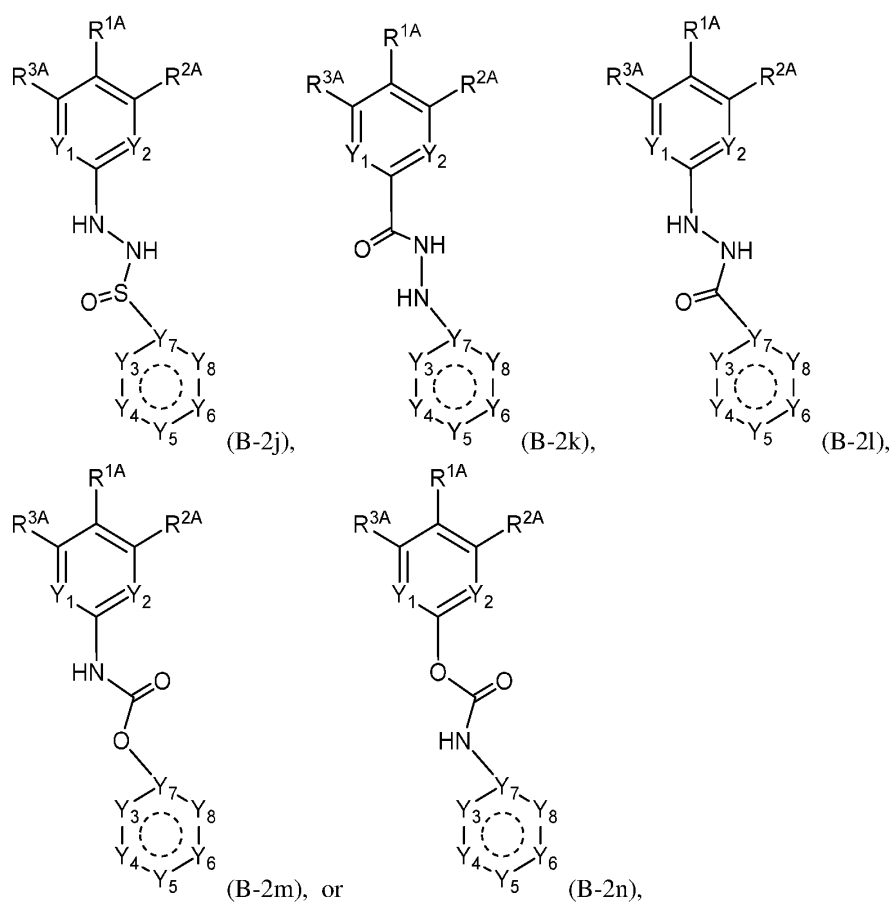
[0090] In some embodiments, the compound of Formula (B) is a compound of Formula (B-1a) or (B-1b):



wherein R^{1A}, R^{2A}, R^{3A}, Y₁, Y₂, Y₃, Y₄, Y₅, Y₆, Y₇, Y₈, and L are as defined for Formula (B).

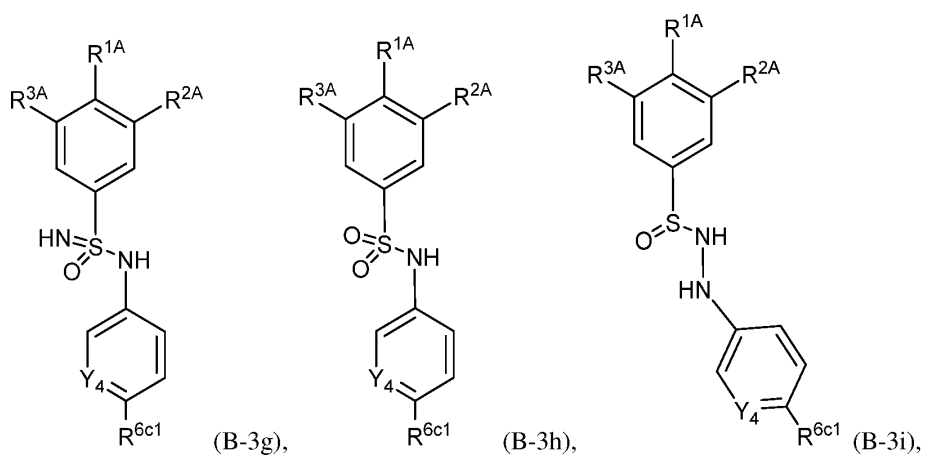
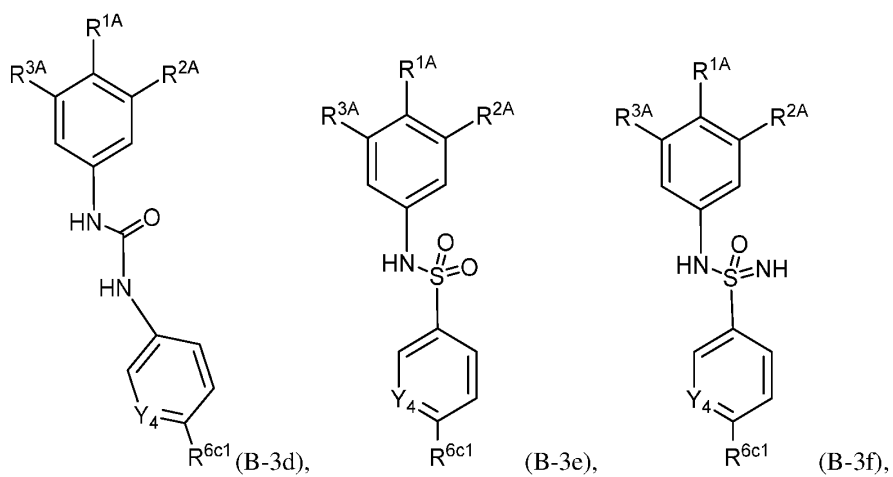
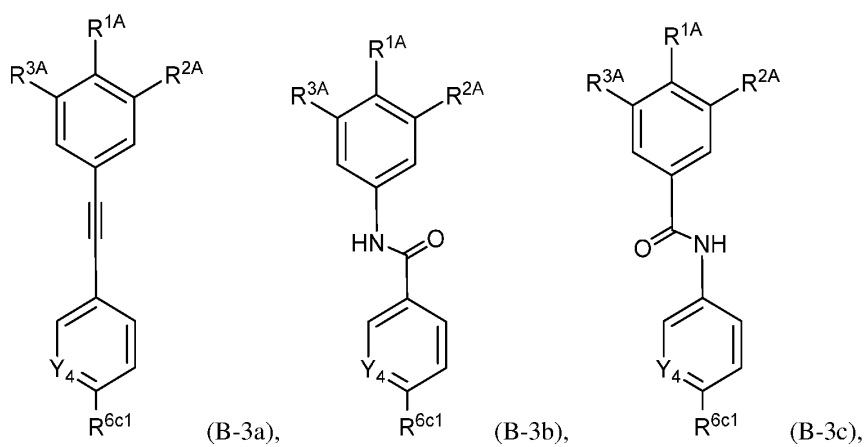
[0091] In some embodiments, the compound of Formula (B) is a compound of Formula (B-2a), (B-2b), (B-2c), (B-2d), (B-2e), (B-2f), (B-2g), (B-2h), (B-2i), (B-2j), (B-2k), (B-2l), (B-2m), or (B-2n):

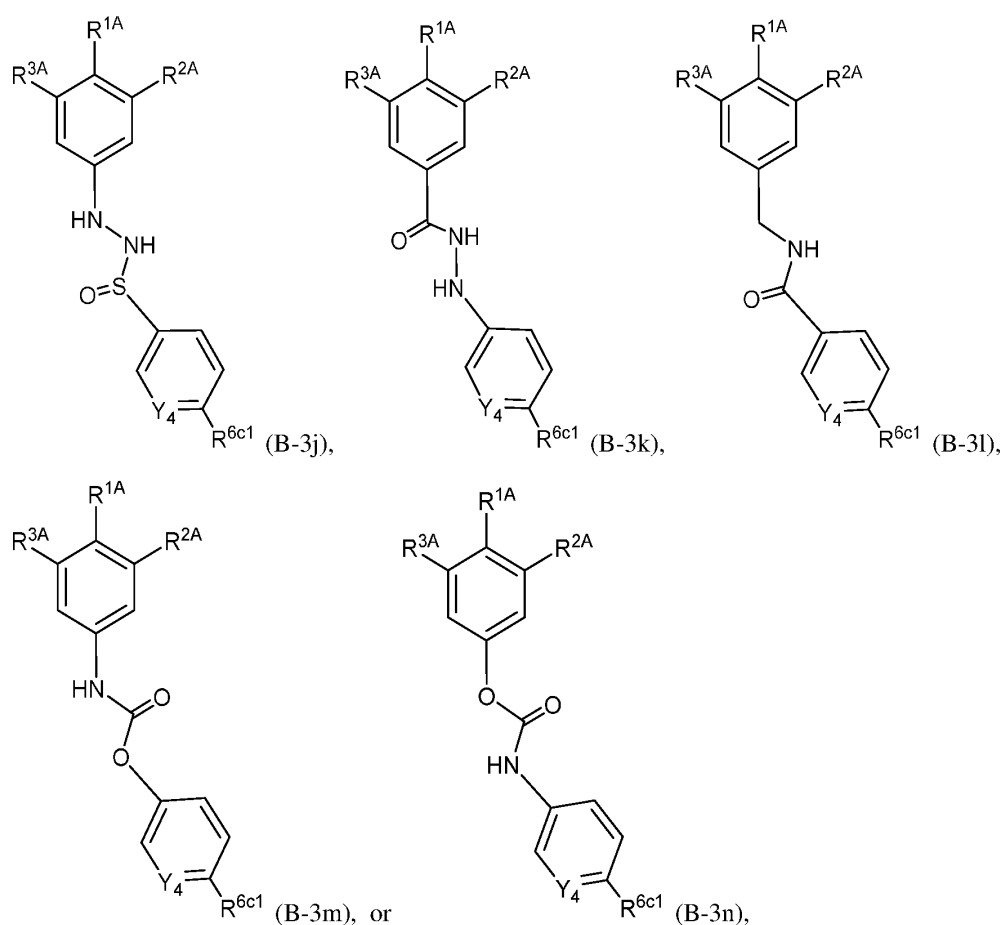




wherein R^{1A} , R^{2A} , R^{3A} , Y_1 , Y_2 , Y_3 , Y_4 , Y_5 , Y_6 , Y_7 , and Y_8 are as defined for Formula (B).

[0092] In some embodiments, the compound of Formula (B) is a compound of Formula (B-3a), (B-3b), (B-3c), (B-3d), (B-3e), (B-3f), (B-3g), (B-3h), (B-3i), (B-3j), (B-3k), (B-3l), (B-3m), or (B-3n):





wherein R^{1A} , R^{2A} , R^{3A} , Y_4 , and R^{6c1} are as defined for Formula (B).

[0093] In some embodiments, when any particular group is substituted, the indicated group is substituted by one or more substituents selected from the group consisting of oxo, C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, halogen, -CN, -OR^{A1}, -SR^{A1}, -NR^{A2}R^{A3}, -NO₂, -C=NH(OR^{A1}), -C(O)R^{A1}, -OC(O)R^{A1}, -C(O)OR^{A1}, -C(O)NR^{A2}R^{A3}, -OC(O)NR^{A2}R^{A3}, -NR^{A1}C(O)R^{A2}, -NR^{A1}C(O)OR^{A2}, -NR^{A1}C(O)NR^{A2}R^{A3}, -S(O)R^{A1}, -S(O)₂R^{A1}, -NR^{A1}S(O)R^{A2}, -C(O)NR^{A1}S(O)R^{A2}, -NR^{A1}S(O)₂R^{A2}, -C(O)NR^{A1}S(O)₂R^{A2}, -S(O)NR^{A2}R^{A3}, -S(O)₂NR^{A2}R^{A3}, -P(O)(OR^{A2})(OR^{A3}), C_3 - C_8 cycloalkyl, 3-12-membered heterocyclyl, 5- to 10-membered heteroaryl, C_6 - C_{14} aryl, -(C₁-C₃ alkylene)CN, -(C₁-C₃ alkylene)OR^{A1}, -(C₁-C₃ alkylene)SR^{A1}, -(C₁-C₃ alkylene)NR^{A2}R^{A3}, -(C₁-C₃ alkylene)CF₃, -(C₁-C₃ alkylene)NO₂, -C=NH(OR^{A1}), -(C₁-

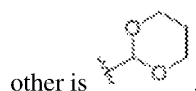
C_3 alkylene)C(O)R^{A1}, -(C₁-C₃ alkylene)OC(O)R^{A1}, -(C₁-C₃ alkylene)C(O)OR^{A1}, -(C₁-C₃ alkylene)C(O)NR^{A2}R^{A3}, -(C₁-C₃ alkylene)OC(O)NR^{A2}R^{A3}, -(C₁-C₃ alkylene)NR^{A1}C(O)R^{A2}, -(C₁-C₃ alkylene)NR^{A1}C(O)OR^{A2}, -(C₁-C₃ alkylene)NR^{A1}C(O)NR^{A2}R^{A3}, -(C₁-C₃ alkylene)S(O)R^{A1}, -(C₁-C₃ alkylene)S(O)₂R^{A1}, -(C₁-C₃ alkylene)NR^{A1}S(O)R^{A2}, -C(O)(C₁-C₃ alkylene)NR^{A1}S(O)R^{A2}, -(C₁-C₃ alkylene)NR^{A1}S(O)₂R^{A2}, -(C₁-C₃ alkylene)C(O)NR^{A1}S(O)₂R^{A2}, -(C₁-C₃ alkylene)S(O)NR^{A2}R^{A3}, -(C₁-C₃ alkylene)S(O)₂NR^{A2}R^{A3}, -(C₁-C₃ alkylene)P(O)(OR^{A2})(OR^{A3}), -(C₁-C₃ alkylene)(C₃-C₈ cycloalkyl), -(C₁-C₃ alkylene)(3-12-membered heterocyclyl), -(C₁-C₃ alkylene)(5-10-membered heteroaryl) and -(C₁-C₃ alkylene)(C₆-C₁₄ aryl), wherein the one or more substituents are each independently unsubstituted or substituted with one or more further substituents selected from the group consisting of halogen, oxo, -OR^{A4}, -NR^{A4}R^{A5}, -C(O)R^{A4}, -CN, -S(O)R^{A4}, -S(O)₂R^{A4}, -P(O)(OR^{A4})(OR^{A5}), -(C₁-C₃ alkylene)OR^{A4}, -(C₁-C₃ alkylene)NR^{A4}R^{A5}, -(C₁-C₃ alkylene)C(O)R^{A4}, -(C₁-C₃ alkylene)S(O)R^{A4}, -(C₁-C₃ alkylene)S(O)₂R^{A4}, -(C₁-C₃ alkylene)P(O)(OR^{A4})(OR^{A5}), C₃-C₈ cycloalkyl, C₁-C₆ alkyl, and C₁-C₆ alkyl substituted by oxo, -OH or halogen; wherein each R^{A1} is independently hydrogen, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₈ cycloalkyl, C₆-C₁₄ aryl, 5-6-membered heteroaryl or 3-6-membered heterocyclyl, wherein the C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₈ cycloalkyl, C₆-C₁₄ aryl, 5-6-membered heteroaryl and 3-6-membered heterocyclyl are independently unsubstituted or substituted by halogen, oxo, -CN, -OR^{A6}, -NR^{A6}R^{A7}, -P(O)(OR^{A6})(OR^{A6}), phenyl, phenyl substituted by halogen, C₁-C₆ alkyl, or C₁-C₆ alkyl substituted by halogen, -OH or oxo; R^{A2} and R^{A3} are each independently hydrogen, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₈ cycloalkyl, C₆-C₁₄ aryl, 5-6-membered heteroaryl or 3-6 membered heterocyclyl, wherein the C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₈ cycloalkyl, C₆-C₁₄ aryl, 5-6-membered heteroaryl and 3-6 membered heterocyclyl are each independently unsubstituted or substituted by halogen, oxo, -CN, -OR^{A6}, -NR^{A6}R^{A7}, C₁-C₆ alkyl, or C₁-C₆ alkyl substituted by halogen, -OH or oxo; and R^{A4}, R^{A5}, R^{A6} and R^{A7} are each independently hydrogen, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ alkyl substituted by one or more halogen, C₂-C₆ alkenyl substituted by one or more halogen, or C₂-C₆ alkynyl substituted by one or more halogen.

[0094] In some embodiments of Formula (B), including Formula (B-1a) and (B-1b), L is -C≡C-. In some embodiments, L is *-NHC(O)-, wherein * represents the point of attachment to Y₇. In some embodiments, L is *-C(O)NH-, wherein * represents the point of attachment to Y₇.

In some embodiments, L is -NHC(O)NH-. In some embodiments, L is *-NHS(O)₂-, wherein * represents the point of attachment to Y₇. In some embodiments, L is *-NHS(O)(=NH)-, wherein * represents the point of attachment to Y₇. In some embodiments, L is *-S(O)(=NH)NH-, wherein * represents the point of attachment to Y₇. In some embodiments, L is *-S(O)₂NH-, wherein * represents the point of attachment to Y₇. In some embodiments, L is *-S(O)NHNH-, wherein * represents the point of attachment to Y₇. In some embodiments, L is *-NHNHS(O)-, wherein * represents the point of attachment to Y₇. In some embodiments, L is *-C(O)NHNH-, wherein * represents the point of attachment to Y₇. In some embodiments, L is *-NHNHC(O)-, wherein * represents the point of attachment to Y₇. In some embodiments, L is *-NHC(O)O-, wherein * represents the point of attachment to Y₇. In some embodiments, L is *-OC(O)NH-, wherein * represents the point of attachment to Y₇.

[0095] In some embodiments of Formula (B), including Formula (B-1a) and (B-1b), L is -C≡C-, and one of R^{1A} and R^{2A} is -OH and the other is -C(O)R^{a1}. In some embodiments, L is -C≡C-, and one of R^{1A} and R^{2A} is -OH and the other is -C(O)H. In some embodiments, L is -C≡C-, and one of R^{1A} and R^{2A} is -OH and the other is -CHNR^{j1}. In some embodiments, L is -C≡C-, and one of R^{1A} and R^{2A} is -OH and the other is -S(O)R^{b1} or -S(O)₂R^{c1}. In some embodiments, L is -C≡C-, and one of R^{1A} and R^{2A} is -OH and the other is -NHC(O)R^{d1} or -NHS(O)₂R^{e1}. In some embodiments, L is -C≡C-, and one of R^{1A} and R^{2A} is -OH and the other is -C₁-C₆alkyl-R^{f1} or -C₂-C₆alkenyl-R^{g1}. In some embodiments, L is -C≡C-, and one of R^{1A} and R^{2A} is -OH and the other is -C(O)H. In some embodiments, L is -C≡C-, and one of R^{1A} and R^{2A} is -OH and the other is -CHNR^{j1}. In some embodiments, L is -C≡C-, and one of R^{1A} and R^{2A} is -OH and the other is -CHNR^{j1}, wherein R^{j1} is C₁-C₆alkyl. In some embodiments, L is -C≡C-, and one of R^{1A} and R^{2A} is -OH and the other is -CHNR^{j1}, wherein R^{j1} is 5- to 6-membered heterocyclyl, unsubstituted or substituted with one or more substituents selected from the group consisting of C₁-C₆alkyl, C₃-C₈cycloalkyl, =O, -C(O)NH-C₁-C₆alkyl, and -C(O)O-C₁-C₆alkyl. In some embodiments, L is -C≡C-, and one of R^{1A} and R^{2A} is -OH and the other is -CHNR^{j1}, wherein R^{j1} is 5- to 6-membered heteroaryl, unsubstituted or substituted with one or more substituents selected from the group consisting of C₁-C₆alkyl, C₃-C₈cycloalkyl, and -C(O)O-C₁-C₆alkyl. In other embodiments, L is -C≡C-, and one of R^{1A} and R^{2A} is -OH and the other is -CHNR^{j1}, wherein R^{j1} is 6- to 12-membered aryl, unsubstituted or substituted with one or more substituents selected from the group consisting of C₁-C₆alkyl, C₃-C₈cycloalkyl, and -C(O)O-C₁-

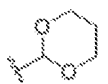
C₆alkyl. In some embodiments, L is -C≡C-, and one of R^{1A} and R^{2A} is -OH and the other is -CHNR^{j1}, wherein R^{j1} is -OR^{k1}, wherein R^{k1} is C₁-C₆alkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, C₃-C₈cycloalkyl, or 6- to 12-membered aryl, wherein the C₁-C₆alkyl is unsubstituted or substituted with 5- to 6-membered heterocyclyl or 5- to 6-membered heteroaryl. In some embodiments, L is -C≡C-, and one of R^{1A} and R^{2A} is -OH and the other is -CHNR^{j1}, wherein R^{j1} is -NHR^{k1} or -N(C₁-C₆alkyl)R^{k1}, wherein R^{k1} is C₁-C₆alkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, C₃-C₈cycloalkyl, or 6- to 12-membered aryl, wherein the C₁-C₆alkyl is unsubstituted or substituted with 5- to 6-membered heterocyclyl or 5- to 6-membered heteroaryl. In some embodiments, L is -C≡C-, and one of R^{1A} and R^{2A} is -OH and the other is -CHNR^{j1}, wherein R^{j1} is -NHC(O)R^{k1}, wherein R^{k1} is C₁-C₆alkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, C₃-C₈cycloalkyl, or 6- to 12-membered aryl, wherein the C₁-C₆alkyl is unsubstituted or substituted with 5- to 6-membered heterocyclyl or 5- to 6-membered heteroaryl. In other embodiments, L is -C≡C-, and one of R^{1A} and R^{2A} is -OH and the other is -CHNR^{j1}, wherein R^{j1} is -NHS(O)₂R^{k1}, wherein R^{k1} is C₁-C₆alkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, C₃-C₈cycloalkyl, or 6- to 12-membered aryl, wherein the C₁-C₆alkyl is unsubstituted or substituted with 5- to 6-membered heterocyclyl or 5- to 6-membered heteroaryl. In yet other embodiments, L is -C≡C-, and one of R^{1A} and R^{2A} is -OH and the other is -CHNR^{j1}, wherein R^{j1} is -NHC(NH)NH₂. In other embodiments, L is -C≡C-, and one of R^{1A} and R^{2A} is -OH and the



[0096] In some embodiments of Formula (B), including Formula (B-1a) and (B-1b), L is *-NHC(O)-, and one of R^{1A} and R^{2A} is -OH and the other is -C(O)H. In some embodiments, L is *-NHC(O)-, and one of R^{1A} and R^{2A} is -OH and the other is -CHNR^{j1}. In some embodiments, L is *-NHC(O)-, and one of R^{1A} and R^{2A} is -OH and the other is -CHNR^{j1}, wherein R^{j1} is C₁-C₆alkyl. In some embodiments, L is *-NHC(O)-, and one of R^{1A} and R^{2A} is -OH and the other is -CHNR^{j1}, wherein R^{j1} is 5- to 6-membered heterocyclyl, unsubstituted or substituted with one or more substituents selected from the group consisting of C₁-C₆alkyl, C₃-C₈cycloalkyl, =O, -C(O)NH-C₁-C₆alkyl, and -C(O)O-C₁-C₆alkyl. In some embodiments, L is *-NHC(O)-, and one of R^{1A} and R^{2A} is -OH and the other is -CHNR^{j1}, wherein R^{j1} is 5- to 6-membered heteroaryl, unsubstituted or substituted with one or more substituents selected from the group consisting of C₁-C₆alkyl, C₃-C₈cycloalkyl, and -C(O)O-C₁-C₆alkyl. In other embodiments, L is *-NHC(O)-, and one of R^{1A} and R^{2A} is -OH and the other is -CHNR^{j1}, wherein R^{j1} is 6- to 12-membered aryl,

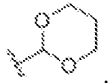
unsubstituted or substituted with one or more substituents selected from the group consisting of C₁-C₆alkyl, C₃-C₈cycloalkyl, and -C(O)O-C₁-C₆alkyl. In some embodiments, L is *-NHC(O)-, and one of R^{1A} and R^{2A} is -OH and the other is -CHNR^{j1}, wherein R^{j1} is -OR^{k1}, wherein R^{k1} is C₁-C₆alkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, C₃-C₈cycloalkyl, or 6- to 12-membered aryl, wherein the C₁-C₆alkyl is unsubstituted or substituted with 5- to 6-membered heterocyclyl or 5- to 6-membered heteroaryl. In some embodiments, L is *-NHC(O)-, and one of R^{1A} and R^{2A} is -OH and the other is -CHNR^{j1}, wherein R^{j1} is -NHR^{k1} or -N(C₁-C₆alkyl)R^{k1}, wherein R^{k1} is C₁-C₆alkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, C₃-C₈cycloalkyl, or 6- to 12-membered aryl, wherein the C₁-C₆alkyl is unsubstituted or substituted with 5- to 6-membered heterocyclyl or 5- to 6-membered heteroaryl. In some embodiments, L is *-NHC(O)-, and one of R^{1A} and R^{2A} is -OH and the other is -CHNR^{j1}, wherein R^{j1} is -NHC(O)R^{k1}, wherein R^{k1} is C₁-C₆alkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, C₃-C₈cycloalkyl, or 6- to 12-membered aryl, wherein the C₁-C₆alkyl is unsubstituted or substituted with 5- to 6-membered heterocyclyl or 5- to 6-membered heteroaryl. In other embodiments, L is *-NHC(O)-, and one of R^{1A} and R^{2A} is -OH and the other is -CHNR^{j1}, wherein R^{j1} is -NHS(O)₂R^{k1}, wherein R^{k1} is C₁-C₆alkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, C₃-C₈cycloalkyl, or 6- to 12-membered aryl, wherein the C₁-C₆alkyl is unsubstituted or substituted with 5- to 6-membered heterocyclyl or 5- to 6-membered heteroaryl. In yet other embodiments, L is *-NHC(O)-, and one of R^{1A} and R^{2A} is -OH and the other is -CHNR^{j1}, wherein R^{j1} is -NHC(NH)NH₂. In other embodiments, L is *-NHC(O)-, and one of R^{1A} and R^{2A}

is -OH and the other is



[0097] In some embodiments of Formula (B), including Formula (B-1a) and (B-1b), L is *-C(O)NH-, and one of R^{1A} and R^{2A} is -OH and the other is -C(O)H. In some embodiments, L is *-C(O)NH-, and one of R^{1A} and R^{2A} is -OH and the other is -CHNR^{j1}. In some embodiments, L is *-C(O)NH-, and one of R^{1A} and R^{2A} is -OH and the other is -CHNR^{j1}, wherein R^{j1} is C₁-C₆alkyl. In some embodiments, L is *-C(O)NH-, and one of R^{1A} and R^{2A} is -OH and the other is -CHNR^{j1}, wherein R^{j1} is 5- to 6-membered heterocyclyl, unsubstituted or substituted with one or more substituents selected from the group consisting of C₁-C₆alkyl, C₃-C₈cycloalkyl, =O, -C(O)NH-C₁-C₆alkyl, and -C(O)O-C₁-C₆alkyl. In some embodiments, L is *-C(O)NH-, and one of R^{1A} and R^{2A} is -OH and the other is -CHNR^{j1}, wherein R^{j1} is 5- to 6-membered heteroaryl, unsubstituted or substituted with one or more substituents selected from the group consisting of

C₁-C₆alkyl, C₃-C₈cycloalkyl, and -C(O)O-C₁-C₆alkyl. In other embodiments, L is *-C(O)NH-, and one of R^{1A} and R^{2A} is -OH and the other is -CHNR^{j1}, wherein R^{j1} is 6- to 12-membered aryl, unsubstituted or substituted with one or more substituents selected from the group consisting of C₁-C₆alkyl, C₃-C₈cycloalkyl, and -C(O)O-C₁-C₆alkyl. In some embodiments, L is *-C(O)NH-, and one of R^{1A} and R^{2A} is -OH and the other is -CHNR^{j1}, wherein R^{j1} is -OR^{k1}, wherein R^{k1} is C₁-C₆alkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, C₃-C₈cycloalkyl, or 6- to 12-membered aryl, wherein the C₁-C₆alkyl is unsubstituted or substituted with 5- to 6-membered heterocyclyl or 5- to 6-membered heteroaryl. In some embodiments, L is *-C(O)NH-, and one of R^{1A} and R^{2A} is -OH and the other is -CHNR^{j1}, wherein R^{j1} is -NHR^{k1} or -N(C₁-C₆alkyl)R^{k1}, wherein R^{k1} is C₁-C₆alkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, C₃-C₈cycloalkyl, or 6- to 12-membered aryl, wherein the C₁-C₆alkyl is unsubstituted or substituted with 5- to 6-membered heterocyclyl or 5- to 6-membered heteroaryl. In some embodiments, L is *-C(O)NH-, and one of R^{1A} and R^{2A} is -OH and the other is -CHNR^{j1}, wherein R^{j1} is -NHC(O)R^{k1}, wherein R^{k1} is C₁-C₆alkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, C₃-C₈cycloalkyl, or 6- to 12-membered aryl, wherein the C₁-C₆alkyl is unsubstituted or substituted with 5- to 6-membered heterocyclyl or 5- to 6-membered heteroaryl. In other embodiments, L is *-C(O)NH-, and one of R^{1A} and R^{2A} is -OH and the other is -CHNR^{j1}, wherein R^{j1} is -NHS(O)₂R^{k1}, wherein R^{k1} is C₁-C₆alkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, C₃-C₈cycloalkyl, or 6- to 12-membered aryl, wherein the C₁-C₆alkyl is unsubstituted or substituted with 5- to 6-membered heterocyclyl or 5- to 6-membered heteroaryl. In yet other embodiments, L is *-C(O)NH-, and one of R^{1A} and R^{2A} is -OH and the other is -CHNR^{j1}, wherein R^{j1} is -NHC(NH)NH₂. In other embodiments, L is *-C(O)NH-, and one of R^{1A} and R^{2A}

is -OH and the other is .

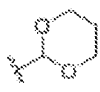
[0098] In some embodiments of Formula (B), including Formula (B-1a) and (B-1b), L is -NHC(O)NH-, and one of R^{1A} and R^{2A} is -OH and the other is -C(O)H. In some embodiments, L is -NHC(O)NH-, and one of R^{1A} and R^{2A} is -OH and the other is -CHNR^{j1}. In some embodiments, L is -NHC(O)NH-, and one of R^{1A} and R^{2A} is -OH and the other is -CHNR^{j1}, wherein R^{j1} is C₁-C₆alkyl. In some embodiments, L is -NHC(O)NH-, and one of R^{1A} and R^{2A} is -OH and the other is -CHNR^{j1}, wherein R^{j1} is 5- to 6-membered heterocyclyl, unsubstituted or substituted with one or more substituents selected from the group consisting of C₁-C₆alkyl, C₃-C₈cycloalkyl, =O, -C(O)NH-C₁-C₆alkyl, and -C(O)O-C₁-C₆alkyl. In some embodiments, L is -

NHC(O)NH-, and one of R^{1A} and R^{2A} is -OH and the other is -CHNR^{j1}, wherein R^{j1} is 5- to 6-membered heteroaryl, unsubstituted or substituted with one or more substituents selected from the group consisting of C₁-C₆alkyl, C₃-C₈cycloalkyl, and -C(O)O-C₁-C₆alkyl. In other embodiments, L is -NHC(O)NH-, and one of R^{1A} and R^{2A} is -OH and the other is -CHNR^{j1}, wherein R^{j1} is 6- to 12-membered aryl, unsubstituted or substituted with one or more substituents selected from the group consisting of C₁-C₆alkyl, C₃-C₈cycloalkyl, and -C(O)O-C₁-C₆alkyl. In some embodiments, L is -NHC(O)NH-, and one of R^{1A} and R^{2A} is -OH and the other is -CHNR^{j1}, wherein R^{j1} is -OR^{k1}, wherein R^{k1} is C₁-C₆alkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, C₃-C₈cycloalkyl, or 6- to 12-membered aryl, wherein the C₁-C₆alkyl is unsubstituted or substituted with 5- to 6-membered heterocyclyl or 5- to 6-membered heteroaryl. In some embodiments, L is -NHC(O)NH-, and one of R^{1A} and R^{2A} is -OH and the other is -CHNR^{j1}, wherein R^{j1} is -NHR^{k1}, wherein R^{k1} is C₁-C₆alkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, C₃-C₈cycloalkyl, or 6- to 12-membered aryl, wherein the C₁-C₆alkyl is unsubstituted or substituted with 5- to 6-membered heterocyclyl or 5- to 6-membered heteroaryl. In some embodiments, L is -NHC(O)NH-, and one of R^{1A} and R^{2A} is -OH and the other is -CHNR^{j1}, wherein R^{j1} is -NHC(O)R^{k1} or -N(C₁-C₆alkyl)R^{k1}, wherein R^{k1} is C₁-C₆alkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, C₃-C₈cycloalkyl, or 6- to 12-membered aryl, wherein the C₁-C₆alkyl is unsubstituted or substituted with 5- to 6-membered heterocyclyl or 5- to 6-membered heteroaryl. In other embodiments, L is -NHC(O)NH-, and one of R^{1A} and R^{2A} is -OH and the other is -CHNR^{j1}, wherein R^{j1} is -NHS(O)₂R^{k1}, wherein R^{k1} is C₁-C₆alkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, C₃-C₈cycloalkyl, or 6- to 12-membered aryl, wherein the C₁-C₆alkyl is unsubstituted or substituted with 5- to 6-membered heterocyclyl or 5- to 6-membered heteroaryl. In yet other embodiments, L is -NHC(O)NH-, and one of R^{1A} and R^{2A} is -OH and the other is -CHNR^{j1}, wherein R^{j1} is -NHC(NH)NH₂. In other embodiments, L is -NHC(O)NH-, and one of

R^{1A} and R^{2A} is -OH and the other is .

[0099] In some embodiments of Formula (B), including Formula (B-1a) and (B-1b), L is *-NHS(O)₂-, and one of R^{1A} and R^{2A} is -OH and the other is -C(O)H. In some embodiments, L is *-NHS(O)₂-, and one of R^{1A} and R^{2A} is -OH and the other is -CHNR^{j1}. In some embodiments, L is *-NHS(O)₂-, and one of R^{1A} and R^{2A} is -OH and the other is -CHNR^{j1}, wherein R^{j1} is C₁-C₆alkyl. In some embodiments, L is *-NHS(O)₂-, and one of R^{1A} and R^{2A} is -OH and the other is -CHNR^{j1}, wherein R^{j1} is 5- to 6-membered heterocyclyl, unsubstituted or substituted with one

or more substituents selected from the group consisting of C₁-C₆alkyl, C₃-C₈cycloalkyl, =O, -C(O)NH-C₁-C₆alkyl, and -C(O)O-C₁-C₆alkyl. In some embodiments, L is *-NHS(O)₂-, and one of R^{1A} and R^{2A} is -OH and the other is -CHNR^{j1}, wherein R^{j1} is 5- to 6-membered heteroaryl, unsubstituted or substituted with one or more substituents selected from the group consisting of C₁-C₆alkyl, C₃-C₈cycloalkyl, and -C(O)O-C₁-C₆alkyl. In other embodiments, L is *-NHS(O)₂-, and one of R^{1A} and R^{2A} is -OH and the other is -CHNR^{j1}, wherein R^{j1} is 6- to 12-membered aryl, unsubstituted or substituted with one or more substituents selected from the group consisting of C₁-C₆alkyl, C₃-C₈cycloalkyl, and -C(O)O-C₁-C₆alkyl. In some embodiments, L is *-NHS(O)₂-, and one of R^{1A} and R^{2A} is -OH and the other is -CHNR^{j1}, wherein R^{j1} is -OR^{k1}, wherein R^{k1} is C₁-C₆alkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, C₃-C₈cycloalkyl, or 6- to 12-membered aryl, wherein the C₁-C₆alkyl is unsubstituted or substituted with 5- to 6-membered heterocyclyl or 5- to 6-membered heteroaryl. In some embodiments, L is *-NHS(O)₂-, and one of R^{1A} and R^{2A} is -OH and the other is -CHNR^{j1}, wherein R^{j1} is -NHR^{k1} or -N(C₁-C₆alkyl)R^{k1}, wherein R^{k1} is C₁-C₆alkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, C₃-C₈cycloalkyl, or 6- to 12-membered aryl, wherein the C₁-C₆alkyl is unsubstituted or substituted with 5- to 6-membered heterocyclyl or 5- to 6-membered heteroaryl. In some embodiments, L is *-NHS(O)₂-, and one of R^{1A} and R^{2A} is -OH and the other is -CHNR^{j1}, wherein R^{j1} is -NHC(O)R^{k1}, wherein R^{k1} is C₁-C₆alkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, C₃-C₈cycloalkyl, or 6- to 12-membered aryl, wherein the C₁-C₆alkyl is unsubstituted or substituted with 5- to 6-membered heterocyclyl or 5- to 6-membered heteroaryl. In other embodiments, L is *-NHS(O)₂-, and one of R^{1A} and R^{2A} is -OH and the other is -CHNR^{j1}, wherein R^{j1} is -NHS(O)₂R^{k1}, wherein R^{k1} is C₁-C₆alkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, C₃-C₈cycloalkyl, or 6- to 12-membered aryl, wherein the C₁-C₆alkyl is unsubstituted or substituted with 5- to 6-membered heterocyclyl or 5- to 6-membered heteroaryl. In yet other embodiments, L is *-NHS(O)₂-, and one of R^{1A} and R^{2A} is -OH and the other is -CHNR^{j1}, wherein R^{j1} is -NHC(NH)NH₂. In other embodiments, L is *-NHS(O)₂-, and one of R^{1A} and R^{2A}

is -OH and the other is .

[0100] In some embodiments of Formula (B), including Formula (B-1a) and (B-1b), L is *-NHS(O)(=NH)- or *-S(O)(=NH)NH-, and one of R^{1A} and R^{2A} is -OH and the other is -C(O)H. In some embodiments, L is *-NHS(O)(=NH)- or *-S(O)(=NH)NH-, and one of R^{1A} and R^{2A} is -OH and the other is -CHNR^{j1}. In some embodiments, L is *-NHS(O)(=NH)- or *-

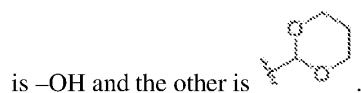
S(O)(=NH)NH-, and one of R^{1A} and R^{2A} is -OH and the other is -CHNR^{j1}, wherein R^{j1} is C₁-C₆alkyl. In some embodiments, L is *-NHS(O)(=NH)- or *-S(O)(=NH)NH-, and one of R^{1A} and R^{2A} is -OH and the other is -CHNR^{j1}, wherein R^{j1} is 5- to 6-membered heterocyclyl, unsubstituted or substituted with one or more substituents selected from the group consisting of C₁-C₆alkyl, C₃-C₈cycloalkyl, =O, -C(O)NH-C₁-C₆alkyl, and -C(O)O-C₁-C₆alkyl. In some embodiments, L is *-NHS(O)(=NH)- or *-S(O)(=NH)NH-, and one of R^{1A} and R^{2A} is -OH and the other is -CHNR^{j1}, wherein R^{j1} is 5- to 6-membered heteroaryl, unsubstituted or substituted with one or more substituents selected from the group consisting of C₁-C₆alkyl, C₃-C₈cycloalkyl, and -C(O)O-C₁-C₆alkyl. In other embodiments, L is *-NHS(O)(=NH)- or *-S(O)(=NH)NH-, and one of R^{1A} and R^{2A} is -OH and the other is -CHNR^{j1}, wherein R^{j1} is 6- to 12-membered aryl, unsubstituted or substituted with one or more substituents selected from the group consisting of C₁-C₆alkyl, C₃-C₈cycloalkyl, and -C(O)O-C₁-C₆alkyl. In some embodiments, L is *-NHS(O)(=NH)- or *-S(O)(=NH)NH-, and one of R^{1A} and R^{2A} is -OH and the other is -CHNR^{j1}, wherein R^{j1} is -OR^{k1}, wherein R^{k1} is C₁-C₆alkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, C₃-C₈cycloalkyl, or 6- to 12-membered aryl, wherein the C₁-C₆alkyl is unsubstituted or substituted with 5- to 6-membered heterocyclyl or 5- to 6-membered heteroaryl. In some embodiments, L is *-NHS(O)(=NH)- or *-S(O)(=NH)NH-, and one of R^{1A} and R^{2A} is -OH and the other is -CHNR^{j1}, wherein R^{j1} is -NHR^{k1} or -N(C₁-C₆alkyl)R^{k1}, wherein R^{k1} is C₁-C₆alkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, C₃-C₈cycloalkyl, or 6- to 12-membered aryl, wherein the C₁-C₆alkyl is unsubstituted or substituted with 5- to 6-membered heterocyclyl or 5- to 6-membered heteroaryl. In some embodiments, L is *-NHS(O)(=NH)- or *-S(O)(=NH)NH-, and one of R^{1A} and R^{2A} is -OH and the other is -CHNR^{j1}, wherein R^{j1} is -NHC(O)R^{k1}, wherein R^{k1} is C₁-C₆alkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, C₃-C₈cycloalkyl, or 6- to 12-membered aryl, wherein the C₁-C₆alkyl is unsubstituted or substituted with 5- to 6-membered heterocyclyl or 5- to 6-membered heteroaryl. In other embodiments, L is *-NHS(O)(=NH)- or *-S(O)(=NH)NH-, and one of R^{1A} and R^{2A} is -OH and the other is -CHNR^{j1}, wherein R^{j1} is -NHS(O)₂R^{k1}, wherein R^{k1} is C₁-C₆alkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, C₃-C₈cycloalkyl, or 6- to 12-membered aryl, wherein the C₁-C₆alkyl is unsubstituted or substituted with 5- to 6-membered heterocyclyl or 5- to 6-membered heteroaryl. In yet other embodiments, L is *-NHS(O)(=NH)- or *-S(O)(=NH)NH-, and one of R^{1A} and R^{2A} is -OH and

the other is $-\text{CHNR}^{j1}$, wherein R^{j1} is $-\text{NHC}(\text{NH})\text{NH}_2$. In other embodiments, L is $^*\text{-NHS}(\text{O})_2-$,

and one of R^{1A} and R^{2A} is $-\text{OH}$ and the other is .

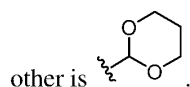
[0101] In some embodiments of Formula (B), including Formula (B-1a) and (B-1b), L is $^*\text{-S}(\text{O})_2\text{NH}-$, and one of R^{1A} and R^{2A} is $-\text{OH}$ and the other is $-\text{C}(\text{O})\text{H}$. In some embodiments, L is $^*\text{-S}(\text{O})_2\text{NH}-$, and one of R^{1A} and R^{2A} is $-\text{OH}$ and the other is $-\text{CHNR}^{j1}$. In some embodiments, L is $^*\text{-S}(\text{O})_2\text{NH}-$, and one of R^{1A} and R^{2A} is $-\text{OH}$ and the other is $-\text{CHNR}^{j1}$, wherein R^{j1} is C_1 - C_6 alkyl. In some embodiments, L is $^*\text{-S}(\text{O})_2\text{NH}-$, and one of R^{1A} and R^{2A} is $-\text{OH}$ and the other is $-\text{CHNR}^{j1}$, wherein R^{j1} is 5- to 6-membered heterocyclyl, unsubstituted or substituted with one or more substituents selected from the group consisting of C_1 - C_6 alkyl, C_3 - C_8 cycloalkyl, $=\text{O}$, $-\text{C}(\text{O})\text{NH}-\text{C}_1$ - C_6 alkyl, and $-\text{C}(\text{O})\text{O}-\text{C}_1$ - C_6 alkyl. In some embodiments, L is $^*\text{-S}(\text{O})_2\text{NH}-$, and one of R^{1A} and R^{2A} is $-\text{OH}$ and the other is $-\text{CHNR}^{j1}$, wherein R^{j1} is 5- to 6-membered heteroaryl, unsubstituted or substituted with one or more substituents selected from the group consisting of C_1 - C_6 alkyl, C_3 - C_8 cycloalkyl, and $-\text{C}(\text{O})\text{O}-\text{C}_1$ - C_6 alkyl. In other embodiments, L is $^*\text{-S}(\text{O})_2\text{NH}-$, and one of R^{1A} and R^{2A} is $-\text{OH}$ and the other is $-\text{CHNR}^{j1}$, wherein R^{j1} is 6- to 12-membered aryl, unsubstituted or substituted with one or more substituents selected from the group consisting of C_1 - C_6 alkyl, C_3 - C_8 cycloalkyl, and $-\text{C}(\text{O})\text{O}-\text{C}_1$ - C_6 alkyl. In some embodiments, L is $^*\text{-S}(\text{O})_2\text{NH}-$, and one of R^{1A} and R^{2A} is $-\text{OH}$ and the other is $-\text{CHNR}^{j1}$, wherein R^{j1} is $-\text{OR}^{k1}$, wherein R^{k1} is C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, C_3 - C_8 cycloalkyl, or 6- to 12-membered aryl, wherein the C_1 - C_6 alkyl is unsubstituted or substituted with 5- to 6-membered heterocyclyl or 5- to 6-membered heteroaryl. In some embodiments, L is $^*\text{-S}(\text{O})_2\text{NH}-$, and one of R^{1A} and R^{2A} is $-\text{OH}$ and the other is $-\text{CHNR}^{j1}$, wherein R^{j1} is $-\text{NHR}^{k1}$ or $-\text{N}(\text{C}_1\text{-}\text{C}_6\text{alkyl})\text{R}^{k1}$, wherein R^{k1} is C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, C_3 - C_8 cycloalkyl, or 6- to 12-membered aryl, wherein the C_1 - C_6 alkyl is unsubstituted or substituted with 5- to 6-membered heterocyclyl or 5- to 6-membered heteroaryl. In some embodiments, L is $^*\text{-S}(\text{O})_2\text{NH}-$, and one of R^{1A} and R^{2A} is $-\text{OH}$ and the other is $-\text{CHNR}^{j1}$, wherein R^{j1} is $-\text{NHC}(\text{O})\text{R}^{k1}$, wherein R^{k1} is C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, C_3 - C_8 cycloalkyl, or 6- to 12-membered aryl, wherein the C_1 - C_6 alkyl is unsubstituted or substituted with 5- to 6-membered heterocyclyl or 5- to 6-membered heteroaryl. In other embodiments, L is $^*\text{-S}(\text{O})_2\text{NH}-$, and one of R^{1A} and R^{2A} is $-\text{OH}$ and the other is $-\text{CHNR}^{j1}$, wherein R^{j1} is $-\text{NHS}(\text{O})_2\text{R}^{k1}$, wherein R^{k1} is C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, C_3 - C_8 cycloalkyl, or 6- to 12-membered aryl, wherein the C_1 - C_6 alkyl is unsubstituted or

substituted with 5- to 6-membered heterocyclyl or 5- to 6-membered heteroaryl. In yet other embodiments, L is $^*-S(O)_2NH-$, and one of R^{1A} and R^{2A} is $-OH$ and the other is $-CHNR^{j1}$, wherein R^{j1} is $-NHC(NH)NH_2$. In other embodiments, L is $^*-S(O)_2NH-$, and one of R^{1A} and R^{2A}



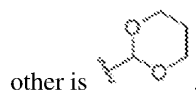
[0102] In some embodiments of Formula (B), including Formula (B-1a) and (B-1b), L is $^*-S(O)NHNH-$ or $^*-NHNHS(O)-$, and one of R^{1A} and R^{2A} is $-OH$ and the other is $-C(O)H$. In some embodiments, L is $^*-S(O)NHNH-$ or $^*-NHNHS(O)-$, and one of R^{1A} and R^{2A} is $-OH$ and the other is $-CHNR^{j1}$. In some embodiments, L is $^*-S(O)NHNH-$ or $^*-NHNHS(O)-$, and one of R^{1A} and R^{2A} is $-OH$ and the other is $-CHNR^{j1}$, wherein R^{j1} is C_1 - C_6 alkyl. In some embodiments, L is $^*-S(O)NHNH-$ or $^*-NHNHS(O)-$, and one of R^{1A} and R^{2A} is $-OH$ and the other is $-CHNR^{j1}$, wherein R^{j1} is 5- to 6-membered heterocyclyl, unsubstituted or substituted with one or more substituents selected from the group consisting of C_1 - C_6 alkyl, C_3 - C_8 cycloalkyl, $=O$, $-C(O)NH-C_1$ - C_6 alkyl, and $-C(O)O-C_1$ - C_6 alkyl. In some embodiments, L is $^*-S(O)NHNH-$ or $^*-NHNHS(O)-$, and one of R^{1A} and R^{2A} is $-OH$ and the other is $-CHNR^{j1}$, wherein R^{j1} is 5- to 6-membered heteroaryl, unsubstituted or substituted with one or more substituents selected from the group consisting of C_1 - C_6 alkyl, C_3 - C_8 cycloalkyl, and $-C(O)O-C_1$ - C_6 alkyl. In other embodiments, L is $^*-S(O)NHNH-$ or $^*-NHNHS(O)-$, and one of R^{1A} and R^{2A} is $-OH$ and the other is $-CHNR^{j1}$, wherein R^{j1} is 6- to 12-membered aryl, unsubstituted or substituted with one or more substituents selected from the group consisting of C_1 - C_6 alkyl, C_3 - C_8 cycloalkyl, and $-C(O)O-C_1$ - C_6 alkyl. In some embodiments, L is $^*-S(O)NHNH-$ or $^*-NHNHS(O)-$, and one of R^{1A} and R^{2A} is $-OH$ and the other is $-CHNR^{j1}$, wherein R^{j1} is $-OR^{k1}$, wherein R^{k1} is C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, C_3 - C_8 cycloalkyl, or 6- to 12-membered aryl, wherein the C_1 - C_6 alkyl is unsubstituted or substituted with 5- to 6-membered heterocyclyl or 5- to 6-membered heteroaryl. In some embodiments, L is $^*-S(O)NHNH-$ or $^*-NHNHS(O)-$, and one of R^{1A} and R^{2A} is $-OH$ and the other is $-CHNR^{j1}$, wherein R^{j1} is $-NHR^{k1}$ or $-N(C_1$ - C_6 alkyl) R^{k1} , wherein R^{k1} is C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, C_3 - C_8 cycloalkyl, or 6- to 12-membered aryl, wherein the C_1 - C_6 alkyl is unsubstituted or substituted with 5- to 6-membered heterocyclyl or 5- to 6-membered heteroaryl. In some embodiments, L is $^*-S(O)NHNH-$ or $^*-NHNHS(O)-$, and one of R^{1A} and R^{2A} is $-OH$ and the other is $-CHNR^{j1}$, wherein R^{j1} is $-NHC(O)R^{k1}$, wherein R^{k1} is C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, C_3 - C_8 cycloalkyl, or 6- to 12-membered aryl, wherein the

C₁-C₆alkyl is unsubstituted or substituted with 5- to 6-membered heterocyclyl or 5- to 6-membered heteroaryl. In other embodiments, L is *-S(O)NHNH- or *-NHNHS(O)-, and one of R^{1A} and R^{2A} is -OH and the other is -CHNR^{j1}, wherein R^{j1} is -NHS(O)₂R^{k1}, wherein R^{k1} is C₁-C₆alkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, C₃-C₈cycloalkyl, or 6- to 12-membered aryl, wherein the C₁-C₆alkyl is unsubstituted or substituted with 5- to 6-membered heterocyclyl or 5- to 6-membered heteroaryl. In yet other embodiments, L is *-S(O)NHNH- or *-NHNHS(O)-, and one of R^{1A} and R^{2A} is -OH and the other is -CHNR^{j1}, wherein R^{j1} is -NHC(NH)NH₂. In other embodiments, L is *-S(O)NHNH- or *-NHNHS(O)-, and one of R^{1A} and R^{2A} is -OH and the



[0103] In some embodiments of Formula (B), including Formula (B-1a) and (B-1b), L is *-C(O)NHNH- or *-NHNHC(O)-, and one of R^{1A} and R^{2A} is -OH and the other is -C(O)H. In some embodiments, L is *-C(O)NHNH- or *-NHNHC(O)-, and one of R^{1A} and R^{2A} is -OH and the other is -CHNR^{j1}. In some embodiments, L is *-C(O)NHNH- or *-NHNHC(O)-, and one of R^{1A} and R^{2A} is -OH and the other is -CHNR^{j1}, wherein R^{j1} is C₁-C₆alkyl. In some embodiments, L is *-C(O)NHNH- or *-NHNHC(O)-, and one of R^{1A} and R^{2A} is -OH and the other is -CHNR^{j1}, wherein R^{j1} is 5- to 6-membered heterocyclyl, unsubstituted or substituted with one or more substituents selected from the group consisting of C₁-C₆alkyl, C₃-C₈cycloalkyl, =O, -C(O)NH-C₁-C₆alkyl, and -C(O)O-C₁-C₆alkyl. In some embodiments, L is *-C(O)NHNH- or *-NHNHC(O)-, and one of R^{1A} and R^{2A} is -OH and the other is -CHNR^{j1}, wherein R^{j1} is 5- to 6-membered heteroaryl, unsubstituted or substituted with one or more substituents selected from the group consisting of C₁-C₆alkyl, C₃-C₈cycloalkyl, and -C(O)O-C₁-C₆alkyl. In other embodiments, L is *-C(O)NHNH- or *-NHNHC(O)-, and one of R^{1A} and R^{2A} is -OH and the other is -CHNR^{j1}, wherein R^{j1} is 6- to 12-membered aryl, unsubstituted or substituted with one or more substituents selected from the group consisting of C₁-C₆alkyl, C₃-C₈cycloalkyl, and -C(O)O-C₁-C₆alkyl. In some embodiments, L is *-C(O)NHNH- or *-NHNHC(O)-, and one of R^{1A} and R^{2A} is -OH and the other is -CHNR^{j1}, wherein R^{j1} is -OR^{k1}, wherein R^{k1} is C₁-C₆alkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, C₃-C₈cycloalkyl, or 6- to 12-membered aryl, wherein the C₁-C₆alkyl is unsubstituted or substituted with 5- to 6-membered heterocyclyl or 5- to 6-membered heteroaryl. In some embodiments, L is *-C(O)NHNH- or *-NHNHC(O)-, and one of R^{1A} and R^{2A} is -OH and the other is -CHNR^{j1}, wherein R^{j1} is -NHR^{k1} or -N(C₁-C₆alkyl)R^{k1}, wherein R^{k1}

is C₁-C₆alkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, C₃-C₈cycloalkyl, or 6- to 12-membered aryl, wherein the C₁-C₆alkyl is unsubstituted or substituted with 5- to 6-membered heterocyclyl or 5- to 6-membered heteroaryl. In some embodiments, L is *-C(O)NHNH- or *-NHNHC(O)-, and one of R^{1A} and R^{2A} is -OH and the other is -CHNR^{j1}, wherein R^{j1} is -NHC(O)R^{k1}, wherein R^{k1} is C₁-C₆alkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, C₃-C₈cycloalkyl, or 6- to 12-membered aryl, wherein the C₁-C₆alkyl is unsubstituted or substituted with 5- to 6-membered heterocyclyl or 5- to 6-membered heteroaryl. In other embodiments, L is *-C(O)NHNH- or *-NHNHC(O)-, and one of R^{1A} and R^{2A} is -OH and the other is -CHNR^{j1}, wherein R^{j1} is -NHS(O)₂R^{k1}, wherein R^{k1} is C₁-C₆alkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, C₃-C₈cycloalkyl, or 6- to 12-membered aryl, wherein the C₁-C₆alkyl is unsubstituted or substituted with 5- to 6-membered heterocyclyl or 5- to 6-membered heteroaryl. In yet other embodiments, L is *-C(O)NHNH- or *-NHNHC(O)-, and one of R^{1A} and R^{2A} is -OH and the other is -CHNR^{j1}, wherein R^{j1} is -NHC(NH)NH₂. In other embodiments, L is *-C(O)NHNH- or *-NHNHC(O)-, and one of R^{1A} and R^{2A} is -OH and the



[0104] In some embodiments of Formula (B), including Formula (B-1a) and (B-1b), L is *-NHC(O)O- or *-OC(O)NH-, and one of R^{1A} and R^{2A} is -OH and the other is -C(O)H. In some embodiments, L is *-NHC(O)O- or *-OC(O)NH-, and one of R^{1A} and R^{2A} is -OH and the other is -CHNR^{j1}. In some embodiments, L is *-NHC(O)O- or *-OC(O)NH-, and one of R^{1A} and R^{2A} is -OH and the other is -CHNR^{j1}, wherein R^{j1} is C₁-C₆alkyl. In some embodiments, L is *-NHC(O)O- or *-OC(O)NH-, and one of R^{1A} and R^{2A} is -OH and the other is -CHNR^{j1}, wherein R^{j1} is 5- to 6-membered heterocyclyl, unsubstituted or substituted with one or more substituents selected from the group consisting of C₁-C₆alkyl, C₃-C₈cycloalkyl, =O, -C(O)NH-C₁-C₆alkyl, and -C(O)O-C₁-C₆alkyl. In some embodiments, L is *-NHC(O)O- or *-OC(O)NH-, and one of R^{1A} and R^{2A} is -OH and the other is -CHNR^{j1}, wherein R^{j1} is 5- to 6-membered heteroaryl, unsubstituted or substituted with one or more substituents selected from the group consisting of C₁-C₆alkyl, C₃-C₈cycloalkyl, and -C(O)O-C₁-C₆alkyl. In other embodiments, L is *-NHC(O)O- or *-OC(O)NH-, and one of R^{1A} and R^{2A} is -OH and the other is -CHNR^{j1}, wherein R^{j1} is 6- to 12-membered aryl, unsubstituted or substituted with one or more substituents selected from the group consisting of C₁-C₆alkyl, C₃-C₈cycloalkyl, and -C(O)O-C₁-C₆alkyl. In some embodiments, L is *-NHC(O)O- or *-OC(O)NH-, and one of R^{1A} and R^{2A} is -OH and the other

is $-\text{CHNR}^{\text{j1}}$, wherein R^{j1} is $-\text{OR}^{\text{k1}}$, wherein R^{k1} is C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, C_3 - C_8 cycloalkyl, or 6- to 12-membered aryl, wherein the C_1 - C_6 alkyl is unsubstituted or substituted with 5- to 6-membered heterocyclyl or 5- to 6-membered heteroaryl. In some embodiments, L is $^*\text{-NHC(O)O-}$ or $^*\text{-OC(O)NH-}$, and one of $\text{R}^{1\text{A}}$ and $\text{R}^{2\text{A}}$ is $-\text{OH}$ and the other is $-\text{CHNR}^{\text{j1}}$, wherein R^{j1} is $-\text{NHR}^{\text{k1}}$ or $-\text{N}(\text{C}_1\text{-C}_6\text{alkyl})\text{R}^{\text{k1}}$, wherein R^{k1} is C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, C_3 - C_8 cycloalkyl, or 6- to 12-membered aryl, wherein the C_1 - C_6 alkyl is unsubstituted or substituted with 5- to 6-membered heterocyclyl or 5- to 6-membered heteroaryl. In some embodiments, L is $^*\text{-NHC(O)O-}$ or $^*\text{-OC(O)NH-}$, and one of $\text{R}^{1\text{A}}$ and $\text{R}^{2\text{A}}$ is $-\text{OH}$ and the other is $-\text{CHNR}^{\text{j1}}$, wherein R^{j1} is $-\text{NHC(O)R}^{\text{k1}}$, wherein R^{k1} is C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, C_3 - C_8 cycloalkyl, or 6- to 12-membered aryl, wherein the C_1 - C_6 alkyl is unsubstituted or substituted with 5- to 6-membered heterocyclyl or 5- to 6-membered heteroaryl. In other embodiments, L is $^*\text{-NHC(O)O-}$ or $^*\text{-OC(O)NH-}$, and one of $\text{R}^{1\text{A}}$ and $\text{R}^{2\text{A}}$ is $-\text{OH}$ and the other is $-\text{CHNR}^{\text{j1}}$, wherein R^{j1} is $-\text{NHS(O)}_2\text{R}^{\text{k1}}$, wherein R^{k1} is C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, C_3 - C_8 cycloalkyl, or 6- to 12-membered aryl, wherein the C_1 - C_6 alkyl is unsubstituted or substituted with 5- to 6-membered heterocyclyl or 5- to 6-membered heteroaryl. In yet other embodiments, L is $^*\text{-NHC(O)O-}$ or $^*\text{-OC(O)NH-}$, and one of $\text{R}^{1\text{A}}$ and $\text{R}^{2\text{A}}$ is $-\text{OH}$ and the other is $-\text{CHNR}^{\text{j1}}$, wherein R^{j1} is $-\text{NHC(NH)NH}_2$. In other embodiments, L is $^*\text{-NHC(O)O-}$ or $^*\text{-}$

OC(O)NH- , and one of $\text{R}^{1\text{A}}$ and $\text{R}^{2\text{A}}$ is $-\text{OH}$ and the other is

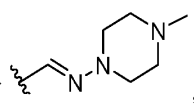


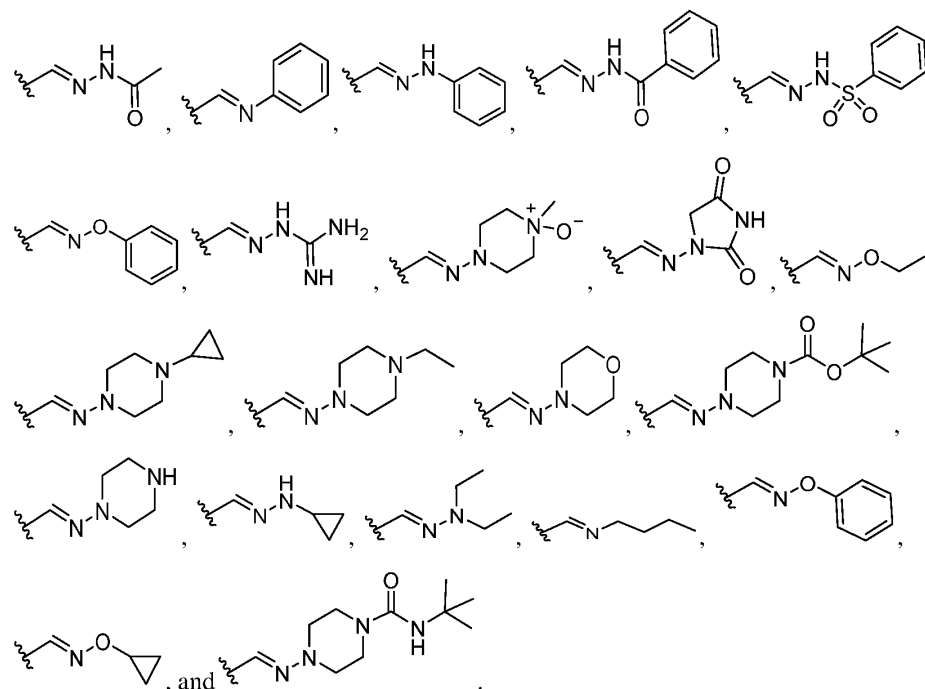
[0105] In some of any of the foregoing embodiments, one of $\text{R}^{1\text{A}}$ and $\text{R}^{2\text{A}}$ is $-\text{OH}$ and the other is $-\text{CHNR}^{\text{j1}}$, wherein R^{j1} is a 5- to 6-membered heterocyclyl, wherein the 5- to 6-membered heterocyclyl of R^{j1} is unsubstituted or substituted with one or more substituents selected from the group consisting of C_1 - C_6 alkyl, C_3 - C_8 cycloalkyl, $=\text{O}$, $-\text{C(O)NH-C}_1\text{-C}_6\text{alkyl}$, and $-\text{C(O)O-C}_1\text{-C}_6\text{alkyl}$. In some embodiments, R^{j1} is selected from the group consisting of pyrrolidinyl, pyrazolidinyl, imidazolidinyl, tetrahydrofuranyl, 1,3-dioxolanyl, tetrahydrothiophenyl, oxathiolanyl, sulfolanyl, piperidinyl, piperazinyl, tetrahydropyranyl, dioxanyl, thianyl, dithianyl, trithianyl, morpholinyl, and thiomorpholinyl, each independently unsubstituted or substituted with one or more substituents selected from the group consisting of C_1 - C_6 alkyl, C_3 - C_8 cycloalkyl, $=\text{O}$, $-\text{C(O)NH-C}_1\text{-C}_6\text{alkyl}$, and $-\text{C(O)O-C}_1\text{-C}_6\text{alkyl}$. In some embodiments, R^{j1} is a 5- to 6-membered heterocyclyl, wherein the nitrogen and/or sulfur atom(s) of the heterocyclyl are optionally oxidized to provide for N-oxide, $-\text{S(O)-}$, or $-\text{SO}_2-$ moieties. In

some of any of the foregoing embodiments, one of R^{1A} and R^{2A} is $-OH$ and the other is $-CHNR^{j1}$, wherein R^{j1} is a 5- to 6-membered heteroaryl, wherein the 5- to 6-membered heteroaryl of R^{j1} is unsubstituted or substituted with one or more substituents selected from the group consisting of C_1 - C_6 alkyl, C_3 - C_8 cycloalkyl, and $-C(O)O$ - C_1 - C_6 alkyl. In some embodiments, R^{j1} is selected from the group consisting of pyrrolyl, pyrazolyl, imidazolyl, triazolyl, tetrazolyl, furanyl, isoxazolyl, oxazolyl, oxadiazolyl, thiophenyl, isothiazolyl, thiazolyl, thiadiazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl, and tetrazinyl, each independently unsubstituted or substituted with one or more substituents selected from the group consisting of C_1 - C_6 alkyl, C_3 - C_8 cycloalkyl, and $-C(O)O$ - C_1 - C_6 alkyl. In some of any of the foregoing embodiments, one of R^{1A} and R^{2A} is $-OH$ and the other is $-CHNR^{j1}$, wherein R^{j1} is a 6- to 12-membered aryl, wherein the 6- to 12-membered aryl of R^{j1} is unsubstituted or substituted with one or more substituents selected from the group consisting of C_1 - C_6 alkyl, C_3 - C_8 cycloalkyl, and $-C(O)O$ - C_1 - C_6 alkyl. In some embodiments, R^{j1} is selected from the group consisting of phenyl and naphthyl, each independently unsubstituted or substituted with one or more substituents selected from the group consisting of C_1 - C_6 alkyl, C_3 - C_8 cycloalkyl, and $-C(O)O$ - C_1 - C_6 alkyl. In some of any of the foregoing embodiments, one of R^{1A} and R^{2A} is $-OH$ and the other is $-CHNR^{j1}$, wherein R^{j1} is unsubstituted $-OC_1$ - C_6 alkyl, or $-OC_1$ - C_6 alkyl substituted with a 5- to 6-membered heterocyclyl or a 5- to 6-membered heteroaryl. In some of any of the foregoing embodiments, one of R^{1A} and R^{2A} is $-OH$ and the other is $-CHNR^{j1}$, wherein R^{j1} is $-OC_2$ - C_6 alkenyl or $-OC_2$ - C_6 alkynyl. In some embodiments, one of R^{1A} and R^{2A} is $-OH$ and the other is $-CHNR^{j1}$, wherein R^{j1} is $-OC_3$ - C_8 cycloalkyl or $-O$ -6- to 12-membered aryl. In some of any of the foregoing embodiments, one of R^{1A} and R^{2A} is $-OH$ and the other is $-CHNR^{j1}$, wherein R^{j1} is $-NHC_1$ - C_6 alkyl, $-NHC(O)C_1$ - C_6 alkyl, or $-NHS(O)_2C_1$ - C_6 alkyl, each unsubstituted or substituted with a 5- to 6-membered heterocyclyl or a 5- to 6-membered heteroaryl. In some of any of the foregoing embodiments, one of R^{1A} and R^{2A} is $-OH$ and the other is $-CHNR^{j1}$, wherein R^{j1} is $-NHC_2$ - C_6 alkenyl, $-NHC_2$ - C_6 alkynyl, $-NHC(O)C_2$ - C_6 alkenyl, $-NHC(O)C_2$ - C_6 alkynyl, $-NHS(O)_2C_2$ - C_6 alkenyl, or $-NHS(O)_2C_2$ - C_6 alkynyl. In some embodiments, one of R^{1A} and R^{2A} is $-OH$ and the other is $-CHNR^{j1}$, wherein R^{j1} is $-NHC_3$ - C_8 cycloalkyl, $-NH$ -6- to 12-membered aryl, $-NHC(O)C_3$ - C_8 cycloalkyl, $-NHC(O)$ -6- to 12-membered aryl, $-NHS(O)_2C_3$ - C_8 cycloalkyl, or $-NHS(O)_2$ -6- to 12-membered aryl. In some of any of the foregoing embodiments, one of R^{1A} and R^{2A} is $-OH$ and the other is $-CHNR^{j1}$, wherein R^{j1} is $-NHC(NH)NH_2$. In some embodiments, one of R^{1A} and R^{2A} is $-OH$ and the other is $-CH=NR^{j1}$, wherein R^{j1} is $-NHC(NH)NHR^{bb}$. In

some embodiments, R^{bb} is unsubstituted or substituted C_1 - C_6 alkyl. In certain embodiments, R^{bb} is C_1 - C_6 alkyl substituted with $-OH$ or $-(OCH_2CH_2)_vOH$, where v is 1, 2, or 3. In some embodiments, R^{bb} is unsubstituted or substituted C_3 - C_8 cycloalkyl. In some embodiments, R^{bb} is unsubstituted or substituted aryl. In some embodiments, R^{bb} is unsubstituted or substituted C_6 - C_{14} aryl. In some embodiments, R^{bb} is unsubstituted or substituted heterocycloalkyl. In some embodiments, R^{bb} is unsubstituted or substituted 3- to 18-membered heterocycloalkyl. In some embodiments, R^{bb} is unsubstituted or substituted 3- to 6-membered heterocycloalkyl. In some embodiments, R^{bb} is unsubstituted or substituted heteroaryl. In some embodiments, R^{bb} is unsubstituted or substituted 5- to 18-membered heteroaryl. In some embodiments, R^{bb} is unsubstituted or substituted 5- to 10-membered heteroaryl. In some embodiments, R^{bb} is C_3 - C_8 cycloalkyl, C_6 - C_{14} aryl, 3- to 18-membered heterocycloalkyl, or 5- to 18-membered heteroaryl, each optionally substituted with C_1 - C_6 alkyl.

[0106] In some of any of the foregoing embodiments, one of R^{1A} and R^{2A} is $-OH$ and the

other is $-CHNR^{j1}$, wherein $-CHNR^{j1}$ is selected from the group consisting of ,



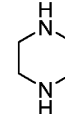
[0107] In some embodiments of Formula (B), including Formula (B-1a), (B-1b), (B-2a), (B-2b), (B-2c), (B-2d), (B-2e), (B-2f), (B-2g), (B-2h), (B-2i), (B-2j), (B-2k), (B-2l), (B-2m), (B-2n), (B-3a), (B-3b), (B-3c), (B-3d), (B-3e), (B-3f), (B-3g), (B-3h), (B-3i), (B-3j), (B-3k), (B-3l), (B-3m), and (B-3n), R^{3A} is H. In some embodiments, R^{3A} is unsubstituted C_1 - C_6 alkyl. In some embodiments, R^{3A} is C_1 - C_6 alkyl substituted with one or more halogen. In some embodiments, R^{3A} is unsubstituted C_1 - C_6 alkoxy. In some embodiments, R^{3A} is C_1 - C_6 alkoxy substituted with one or more halogen. In other embodiments, R^{3A} is halogen.

[0108] In some embodiments of Formula (B), including Formula (B-1a), (B-1b), (B-2a), (B-2b), (B-2c), (B-2d), (B-2e), (B-2f), (B-2g), (B-2h), (B-2i), (B-2j), (B-2k), (B-2l), (B-2m), (B-2n), (B-3a), (B-3b), (B-3c), (B-3d), (B-3e), (B-3f), (B-3g), (B-3h), (B-3i), (B-3j), (B-3k), (B-3l), (B-3m), and (B-3n), one of R^{1A} and R^{2A} is $-OH$ and the other is $-C(O)H$. In some embodiments, R^{1A} is $-OH$, R^{2A} is $-C(O)H$, and R^{3A} is H. In some embodiments, R^{1A} is $-OH$, R^{2A} is $-C(O)H$, and R^{3A} is unsubstituted C_1 - C_6 alkyl. In some embodiments, R^{1A} is $-OH$, R^{2A} is $-C(O)H$, and R^{3A} is C_1 - C_6 haloalkyl. In some embodiments, R^{1A} is $-OH$, R^{2A} is $-C(O)H$, and R^{3A} is unsubstituted C_1 - C_6 alkoxy. In some embodiments, R^{1A} is $-OH$, R^{2A} is $-C(O)H$, and R^{3A} is C_1 - C_6 alkoxy substituted with one or more halogen. In other embodiments, R^{1A} is $-OH$, R^{2A} is $-C(O)H$, and R^{3A} is halogen. In certain embodiments, R^{1A} is $-OH$, R^{2A} is $-C(O)H$, and R^{3A} is fluoro. In certain embodiments, R^{1A} is $-OH$, R^{2A} is $-C(O)H$, and R^{3A} is methyl. In some embodiments, R^{1A} is $-OH$, R^{2A} is $-C(O)H$, and R^{3A} is methoxy. In some embodiments, R^{2A} is $-OH$, R^{1A} is $-C(O)H$, and R^{3A} is H. In some embodiments, R^{2A} is $-OH$, R^{1A} is $-C(O)H$, and R^{3A} is unsubstituted C_1 - C_6 alkyl. In some embodiments, R^{2A} is $-OH$, R^{1A} is $-C(O)H$, and R^{3A} is C_1 - C_6 haloalkyl. In some embodiments, R^{2A} is $-OH$, R^{1A} is $-C(O)H$, and R^{3A} is unsubstituted C_1 - C_6 alkoxy. In some embodiments, R^{2A} is $-OH$, R^{1A} is $-C(O)H$, and R^{3A} is C_1 - C_6 alkoxy substituted with one or more halogen. In other embodiments, R^{2A} is $-OH$, R^{1A} is $-C(O)H$, and R^{3A} is halogen. In certain embodiments, R^{2A} is $-OH$, R^{1A} is $-C(O)H$, and R^{3A} is fluoro. In certain embodiments, R^{2A} is $-OH$, R^{1A} is $-C(O)H$, and R^{3A} is methyl. In some embodiments, R^{2A} is $-OH$, R^{1A} is $-C(O)H$, and R^{3A} is methoxy.

[0109] In some embodiments of Formula (B), including Formula (B-1a), (B-1b), (B-2a), (B-2b), (B-2c), (B-2d), (B-2e), (B-2f), (B-2g), (B-2h), (B-2i), (B-2j), (B-2k), (B-2l), (B-2m), and (B-2n), Y_1 and Y_2 are each independently CR^x , wherein R^x is H or halogen. In some embodiments, Y_1 and Y_2 are each independently CH, CF, CCl, or CBr. In some embodiments,

Y_1 and Y_2 are each CH. In a particular embodiment, Y_1 is CF and Y_2 is CH. In another embodiment, Y_1 is CH and Y_2 is CF. In some embodiments, Y_1 is CR^x and Y_2 is N. For instance, in some embodiments, Y_1 is CH, CF, CCl, or CBr, and Y_2 is N. In some embodiments, Y_1 is N and Y_2 is CR^x . For instance, in some embodiments, Y_1 is N and Y_2 is CH, CF, CCl, or CBr. In other embodiments, Y_1 and Y_2 are each N.

[0110] In some embodiments of Formula (B), including Formula (B-1a), (B-1b), (B-2a), (B-2b), (B-2c), (B-2d), (B-2e), (B-2f), (B-2g), (B-2h), (B-2i), (B-2j), (B-2k), (B-2l), (B-2m), and (B-2n), the ring bearing  is saturated, such that the ring consists entirely of single bonds.

Examples of saturated rings include, but are not limited to, , , , , , , , , , , , , , , , , , , , , and . In some embodiments, the ring bearing  is partially

unsaturated, such that the ring is nonaromatic and comprises at least one double bond, such as one or two double bonds. Examples of partially unsaturated rings include, but are not limited to,

, , , , , , , , , , , , , , , , , and . In other embodiments, the ring bearing  is fully unsaturated and comprises

two or three double bonds. In certain embodiments, the ring bearing  is fully unsaturated. In certain embodiments, the ring bearing  is fully unsaturated and aromatic. Examples of fully

unsaturated rings include, but are not limited to , , , , , , , and .

[0111] In some embodiments of Formula (B), including Formula (B-1a), (B-1b), (B-2a), (B-2b), (B-2c), (B-2d), (B-2e), (B-2f), (B-2g), (B-2h), (B-2i), (B-2j), (B-2k), (B-2l), (B-2m), and (B-2n), Y₃ is CH(X_{1A}-R^{6a1}) or C(X_{1A}-R^{6a1}), Y₄ is CH(X_{2A}-R^{6b1}) or C(X_{2A}-R^{6b1}), Y₅ is CH(X_{3A}-R^{6c1}) or C(X_{3A}-R^{6c1}), Y₆ is CH(X_{4A}-R^{6d1}) or C(X_{4A}-R^{6d1}), and the ring bearing  is partially unsaturated. In some embodiments, Y₃ is C(X_{1A}-R^{6a1}), Y₄ is C(X_{2A}-R^{6b1}), Y₅ is C(X_{3A}-R^{6c1}), Y₆ is C(X_{4A}-R^{6d1}), and the ring bearing  is fully unsaturated. In some embodiments, Y₃ is CH(X_{1A}-R^{6a1}), Y₄ is CH(X_{2A}-R^{6b1}), Y₅ is CH(X_{3A}-R^{6c1}), Y₆ is CH(X_{4A}-R^{6d1}), and the ring bearing  is saturated. In other embodiments, Y₃ is CH(X_{1A}-R^{6a1}) or C(X_{1A}-R^{6a1}), Y₄ is CH(X_{2A}-R^{6b1}) or C(X_{2A}-R^{6b1}), Y₅ is CH(X_{3A}-R^{6c1}) or C(X_{3A}-R^{6c1}), and Y₆ is absent.

[0112] In some embodiments of Formula (B), including Formula (B-1a), (B-1b), (B-2a), (B-2b), (B-2c), (B-2d), (B-2e), (B-2f), (B-2g), (B-2h), (B-2i), (B-2j), (B-2k), (B-2l), (B-2m), and (B-2n), Y₃ is CH(X_{1A}-R^{6a1}) or C(X_{1A}-R^{6a1}), Y₄ is N or N(X_{2A}-R^{6b1}), Y₅ is CH(X_{3A}-R^{6c1}) or C(X_{3A}-R^{6c1}), Y₆ is CH(X_{4A}-R^{6d1}) or C(X_{4A}-R^{6d1}), and the ring bearing  is partially unsaturated. In some embodiments, Y₃ is C(X_{1A}-R^{6a1}), Y₄ is N, Y₅ is C(X_{3A}-R^{6c1}), Y₆ is C(X_{4A}-R^{6d1}), and the ring bearing  is fully unsaturated. In some embodiments, Y₃ is CH(X_{1A}-R^{6a1}), Y₄ is N(X_{2A}-R^{6b1}), Y₅ is CH(X_{3A}-R^{6c1}), Y₆ is CH(X_{4A}-R^{6d1}), and the ring bearing  is saturated. In other embodiments, Y₃ is CH(X_{1A}-R^{6a1}) or C(X_{1A}-R^{6a1}), Y₄ is N or N(X_{2A}-R^{6b1}), Y₅ is CH(X_{3A}-R^{6c1}) or C(X_{3A}-R^{6c1}), and Y₆ is absent.

[0113] In some embodiments of Formula (B), including Formula (B-1a), (B-1b), (B-2a), (B-2b), (B-2c), (B-2d), (B-2e), (B-2f), (B-2g), (B-2h), (B-2i), (B-2j), (B-2k), (B-2l), (B-2m), and (B-2n), Y₃ is N or N(X_{1A}-R^{6a1}), Y₄ is CH(X_{2A}-R^{6b1}) or C(X_{2A}-R^{6b1}), Y₅ is CH(X_{3A}-R^{6c1}) or C(X_{3A}-R^{6c1}), Y₆ is CH(X_{4A}-R^{6d1}) or C(X_{4A}-R^{6d1}), and the ring bearing  is partially unsaturated. In some embodiments, Y₃ is N, Y₄ is C(X_{2A}-R^{6b1}), Y₅ is C(X_{3A}-R^{6c1}), Y₆ is C(X_{4A}-R^{6d1}), and the ring bearing  is fully unsaturated. In some embodiments, Y₃ is N(X_{1A}-R^{6a1}), Y₄ is CH(X_{2A}-R^{6b1}), Y₅ is CH(X_{3A}-R^{6c1}), Y₆ is CH(X_{4A}-R^{6d1}), and the ring bearing  is saturated. In other embodiments, Y₃ is N or N(X_{1A}-R^{6a1}), Y₄ is CH(X_{2A}-R^{6b1}) or C(X_{2A}-R^{6b1}), Y₅ is CH(X_{3A}-R^{6c1}) or C(X_{3A}-R^{6c1}), and Y₆ is absent.

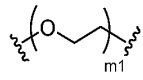
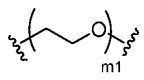
[0114] In some embodiments of Formula (B), including Formula (B-1a), (B-1b), (B-2a), (B-2b), (B-2c), (B-2d), (B-2e), (B-2f), (B-2g), (B-2h), (B-2i), (B-2j), (B-2k), (B-2l), (B-2m), and

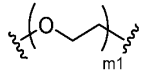
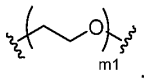
(B-2n), Y_3 is $CH(X_{1A}-R^{6a1})$ or $C(X_{1A}-R^{6a1})$, Y_4 is $CH(X_{2A}-R^{6b1})$ or $C(X_{2A}-R^{6b1})$, Y_5 is N or $N(X_{3A}-R^{6c1})$, Y_6 is $CH(X_{4A}-R^{6d1})$ or $C(X_{4A}-R^{6d1})$, and the ring bearing  is partially unsaturated. In some embodiments, Y_3 is $C(X_{1A}-R^{6a1})$, Y_4 is $C(X_{2A}-R^{6b1})$, Y_5 is N, Y_6 is $C(X_{4A}-R^{6d1})$, and the ring bearing  is fully unsaturated. In some embodiments, Y_3 is $CH(X_{1A}-R^{6a1})$, Y_4 is $CH(X_{2A}-R^{6b1})$, Y_5 is $N(X_{3A}-R^{6c1})$, Y_6 is $CH(X_{4A}-R^{6d1})$, and the ring bearing  is saturated. In other embodiments, Y_3 is $CH(X_{1A}-R^{6a1})$ or $C(X_{1A}-R^{6a1})$, Y_4 is $CH(X_{2A}-R^{6b1})$ or $C(X_{2A}-R^{6b1})$, Y_5 is N or $N(X_{3A}-R^{6c1})$, and Y_6 is absent.

[0115] In other embodiments of Formula (B), including Formula (B-1a), (B-1b), (B-2a), (B-2b), (B-2c), (B-2d), (B-2e), (B-2f), (B-2g), (B-2h), (B-2i), (B-2j), (B-2k), (B-2l), (B-2m), and (B-2n), Y_3 is N or $N(X_{1A}-R^{6a1})$, Y_4 is $CH(X_{2A}-R^{6b1})$ or $C(X_{2A}-R^{6b1})$, Y_5 is N or $N(X_{1A}-R^{6c1})$, Y_6 is $CH(X_{4A}-R^{6d1})$ or $C(X_{4A}-R^{6d1})$, and the ring bearing  is partially unsaturated. In some embodiments, Y_3 is N, Y_4 is $C(X_{2A}-R^{6b1})$, Y_5 is N, Y_6 is $C(X_{4A}-R^{6d1})$, and the ring bearing  is fully unsaturated. In some embodiments, Y_3 is $N(X_{1A}-R^{6a1})$, Y_4 is $CH(X_{2A}-R^{6b1})$, Y_5 is $N(X_{1A}-R^{6c1})$, Y_6 is $CH(X_{4A}-R^{6d1})$, and the ring bearing  is saturated. In other embodiments, Y_3 is N or $N(X_{1A}-R^{6a1})$, Y_4 is $CH(X_{2A}-R^{6b1})$ or $C(X_{2A}-R^{6b1})$, Y_5 is N or $N(X_{1A}-R^{6c1})$, and Y_6 is absent.

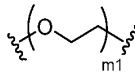
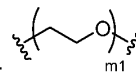
[0116] In certain embodiments of Formula (B), including Formula (B-1a), (B-1b), (B-2a), (B-2b), (B-2c), (B-2d), (B-2e), (B-2f), (B-2g), (B-2h), (B-2i), (B-2j), (B-2k), (B-2l), (B-2m), and (B-2n), R^4 and R^5 come together to form $-S-$, Y_3 is $CH(X_{1A}-R^{6a1})$, Y_4 is $N(X_{2A}-R^{6b1})$, Y_5 is $CH(X_{1A}-R^{6a1})$, Y_6 is $CH(X_{1A}-R^{6a1})$, and the ring bearing  is a saturated ring. In certain embodiments, R^4 and R^5 come together to form $-S-$, Y_3 , Y_5 , and Y_6 are each CH_2 , Y_4 is $N(X_{2A}-R^{6b1})$, and the ring bearing  is a saturated ring.

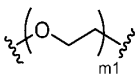
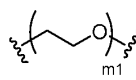
[0117] In some embodiments of Formula (B), including Formula (B-1a), (B-1b), (B-2a), (B-2b), (B-2c), (B-2d), (B-2e), (B-2f), (B-2g), (B-2h), (B-2i), (B-2j), (B-2k), (B-2l), (B-2m), and (B-2n), Y_3 is $CH(X_{1A}-R^{6a1})$ or $C(X_{1A}-R^{6a1})$, wherein X_{1A} is absent. In some embodiments, Y_3 is

$CH(X_{1A}-R^{6a1})$ or $C(X_{1A}-R^{6a1})$, wherein X_{1A} is  or , and m_1 is 1-6. In some embodiments, Y_3 is N. In other embodiments, Y_3 is $N(X_{1A}-R^{6a1})$, wherein X_{1A} is absent. In

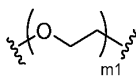
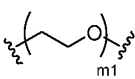
some embodiments, Y_3 is $N(X_{1A}-R^{6a1})$, wherein X_{1A} is  or , and m_1 is

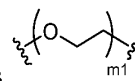
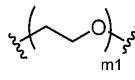
1-6. In some embodiments, Y_3 is S. In other embodiments, Y_3 is O. In some embodiments, Y_3

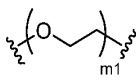
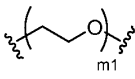
is $CH(X_{1A}-R^{6a1})$ or $C(X_{1A}-R^{6a1})$; X_{1A} is absent, , or ; m_1 is 1-6; R^{6a1} is hydrogen, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, halo, C_6 - C_{12} aryl, 3- to 10-membered heterocyclyl, or 5- to 10-membered heteroaryl. In some embodiments, Y_3 is N or $N(X_{1A}-R^{6a1})$; X_{1A} is absent,

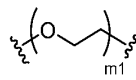
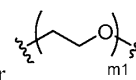
, or ; m_1 is 1-6; and R^{6a1} is hydrogen, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, halo, C_6 - C_{12} aryl, 3- to 10-membered heterocyclyl, or 5- to 10-membered heteroaryl.

[0118] In some embodiments of Formula (B), including Formula (B-1a), (B-1b), (B-2a), (B-2b), (B-2c), (B-2d), (B-2e), (B-2f), (B-2g), (B-2h), (B-2i), (B-2j), (B-2k), (B-2l), (B-2m), (B-2n), (B-3a), (B-3b), (B-3c), (B-3d), (B-3e), (B-3f), (B-3g), (B-3h), (B-3i), (B-3j), (B-3k), (B-3l), (B-3m), and (B-3n), Y_4 is $CH(X_{2A}-R^{6b1})$ or $C(X_{2A}-R^{6b1})$, wherein X_{2A} is absent. In some

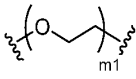
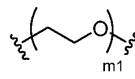
embodiments, Y_4 is $CH(X_{2A}-R^{6b1})$ or $C(X_{2A}-R^{6b1})$, wherein X_{2A} is  or , and m_1 is 1-6. In some embodiments, Y_4 is N. In other embodiments, Y_4 is $N(X_{2A}-R^{6b1})$,

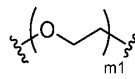
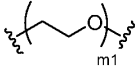
wherein X_{2A} is absent. In some embodiments, Y_4 is $N(X_{2A}-R^{6b1})$, wherein X_{2A} is  or , and m_1 is 1-6. In some embodiments, Y_4 is S. In other embodiments, Y_4 is O.

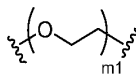
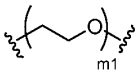
In some embodiments, Y_4 is $CH(X_{2A}-R^{6b1})$ or $C(X_{2A}-R^{6b1})$; X_{2A} is absent, , or ; m_1 is 1-6; and R^{6b1} is hydrogen, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, halo, C_6 - C_{12} aryl, 3- to 10-membered heterocyclyl, or 5- to 10-membered heteroaryl. In some embodiments, Y_4 is N

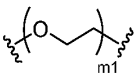
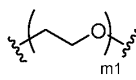
or $N(X_{2A}-R^{6b1})$; X_{2A} is absent, , or ; m_1 is 1-6; and R^{6b1} is hydrogen, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, halo, C_6 - C_{12} aryl, 3- to 10-membered heterocyclyl, or 5- to 10-membered heteroaryl.

In some embodiments, Y_5 is $CH(X_{3A}-R^{6c1})$ or $C(X_{3A}-R^{6c1})$, wherein X_{3A} is absent. In some

embodiments, Y_5 is $CH(X_{3A}-R^{6c1})$ or $C(X_{3A}-R^{6c1})$, wherein X_{3A} is  or , and m_1 is 1-6. In some embodiments, Y_5 is N. In other embodiments, Y_5 is $N(X_{3A}-R^{6c1})$,

wherein X_{3A} is absent. In some embodiments, Y_5 is $N(X_{3A}-R^{6c1})$, wherein X_{3A} is  or , and m_1 is 1-6. In some embodiments, Y_5 is S. In other embodiments, Y_5 is O. In

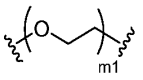
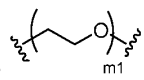
some embodiments, Y_5 is $CH(X_{3A}-R^{6c1})$ or $C(X_{3A}-R^{6c1})$; X_{3A} is absent, , or ; m_1 is 1-6; and R^{6c1} is hydrogen, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, halo, C_6 - C_{12} aryl, 3- to 10-membered heterocyclyl, or 5- to 10-membered heteroaryl. In some embodiments, Y_5 is N

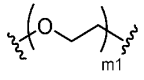
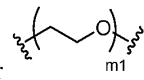
or $N(X_{3A}-R^{6c1})$; X_{3A} is absent,  or ; m_1 is 1-6; and R^{6c1} is hydrogen, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, halo, C_6 - C_{12} aryl, 3- to 10-membered heterocyclyl, or 5- to 10-membered heteroaryl.

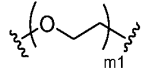
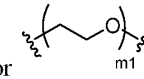
[0119] In some embodiments of Formula (B), including Formula (B-1a), (B-1b), (B-2a), (B-2b), (B-2c), (B-2d), (B-2e), (B-2f), (B-2g), (B-2h), (B-2i), (B-2j), (B-2k), (B-2l), (B-2m), and (B-2n), one of Y_3 , Y_4 , Y_5 , and Y_6 is S or O. In some embodiments, one of Y_3 , Y_4 , and Y_5 is S or O. In some embodiments, Y_3 is S. In some embodiments, Y_3 is O. In some embodiments, Y_4 is S. In some embodiments, Y_4 is O. In some embodiments, Y_5 is S. In some embodiments, Y_5 is O. In some embodiments, Y_6 is S. In some embodiments, Y_6 is O.

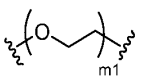
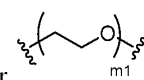
[0120] In some embodiments of Formula (B), including Formula (B-1a), (B-1b), (B-2a), (B-2b), (B-2c), (B-2d), (B-2e), (B-2f), (B-2g), (B-2h), (B-2i), (B-2j), (B-2k), (B-2l), (B-2m), and (B-2n), one of Y_3 , Y_4 , Y_5 , Y_6 , Y_7 , and Y_8 is N. In some embodiments, two of Y_3 , Y_4 , Y_5 , Y_6 , Y_7 , and Y_8 are N. In other embodiments, three of Y_3 , Y_4 , Y_5 , Y_6 , Y_7 , and Y_8 are N.

[0121] In some embodiments of Formula (B), including Formula (B-1a), (B-1b), (B-2a), (B-2b), (B-2c), (B-2d), (B-2e), (B-2f), (B-2g), (B-2h), (B-2i), (B-2j), (B-2k), (B-2l), (B-2m), and (B-2n), Y_6 is $CH(X_{4A}-R^{6d1})$ or $C(X_{4A}-R^{6d1})$, wherein X_{4A} is absent. In some embodiments, Y_6 is

CH(X_{4A}-R^{6d1}) or C(X_{4A}-R^{6d1}), wherein X_{4A} is  or , and m1 is 1-6. In some embodiments, Y₆ is N. In other embodiments, Y₆ is N(X_{4A}-R^{6d1}), wherein X_{4A} is absent. In

some embodiments, Y₆ is N(X_{4A}-R^{6d1}), wherein X_{4A} is  or , and m1 is 1-6. In some embodiments, Y₆ is S. In other embodiments, Y₆ is O. In some embodiments, Y₆

is CH(X_{4A}-R^{6d1}) or C(X_{4A}-R^{6d1}); X_{4A} is absent, , or ; m1 is 1-6; and R^{6d1} is hydrogen, C₁-C₆alkyl, C₁-C₆haloalkyl, halo, C₆-C₁₂ aryl, 3- to 10-membered heterocyclyl, or 5- to 10-membered heteroaryl. In some embodiments, Y₆ is N or N(X_{4A}-R^{6d1}); X_{4A} is absent,

, or ; m1 is 1-6; and R^{6d1} is hydrogen, C₁-C₆alkyl, C₁-C₆haloalkyl, halo, C₆-C₁₂ aryl, 3- to 10-membered heterocyclyl, or 5- to 10-membered heteroaryl.

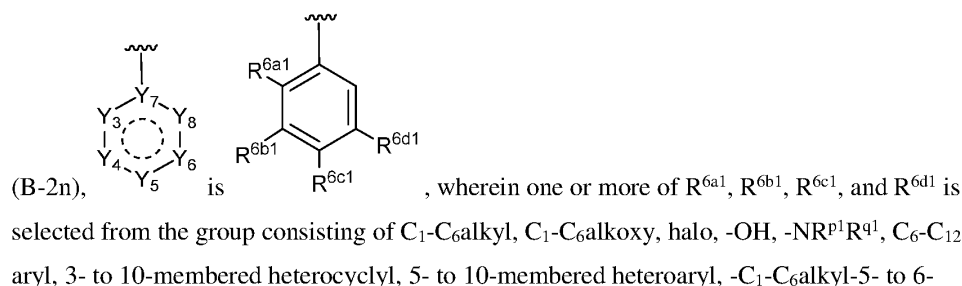
[0122] In some embodiments of Formula (B), including Formula (B-1a), (B-1b), (B-2a), (B-2b), (B-2c), (B-2d), (B-2e), (B-2f), (B-2g), (B-2h), (B-2i), (B-2j), (B-2k), (B-2l), (B-2m), and (B-2n), Y₅ is CH(X_{3A}-R^{6c1}), Y₆ is CH(X_{4A}-R^{6d1}), ring  is saturated, and R^{6c1} and R^{6d1} are taken together with the carbon atoms to which they are attached to form a 6-membered heterocyclyl ring; wherein the heterocyclyl ring is unsubstituted or substituted with one or more groups selected from the group consisting of C₁-C₆alkyl and -C(O)O-C₁-C₆alkyl. In some embodiments, Y₅ is C(X_{3A}-R^{6c1}), Y₆ is C(X_{4A}-R^{6d1}),  is partially unsaturated or fully unsaturated, and R^{6c1} and R^{6d1} are taken together with the carbon atoms to which they are attached to form a 6-membered aryl, 6-membered heterocyclyl, or 6-membered heteroaryl ring; wherein the 6-membered aryl, 6-membered heterocyclyl, and 6-membered heteroaryl rings are each independently unsubstituted or substituted with one or more groups selected from the group consisting of C₁-C₆alkyl and -C(O)O-C₁-C₆alkyl. In some embodiments, Y₅ is C(X_{3A}-R^{6c1}), Y₆ is C(X_{4A}-R^{6d1}),  is fully unsaturated, and R^{6c1} and R^{6d1} are taken together with the carbon atoms to which they are attached to form a 6-membered aryl, a 6-membered heterocyclyl, or a 6-membered heteroaryl ring; wherein the 6-membered aryl, 6-membered heterocyclyl, and 6-membered heteroaryl rings are each independently unsubstituted or substituted with one or more groups selected from the group consisting of C₁-C₆alkyl and -C(O)O-C₁-C₆alkyl. In some

embodiments, R^{6c1} and R^{6d1} come together with the carbon atoms to which they are attached to form a phenyl ring. In some embodiments, R^{6c1} and R^{6d1} are taken together with the carbon atoms to which they are attached to form a 6-membered heterocyclyl or 6-membered heteroaryl ring, wherein the 6-membered heterocyclyl or 6-membered heteroaryl ring each contains one, two, or three heteroatoms independently selected from the group consisting of N, S, and O. In some embodiments, R^{6c1} and R^{6d1} are taken together with the carbon atoms to which they are attached to form an unsubstituted 6-membered aryl, 6-membered heterocyclyl, or 6-membered heteroaryl ring. In some embodiments, R^{6c1} and R^{6d1} are taken together with the carbon atoms to which they are attached to form a 6-membered aryl, 6-membered heterocyclyl, or 6-membered heteroaryl ring, wherein the 6-membered aryl, 6-membered heterocyclyl, or 6-membered heteroaryl ring are each independently substituted with one or more substituents selected from the group consisting of C_1 - C_6 alkyl and $-C(O)O$ - C_1 - C_6 alkyl.

[0123] In some embodiments of Formula (B), including Formula (B-1a), (B-1b), (B-2a), (B-2b), (B-2c), (B-2d), (B-2e), (B-2f), (B-2g), (B-2h), (B-2i), (B-2j), (B-2k), (B-2l), (B-2m), and (B-2n), Y_7 is N. In some embodiments, Y_7 is C. In other embodiments, Y_7 is CH. In some embodiments, Y_8 is N. In some embodiments, Y_8 is NH. In some embodiments, Y_8 is C. In other embodiments, Y_8 is CH.

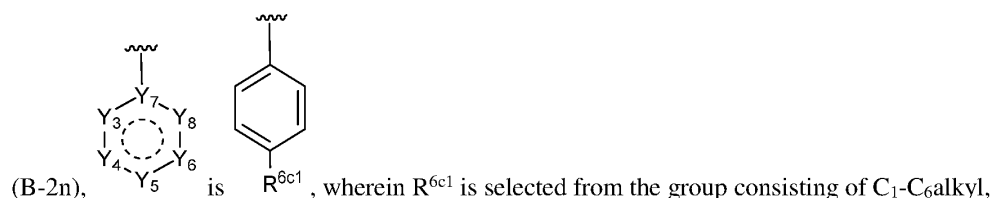
[0124] In some embodiments, Y_3 is $CH(X_{1A}-R^{6a1})$, $C(X_{1A}-R^{6a1})$, N, $N(X_{1A}-R^{6a1})$, S, or O; Y_4 is $CH(X_{2A}-R^{6b1})$, $C(X_{2A}-R^{6b1})$, N, $N(X_{2A}-R^{6b1})$, S, or O; Y_5 is $CH(X_{3A}-R^{6c1})$, $C(X_{3A}-R^{6c1})$, N, $N(X_{3A}-R^{6c1})$, S, or O; Y_6 is $CH(X_{4A}-R^{6d1})$, $C(X_{4A}-R^{6d1})$, N, $N(X_{4A}-R^{6d1})$, S, O, or absent; and G_7 is N, C, or CH, wherein Y_1 , Y_2 , Y_3 , Y_4 , Y_5 , Y_6 , and Y_7 each have a charge of zero (e.g., the nitrogen of Y_1 , Y_2 , Y_3 , Y_4 , Y_5 , Y_6 , and Y_7 is not cationic).

[0125] In some embodiments of Formula (B), including Formula (B-1a), (B-1b), (B-2a), (B-2b), (B-2c), (B-2d), (B-2e), (B-2f), (B-2g), (B-2h), (B-2i), (B-2j), (B-2k), (B-2l), (B-2m), and



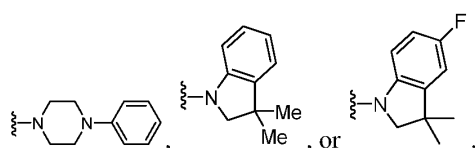
membered heterocyclyl, -OC(O)-5- to 6-membered heterocyclyl, -C(O)R^{h1}, -S(O)₂NR^{w1a}R^{w2a}, -S(O)₂R^{y1}, and -NR^{z1a}S(O)₂R^{z2a}.

[0126] In some embodiments of Formula (B), including Formula (B-1a), (B-1b), (B-2a), (B-2b), (B-2c), (B-2d), (B-2e), (B-2f), (B-2g), (B-2h), (B-2i), (B-2j), (B-2k), (B-2l), (B-2m), and

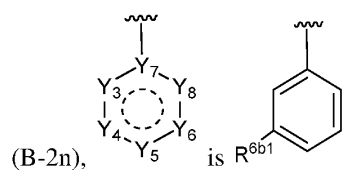


C₁-C₆alkoxy, halo, -OH, -NR^{p1}R^{q1}, C₆-C₁₂ aryl, 3- to 10-membered heterocyclyl, 5- to 10-membered heteroaryl, -C₁-C₆alkyl-5- to 6-membered heterocyclyl, -OC(O)-5- to 6-membered heterocyclyl, -C(O)R^{h1}, -S(O)₂NR^{w1a}R^{w2a}, -S(O)₂R^{y1}, or -NR^{z1a}S(O)₂R^{z2a}. In some embodiments, R^{6c1} is unsubstituted C₁-C₆alkyl. For instance, in some embodiments, R^{6c1} is methyl, ethyl, propyl, isopropyl, butyl, isobutyl, secbutyl, and tertbutyl. In some embodiments, R^{6c1} is C₁-C₆alkyl substituted with one or more groups selected from the group consisting of C₃-C₈ cycloalkyl and halogen. In some embodiments, R^{6c1} is C₁-C₆alkoxy. For instance, in some embodiments, R^{6c1} is methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, secbutoxy, and tertbutoxy. In some embodiments, R^{6c1} is C₁-C₆alkoxy substituted with one or more groups selected from the group consisting of C₃-C₈ cycloalkyl and halogen. In some embodiments, R^{6c1} is halo. For instance, in some embodiments, R^{6c1} is fluoro, chloro, or bromo. In other embodiments, R^{6c1} is C₁-C₆haloalkyl. For instance, in some embodiments, R^{6c1} is fluoroethyl, trifluoromethyl, difluoromethyl, trifluoroethyl, and trichloromethyl. In some embodiments, R^{6c1} is -C(O)R^{h1}, wherein R^{h1} is H, C₁-C₆alkyl, C₁-C₆alkoxy, C₃-C₈cycloalkyl, or -NR^{r1}R^{s1}. For instance, in some embodiments, R^{6c1} is -C(O)H, -C(O)CH₃, -C(O)OC(CH₃)₃, or -C(O)-cyclopropyl. In some embodiments, R^{6c1} is an unsubstituted 5- to 6-membered heterocycle. In some embodiments, R^{6c1} is a 5- to 6-membered heterocycle, substituted with one or more groups selected from the group consisting of C₁-C₆alkyl, C₁-C₆alkoxy, -OH, C₁-C₆alkyl-OH, =O, =S, halo, C₃-C₈cycloalkyl, -C(O)NH-C₃-C₈cycloalkyl, C₆-C₁₂ aryl, and 5- to 6-membered heterocyclyl. In some embodiments, R^{6c1} is a 5- to 6-membered heterocycle, substituted with one or more groups selected from the group consisting of C₁-C₆alkyl, C₁-C₆alkoxy, -OH, C₁-C₆alkyl-OH, =O, and =S. In some embodiments, R^{6c1} is pyrrolidinyl, pyrazolidinyl, imidazolidinyl, tetrahydrofuranyl, 1,3-dioxolanyl, tetrahydrothiophenyl, oxathiolanyl,

sulfolanyl, piperidinyl, piperazinyl, tetrahydropyranyl, dioxanyl, thianyl, dithianyl, trithianyl, morpholinyl, or thiomorpholinyl. In some embodiments, R^{6c1} is piperazinyl substituted with phenyl. In some embodiments, R^{6c1} is pyrrolidinyl. In certain embodiments, R^{6c1} is 4-pyrrolidin-1-yl. In some embodiments, R^{6c1} is a 5- to 10-membered heterocyclyl, substituted with one or more groups selected from the group consisting of C_1 - C_6 alkyl, C_1 - C_6 alkoxy, -OH, C_1 - C_6 alkyl-OH, =O, =S, halo, C_3 - C_8 cycloalkyl, -C(O)NH- C_3 - C_8 cycloalkyl, C_6 - C_{12} aryl, and 5- to 6-membered heterocyclyl. In some embodiments, R^{6c1} is azabicyclo[3.1.0]hexanyl, furo[3,4-c]pyrrolyl, azaspiro[3.3]heptane, 6-oxo-5-azaspiro[2.4]heptanyl, azaspiro[2.4]heptanyl, isoindolinyl, dihydroisoquinolinyl, pyrrolidin-1-yl)piperidinyl, indolinyl, benzo[b][1,4]oxazinyl, adamantan-1-yl)(methyl)amino, azabicyclo[2.2.1]heptanyl, azabicyclo[3.2.1]octanyl, or hexahydrocyclopenta[c]pyrrolyl, each optionally substituted with one or more substituents selected from the group consisting of C_1 - C_6 alkyl, C_1 - C_6 alkoxy, -OH, C_1 - C_6 alkyl-OH, =O, =S, halo, C_3 - C_8 cycloalkyl, -C(O)NH- C_3 - C_8 cycloalkyl, C_6 - C_{12} aryl, and 5- to 6-membered heterocyclyl. In some embodiments, R^{6c1} is an indolinyl, substituted with one or more groups selected from the group consisting of C_1 - C_6 alkyl, C_1 - C_6 alkoxy, -OH, C_1 - C_6 alkyl-OH, =O, =S, halo, C_3 - C_8 cycloalkyl, -C(O)NH- C_3 - C_8 cycloalkyl, C_6 - C_{12} aryl, and 5- to 6-membered heterocyclyl. In certain embodiments, R^{6c1} is an indolinyl, substituted with one or more independently selected C_1 - C_6 alkyl and halo groups. In some embodiments, R^{6c1} is an unsubstituted 5- to 10-membered heteroaryl. In some embodiments, R^{6c1} is a 5- to 10-membered heteroaryl, substituted with one or more groups selected from the group consisting of C_1 - C_6 alkyl, C_1 - C_6 alkoxy, -OH, and C_1 - C_6 alkyl-OH. In some embodiments, R^{6c1} is pyrrolyl, pyrazolyl, imidazolyl, triazolyl, tetrazolyl, furanyl, isoxazolyl, oxazolyl, oxadiazolyl, thiophenyl, isothiazolyl, thiazolyl, thiadiazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl, or tetrazinyl. In some embodiments, R^{6c1} is -N(CH₃)CH₂C(CH₃)₃. In some embodiments, R^{6c1} is

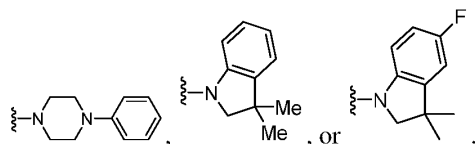


[0127] In some embodiments of Formula (B), including Formula (B-1a), (B-1b), (B-2a), (B-2b), (B-2c), (B-2d), (B-2e), (B-2f), (B-2g), (B-2h), (B-2i), (B-2j), (B-2k), (B-2l), (B-2m), and

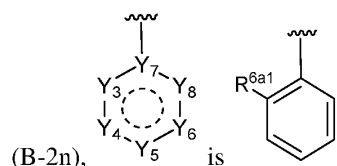


, wherein R^{6b1} is selected from the group consisting of C_1 - C_6 alkyl, C_1 - C_6 alkoxy, halo, -OH, $-NR^{p1}R^{q1}$, C_6 - C_{12} aryl, 3- to 10-membered heterocyclyl, 5- to 10-membered heteroaryl, $-C_1$ - C_6 alkyl-5- to 6-membered heterocyclyl, $-OC(O)$ -5- to 6-membered heterocyclyl, $-C(O)R^{h1}$, $-S(O)_2NR^{w1a}R^{w2a}$, $-S(O)_2R^{y1}$, or $-NR^{z1a}S(O)_2R^{z2a}$. In some embodiments, R^{6b1} is unsubstituted C_1 - C_6 alkyl. For instance, in some embodiments, R^{6b1} is methyl, ethyl, propyl, isopropyl, butyl, isobutyl, secbutyl, and tertbutyl. In some embodiments, R^{6b1} is C_1 - C_6 alkyl substituted with one or more groups selected from the group consisting of C_3 - C_8 cycloalkyl and halogen. In some embodiments, R^{6b1} is C_1 - C_6 alkoxy. For instance, in some embodiments, R^{6b1} is methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, secbutoxy, and tertbutoxy. In some embodiments, R^{6b1} is C_1 - C_6 alkoxy substituted with one or more groups selected from the group consisting of C_3 - C_8 cycloalkyl and halogen. In some embodiments, R^{6b1} is halo. For instance, in some embodiments, R^{6b1} is fluoro, chloro, or bromo. In other embodiments, R^{6b1} is C_1 - C_6 haloalkyl. For instance, in some embodiments, R^{6b1} is fluoroethyl, trifluoromethyl, difluoromethyl, trifluoroethyl, and trichloromethyl. In some embodiments, R^{6b1} is $-C(O)R^{h1}$, wherein R^{h1} is H, C_1 - C_6 alkyl, C_1 - C_6 alkoxy, C_3 - C_8 cycloalkyl, or $-NR^{r1}R^{s1}$. For instance, in some embodiments, R^{6b1} is $-C(O)H$, $-C(O)CH_3$, $-C(O)OC(CH_3)_3$, or $-C(O)$ -cyclopropyl. In some embodiments, R^{6b1} is a 5- to 10-membered heterocyclyl, substituted with one or more groups selected from the group consisting of C_1 - C_6 alkyl, C_1 - C_6 alkoxy, -OH, C_1 - C_6 alkyl-OH, =O, =S, halo, C_3 - C_8 cycloalkyl, $-C(O)NH$ - C_3 - C_8 cycloalkyl, C_6 - C_{12} aryl, and 5- to 6-membered heterocyclyl. In some embodiments, R^{6b1} is azabicyclo[3.1.0]hexanyl, furo[3,4-c]pyrrolyl, azaspiro[3.3]heptane, 6-oxo-5-azaspiro[2.4]heptanyl, azaspiro[2.4]heptanyl, isoindoliny, dihydroisoquinoliny, pyrrolidin-1-yl)piperidiny, indoliny, benzo[b][1,4]oxaziny, adamantan-1-yl)(methyl)amino, azabicyclo[2.2.1]heptanyl, azabicyclo[3.2.1]octanyl, or hexahydrocyclopenta[c]pyrrolyl, each optionally substituted with one or more substituents selected from the group consisting of C_1 - C_6 alkyl, C_1 - C_6 alkoxy, -OH, C_1 - C_6 alkyl-OH, =O, =S, halo, C_3 - C_8 cycloalkyl, $-C(O)NH$ - C_3 - C_8 cycloalkyl, C_6 - C_{12} aryl, and 5- to 6-membered heterocyclyl. In some embodiments, R^{6b1} is an indoliny, substituted with one or more groups selected from the group consisting of C_1 - C_6 alkyl, C_1 - C_6 alkoxy, -OH, C_1 - C_6 alkyl-OH, =O, =S, halo, C_3 - C_8 cycloalkyl, $-C(O)NH$ - C_3 - C_8 cycloalkyl, C_6 - C_{12} aryl, and 5- to 6-membered

heterocyclyl. In certain embodiments, R^{6b1} is an indolinyl, substituted with one or more independently selected C_1 - C_6 alkyl and halo groups. In some embodiments, R^{6b1} is an unsubstituted 5- to 6-membered heterocycle. In some embodiments, R^{6b1} is a 5- to 6-membered heterocycle, substituted with one or more groups selected from the group consisting of C_1 - C_6 alkyl, C_1 - C_6 alkoxy, -OH, C_1 - C_6 alkyl-OH, =O, =S, halo, C_3 - C_8 cycloalkyl, -C(O)NH- C_3 - C_8 cycloalkyl, C_6 - C_{12} aryl, and 5- to 6-membered heterocyclyl. In some embodiments, R^{6b1} is a 5- to 6-membered heterocycle, substituted with one or more groups selected from the group consisting of C_1 - C_6 alkyl, C_1 - C_6 alkoxy, -OH, C_1 - C_6 alkyl-OH, =O, and =S. In some embodiments, R^{6b1} is pyrrolidinyl, pyrazolidinyl, imidazolidinyl, tetrahydrofuranyl, 1,3-dioxolanyl, tetrahydrothiophenyl, oxathiolanyl, sulfolanyl, piperidinyl, piperazinyl, tetrahydropyranyl, dioxanyl, thianyl, dithianyl, trithianyl, morpholinyl, or thiomorpholinyl. In some embodiments, R^{6b1} is piperazinyl substituted with phenyl. In some embodiments, R^{6b1} is an unsubstituted 5- to 10-membered heteroaryl. In some embodiments, R^{6b1} is a 5- to 10-membered heteroaryl, substituted with one or more groups selected from the group consisting of C_1 - C_6 alkyl, C_1 - C_6 alkoxy, -OH, and C_1 - C_6 alkyl-OH. In some embodiments, R^{6b1} is pyrrolyl, pyrazolyl, imidazolyl, triazolyl, tetrazolyl, furanyl, isoxazolyl, oxazolyl, oxadiazolyl, thiophenyl, isothiazolyl, thiazolyl, thiadiazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl, or tetrazinyl. In some embodiments, R^{6b1} is -N(CH₃)CH₂C(CH₃)₃. In some embodiments, R^{6b1} is



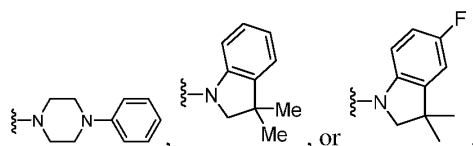
[0128] In some embodiments of Formula (B), including Formula (B-1a), (B-1b), (B-2a), (B-2b), (B-2c), (B-2d), (B-2e), (B-2f), (B-2g), (B-2h), (B-2i), (B-2j), (B-2k), (B-2l), (B-2m), and



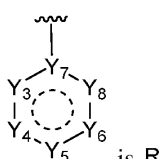
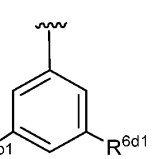
(B-2n), is , wherein R^{6a1} is selected from the group consisting of C_1 - C_6 alkyl, C_1 - C_6 alkoxy, halo, -OH, -NR^{p1}R^{q1}, C_6 - C_{12} aryl, 3- to 10-membered heterocyclyl, 5- to 10-membered heteroaryl, - C_1 - C_6 alkyl-5- to 6-membered heterocyclyl, -OC(O)-5- to 6-membered heterocyclyl, -C(O)R^{h1}, -S(O)₂NR^{w1a}R^{w2a}, -S(O)₂R^{y1}, or -NR^{z1a}S(O)₂R^{z2a}. In some embodiments, R^{6a1} is unsubstituted C_1 - C_6 alkyl. For instance, in some embodiments, R^{6a1} is

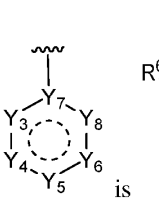
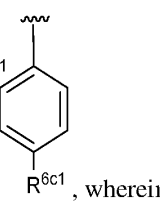
methyl, ethyl, propyl, isopropyl, butyl, isobutyl, secbutyl, and tertbutyl. In some embodiments, R^{6a1} is C_1 - C_6 alkyl substituted with one or more groups selected from the group consisting of C_3 - C_8 cycloalkyl and halogen. In some embodiments, R^{6a1} is C_1 - C_6 alkoxy. For instance, in some embodiments, R^{6a1} is methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, secbutoxy, and tertbutoxy. In some embodiments, R^{6a1} is C_1 - C_6 alkoxy substituted with one or more groups selected from the group consisting of C_3 - C_8 cycloalkyl and halogen. In some embodiments, R^{6a1} is halo. For instance, in some embodiments, R^{6a1} is fluoro, chloro, or bromo. In other embodiments, R^{6a1} is C_1 - C_6 haloalkyl. For instance, in some embodiments, R^{6a1} is fluoroethyl, trifluoromethyl, difluoromethyl, trifluoroethyl, and trichloromethyl. In some embodiments, R^{6a1} is $-C(O)R^{h1}$, wherein R^{h1} is H, C_1 - C_6 alkyl, C_1 - C_6 alkoxy, C_3 - C_8 cycloalkyl, or $-NR^{r1}R^{s1}$. For instance, in some embodiments, R^{6a1} is $-C(O)H$, $-C(O)CH_3$, $-C(O)OC(CH_3)_3$, or $-C(O)$ -cyclopropyl. In some embodiments, R^{6a1} is an unsubstituted 5- to 6-membered heterocycle. In some embodiments, R^{6a1} is a 5- to 6-membered heterocycle, substituted with one or more groups selected from the group consisting of C_1 - C_6 alkyl, C_1 - C_6 alkoxy, $-OH$, C_1 - C_6 alkyl- $-OH$, $=O$, $=S$, halo, C_3 - C_8 cycloalkyl, $-C(O)NH$ - C_3 - C_8 cycloalkyl, C_6 - C_{12} aryl, and 5- to 6-membered heterocyclyl. In some embodiments, R^{6a1} is a 5- to 6-membered heterocycle, substituted with one or more groups selected from the group consisting of C_1 - C_6 alkyl, C_1 - C_6 alkoxy, $-OH$, C_1 - C_6 alkyl- $-OH$, $=O$, and $=S$. In some embodiments, R^{6a1} is pyrrolidinyl, pyrazolidinyl, imidazolidinyl, tetrahydrofuranyl, 1,3-dioxolanyl, tetrahydrothiophenyl, oxathiolanyl, sulfolanyl, piperidinyl, piperazinyl, tetrahydropyranyl, dioxanyl, thianyl, dithianyl, trithianyl, morpholinyl, or thiomorpholinyl. In some embodiments, R^{6a1} is piperazinyl substituted with phenyl. In some embodiments, R^{6a1} is a 5- to 10-membered heterocyclyl, substituted with one or more groups selected from the group consisting of C_1 - C_6 alkyl, C_1 - C_6 alkoxy, $-OH$, C_1 - C_6 alkyl- $-OH$, $=O$, $=S$, halo, C_3 - C_8 cycloalkyl, $-C(O)NH$ - C_3 - C_8 cycloalkyl, C_6 - C_{12} aryl, and 5- to 6-membered heterocyclyl. In some embodiments, R^{6a1} is an indolinyl, substituted with one or more groups selected from the group consisting of C_1 - C_6 alkyl, C_1 - C_6 alkoxy, $-OH$, C_1 - C_6 alkyl- $-OH$, $=O$, $=S$, halo, C_3 - C_8 cycloalkyl, $-C(O)NH$ - C_3 - C_8 cycloalkyl, C_6 - C_{12} aryl, and 5- to 6-membered heterocyclyl. In some embodiments, R^{6a1} is azabicyclo[3.1.0]hexanyl, furo[3,4-c]pyrrolyl, azaspiro[3.3]heptane, 6-oxo-5-azaspiro[2.4]heptanyl, azaspiro[2.4]heptanyl, isoindolinyl, dihydroisoquinolinyl, pyrrolidin-1-yl)piperidinyl, indolinyl, benzo[b][1,4]oxazinyl, adamantan-1-yl)(methyl)amino, azabicyclo[2.2.1]heptanyl, azabicyclo[3.2.1]octanyl, or hexahydrocyclopenta[c]pyrrolyl, each optionally substituted with one or more substituents

selected from the group consisting of C₁-C₆alkyl, C₁-C₆alkoxy, -OH, C₁-C₆alkyl-OH, =O, =S, halo, C₃-C₈cycloalkyl, -C(O)NH-C₃-C₈cycloalkyl, C₆-C₁₂ aryl, and 5- to 6-membered heterocyclyl. In certain embodiments, R^{6a1} is an indolinyl, substituted with one or more independently selected C₁-C₆alkyl and halo groups. In some embodiments, R^{6a1} is an unsubstituted 5- to 10-membered heteroaryl. In some embodiments, R^{6a1} is a 5- to 10-membered heteroaryl, substituted with one or more groups selected from the group consisting of C₁-C₆alkyl, C₁-C₆alkoxy, -OH, and C₁-C₆alkyl-OH. In some embodiments, R^{6a1} is pyrrolyl, pyrazolyl, imidazolyl, triazolyl, tetrazolyl, furanyl, isoxazolyl, oxazolyl, oxadiazolyl, thiophenyl, isothiazolyl, thiazolyl, thiadiazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl, or tetrazinyl. In some embodiments, R^{6a1} is -N(CH₃)CH₂C(CH₃)₃. In some embodiments, R^{6a1} is

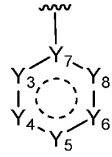
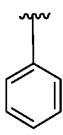


[0129] In some embodiments of Formula (B), including Formula (B-1a), (B-1b), (B-2a), (B-2b), (B-2c), (B-2d), (B-2e), (B-2f), (B-2g), (B-2h), (B-2i), (B-2j), (B-2k), (B-2l), (B-2m), and

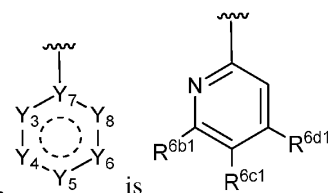
(B-2n),  is , wherein R^{6b1} and R^{6d1} are each independently selected from the group consisting of C₁-C₆alkyl, C₁-C₆alkoxy, halo, -OH, -NR^{p1}R^{q1}, C₆-C₁₂ aryl, 3- to 10-membered heterocyclyl, 5- to 10-membered heteroaryl, -C₁-C₆alkyl-5- to 6-membered heterocyclyl, -OC(O)-5- to 6-membered heterocyclyl, -C(O)R^{h1}, -S(O)₂NR^{w1a}R^{w2a}, -S(O)₂R^{y1}, or

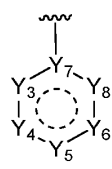
-NR^{z1a}S(O)₂R^{z2a}. In some embodiments,  is , wherein R^{6a1} and R^{6c1} are each independently selected from the group consisting of C₁-C₆alkyl, C₁-C₆alkoxy, halo, -OH, -NR^{p1}R^{q1}, C₆-C₁₂ aryl, 3- to 10-membered heterocyclyl, 5- to 10-membered heteroaryl, -C₁-

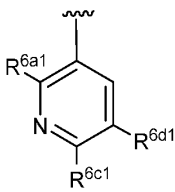
C₆alkyl-5- to 6-membered heterocyclyl, -OC(O)-5- to 6-membered heterocyclyl, -C(O)R^{h1}, -

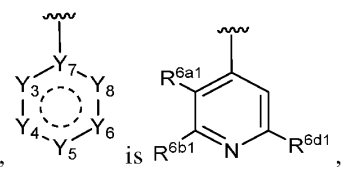
S(O)₂NR^{w1a}R^{w2a}, -S(O)₂R^{y1}, or -NR^{z1a}S(O)₂R^{z2a}. In some embodiments,  is .

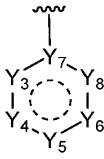
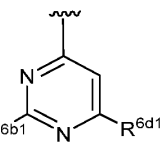
[0130] In some embodiments of Formula (B), including Formula (B-1a), (B-1b), (B-2a), (B-2b), (B-2c), (B-2d), (B-2e), (B-2f), (B-2g), (B-2h), (B-2i), (B-2j), (B-2k), (B-2l), (B-2m), and

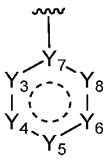
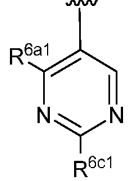
(B-2n), , wherein one or more of R^{6b1}, R^{6c1}, and R^{6d1} is selected from the group consisting of C₁-C₆alkyl, C₁-C₆haloalkyl, halo, C₆-C₁₂ aryl, 3- to 10-membered

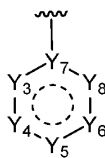
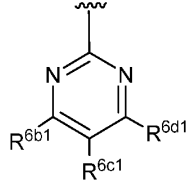
heterocyclyl, and 5- to 10-membered heteroaryl. In some embodiments,  is

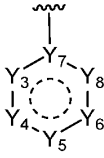
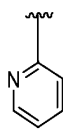
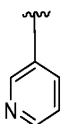
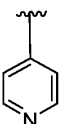
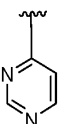
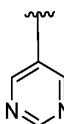
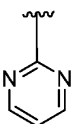
, wherein one or more of R^{6a1}, R^{6c1}, and R^{6d1} is selected from the group consisting of C₁-C₆alkyl, C₁-C₆haloalkyl, halo, C₆-C₁₂ aryl, 3- to 10-membered heterocyclyl,

and 5- to 10-membered heteroaryl. In some embodiments, , wherein one or more of R^{6a1}, R^{6b1}, and R^{6d1} is selected from the group consisting of C₁-C₆alkyl, C₁-C₆haloalkyl, halo, C₆-C₁₂ aryl, 3- to 10-membered heterocyclyl, and 5- to 10-membered

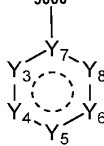
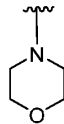
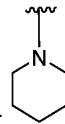
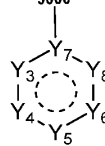
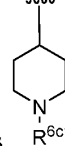
heteroaryl. In some embodiments,  is , wherein one or both of R^{6b1} and R^{6d1} is selected from the group consisting of C₁-C₆alkyl, C₁-C₆haloalkyl, halo, C₆-C₁₂ aryl, 3- to 10-membered heterocyclyl, and 5- to 10-membered heteroaryl. In some embodiments,

 is , wherein one or both of R^{6a1} and R^{6c1} is selected from the group consisting of C₁-C₆alkyl, C₁-C₆haloalkyl, halo, C₆-C₁₂ aryl, 3- to 10-membered heterocyclyl,

and 5- to 10-membered heteroaryl. In some embodiments,  is , wherein one or more of R^{6b1}, R^{6c1}, and R^{6d1} is selected from the group consisting of C₁-C₆alkyl, C₁-C₆haloalkyl, halo, C₆-C₁₂ aryl, 3- to 10-membered heterocyclyl, and 5- to 10-membered

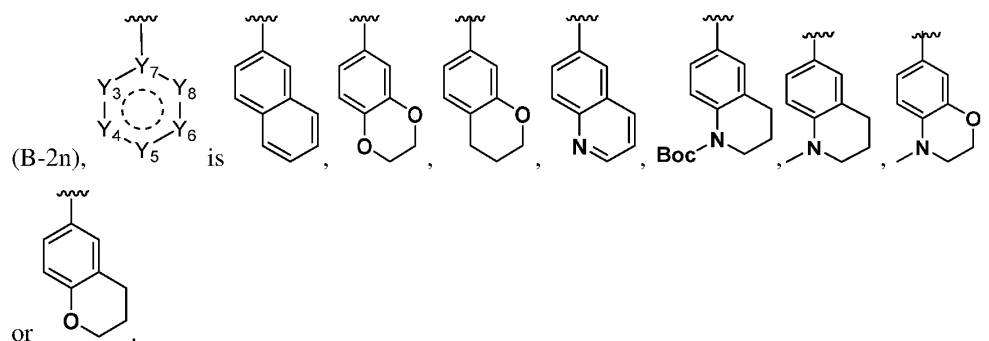
heteroaryl. In some embodiments,  is selected from the group consisting of , , , , , and .

[0131] In some embodiments of Formula (B), including Formula (B-1a), (B-1b), (B-2a), (B-2b), (B-2c), (B-2d), (B-2e), (B-2f), (B-2g), (B-2h), (B-2i), (B-2j), (B-2k), (B-2l), (B-2m), and

(B-2n),  is  or . In some embodiments,  is , wherein R^{6c1}

is selected from the group consisting of hydrogen, C₁-C₆alkyl, C₁-C₆alkoxy, halo, -OH, -NR^{p1}R^{q1}, C₆-C₁₂ aryl, 3- to 10-membered heterocyclyl, 5- to 10-membered heteroaryl, -C₁-C₆alkyl-5- to 6-membered heterocyclyl, -OC(O)-5- to 6-membered heterocyclyl, -C(O)R^{h1}, -S(O)₂NR^{w1a}R^{w2a}, -S(O)₂R^{y1}, and -NR^{z1a}S(O)₂R^{z2a}. In certain embodiments, R^{6c1} is -C(O)OC(CH₃)₃.

[0132] In some embodiments of Formula (B), including Formula (B-1a), (B-1b), (B-2a), (B-2b), (B-2c), (B-2d), (B-2e), (B-2f), (B-2g), (B-2h), (B-2i), (B-2j), (B-2k), (B-2l), (B-2m), and



[0133] In any of the foregoing embodiments, one or more of R^{6a1}, R^{6b1}, R^{6c1}, and R^{6d1} is selected from the group consisting of C₁-C₆alkyl, C₁-C₆haloalkyl, halo, C₆-C₁₂ aryl, 3- to 10-membered heterocyclyl, and 5- to 10-membered heteroaryl. In some embodiments, one or more of R^{6a1}, R^{6b1}, R^{6c1}, and R^{6d1} is C₆-C₁₂ aryl, unsubstituted or substituted with one or more groups selected from the group consisting of C₁-C₆alkyl, C₁-C₆alkoxy, -OH, and C₁-C₆alkyl-OH. For instance, in some embodiments, one of R^{6a1}, R^{6b1}, R^{6c1}, and R^{6d1} is phenyl or naphthyl. In some embodiments, one or more of R^{6a1}, R^{6b1}, R^{6c1}, and R^{6d1} is 3- to 10-membered heterocyclyl, unsubstituted or substituted with one or more groups selected from the group consisting of C₁-C₆alkyl, C₁-C₆alkoxy, -OH, C₁-C₆alkyl-OH, =O, =S, halo, C₃-C₈cycloalkyl, -C(O)NH-C₃-C₈cycloalkyl, C₆-C₁₂ aryl, and 5- to 6-membered heterocyclyl. In some embodiments, one or more of R^{6a1}, R^{6b1}, R^{6c1}, and R^{6d1} is 3- to 10-membered heterocyclyl, unsubstituted or substituted with one or more groups selected from the group consisting of C₁-C₆alkyl, C₁-C₆alkoxy, -OH, C₁-C₆alkyl-OH, =O, and =S. For instance, in some embodiments, one of R^{6a1}, R^{6b1}, R^{6c1}, and R^{6d1} is pyrrolidinyl, pyrazolidinyl, imidazolidinyl, tetrahydrofuranyl, 1,3-dioxolanyl, tetrahydrothiophenyl, oxathiolanyl, sulfolanyl, piperidinyl, piperazinyl, tetrahydropyranyl, dioxanyl, thianyl, dithianyl, trithianyl, morpholinyl, thiomorpholinyl, tetrahydroquinolinyl,

tetrahydroisoquinoliny, decahydroquinoliny, decahydroisoquinoliny, indoliny, isoindoliny, tetrahydronaphthyridiny or hexahydrobenzoimidazoliny, each independently unsubstituted or substituted with one or more groups selected from the group consisting of C₁-C₆alkyl, C₁-C₆alkoxy, -OH, C₁-C₆alkyl-OH, =O, =S, halo, C₃-C₈cycloalkyl, -C(O)NH-C₃-C₈cycloalkyl, C₆-C₁₂ aryl, and 5- to 6-membered heterocyclyl. For instance, in some embodiments, one of R^{6a1}, R^{6b1}, R^{6c1}, and R^{6d1} is pyrrolidinyl, pyrazolidinyl, imidazolidinyl, tetrahydrofuranyl, 1,3-dioxolanyl, tetrahydrothiophenyl, oxathiolanyl, sulfolanyl, piperidinyl, piperazinyl, tetrahydropyranyl, dioxanyl, thianyl, dithianyl, trithianyl, morpholiny, thiomorpholiny, tetrahydroquinoliny, tetrahydroisoquinoliny, decahydroquinoliny, decahydroisoquinoliny, indoliny, isoindoliny, tetrahydronaphthyridiny or hexahydrobenzoimidazoliny, each independently unsubstituted or substituted with one or more groups selected from the group consisting of C₁-C₆alkyl, C₁-C₆alkoxy, -OH, C₁-C₆alkyl-OH, =O, and =S.

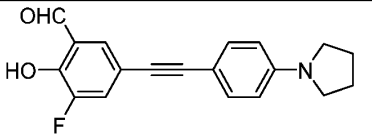
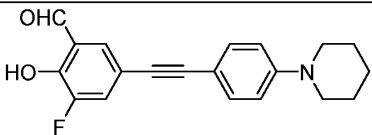
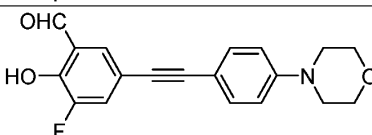
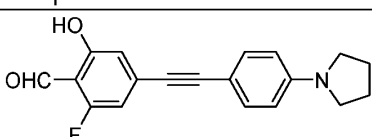
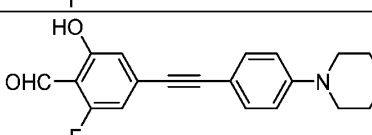
[0134] In some embodiments of Formula (B), including Formula (B-1a), (B-1b), (B-2a), (B-2b), (B-2c), (B-2d), (B-2e), (B-2f), (B-2g), (B-2h), (B-2i), (B-2j), (B-2k), (B-2l), (B-2m), and (B-2n), one of R^{6a1}, R^{6b1}, R^{6c1}, and R^{6d1} is selected from the group consisting of C₁-C₆alkyl, C₁-C₆haloalkyl, halo, C₆-C₁₂ aryl, 3- to 10-membered heterocyclyl, and 5- to 10-membered heteroaryl. In certain embodiments, one of R^{6a1}, R^{6b1}, R^{6c1}, and R^{6d1} is selected from the group consisting of methyl, ethyl, F, Cl, -CF₃, pyrrolidinyl, piperidinyl, morpholiny, piperazinyl, pyrazolyl, and triazolyl. In certain embodiments, one of R^{6a1}, R^{6b1}, R^{6c1}, and R^{6d1} is selected from the group consisting of pyrrolidinyl, piperidinyl, morpholiny, piperazinyl, pyrazolyl, and triazolyl, each optionally substituted with one or more groups selected from the group consisting of C₁-C₆alkyl, C₁-C₆alkoxy, -OH, C₁-C₆alkyl-OH, =O, =S, halo, C₃-C₈cycloalkyl, -C(O)NH-C₃-C₈cycloalkyl, C₆-C₁₂ aryl, and 5- to 6-membered heterocyclyl. In certain embodiments, one of R^{6a1}, R^{6b1}, R^{6c1}, and R^{6d1} is selected from the group consisting of pyrrolidinyl, piperidinyl, morpholiny, piperazinyl, pyrazolyl, and triazolyl, each optionally substituted with one or more groups selected from the group consisting of C₁-C₆alkyl, C₁-C₆alkoxy, -OH, C₁-C₆alkyl-OH, =O, and =S. In some embodiments, two or three of R^{6a1}, R^{6b1}, R^{6c1}, and R^{6d1} is selected from the group consisting of methyl, ethyl, F, Cl, -CF₃, pyrrolidinyl, piperidinyl, morpholiny, piperazinyl, pyrazolyl, and triazolyl. In other embodiments, R^{6a1}, R^{6b1}, R^{6c1}, and R^{6d1} are each H.

[0135] In some embodiments of Formula (B), including Formula (B-1a), (B-1b), (B-2a), (B-2b), (B-2c), (B-2d), (B-2e), (B-2f), (B-2g), (B-2h), (B-2i), (B-2j), (B-2k), (B-2l), (B-2m), and

(B-2n), one of R^{6a1} , R^{6b1} , R^{6c1} , and R^{6d1} is indolinyl optionally substituted with one or more groups selected from the group consisting of C_1 - C_6 alkyl, C_1 - C_6 alkoxy, -OH, C_1 - C_6 alkyl-OH, =O, =S, halo, C_3 - C_8 cycloalkyl, -C(O)NH- C_3 - C_8 cycloalkyl, C_6 - C_{12} aryl, and 5- to 6-membered heterocyclyl. In some embodiments, one of R^{6a1} , R^{6b1} , R^{6c1} , and R^{6d1} is indolinyl optionally substituted with one or more independently selected C_1 - C_6 alkyl and halo groups. In some embodiments, one of R^{6a1} , R^{6b1} , R^{6c1} , and R^{6d1} is 3,3-dimethylindolin-1-yl or 5-fluoro-3,3-dimethylindolin-1-yl. In some embodiments, R^{6c1} is 3,3-dimethylindolin-1-yl or 5-fluoro-3,3-dimethylindolin-1-yl. In some embodiments, one of R^{6a1} , R^{6b1} , R^{6c1} , and R^{6d1} is piperazinyl optionally substituted with phenyl. In some embodiments, one of R^{6a1} , R^{6b1} , R^{6c1} , and R^{6d1} is 4-phenylpiperazinyl. In some embodiments, R^{6c1} is 4-phenylpiperazinyl.

[0136] In some embodiments, provided herein are compounds and salts thereof described in Table 1B.

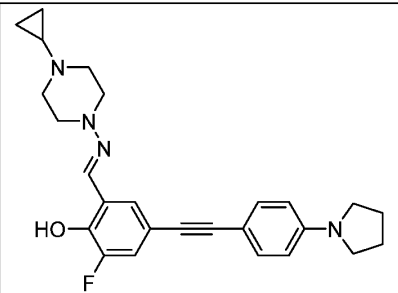
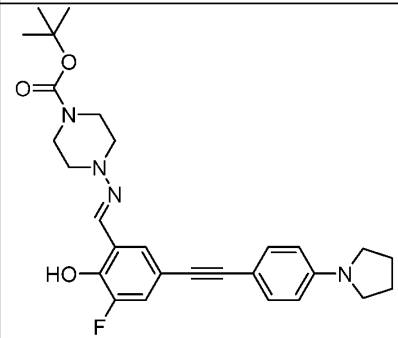
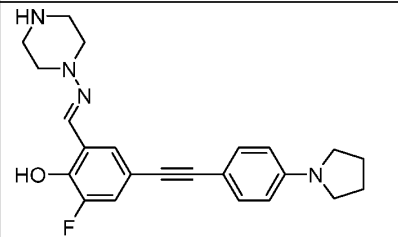
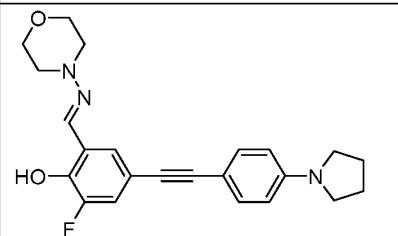
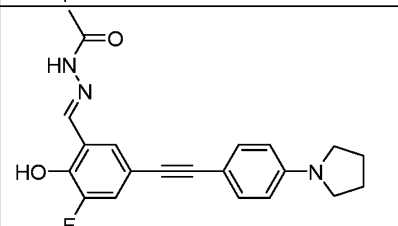
Table 1B.

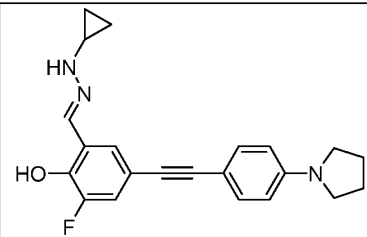
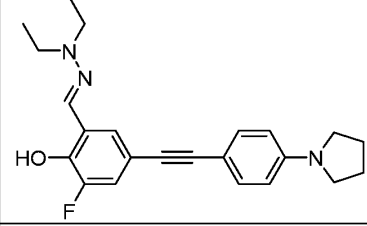
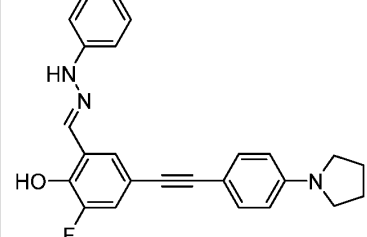
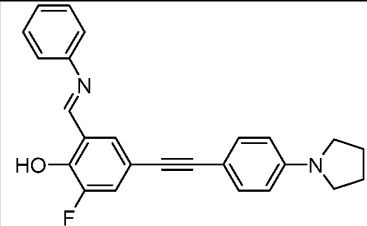
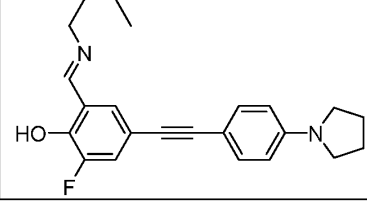
Compo und No.	Chemical Structure	Chemical Name
B1		3-fluoro-2-hydroxy-5-((4-(pyrrolidin-1-yl)phenyl)ethynyl)benzaldehyde
B2		3-fluoro-2-hydroxy-5-((4-(piperidin-1-yl)phenyl)ethynyl)benzaldehyde
B3		3-fluoro-2-hydroxy-5-((4-morpholinophenyl)ethynyl)benzaldehyde
B4		2-fluoro-6-hydroxy-4-((4-(pyrrolidin-1-yl)phenyl)ethynyl)benzaldehyde
B5		2-fluoro-6-hydroxy-4-((4-(piperidin-1-yl)phenyl)ethynyl)benzaldehyde

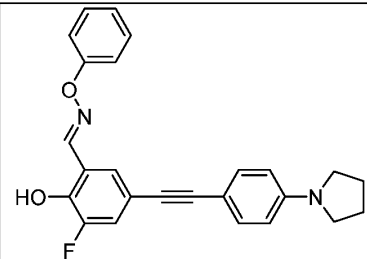
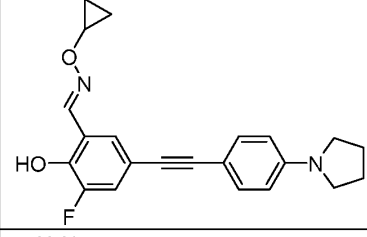
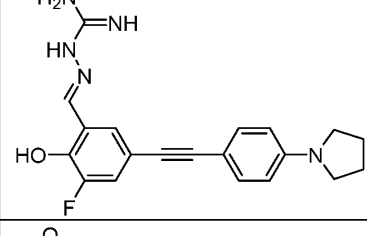
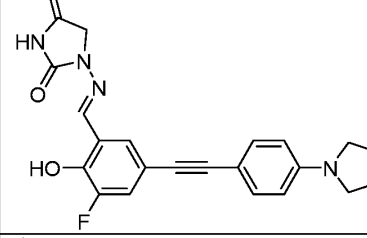
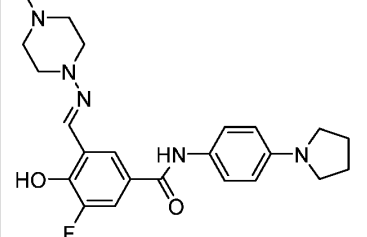
B6		2-fluoro-6-hydroxy-4-((4-morpholinophenyl)ethynyl)benzaldehyde
B7		2-hydroxy-6-methoxy-4-((4-(pyrrolidin-1-yl)phenyl)ethynyl)benzaldehyde
B8		2-hydroxy-3-methoxy-5-((4-morpholinophenyl)ethynyl)benzaldehyde
B9		N-(3-fluoro-5-formyl-4-hydroxyphenyl)benzamide
B10		1-(3-fluoro-5-formyl-4-hydroxyphenyl)-3-phenylurea
B11		3-fluoro-5-formyl-4-hydroxy-N-phenylbenzamide
B12		3-fluoro-5-formyl-4-hydroxy-N-(4-(pyrrolidin-1-yl)phenyl)benzamide
B13		3-fluoro-5-formyl-4-hydroxy-N-(4-(trifluoromethyl)phenyl)benzamide
B14		N-(3-chloro-4-(trifluoromethyl)phenyl)-3-fluoro-5-formyl-4-hydroxybenzamide
B15		3-fluoro-5-formyl-4-hydroxy-N-phenylbenzenesulfonamide

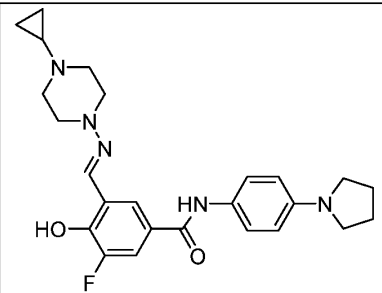
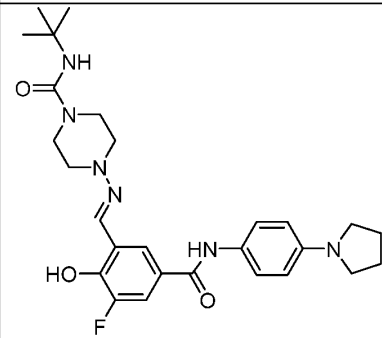
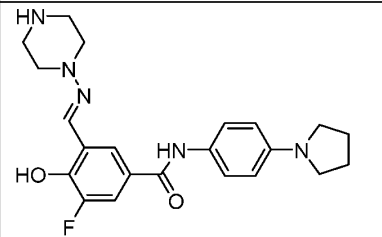
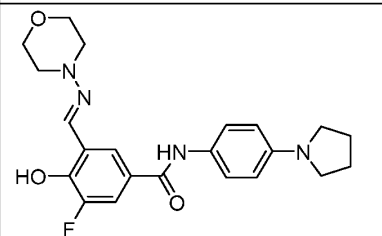
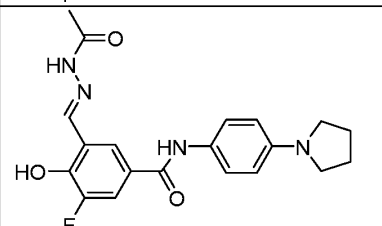
B16		3-fluoro-N-(4-fluorophenyl)-5-formyl-4-hydroxybenzenesulfonamide
B17		3-fluoro-5-formyl-4-hydroxy-N-(4-(pyrrolidin-1-yl)phenyl)benzenesulfonamide
B18		N-(3-fluoro-5-formyl-4-hydroxyphenyl)benzenesulfonamide
B19		N-(3-fluoro-5-formyl-4-hydroxyphenyl)-4-(pyrrolidin-1-yl)benzenesulfonamide
B20		3-fluoro-5-formyl-4-hydroxy-N-(4-(pyrrolidin-1-yl)phenyl)benzenesulfonimide
B21		3-fluoro-N'-(4-fluorophenyl)-5-formyl-4-hydroxybenzohydrazide
B22		phenyl (3-formyl-4-hydroxy-5-methoxyphenyl)carbamate
B23		4-(trifluoromethyl)phenyl (3-fluoro-5-formyl-4-hydroxyphenyl)carbamate

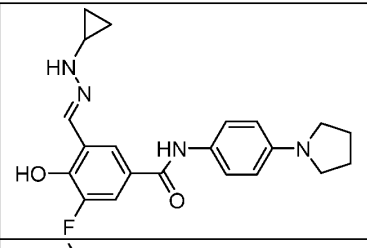
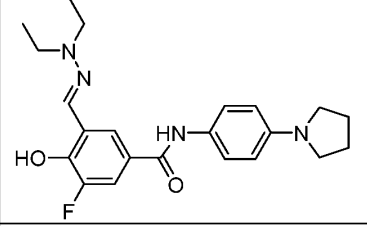
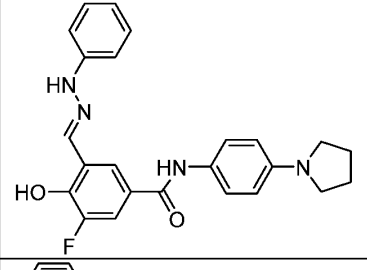
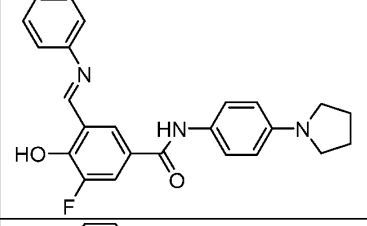
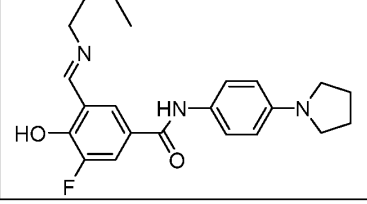
B24		4-fluoro-N'-(3-formyl-4-hydroxy-5-methoxyphenyl)benzohydrazide
B25		1-(3-formyl-4-hydroxy-5-methoxyphenyl)-3-(pyridin-3-yl)urea
B26		3-fluoro-5-formyl-4-hydroxy-N-(4-methyl-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)benzamide
B27		N-(chroman-7-yl)-3-fluoro-5-formyl-4-hydroxybenzamide
B28		N-(3-(2-ethoxyethoxy)phenyl)-3-formyl-4-hydroxy-5-methoxybenzamide
B29		2-fluoro-6-(((4-methylpiperazin-1-yl)imino)methyl)-4-((4-(pyrrolidin-1-yl)phenyl)ethynyl)phenol

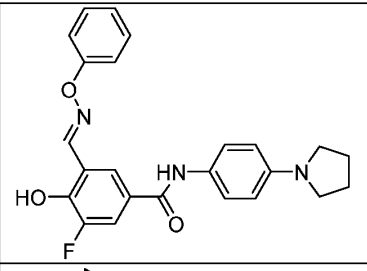
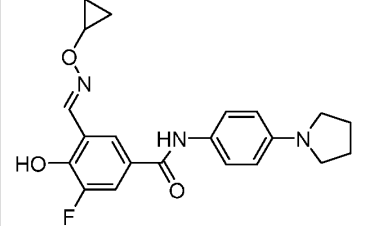
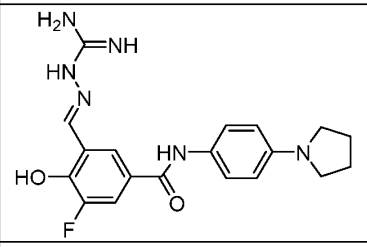
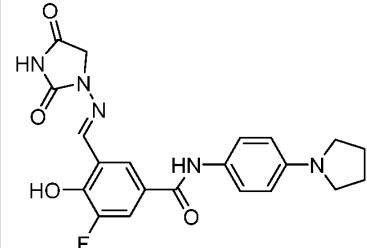
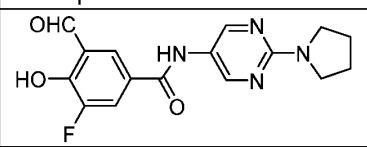
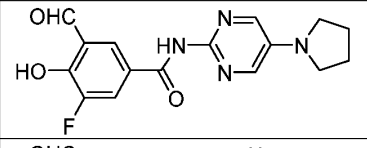
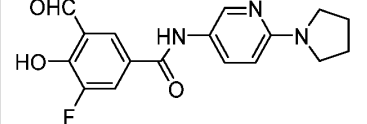
B30		2-(((4-cyclopropylpiperazin-1-yl)imino)methyl)-6-fluoro-4-((4-(pyrrolidin-1-yl)phenyl)ethynyl)phenol
B31		tert-butyl 4-((3-fluoro-2-hydroxy-5-((4-(pyrrolidin-1-yl)phenyl)ethynyl)benzylidene)amino)piperazine-1-carboxylate
B32		2-fluoro-6-((piperazin-1-ylimino)methyl)-4-((4-(pyrrolidin-1-yl)phenyl)ethynyl)phenol
B33		2-fluoro-6-((morpholinoimino)methyl)-4-((4-(pyrrolidin-1-yl)phenyl)ethynyl)phenol
B34		N'-(3-fluoro-2-hydroxy-5-((4-(pyrrolidin-1-yl)phenyl)ethynyl)benzylidene)acetohydrazide

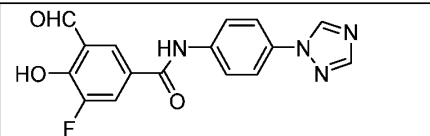
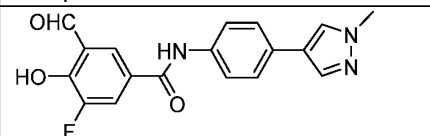
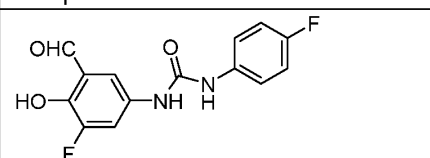
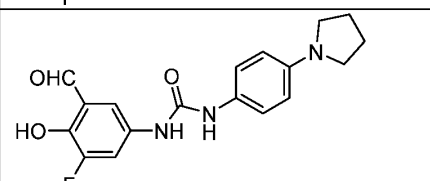
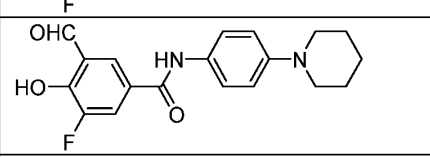
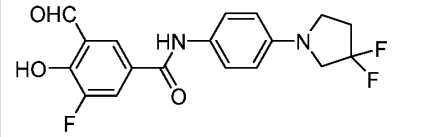
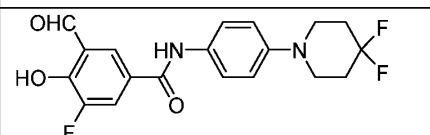
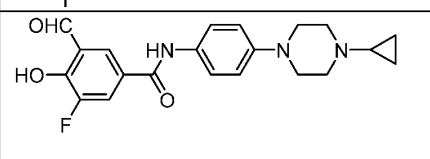
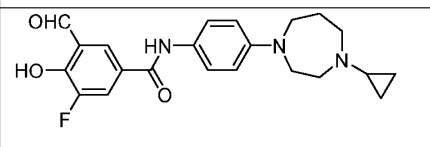
B35		2-((2-cyclopropylhydrazono)methyl)-6-fluoro-4-((4-(pyrrolidin-1-yl)phenyl)ethynyl)phenol
B36		(2-((2,2-diethylhydrazono)methyl)-6-fluoro-4-((4-(pyrrolidin-1-yl)phenyl)ethynyl)phenol
B37		2-fluoro-6-((2-phenylhydrazono)methyl)-4-((4-(pyrrolidin-1-yl)phenyl)ethynyl)phenol
B38		2-fluoro-6-((phenylimino)methyl)-4-((4-(pyrrolidin-1-yl)phenyl)ethynyl)phenol
B39		2-((butylimino)methyl)-6-fluoro-4-((4-(pyrrolidin-1-yl)phenyl)ethynyl)phenol

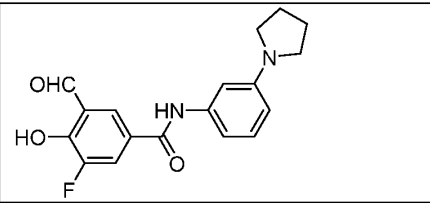
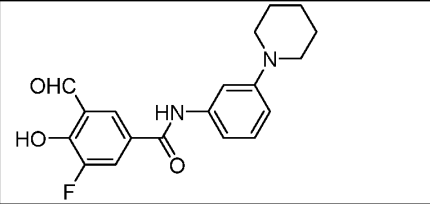
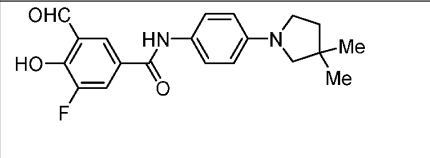
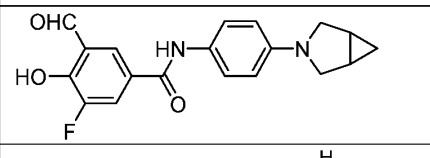
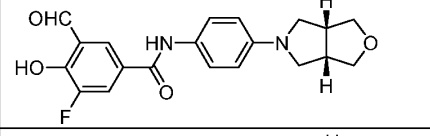
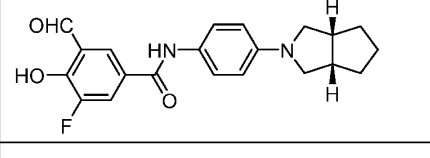
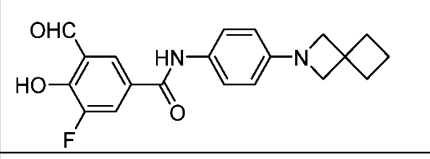
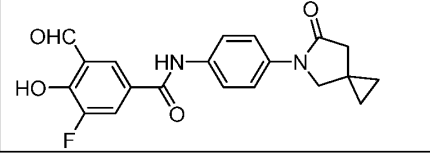
B40		3-fluoro-2-hydroxy-5-((4-(pyrrolidin-1-yl)phenyl)ethynyl)benzaldehyde O-phenyl oxime
B41		3-fluoro-2-hydroxy-5-((4-(pyrrolidin-1-yl)phenyl)ethynyl)benzaldehyde O-cyclopropyl oxime
B42		2-(3-fluoro-2-hydroxy-5-((4-(pyrrolidin-1-yl)phenyl)ethynyl)benzylidene)hydrazine-1-carboximidamide
B43		1-((3-fluoro-2-hydroxy-5-((4-(pyrrolidin-1-yl)phenyl)ethynyl)benzylidene)amino)imidazolidine-2,4-dione
B44		3-fluoro-4-hydroxy-5-(((4-methylpiperazin-1-yl)imino)methyl)-N-(4-(pyrrolidin-1-yl)phenyl)benzamide

B45		3-(((4-cyclopropylpiperazin-1-yl)imino)methyl)-5-fluoro-4-hydroxy-N-(4-(pyrrolidin-1-yl)phenyl)benzamide
B46		N-(tert-butyl)-4-((3-fluoro-2-hydroxy-5-((4-(pyrrolidin-1-yl)phenyl)carbamoyl)benzylidene)amino)piperazine-1-carboxamide
B47		3-fluoro-4-hydroxy-5-((piperazin-1-ylimino)methyl)-N-(4-(pyrrolidin-1-yl)phenyl)benzamide
B48		3-fluoro-4-hydroxy-5-((morpholinoimino)methyl)-N-(4-(pyrrolidin-1-yl)phenyl)benzamide
B49		3-((2-acetylhydrazono)methyl)-5-fluoro-4-hydroxy-N-(4-(pyrrolidin-1-yl)phenyl)benzamide

B50		3-((2-cyclopropylhydrazono)methyl)-5-fluoro-4-hydroxy-N-(4-(pyrrolidin-1-yl)phenyl)benzamide
B51		3-((2,2-diethylhydrazono)methyl)-5-fluoro-4-hydroxy-N-(4-(pyrrolidin-1-yl)phenyl)benzamide
B52		3-fluoro-4-hydroxy-5-((2-phenylhydrazono)methyl)-N-(4-(pyrrolidin-1-yl)phenyl)benzamide
B53		3-fluoro-4-hydroxy-5-((phenylimino)methyl)-N-(4-(pyrrolidin-1-yl)phenyl)benzamide
B54		3-((butylimino)methyl)-5-fluoro-4-hydroxy-N-(4-(pyrrolidin-1-yl)phenyl)benzamide

B55		3-fluoro-4-hydroxy-5-((phenoxymino)methyl)-N-(4-(pyrrolidin-1-yl)phenyl)benzamide
B56		3-((cyclopropoxymino)methyl)-5-fluoro-4-hydroxy-N-(4-(pyrrolidin-1-yl)phenyl)benzamide
B57		3-((2-carbamimidoylhydrazono)methyl)-5-fluoro-4-hydroxy-N-(4-(pyrrolidin-1-yl)phenyl)benzamide
B58		3-(((2,4-dioxoimidazolidin-1-yl)imino)methyl)-5-fluoro-4-hydroxy-N-(4-(pyrrolidin-1-yl)phenyl)benzamide
B59		3-fluoro-5-formyl-4-hydroxy-N-(2-(pyrrolidin-1-yl)pyrimidin-5-yl)benzamide
B60		3-fluoro-5-formyl-4-hydroxy-N-(5-(pyrrolidin-1-yl)pyrimidin-2-yl)benzamide
B61		3-fluoro-5-formyl-4-hydroxy-N-(6-(pyrrolidin-1-yl)pyridin-3-yl)benzamide

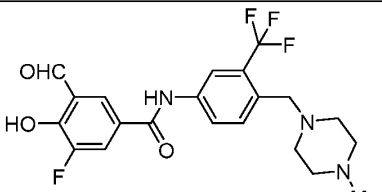
B62		N-(4-(1H-1,2,4-triazol-1-yl)phenyl)-3-fluoro-5-formyl-4-hydroxybenzamide
B63		3-fluoro-5-formyl-4-hydroxy-N-(4-(1-methyl-1H-pyrazol-4-yl)phenyl)benzamide
B64		1-(3-fluoro-5-formyl-4-hydroxyphenyl)-3-(4-fluorophenyl)urea
B65		1-(3-fluoro-5-formyl-4-hydroxyphenyl)-3-(4-(pyrrolidin-1-yl)phenyl)urea
B66		3-fluoro-5-formyl-4-hydroxy-N-(4-(piperidin-1-yl)phenyl)benzamide
B67		N-(4-(3,3-difluoropyrrolidin-1-yl)phenyl)-3-fluoro-5-formyl-4-hydroxybenzamide
B68		N-(4-(4,4-difluoropiperidin-1-yl)phenyl)-3-fluoro-5-formyl-4-hydroxybenzamide
B69		N-(4-(4-cyclopropylpiperazin-1-yl)phenyl)-3-fluoro-5-formyl-4-hydroxybenzamide
B70		N-(4-(4-cyclopropyl-1,4-diazepan-1-yl)phenyl)-3-fluoro-5-formyl-4-hydroxybenzamide

B71		3-fluoro-5-formyl-4-hydroxy-N-(3-(pyrrolidin-1-yl)phenyl)benzamide
B72		3-fluoro-5-formyl-4-hydroxy-N-(3-(piperidin-1-yl)phenyl)benzamide
B73		N-(4-(3,3-dimethylpyrrolidin-1-yl)phenyl)-3-fluoro-5-formyl-4-hydroxybenzamide
B74		N-(4-(3-azabicyclo[3.1.0]hexan-3-yl)phenyl)-3-fluoro-5-formyl-4-hydroxybenzamide
B75		3-fluoro-5-formyl-4-hydroxy-N-(4-((3aR,6aS)-tetrahydro-1H-furo[3,4-c]pyrrol-5(3H)-yl)phenyl)benzamide
B76		3-fluoro-5-formyl-N-(4-((3aR,6aS)-hexahydrocyclopenta[c]pyrrol-2(1H)-yl)phenyl)-4-hydroxybenzamide
B77		N-(4-(2-azaspiro[3.3]heptan-2-yl)phenyl)-3-fluoro-5-formyl-4-hydroxybenzamide
B78		3-fluoro-5-formyl-4-hydroxy-N-(4-(6-oxo-5-azaspiro[2.4]heptan-5-yl)phenyl)benzamide

B79		N-(4-(5-azaspiro[2.4]heptan-5-yl)phenyl)-3-fluoro-5-formyl-4-hydroxybenzamide
B80		N-cyclopropyl-4-((3-fluoro-5-formyl-4-hydroxyphenyl)ethynyl)benzamide
B81		3-fluoro-5-formyl-4-hydroxy-N-(4-(isoindolin-2-yl)phenyl)benzamide
B82		N-(4-(3,4-dihydroisoquinolin-2(1H)-yl)phenyl)-3-fluoro-5-formyl-4-hydroxybenzamide
B83		3-fluoro-5-formyl-4-hydroxy-N-(4-(4-phenylpiperazin-1-yl)phenyl)benzamide
B84		3-fluoro-5-formyl-4-hydroxy-N-(4-(4-(pyrrolidin-1-yl)piperidin-1-yl)phenyl)benzamide
B85		3-fluoro-5-formyl-4-hydroxy-N-(4-(4-(pyrrolidin-1-yl)piperidin-1-yl)phenyl)benzamide
B86		3-fluoro-5-formyl-4-hydroxy-N-(6-(isoindolin-2-yl)pyridin-3-yl)benzamide
B87		N-(6-(3,3-dimethylindolin-1-yl)pyridin-3-yl)-3-fluoro-5-formyl-4-hydroxybenzamide

B88		N-(4-(3,3-dimethylindolin-1-yl)phenyl)-3-fluoro-5-formyl-4-hydroxybenzamide
B89		N-(4-(3,3-dimethyl-2-oxoindolin-1-yl)phenyl)-3-fluoro-5-formyl-4-hydroxybenzamide
B90		N-(4-(2,3-dihydro-4H-benzo[b][1,4]oxazin-4-yl)phenyl)-3-fluoro-5-formyl-4-hydroxybenzamide
B91		3-fluoro-5-formyl-4-hydroxy-N-(4-(pyrrolidin-1-yl)-3-(trifluoromethyl)phenyl)benzamide
B92		3-fluoro-5-formyl-4-hydroxy-N-(3-(pyrrolidin-1-yl)-4-(trifluoromethyl)phenyl)benzamide
B93		N-(4-(((3s,5s,7s)-adamantan-1-yl)(methyl)amino)phenyl)-3-fluoro-5-formyl-4-hydroxybenzamide
B94		3-fluoro-5-formyl-4-hydroxy-N-(4-(methyl(neopentyl)amino)phenyl)benzamide
B95		N-(4-(((1s,4s)-7-azabicyclo[2.2.1]heptan-7-yl)phenyl)-3-fluoro-5-formyl-4-hydroxybenzamide

B96		N-(4-((1R,5S)-8-azabicyclo[3.2.1]octan-8-yl)phenyl)-3-fluoro-5-formyl-4-hydroxybenzamide
B97		3-fluoro-N-(6-(5-fluoroisindolin-2-yl)pyridin-3-yl)-5-formyl-4-hydroxybenzamide
B98		N-(6-(3,3-dimethylindolin-1-yl)-5-(trifluoromethyl)pyridin-3-yl)-3-fluoro-5-formyl-4-hydroxybenzamide
B99		3-fluoro-N-(6-(5-fluoro-3,3-dimethylindolin-1-yl)pyridin-3-yl)-5-formyl-4-hydroxybenzamide
B100		3-fluoro-5-formyl-4-hydroxy-N-(6-(spiro[cyclopropane-1,3'-indolin]-1'-yl)pyridin-3-yl)benzamide
B101		N-(6-(2-azaspiro[3.3]heptan-2-yl)pyridin-3-yl)-3-fluoro-5-formyl-4-hydroxybenzamide
B102		3-fluoro-5-formyl-4-hydroxy-N-(6-(4-phenylpiperazin-1-yl)pyridin-3-yl)benzamide
B103		3-fluoro-5-formyl-N-(6-((3aR,6aS)-hexahydrocyclopenta[c]pyrrol-2(1H)-yl)pyridin-3-yl)-4-hydroxybenzamide

B104		3-fluoro-5-formyl-4-hydroxy-N-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)benzamide
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and pharmaceutically acceptable salts thereof.

[0137] Any formula or compound given herein, such as Formula (I), Formula (A), or Formula (B), or compounds of Table 1A and Table 1B, is intended to represent compounds having structures depicted by the structural formula as well as certain variations or forms. In particular, compounds of any formula given herein may contain bonds with restricted rotation and therefore exist in different geometric configurations. Additionally, compounds of any formula provided herein may have asymmetric centers and therefore exist in different enantiomeric or diastereomeric forms. All optical isomers and stereoisomers of the compounds of the general formula, and mixtures thereof in any ratio, are considered within the scope of the formula. Thus, any formula given herein is intended to represent a racemate, one or more enantiomeric forms, one or more diastereomeric forms, one or more atropisomeric forms (e.g., geoisomeric forms), and mixtures thereof in any ratio. Where a compound of Table 1A or Table 1B is depicted with a particular stereochemical configuration, also provided herein is any alternative stereochemical configuration of the compound, as well as a mixture of stereoisomers of the compound in any ratio. Any compound of Table 1A or Table 1B is intended to represent a racemate, one or more enantiomeric forms, one or more diastereomeric forms, one or more atropisomeric forms (e.g., geoisomeric forms), and mixtures thereof in any ratio. Furthermore, certain structures may exist as tautomers or as atropisomers. Additionally, any formula given herein is intended to refer to hydrates, solvates, and amorphous forms of such compounds, and mixtures thereof, even if such forms are not listed explicitly. In some embodiments, the solvent is water and the solvates are hydrates.

[0138] The compounds of Formula (A) and Formula (B), or Table 1A and Table 1B may be prepared and/or formulated as pharmaceutically acceptable salts. In some embodiments, pharmaceutically acceptable salts include acid addition salts, formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like; or formed with organic acids such as acetic acid, oxalic acid, propionic acid, succinic acid,

maleic acid, tartaric acid and the like. These salts may be derived from inorganic or organic acids. Non-limiting examples of pharmaceutically acceptable salts include sulfates, pyrosulfates, bisulfates, sulfites, bisulfites, phosphates, monohydrogen-phosphates, dihydrogenphosphates, metaphosphates, pyrophosphates, chlorides, bromides, iodides, acetates, propionates, decanoates, caprylates, acrylates, formates, isobutyrate, caproates, heptanoates, propiolates, oxalates, malonates, succinates, suberates, sebacates, fumarates, maleates, butyne-1,4-dioates, hexyne-1,6-dioates, benzoates, chlorobenzoates, methylbenzoates, dinitrobenzoates, hydroxybenzoates, methoxybenzoates, phthalates, sulfonates, methylsulfonates, propylsulfonates, besylates, xylenesulfonates, naphthalene-1-sulfonates, naphthalene-2-sulfonates, phenylacetates, phenylpropionates, phenylbutyrates, citrates, lactates, γ -hydroxybutyrates, glycolates, tartrates, and mandelates. In some embodiments, pharmaceutically acceptable salts are formed when an acidic proton present in the parent compound either is replaced by a metal ion, e.g., an alkali metal ion, an alkaline earth ion, or an aluminum ion; or coordinates with an organic base. Salts derived from pharmaceutically acceptable organic non-toxic bases include salts of primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines and basic ion exchange resins, such as isopropylamine, trimethylamine, diethylamine, triethylamine, tripropylamine, ethanolamine, 2-diethylaminoethanol, tromethamine, trimethamine, dicyclohexylamine, caffeine, procaine, hydrabamine, choline, betaine, ethylenediamine, glucosamine, N-ethylglucamine, N-methylglucamine, theobromine, purines, piperazine, piperidine, N-ethylpiperidine, polyamine resins, amino acids such as lysine, arginine, histidine, and the like. Examples of pharmaceutically acceptable base addition salts include those derived from inorganic bases such as sodium, potassium, lithium, ammonium, calcium, magnesium, iron, zinc, copper, manganese, aluminum salts and the like. In some embodiments, the organic non-toxic bases are L-amino acids, such as L-lysine and L-arginine, tromethamine, N-ethylglucamine and N-methylglucamine. Acceptable inorganic bases include aluminum hydroxide, calcium hydroxide, potassium hydroxide, sodium carbonate, sodium hydroxide, and the like. Lists of other suitable pharmaceutically acceptable salts are found in Remington's Pharmaceutical Sciences, 17th Edition, Mack Publishing Company, Easton, Pa., 1985.

[0139] For a compound described herein that contains a basic nitrogen, a pharmaceutically acceptable salt may be prepared by any suitable method available in the art, for example,

treatment of the free base with an inorganic acid, such as hydrochloric acid, hydrobromic acid, sulfuric acid, sulfamic acid, nitric acid, boric acid, phosphoric acid, and the like, or with an organic acid, such as acetic acid, phenylacetic acid, propionic acid, stearic acid, lactic acid, ascorbic acid, maleic acid, hydroxymaleic acid, isethionic acid, succinic acid, valeric acid, fumaric acid, malonic acid, pyruvic acid, oxalic acid, glycolic acid, salicylic acid, oleic acid, palmitic acid, lauric acid, a pyranosidyl acid, such as glucuronic acid or galacturonic acid, an alpha-hydroxy acid, such as mandelic acid, citric acid, or tartaric acid, an amino acid, such as aspartic acid or glutamic acid, an aromatic acid, such as benzoic acid, 2-acetoxybenzoic acid, naphthoic acid, or cinnamic acid, a sulfonic acid, such as laurylsulfonic acid, p-toluenesulfonic acid, methanesulfonic acid, benzenesulfonic acid, or ethanesulfonic acid, or any compatible mixture of acids such as those given as examples herein, and any other acid and mixture thereof that are regarded as equivalents or acceptable substitutes in light of the ordinary level of skill in this technology.

[0140] The compounds depicted herein may be present as salts even if salts are not depicted, and it is understood that the compositions and methods provided herein embrace all salts and solvates of the compounds depicted here, as well as the non-salt and non-solvate form of the compound, as is well understood by the skilled artisan. In some embodiments, the salts of the compounds provided herein are pharmaceutically acceptable salts.

[0141] Representative examples of compounds detailed herein, including intermediates and final compounds, are depicted in the tables and elsewhere herein. It is understood that in one aspect, any of the compounds may be used in the methods detailed herein, including, where applicable, intermediate compounds that may be isolated and administered to an individual.

[0142] In one variation, the compounds herein are synthetic compounds prepared for administration to an individual. In another variation, compositions are provided containing a compound in substantially pure form. In another variation, provided are pharmaceutical compositions comprising a compound detailed herein and a pharmaceutically acceptable carrier. In another variation, methods of administering a compound are provided. The purified forms, pharmaceutical compositions and methods of administering the compounds are suitable for any compound or form thereof detailed herein.

[0143] Any variation or embodiment of $R^1, R^2, R^3, R^4, Y^1, Y^2, Y^3, Y^4, Y^5, G_1, G_2, G_3, G_4, G_5, G_6, G_7, R^a, R^b, R^c, R^d, R^e, R^f, R^g, R^h, R^i, R^j, R^k, R^m, R^n, R^p, R^q, R^r, R^s, R^t, R^u, R^v, R^{w1}, R^{w2}, R^x, R^y, R^{z1}, R^{z2}, X_1, X_2, X_3, X_4, m, n, R^{6a}, R^{6b}, R^{6c},$ and R^{6d} provided herein can be combined with every other variation or embodiment of $R^1, R^2, R^3, R^4, Y^1, Y^2, Y^3, Y^4, Y^5, G_1, G_2, G_3, G_4, G_5, G_6, G_7, R^a, R^b, R^c, R^d, R^e, R^f, R^g, R^h, R^i, R^j, R^k, R^m, R^n, R^p, R^q, R^r, R^s, R^t, R^u, R^v, R^{w1}, R^{w2}, R^x, R^y, R^{z1}, R^{z2}, X_1, X_2, X_3, X_4, m, n, R^{6a}, R^{6b}, R^{6c},$ and R^{6d} as if each combination had been individually and specifically described.

[0144] Any variation or embodiment of $R^{1A}, R^{2A}, R^{3A}, L, Y_1, Y_2, Y_3, Y_4, Y_5, Y_6, Y_7, Y_8, R^{a1}, R^{b1}, R^{c1}, R^{d1}, R^{e1}, R^{f1}, R^{g1}, R^{h1}, R^{i1}, R^{j1}, R^{k1}, R^{m1}, R^{n1}, R^{p1}, R^{q1}, R^{r1}, R^{s1}, R^{t1}, R^{u1}, R^{v1}, R^{w1a}, R^{w2a}, R^x, R^{y1}, R^{z1a}, R^{z2a}, X_{1A}, X_{2A}, X_{3A}, X_{4A}, m1, R^{6a1}, R^{6b1}, R^{6c1},$ and R^{6d1} provided herein can be combined with every other variation or embodiment of $R^{1A}, R^{2A}, R^{3A}, L, Y_1, Y_2, Y_3, Y_4, Y_5, Y_6, Y_7, Y_8, R^{a1}, R^{b1}, R^{c1}, R^{d1}, R^{e1}, R^{f1}, R^{g1}, R^{h1}, R^{i1}, R^{j1}, R^{k1}, R^{m1}, R^{n1}, R^{p1}, R^{q1}, R^{r1}, R^{s1}, R^{t1}, R^{u1}, R^{v1}, R^{w1a}, R^{w2a}, R^x, R^{y1}, R^{z1a}, R^{z2a}, X_{1A}, X_{2A}, X_{3A}, X_{4A}, m1, R^{6a1}, R^{6b1}, R^{6c1},$ and R^{6d1} , as if each combination had been individually and specifically described.

[0145] Any variation or embodiment of $R^1, R^2, R^3, R^4, Y^1, Y^2, Y^3, Y^4, Y^5, G_1, G_2, G_3, G_4, G_5, G_6, G_7, R^a, R^b, R^c, R^d, R^e, R^f, R^g, R^h, R^i, R^j, R^k, R^m, R^n, R^p, R^q, R^r, R^s, R^t, R^u, R^v, R^{w1}, R^{w2}, R^x, R^y, R^{z1}, R^{z2}, X_1, X_2, X_3, X_4, m, n, R^{6a}, R^{6b}, R^{6c}, R^{6d}, R^{1A}, R^{2A}, R^{3A}, L, Y_1, Y_2, Y_3, Y_4, Y_5, Y_6, Y_7, Y_8, R^{a1}, R^{b1}, R^{c1}, R^{d1}, R^{e1}, R^{f1}, R^{g1}, R^{h1}, R^{i1}, R^{j1}, R^{k1}, R^{m1}, R^{n1}, R^{p1}, R^{q1}, R^{r1}, R^{s1}, R^{t1}, R^{u1}, R^{v1}, R^{w1a}, R^{w2a}, R^x, R^{y1}, R^{z1a}, R^{z2a}, X_{1A}, X_{2A}, X_{3A}, X_{4A}, m1, R^{6a1}, R^{6b1}, R^{6c1},$ and R^{6d1} provided herein can be combined with every other variation or embodiment of $R^1, R^2, R^3, R^4, Y^1, Y^2, Y^3, Y^4, Y^5, G_1, G_2, G_3, G_4, G_5, G_6, G_7, R^a, R^b, R^c, R^d, R^e, R^f, R^g, R^h, R^i, R^j, R^k, R^m, R^n, R^p, R^q, R^r, R^s, R^t, R^u, R^v, R^{w1}, R^{w2}, R^x, R^y, R^{z1}, R^{z2}, X_1, X_2, X_3, X_4, m, n, R^{6a}, R^{6b}, R^{6c}, R^{6d}, R^{1A}, R^{2A}, R^{3A}, L, Y_1, Y_2, Y_3, Y_4, Y_5, Y_6, Y_7, Y_8, R^{a1}, R^{b1}, R^{c1}, R^{d1}, R^{e1}, R^{f1}, R^{g1}, R^{h1}, R^{i1}, R^{j1}, R^{k1}, R^{m1}, R^{n1}, R^{p1}, R^{q1}, R^{r1}, R^{s1}, R^{t1}, R^{u1}, R^{v1}, R^{w1a}, R^{w2a}, R^x, R^{y1}, R^{z1a}, R^{z2a}, X_{1A}, X_{2A}, X_{3A}, X_{4A}, m1, R^{6a1}, R^{6b1}, R^{6c1},$ and R^{6d1} as if each combination had been individually and specifically described.

[0146] The embodiments also relate to pharmaceutically acceptable prodrugs of the compounds described herein, and treatment methods employing such pharmaceutically acceptable prodrugs. The term “prodrug” means a precursor of a designated compound that, following administration to a subject, yields the compound *in vivo* via a chemical or physiological process such as solvolysis or enzymatic cleavage, or under physiological conditions (e.g., a prodrug on being brought to physiological pH is converted to the compound

of Formula (A) of Formula (B)). A "pharmaceutically acceptable prodrug" is a prodrug that is non-toxic, biologically tolerable, and otherwise biologically suitable for administration to the subject. Illustrative procedures for the selection and preparation of suitable prodrug derivatives are described, for example, in "Design of Prodrugs", ed. H. Bundgaard, Elsevier, 1985.

[0147] The embodiments also relate to pharmaceutically active metabolites of compounds described herein, and uses of such metabolites in the methods provided herein. A "pharmaceutically active metabolite" means a pharmacologically active product of metabolism in the body of a compound described herein or salt thereof. Prodrugs and active metabolites of a compound may be determined using routine techniques known or available in the art. See, e.g., Bertolini et al., *J. Med. Chem.* 1997, 40, 2011-2016; Shan et al., *J. Pharm. Sci.* 1997, 86 (7), 765-767; Bagshawe, *Drug Dev. Res.* 1995, 34, 220-230; Bodor, *Adv. Drug Res.* 1984, 13, 255-331; Bundgaard, *Design of Prodrugs* (Elsevier Press, 1985); and Larsen, *Design and Application of Prodrugs, Drug Design and Development* (Krogsgaard-Larsen et al., eds., Harwood Academic Publishers, 1991).

Chemical Definitions

[0148] The following terms have the following meanings unless otherwise indicated. Any undefined terms have their art recognized meanings.

[0149] The term "alkyl" refers to a straight- or branched-chain univalent saturated hydrocarbon group, or combination thereof, having the number of carbon atoms designated (*i.e.*, C₁-C₁₀ means one to ten carbon atoms). Examples of alkyl groups include, but are not limited to, methyl (Me), ethyl (Et), n-propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl (tBu), pentyl, isopentyl, tert-pentyl, hexyl, isohexyl, and groups that in light of the ordinary skill in the art and the teachings provided herein would be considered equivalent to any one of the foregoing examples.

[0150] The term "alkoxy" refers to an -O-alkyl. Examples of alkoxy include, but are not limited to, methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, iso-butoxy, sec-butoxy, and tert-butoxy.

[0151] The term "alkenyl" refers to an unsaturated straight- or branched-chain hydrocarbon group, or combination thereof, having the indicated number of carbon atoms, and having one or

more double bonds. Examples of alkenyl groups include, but are not limited to, ethenyl (or vinyl), allyl, and but-3-en-1-yl. Included within this term are cis and trans isomers and mixtures thereof.

[0152] The term “alkynyl” refers to an unsaturated straight- or branched-chain hydrocarbon group having the indicated number of carbon atoms (e.g., 2 to 8 or 2 to 6 carbon atoms) and at least one carbon-carbon triple bond. Examples of alkynyl groups include, but are not limited to, acetylenyl ($\text{-C}\equiv\text{CH}$) and propargyl ($\text{-CH}_2\text{C}\equiv\text{CH}$).

[0153] The term “alkylene” refers to a divalent group that is a radical of an alkane. The alkylene can be a straight- or branched-chain divalent alkyl radical. “C₁₋₄ alkylene” refers to alkylene groups with 1 to 4 carbon atoms.

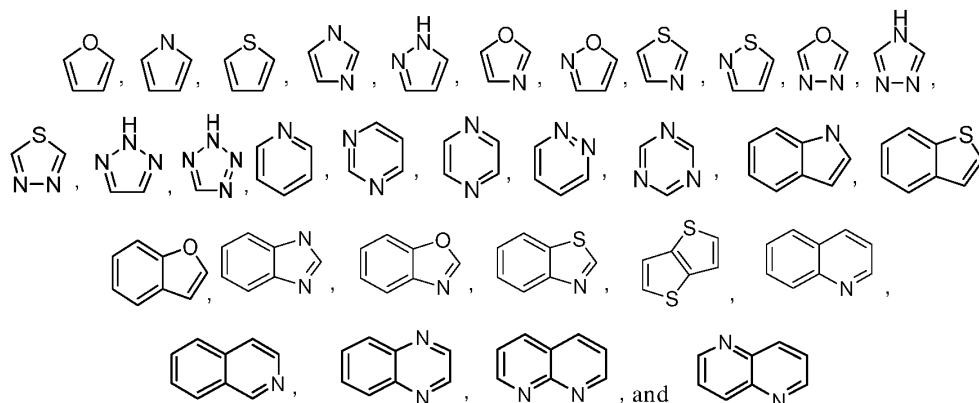
[0154] The term “aryl” refers to a monovalent aromatic carbocyclic group of from 6 to 18 annular carbon atoms having a single ring (a phenyl group) or a multiple condensed ring (such as naphthyl, anthracenyl, or indanyl), in which condensed rings are optionally aromatic, provided that the point of attachment of the aryl group to the parent structure is through an atom of an aromatic ring. “Aryl” as defined herein encompasses groups such as phenyl and fluorenyl.

[0155] The term “cycloalkyl” refers to cyclic hydrocarbon groups of from 3 to 10 annular carbon atoms having single or multiple cyclic rings including fused, bridged, and spiro ring systems. Examples of suitable cycloalkyl groups include, for instance, adamantyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclooctyl and the like. Such cycloalkyl groups include, by way of example, single ring structures such as cyclopropyl, cyclobutyl, cyclopentyl, cyclooctyl, and the like, or multiple ring structures such as adamantanyl, and the like. In some instances, the cycloalkyl is a monocyclic ring. In some instances, cycloalkyl is a 3- to 6-membered ring.

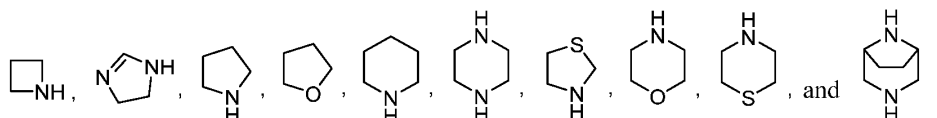
[0156] The term “cycloalkenyl” refers to a cyclic alkenyl group of from 4 to 10 annular carbon atoms having a single cyclic ring and at least one point of internal unsaturation which can be optionally substituted with from 1 to 3 alkyl groups. Examples of suitable cycloalkenyl groups include, for instance, cyclopent-3-enyl, cyclohex-2-enyl, cyclooct-3-enyl and the like.

[0157] The term “haloalkyl” refers to an alkyl group as described above, wherein one or more hydrogen atoms on the alkyl group have been replaced with a halo group. Examples of such groups include, without limitation, fluoroalkyl groups, such as fluoroethyl, trifluoromethyl, difluoromethyl, trifluoroethyl, and the like.

[0158] The term “heteroaryl” refers to a monocyclic, fused bicyclic, or fused polycyclic aromatic heterocycle (ring structure having ring atoms selected from carbon atoms and up to four heteroatoms selected from nitrogen, oxygen, and sulfur) having from 3 to 12 ring atoms per heterocycle. Illustrative examples of heteroaryl groups include the following entities, in the form of properly bonded moieties:



[0159] The terms “heterocyclyl” or “heterocycloalkyl” refer to a saturated or partially unsaturated group having a single ring or multiple condensed rings, including fused, bridged, or spiro ring systems, and having from 3 to 20 ring atoms, including 1 to 10 heteroatoms. These ring atoms are selected from the group consisting of carbon, nitrogen, sulfur, or oxygen. In certain embodiments, the nitrogen and/or sulfur atom(s) of the heterocyclic group are optionally oxidized to provide for N-oxide, -S(O)-, or -SO₂- moieties. Illustrative examples of heterocyclic groups include the following entities, in the form of properly bonded moieties:



[0160] The term “halogen” represents chlorine, fluorine, bromine, or iodine. The term “halo” represents chloro, fluoro, bromo, or iodo.

[0161] The term “oxo” represents a carbonyl oxygen. For example, a cyclopentyl substituted with oxo is cyclopentanone.

[0162] Those skilled in the art will recognize that the species listed or illustrated above are not exhaustive, and that additional species within the scope of these defined terms may also be selected.

[0163] The term “substituted” means that the specified group or moiety bears one or more substituents including, but not limited to, substituents such as alkoxy, acyl, acyloxy, carbonylalkoxy, acylamino, amino, aminoacyl, aminocarbonylamino, aminocarbonyloxy, cycloalkyl, cycloalkenyl, aryl, heteroaryl, aryloxy, cyano, azido, halo, hydroxyl, nitro, carboxyl, thiol, thioalkyl, cycloalkyl, cycloalkenyl, alkyl, alkenyl, alkynyl, heterocyclyl, aralkyl, aminosulfonyl, sulfonylamino, sulfonyl, oxo, carbonylalkylenealkoxy and the like. The term “unsubstituted” means that the specified group bears no substituents. The term “optionally substituted” means that the specified group is unsubstituted or substituted by one or more substituents. Where the term “substituted” is used to describe a structural system, the substitution is meant to occur at any valency-allowed position on the system. When a group or moiety bears more than one substituent, it is understood that the substituents may be the same or different from one another. In some embodiments, a substituted group or moiety bears from one to five substituents. In some embodiments, a substituted group or moiety bears one substituent. In some embodiments, a substituted group or moiety bears two substituents. In some embodiments, a substituted group or moiety bears three substituents. In some embodiments, a substituted group or moiety bears four substituents. In some embodiments, a substituted group or moiety bears five substituents.

[0164] Any formula depicted herein is intended to represent a compound of that structural formula as well as certain variations or forms. For example, a formula given herein is intended to include a racemic form, or one or more enantiomeric, diastereomeric, or geometric isomers, or a mixture thereof. Additionally, any formula given herein is intended to refer also to a hydrate, solvate, or polymorph of such a compound, or a mixture thereof.

[0165] Any formula given herein is also intended to represent unlabeled forms as well as isotopically labeled forms of the compounds. Isotopically labeled compounds have structures depicted by the formulas given herein except that one or more atoms are replaced by an atom having a selected atomic mass or mass number. Examples of isotopes that can be incorporated into compounds of the present disclosure include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, fluorine, chlorine, and iodine, such as ^2H , ^3H , ^{11}C , ^{13}C , ^{14}C , ^{15}N , ^{18}O , ^{17}O ,

³¹P, ³²P, ³⁵S, ¹⁸F, ³⁶Cl, and ¹²⁵I, respectively. Such isotopically labelled compounds are useful in metabolic studies (preferably with ¹⁴C), reaction kinetic studies (with, for example ²H or ³H), detection or imaging techniques [such as positron emission tomography (PET) or single-photon emission computed tomography (SPECT)] including drug or substrate tissue distribution assays, or in radioactive treatment of patients. In particular, an ¹⁸F or ¹¹C labeled compound may be particularly preferred for PET or SPECT studies. PET and SPECT studies may be performed as described, for example, by Brooks, D.J., "Positron Emission Tomography and Single-Photon Emission Computed Tomography in Central Nervous System Drug Development," *NeuroRx* 2005, 2(2), 226-236, and references cited therein. Further, substitution with heavier isotopes such as deuterium (i.e., ²H) may afford certain therapeutic advantages resulting from greater metabolic stability, for example increased *in vivo* half-life or reduced dosage requirements. Isotopically labeled compounds of the present disclosure and prodrugs thereof can generally be prepared by carrying out the procedures disclosed in the schemes or in the examples and preparations described below by substituting a readily available isotopically labeled reagent for a non-isotopically labeled reagent.

[0166] The nomenclature "C_{i-j}" with $j > i$, when applied herein to a class of substituents, is meant to refer to embodiments of the present disclosure for which each and every one of the number of carbon members, from i to j including i and j , is independently realized. By way of example, the term C₁₋₃ refers independently to embodiments that have one carbon member (C₁), embodiments that have two carbon members (C₂), and embodiments that have three carbon members (C₃).

[0167] Any disubstituent referred to herein is meant to encompass the various attachment possibilities when more than one of such possibilities are allowed. For example, reference to disubstituent -A-B-, where $A \neq B$, refers herein to such disubstituent with A attached to a first substituted member and B attached to a second substituted member, and it also refers to such disubstituent with A attached to the second substituted member and B attached to the first substituted member.

[0168] The present disclosure also includes pharmaceutically acceptable salts of the compounds represented by Formula (A) and Formula (B), or the compounds of Table 1A and Table 1B, and pharmaceutical compositions comprising such salts, and methods of using such salts.

[0169] A “pharmaceutically acceptable salt” is intended to mean a salt of a free acid or base of a compound represented herein that is non-toxic, biologically tolerable, or otherwise biologically suitable for administration to the subject. See, generally, S.M. Berge, et al., “Pharmaceutical Salts,” J. Pharm. Sci., 1977, 66, 1-19. Particular pharmaceutically acceptable salts are those that are pharmacologically effective and suitable for contact with the tissues of subjects without undue toxicity, irritation, or allergic response. A compound described herein may possess a sufficiently acidic group, a sufficiently basic group, both types of functional groups, or more than one of each type, and accordingly react with a number of inorganic or organic bases, and inorganic and organic acids, to form a pharmaceutically acceptable salt.

[0170] Examples of pharmaceutically acceptable salts include sulfates, pyrosulfates, bisulfates, sulfites, bisulfites, phosphates, monohydrogen-phosphates, dihydrogenphosphates, metaphosphates, pyrophosphates, chlorides, bromides, iodides, acetates, propionates, decanoates, caprylates, acrylates, formates, isobutyrate, caproates, heptanoates, propiolates, oxalates, malonates, succinates, suberates, sebacates, fumarates, maleates, butyne-1,4-dioates, hexyne-1,6-dioates, benzoates, chlorobenzoates, methylbenzoates, dinitrobenzoates, hydroxybenzoates, methoxybenzoates, phthalates, sulfonates, methylsulfonates, propylsulfonates, besylates, xylenesulfonates, naphthalene-1-sulfonates, naphthalene-2-sulfonates, phenylacetates, phenylpropionates, phenylbutyrates, citrates, lactates, γ -hydroxybutyrates, glycolates, tartrates, and mandelates. Lists of other suitable pharmaceutically acceptable salts are found in Remington's Pharmaceutical Sciences, 17th Edition, Mack Publishing Company, Easton, Pa., 1985.

[0171] For a compound of Formula (A) or Formula (B), or a compound of Table 1A or Table 1B that contains a basic nitrogen, a pharmaceutically acceptable salt may be prepared by any suitable method available in the art, for example, treatment of the free base with an inorganic acid, such as hydrochloric acid, hydrobromic acid, sulfuric acid, sulfamic acid, nitric acid, boric acid, phosphoric acid, and the like, or with an organic acid, such as acetic acid, phenylacetic acid, propionic acid, stearic acid, lactic acid, ascorbic acid, maleic acid, hydroxymaleic acid, isethionic acid, succinic acid, valeric acid, fumaric acid, malonic acid, pyruvic acid, oxalic acid, glycolic acid, salicylic acid, oleic acid, palmitic acid, lauric acid, a pyranosidyl acid, such as glucuronic acid or galacturonic acid, an alpha-hydroxy acid, such as mandelic acid, citric acid, or tartaric acid, an amino acid, such as aspartic acid or glutamic acid, an aromatic acid, such as

benzoic acid, 2-acetoxybenzoic acid, naphthoic acid, or cinnamic acid, a sulfonic acid, such as laurylsulfonic acid, p-toluenesulfonic acid, methanesulfonic acid, or ethanesulfonic acid, or any compatible mixture of acids such as those given as examples herein, and any other acid and mixture thereof that are regarded as equivalents or acceptable substitutes in light of the ordinary level of skill in this technology.

[0172] The present disclosure also relates to pharmaceutically acceptable prodrugs of the compounds of Formula (A) or Formula (B), or the compounds of Table 1A and Table 1B, and treatment methods employing such pharmaceutically acceptable prodrugs. The term "prodrug" means a precursor of a designated compound that, following administration to a subject, yields the compound *in vivo* via a chemical or physiological process such as solvolysis or enzymatic cleavage, or under physiological conditions (e.g., a prodrug on being brought to physiological pH is converted to the formula compound). A "pharmaceutically acceptable prodrug" is a prodrug that is non-toxic, biologically tolerable, and otherwise biologically suitable for administration to the subject. Illustrative procedures for the selection and preparation of suitable prodrug derivatives are described, for example, in "Design of Prodrugs", ed. H. Bundgaard, Elsevier, 1985.

[0173] The present disclosure also relates to pharmaceutically active metabolites of compounds of Formula (A) or Formula (B), or the compounds of Table 1A and Table 1B, and uses of such metabolites in the methods provided herein. A "pharmaceutically active metabolite" means a pharmacologically active product of metabolism in the body of a compound of Formula (A) or Formula (B), or the compounds of Table 1A and Table 1B, or a salt of any of the foregoing. Prodrugs and active metabolites of a compound may be determined using routine techniques known or available in the art. See, e.g., Bertolini et al., *J. Med. Chem.* 1997, 40, 2011-2016; Shan et al., *J. Pharm. Sci.* 1997, 86 (7), 765-767; Bagshawe, *Drug Dev. Res.* 1995, 34, 220-230; Bodor, *Adv. Drug Res.* 1984, 13, 255-331; Bundgaard, *Design of Prodrugs* (Elsevier Press, 1985); and Larsen, *Design and Application of Prodrugs*, Drug Design and Development (Krogsgaard-Larsen et al., eds., Harwood Academic Publishers, 1991).

Pharmaceutical Compositions

[0174] For treatment purposes, pharmaceutical compositions comprising the compounds described herein may further comprise one or more pharmaceutically-acceptable excipients. A

pharmaceutically-acceptable excipient is a substance that is non-toxic and otherwise biologically suitable for administration to a subject. Such excipients facilitate administration of the compounds described herein and are compatible with the active ingredient. Examples of pharmaceutically-acceptable excipients include stabilizers, lubricants, surfactants, diluents, anti-oxidants, binders, coloring agents, bulking agents, emulsifiers, or taste-modifying agents. In particular embodiments, pharmaceutical compositions according to the present disclosure are sterile compositions. Pharmaceutical compositions may be prepared using compounding techniques known or that become available to those skilled in the art.

[0175] Sterile compositions are also contemplated by the present disclosure, including compositions that are in accord with national and local regulations governing such compositions.

[0176] The pharmaceutical compositions and compounds described herein may be formulated as solutions, emulsions, suspensions, or dispersions in suitable pharmaceutical solvents or carriers, or as pills, tablets, lozenges, suppositories, sachets, dragees, granules, powders, powders for reconstitution, or capsules along with solid carriers according to conventional methods known in the art for preparation of various dosage forms. Pharmaceutical compositions of the present disclosure may be administered by a suitable route of delivery, such as oral, parenteral, rectal, nasal, topical, or ocular routes, or by inhalation. In some embodiments, the compositions are formulated for intravenous or oral administration.

[0177] For oral administration, the compounds of the present disclosure may be provided in a solid form, such as a tablet or capsule, or as a solution, emulsion, or suspension. To prepare the oral compositions, the compounds of the present disclosure may be formulated to yield a dosage of, *e.g.*, from about 0.01 to about 50 mg/kg daily, or from about 0.05 to about 20 mg/kg daily, or from about 0.1 to about 10 mg/kg daily. Additional dosages include from about 0.1 mg to 1 g daily, from about 1 mg to about 10 mg daily, from about 10 mg to about 50 mg daily, from about 50 mg to about 250 mg daily, or from about 250 mg to 1 g daily. Oral tablets may include the active ingredient(s) mixed with compatible pharmaceutically acceptable excipients such as diluents, disintegrating agents, binding agents, lubricating agents, sweetening agents, flavoring agents, coloring agents and preservative agents. Suitable inert fillers include sodium and calcium carbonate, sodium and calcium phosphate, lactose, starch, sugar, glucose, methyl cellulose, magnesium stearate, mannitol, sorbitol, and the like. Exemplary liquid oral excipients include ethanol, glycerol, water, and the like. Starch, polyvinyl-pyrrolidone (PVP), sodium

starch glycolate, microcrystalline cellulose, and alginic acid are exemplary disintegrating agents. Binding agents may include starch and gelatin. The lubricating agent, if present, may be magnesium stearate, stearic acid, or talc. If desired, the tablets may be coated with a material such as glyceryl monostearate or glyceryl distearate to delay absorption in the gastrointestinal tract, or may be coated with an enteric coating.

[0178] Capsules for oral administration include hard and soft gelatin capsules. To prepare hard gelatin capsules, active ingredient(s) may be mixed with a solid, semi-solid, or liquid diluent. Soft gelatin capsules may be prepared by mixing the active ingredient with water, an oil such as peanut oil or olive oil, liquid paraffin, a mixture of mono and di-glycerides of short chain fatty acids, polyethylene glycol 400, or propylene glycol.

[0179] Liquids for oral administration may be in the form of suspensions, solutions, emulsions, or syrups, or may be lyophilized or presented as a dry product for reconstitution with water or other suitable vehicle before use. Such liquid compositions may optionally contain: pharmaceutically-acceptable excipients such as suspending agents (for example, sorbitol, methyl cellulose, sodium alginate, gelatin, hydroxyethylcellulose, carboxymethylcellulose, aluminum stearate gel and the like); non-aqueous vehicles, e.g., oil (for example, almond oil or fractionated coconut oil), propylene glycol, ethyl alcohol, or water; preservatives (for example, methyl or propyl p-hydroxybenzoate or sorbic acid); wetting agents such as lecithin; and, if desired, flavoring or coloring agents.

[0180] The inventive compositions may be formulated for rectal administration as a suppository. For parenteral use, including intravenous, intramuscular, intraperitoneal, intranasal, or subcutaneous routes, the agents of the present disclosure may be provided in sterile aqueous solutions or suspensions, buffered to an appropriate pH and isotonicity or in parenterally acceptable oil. Suitable aqueous vehicles include Ringer's solution and isotonic sodium chloride. Such forms may be presented in unit-dose form such as ampoules or disposable injection devices, in multi-dose forms such as vials from which the appropriate dose may be withdrawn, or in a solid form or pre-concentrate that can be used to prepare an injectable formulation. Illustrative infusion doses range from about 1 to 1000 $\mu\text{g/kg/minute}$ of agent admixed with a pharmaceutical carrier over a period ranging from several minutes to several days.

[0181] For nasal, inhaled, or oral administration, the inventive pharmaceutical compositions may be administered using, for example, a spray formulation also containing a suitable carrier.

[0182] For topical applications, the compounds of the present disclosure may be formulated as creams or ointments or a similar vehicle suitable for topical administration. For topical administration, the inventive compounds may be mixed with a pharmaceutical carrier at a concentration of about 0.1% to about 10% of drug to vehicle. Another mode of administering the agents of the present disclosure may utilize a patch formulation to effect transdermal delivery.

[0183] As used herein, “treatment” or “treating” is an approach for obtaining a beneficial or desired result, including clinical results. For purposes of this disclosure, beneficial or desired results include, but are not limited to: reducing the severity of or suppressing the worsening of a disease, symptom, or condition, alleviating a symptom and/or diminishing the extent of a symptom and/or preventing a worsening of a symptom associated with a condition, arresting the development of a disease, symptom, or condition, relieving the disease, symptom, or condition, causing regression of the disease, disorder, or symptom (in terms of severity or frequency of negative symptoms), or stopping the symptoms of the disease or condition. Beneficial or desired results can also be slowing, halting, or reversing the progressive course of a disease or condition. For example, beneficial effects may include slowing the progression of Parkinson’s disease from an earlier stage (e.g., prodromal stage or stage 1, 2 or 3) to a later stage (e.g., stage 4 or 5), or halting Parkinson’s disease at a prodromal or early stage.

[0184] As used herein, “delaying” development of a disease or condition means to defer, hinder, slow, retard, stabilize and/or postpone development of the disease or condition. This delay can be of varying lengths of time, depending on the history of the disease and/or individual being treated. As is evident to one skilled in the art, a sufficient or significant delay can, in effect, encompass prevention, in that the individual does not develop the disease or condition. For example, a method that “delays” development of Parkinson’s disease (e.g., in a prodromal individual) is a method that reduces probability of disease development in a given time frame and/or reduces extent of the disease in a given time frame, when compared to not using the method.

[0185] The term “subject” refers to a mammalian patient in need of such treatment, such as a human. A “subject” may be a human, or may be a cat, dog, cow, rat, mouse, horse, rabbit, or other domesticated mammal.

[0186] Exemplary diseases that are characterized by protein aggregation include Alzheimer’s disease, Parkinson’s disease, fronto-temporal dementia, dementia with Lewy bodies (Lewy body disease), Parkinson’s disease with dementia, multiple system atrophy, amyotrophic lateral sclerosis, Huntington’s disease, Progressive Supranuclear Palsy (PSP), and Niemann-Pick disease type C, as well inflammatory diseases, such as asthma, chronic obstructive pulmonary disease (COPD), chronic peptic ulcers, irritable bowel disease, tuberculosis, rheumatoid arthritis, osteoarthritis, chronic sinusitis, hepatitis (such as hepatitis B or C), gout, lupus, pleurisy, eczema, gastritis, psoriasis, psoriatic arthritis, vasculitis, laryngitis, allergic reactions, multiple sclerosis, Crohn’s disease, traumatic brain injury, CIDP (chronic inflammatory demyelinating polyneuropathy), stroke, ischemic heart disease, atopic dermatitis, acne vulgaris, rosacea, non-alcoholic fatty liver disease, non-alcoholic steatohepatitis, corneal wounds, corneal disorders, corneal HSV, Stargardt disease (Juvenile macular degeneration), age-related macular degeneration, sepsis, diabetic wounds, herpes simplex virus, and anti-fungal, anti-bacterial, antiviral and antitumor diseases or conditions.

[0187] In one aspect, the compounds and pharmaceutical compositions of the present disclosure specifically target TLR2 protein dimers. Thus, these compounds and pharmaceutical compositions can be used to prevent, reverse, slow, or inhibit dimerization of TLR2 proteins with other natural protein ligands, and are used in methods of the present disclosure to treat neurological and inflammatory diseases related to or caused by such dimerization. In some embodiments, methods of treatment target Parkinson’s disease, Alzheimer’s disease, Lewy body disease, multiple system atrophy, atopic dermatitis, traumatic brain injury, or multiple sclerosis. The compounds, compositions, and method of the present disclosure are also used to mitigate deleterious effects that are secondary to protein dimerization and/or misfolding, such as neuronal cell death. In another aspect, the compounds and pharmaceutical compositions of the present disclosure are inhibitors of TLR9. In some embodiments, the compounds and pharmaceutical compositions of the present disclosure are used in methods of the present disclosure to treat central nervous system (CNS) and peripheral disorders. In some embodiments, methods of

treatment target Parkinson's disease, Amyotrophic lateral sclerosis, Guillain-Barre syndrome, spinal cord injury, multiple sclerosis, multiple forms of tissue injury, chronic pain, or psoriasis.

[0188] In some aspects, the compounds, compositions, and methods of the present disclosure are used to inhibit TLR2 dimerization. In alternative aspects, the compounds, compositions, and methods of the present disclosure are used to inhibit TLR2 dimerization with TLR1, or with TLR6, or both.

[0189] In the inhibitory methods of the present disclosure, an "effective amount" means an amount sufficient to reduce, slow the progression of, or reverse TLR2 dimerization. Measuring the amount of dimerization may be performed by routine analytical methods such as those described below. Such modulation is useful in a variety of settings, including *in vitro* assays. In some embodiments of such methods, the cell is a nerve cell or an HEK or THP cell.

[0190] In treatment methods according to the present disclosure, an "effective amount" means an amount or dose sufficient to generally bring about the desired therapeutic benefit in subjects needing such treatment. Effective amounts or doses of the compounds of the present disclosure may be ascertained by routine methods, such as modeling, dose escalation, or clinical trials, taking into account routine factors, e.g., the mode or route of administration or drug delivery, the pharmacokinetics of the agent, the severity and course of the infection, the subject's health status, condition, and weight, and the judgment of the treating physician. An exemplary dose is in the range of about 1 µg to 2 mg of active agent per kilogram of subject's body weight per day, such as about 0.05 to 100 mg/kg/day, or about 1 to 35 mg/kg/day, or about 0.1 to 10 mg/kg/day. In alternative embodiments an exemplary dose is in the range of about 1 mg to about 1 g per day, or about 1-500, 1-250, 1-100, 1-50, 50-500, or 250-500 mg per day. The total dosage may be given in single or divided dosage units (e.g., BID, TID, QID).

[0191] Once improvement of the patient's disease has occurred, the dose may be adjusted for preventative or maintenance treatment. For example, the dosage or the frequency of administration, or both, may be reduced as a function of the symptoms, to a level at which the desired therapeutic or prophylactic effect is maintained. Of course, if symptoms have been alleviated to an appropriate level, treatment may cease. Patients may, however, require intermittent treatment on a long-term basis upon any recurrence of symptoms. Patients may also require chronic treatment on a long-term basis.

Drug Combinations

[0192] The inventive compounds described herein may be used in pharmaceutical compositions or methods in combination with one or more additional active ingredients in the treatment of neurodegenerative disorders. Further additional active ingredients for cancer applications include other cancer therapeutics or agents that mitigate adverse effects of cancer chemotherapeutic agents. Such combinations may serve to increase efficacy, ameliorate other disease symptoms, decrease one or more side effects, or decrease the required dose of an inventive compound. The additional active ingredients may be administered in a separate pharmaceutical composition from a compound of the present disclosure or may be included with a compound of the present disclosure in a single pharmaceutical composition. The additional active ingredients may be administered simultaneously with, prior to, or after administration of a compound of the present disclosure.

[0193] Combination agents include additional active ingredients are those that are known or discovered to be effective in treating the diseases, disorders, conditions, and symptoms discussed herein, including those active against another target associated with the disease, disorder, or symptom such as but not limited to, a) compounds that address protein misfolding (such as drugs which reduce the production of these proteins, which increase their clearance or which alter their aggregation and/or propagation); b) compounds that treat symptoms of such disorders (e.g., dopamine replacement therapies); and c) drugs that act as neuroprotectants by complementary mechanisms (e.g., those targeting autophagy, those that are anti-oxidants, and those acting by other mechanisms such as adenosine A2A antagonists).

[0194] For example, compositions and formulations of the present disclosure, as well as methods of treatment, can further comprise other drugs or pharmaceuticals, e.g., other active agents useful for treating or palliative for a neurological or inflammatory diseases related to or caused by TLR2 dimerization, e.g., Parkinson's disease, Alzheimer's Disease (AD), Lewy body disease (LBD) and multiple system atrophy (MSA), or related symptoms or conditions. For example, the pharmaceutical compositions of the present disclosure may additionally comprise one or more of such active agents, and methods of treatment may additionally comprise administering an effective amount of one or more of such active agents. In certain embodiments, additional active agents may be antibiotics (e.g., antibacterial or bacteriostatic

peptides or proteins), e.g., those effective against gram positive or negative bacteria, fluids, cytokines, immunoregulatory agents, anti-inflammatory agents, complement activating agents, such as peptides or proteins comprising collagen-like domains or fibrinogen-like domains (e.g., a ficolin), carbohydrate-binding domains, and the like and combinations thereof. Additional active agents include those useful in such compositions and methods include dopamine therapy drugs, catechol-O-methyl transferase (COMT) inhibitors, monamine oxidase inhibitors, cognition enhancers (such as acetylcholinesterase inhibitors or memantine), adenosine 2A receptor antagonists, beta-secretase inhibitors, or gamma-secretase inhibitors. In particular embodiments, at least one compound of the present disclosure may be combined in a pharmaceutical composition or a method of treatment with one or more drugs selected from the group consisting of: tacrine (Cognex), donepezil (Aricept), rivastigmine (Exelon) galantamine (Reminyl), physostigmine, neostigmine, Icopezil (CP-118954, 5,7-dihydro-3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]-6H-pyrrolo-[4,5-f]-1,2-benzisoxazol-6-one maleate), ER-127528 (4-[(5,6-dimethoxy-2-fluoro-1-indanon)-2-yl]methyl-1-(3-fluorobenzyl)piperidine hydrochloride), zanapezil (TAK-147; 3-[1-(phenylmethyl)piperidin-4-yl]-1-(2,3,4,5-tetrahydro-1H-1-benzazepin-8-yl)-1-propane fumarate), Metrifonate (T-588; (-)-R-.alpha.-[[2-(dimethylamino)ethoxy]methyl] benzo[b]thiophene-5-methanol hydrochloride), FK-960 (N-(4-acetyl-1-piperazinyl)-p-fluorobenzamide-hydrate), TCH-346 (N-methyl-N-2-pyropinyldibenz[b,f]oxepine-10-methanamine), SDZ-220-581 ((S)-alpha-amino-5-(phosphonomethyl)-[1,1'-biphenyl]-3-propionic acid), memantine (Namenda/Exiba) and 1,3,3,5,5-pentamethylcyclohexan-1-amine (Neramexane), tarenflurbil (Flurizan), tramiprosate (Alzhemed), clioquinol, PBT-2 (an 8-hydroxyquinilone derivative), 1-(2-(2-Naphthyl)ethyl)-4-(3-trifluoromethylphenyl)-1,2,3,6-tetrahydropyridine, Huperzine A, posatiorelin, leuprolide or derivatives thereof, ispronicline, (3-aminopropyl)(n-butyl)phosphinic acid (SGS-742), N-methyl-5-(3-(5-isopropoxy-pyridinyl))-4-penten-2-amine (ispronicline), 1-decanaminium, N-(2-hydroxy-3-sulfopropyl)-N-methyl-N-octyl-, inner salt (zt-1), salicylates, aspirin, amoxiprin, benorilate, choline magnesium salicylate, diflunisal, faislamine, methyl salicylate, magnesium salicylate, salicyl salicylate, diclofenac, aceclofenac, acemetacin, bromfenac, etodolac, indometacin, nabumetone, sulindac, tolmetin, ibuprofen, carprofen, fenbufen, fenoprofen, flurbiprofen, ketoprofen, ketorolac, loxoprofen, naproxen, tiaprofenic acid, suprofen, mefenamic acid, meclofenamic acid, phenylbutazone, azapropazone, metamizole, oxyphenbutazone, sulfinprazone, piroxicam, lornoxicam, meloxicam, tenoxicam, celecoxib, etoricoxib,

lumiracoxib, parecoxib, rofecoxib, valdecoxib, nimesulide, arylalkanoic acids, 2-arylpropionic acids (profens), N-arylanthranilic acids (fenamic acids), pyrazolidine derivatives, oxicams, COX-2 inhibitors, sulphonanilides, essential fatty acids, and Minozac (2-(4-(4-methyl-6-phenylpyridazin-3-yl)piperazin-1-yl)pyrimidine dihydrochloride hydrate), or a combination thereof.

Methods of Use

[0195] The compounds and pharmaceutical compositions herein may be used to treat or prevent a disease or condition in an individual. In some embodiments, provided are methods of treating a disease or condition associated with TLR2 heterodimerization, comprising administering to the individual in need thereof a compound of Formula (A) or Formula (B), or a compound of Table 1A or Table 1B, or a tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing. In some embodiments, provided are methods of treating a disease or condition associated with TLR2 heterodimerization comprising administering to the subject a therapeutically effective amount of at least one chemical entity as described herein.

[0196] In some embodiments, provided are compositions containing one or more compounds of Formula (A) or Formula (B), or a compound of Table 1A or Table 1B, or a tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, for use in the treatment of a disease or condition associated with TLR2 heterodimerization. In some embodiments, provided are compositions containing at least one chemical entity as described herein for use in the treatment of a disease or condition associated with TLR2 heterodimerization.

[0197] Also provided herein is the use of a compound of Formula (A) or Formula (B), or a compound of Table 1A or Table 1B, or a tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, in the manufacture of a medicament for treatment of a disease or condition associated with TLR2 heterodimerization. In some embodiments, provided is the use of at least one chemical entity as described herein in the manufacture of a medicament for treatment of a disease or condition associated with TLR2 heterodimerization.

[0198] In some embodiments, the disease or condition is selected from Alzheimer's disease, Parkinson's disease, fronto-temporal dementia, dementia with Lewy bodies (Lewy body

disease), Parkinson's disease with dementia, multiple system atrophy, amyotrophic lateral sclerosis, Huntington's disease, Progressive Supranuclear Palsy (PSP), Niemann-Pick disease type C, inflammatory diseases, asthma, chronic obstructive pulmonary disease (COPD), chronic peptic ulcers, irritable bowel disease, tuberculosis, rheumatoid arthritis, osteoarthritis, chronic sinusitis, hepatitis, hepatitis B, hepatitis C, gout, lupus, pleurisy, eczema, gastritis, psoriasis, psoriatic arthritis, vasculitis, laryngitis, allergic reactions, multiple sclerosis, Crohn's disease, traumatic brain injury, CIDP (chronic inflammatory demyelinating polyneuropathy), stroke, ischemic heart disease, atopic dermatitis, acne vulgaris, rosacea, non-alcoholic fatty liver disease, non-alcoholic steatohepatitis, corneal wounds, corneal disorders, corneal HSV, Stargardt disease (Juvenile macular degeneration), age-related macular degeneration, sepsis, diabetic wounds, herpes simplex virus, and anti-fungal, anti-bacterial, antiviral and antitumor diseases or conditions. In some embodiments, the disease or condition is selected from Alzheimer's disease, Parkinson's disease, fronto-temporal dementia, dementia with Lewy bodies (Lewy body disease), Parkinson's disease with dementia, multiple system atrophy, amyotrophic lateral sclerosis, Huntington's disease, inflammatory diseases, asthma, chronic obstructive pulmonary disease (COPD), chronic peptic ulcers, tuberculosis, rheumatoid arthritis, chronic sinusitis, hepatitis, hepatitis B, hepatitis C, gout, lupus, pleurisy, eczema, gastritis, psoriasis, psoriatic arthritis, vasculitis, laryngitis, allergic reactions, multiple sclerosis, Crohn's disease, and traumatic brain injury.

[0199] Also provided are methods for interfering with the heterodimerization of TLR2 in a cell, or modulating, preventing, slowing, reversing, or inhibiting TLR2 heterodimerization in a cell which involves contacting the cell with an effective amount of at least one compound of Formula (A) or Formula (B), or a compound of Table 1A or Table 1B, or a tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing. In some embodiments, provided are methods for interfering with the heterodimerization of TLR2 in a cell, or modulating, preventing, slowing, reversing, or inhibiting TLR2 heterodimerization in a cell which involves contacting the cell with an effective amount of at least one chemical entity as described herein. In some embodiments, provided are methods of inhibiting TLR2 activation in a cell, comprising contacting the cell with an effective amount of at least one compound of Formula (A) or Formula (B), or a compound of Table 1A or Table 1B, or a tautomer thereof, or a pharmaceutically

acceptable salt of any of the foregoing, or a pharmaceutical composition comprising any of the foregoing, wherein the contacting is *in vitro*, *ex vivo*, or *in vivo*.

[0200] Also provided herein are compositions containing one or more compounds of Formula (A) or Formula (B), or a compound of Table 1A or Table 1B, or a tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, for use in interfering with the heterodimerization of TLR2 in a cell, or modulating, preventing, slowing, reversing, or inhibiting TLR2 heterodimerization in a cell. In some embodiments, provided are compositions containing at least one chemical entity as described herein for use in interfering with the heterodimerization of TLR2 in a cell, or modulating, preventing, slowing, reversing, or inhibiting TLR2 heterodimerization in a cell.

[0201] Additionally provided herein is the use of at least one chemical entity as described herein, such as a compound of Formula (A) or Formula (B), or a compound of Table 1A or Table 1B, or a tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, in the manufacture of a medicament for interfering with the heterodimerization of TLR2, or modulating, preventing, slowing, reversing, or inhibiting TLR2 heterodimerization.

[0202] In some embodiments, provided are methods of treating a disease or condition associated with inhibition of TLR9, comprising administering to the individual in need thereof a compound of Formula (A) or Formula (B), or a compound of Table 1A or Table 1B, or a tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing.

[0203] In some embodiments, provided are compositions containing one or more compounds of Formula (A) or Formula (B), or a compound of Table 1A or Table 1B, or a tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, for use in the treatment of a disease or condition associated with inhibition of TLR9. In some embodiments, provided are compositions containing at least one chemical entity as described herein for use in the treatment of a disease or condition associated with inhibition of TLR9.

[0204] Also provided herein is the use of a compound of Formula (A) or Formula (B), or a compound of Table 1A or Table 1B, or a tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, in the manufacture of a medicament for treatment of a disease or condition associated with inhibition of TLR9. In some embodiments, provided is the use of at

least one chemical entity as described herein in the manufacture of a medicament for treatment of a disease or condition associated with inhibition of TLR9.

[0205] In some embodiments, the disease or condition is central nervous system (CNS) or peripheral disorder. In some embodiments, the disease or condition is Parkinson's disease, Amyotrophic lateral sclerosis, Guillain-Barre syndrome, spinal cord injury, multiple sclerosis, multiple forms of tissue injury, chronic pain, or psoriasis.

[0206] Also provided are methods of inhibiting TLR9 in a cell, which involves contacting the cell with an effective amount of at least one compound of Formula (A) or Formula (B), or a compound of Table 1A or Table 1B, or a tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing. In some embodiments, provided are methods for inhibiting TLR9 in a cell, which involves contacting the cell with an effective amount of at least one chemical entity as described herein. In some embodiments, provided are methods of inhibiting TLR9 activation in a cell, comprising contacting the cell with an effective amount of at least one compound of Formula (A) or Formula (B), or a compound of Table 1A or Table 1B, or a tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or a pharmaceutical composition comprising any of the foregoing, wherein the contacting is *in vitro*, *ex vivo*, or *in vivo*.

[0207] Also provided herein are compositions containing one or more compounds of Formula (A) or Formula (B), or a compound of Table 1A or Table 1B, or a tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, for use in inhibiting TLR9 in a cell. In some embodiments, provided are compositions containing at least one chemical entity as described herein for use in inhibiting TLR9 in a cell.

[0208] Additionally provided herein is the use of at least one chemical entity as described herein, such as a compound of Formula (A) or Formula (B), or a compound of Table 1A or Table 1B, or a tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, in the manufacture of a medicament for inhibiting TLR9.

[0209] In some embodiments, compounds described herein, such as a compound of Formula (A) or Formula (B), or a compound of Table 1A or Table 1B, or a tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, inhibit both TLR2 and TLR9. In some embodiments, provided are methods of treating a disease or condition associated with TLR2 heterodimerization and/or inhibition of TLR9, comprising administering to the individual in

need thereof a compound of Formula (A) or Formula (B), or a compound of Table 1A or Table 1B, or a tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing. In some embodiments, provided are methods of treating a disease or condition associated with TLR2 heterodimerization and/or inhibition of TLR9 comprising administering to the subject a therapeutically effective amount of at least one chemical entity as described herein.

[0210] In some embodiments, provided are compositions containing one or more compounds of Formula (A) or Formula (B), or a compound of Table 1A or Table 1B, or a tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, for use in the treatment of a disease or condition associated with TLR2 heterodimerization and/or inhibition of TLR9. In some embodiments, provided are compositions containing at least one chemical entity as described herein for use in the treatment of a disease or condition associated with TLR2 heterodimerization and/or inhibition of TLR9.

[0211] Also provided herein is the use of a compound of Formula (A) or Formula (B), or a compound of Table 1A or Table 1B, or a tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, in the manufacture of a medicament for treatment of a disease or condition associated with TLR2 heterodimerization and/or inhibition of TLR9. In some embodiments, provided is the use of at least one chemical entity as described herein in the manufacture of a medicament for treatment of a disease or condition associated with TLR2 heterodimerization and/or inhibition of TLR9.

Kits

[0212] Also provided are articles of manufacture and kits containing any of the compounds or pharmaceutical compositions provided herein. The article of manufacture may comprise a container with a label. Suitable containers include, for example, bottles, vials, and test tubes. The containers may be formed from a variety of materials such as glass or plastic. The container may hold a pharmaceutical composition provided herein. The label on the container may indicate that the pharmaceutical composition is used for preventing, treating or suppressing a condition described herein, and may also indicate directions for either *in vivo* or *in vitro* use.

[0213] In one aspect, provided herein are kits containing a compound or composition described herein and instructions for use. The kits may contain instructions for use in the

treatment of a disease or condition associated with TLR2 heterodimerization in an individual in need thereof and/or instructions for use in the treatment of a disease or condition associated with inhibition of TLR9 in an individual in need thereof. A kit may additionally contain any materials or equipment that may be used in the administration of the compound or composition, such as vials, syringes, or IV bags. A kit may also contain sterile packaging.

General Synthetic methods

[0214] The compounds of the present disclosure may be prepared by a number of processes as generally described below and more specifically in the Examples hereinafter (such as the schemes provided in the Examples below). In the following process descriptions, the symbols when used in the formulae depicted are to be understood to represent those groups described above in relation to the formulae herein.

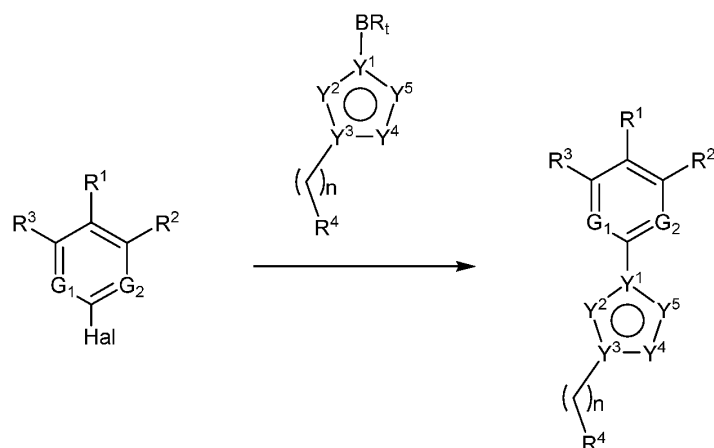
[0215] Where it is desired to obtain a particular enantiomer of a compound, this may be accomplished from a corresponding mixture of enantiomers using any suitable conventional procedure for separating or resolving enantiomers. Thus, for example, diastereomeric derivatives may be produced by reaction of a mixture of enantiomers, *e.g.*, a racemate, and an appropriate chiral compound. The diastereomers may then be separated by any convenient means, for example by crystallization and the desired enantiomer recovered. In another resolution process, a racemate may be separated using chiral High Performance Liquid Chromatography. Alternatively, if desired a particular enantiomer may be obtained by using an appropriate chiral intermediate in one of the processes described.

[0216] Chromatography, recrystallization and other conventional separation procedures may also be used with intermediates or final products where it is desired to obtain a particular isomer of a compound or to otherwise purify a product of a reaction.

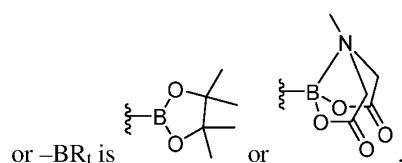
[0217] Solvates of a compound provided herein or a pharmaceutically acceptable salt thereof are also contemplated. Solvates contain either stoichiometric or non-stoichiometric amounts of a solvent, and are often formed during the process of crystallization. Hydrates are formed when the solvent is water, or alcoholates are formed when the solvent is alcohol.

[0218] In some embodiments, compounds of the Formula (A) may be synthesized according to Scheme A-1.

Scheme A-1.

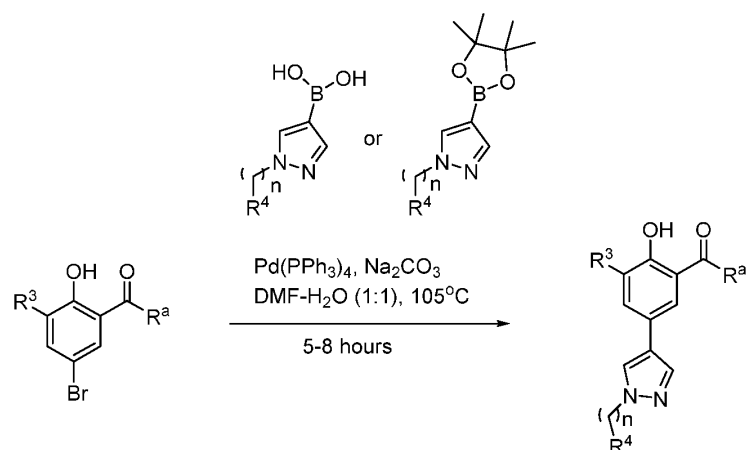


wherein R^1 , R^2 , R^3 , R^4 , G_1 , G_2 , Y^1 , Y^2 , Y^3 , Y^4 , Y^5 , and n are as defined for Formula (A), or any variation thereof detailed herein; Hal is a halogen; t is 2 or 3; and R is $-OH$, $-Oalkyl$, or halogen,



[0219] In some variations of the foregoing Scheme A-1, compounds of the Formula (A) may be synthesized according to Scheme A-1a.

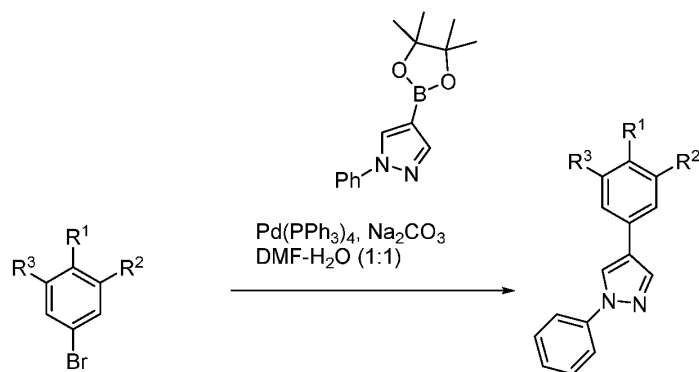
Scheme A-1a.



wherein R^3 , R^4 , R^a , and n are as defined for Formula (A), or any variation thereof detailed herein.

[0220] In some variations of the foregoing Scheme A-1, compounds of the Formula (A) may be synthesized according to Scheme A-1b.

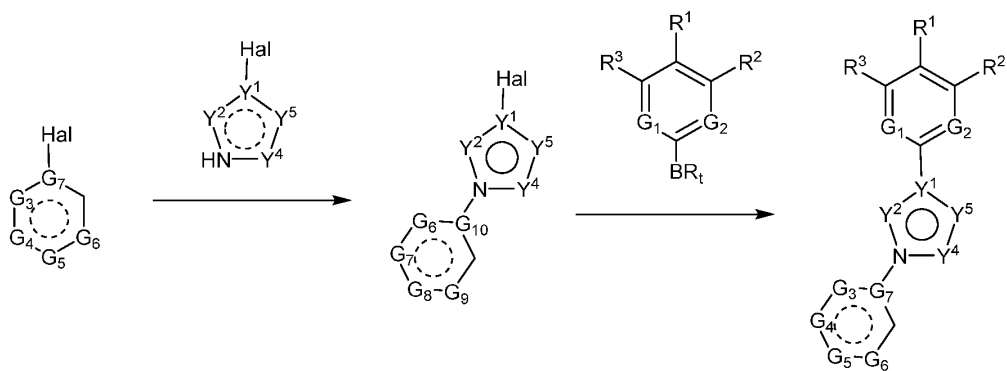
Scheme A-1b.



wherein R^1 , R^2 , and R^3 are as defined for Formula (A), or any variation thereof detailed herein

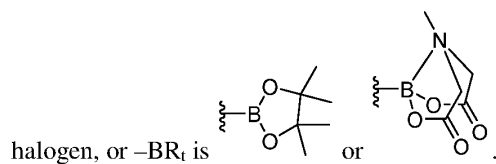
[0221] In some embodiments, compounds of the Formula (A) may be synthesized according to Scheme A-2.

Scheme A-2.



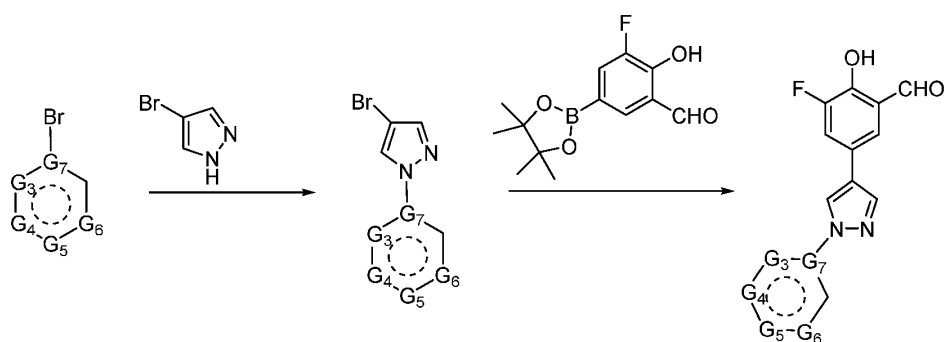
wherein R^1 , R^2 , R^3 , Y^1 , Y^2 , Y^4 , Y^5 , G_1 , G_2 , G_3 , G_4 , G_5 , G_6 , and G_7 are as defined for Formula (A),

or any variation thereof detailed herein; Hal is a halogen; t is 2 or 3; and R is -OH, -Oalkyl, or



[0222] In some variations of the foregoing Scheme A-2, compounds of the Formula (A) may be synthesized according to Scheme A-2a.

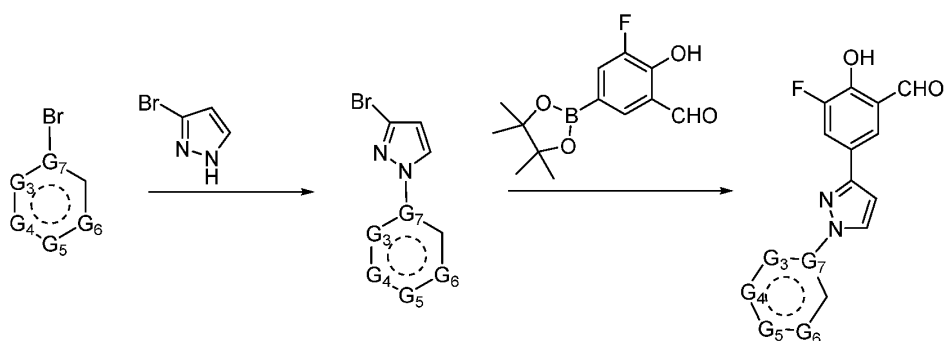
Scheme A-2a.



wherein G₃, G₄, G₅, G₆, and G₇ are as defined for Formula (A), or any variation thereof detailed herein.

[0223] In some variations of the foregoing Scheme A-2, compounds of the Formula (A) may be synthesized according to Scheme A-2b.

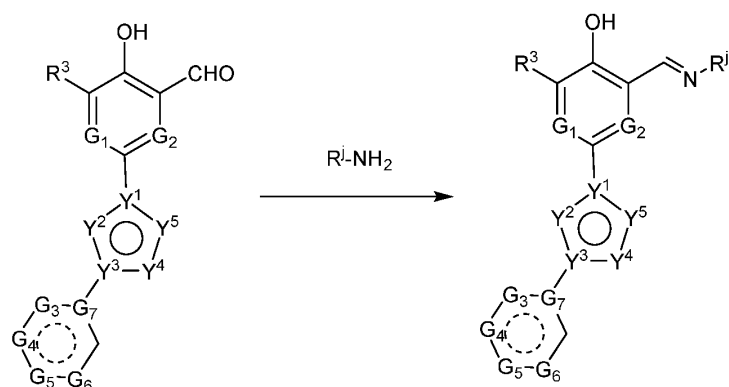
Scheme A-2b.



wherein G_3 , G_4 , G_5 , G_6 , and G_7 are as defined for Formula (A), or any variation thereof detailed herein.

[0224] In some embodiments, compounds of the Formula (A) may be synthesized according to Scheme A-3.

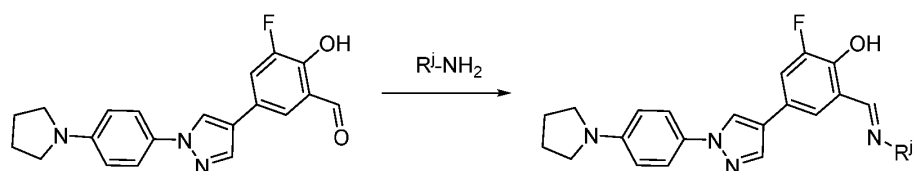
Scheme A-3.



wherein R^3 , R^j , Y^1 , Y^2 , Y^3 , Y^4 , Y^5 , G_1 , G_2 , G_3 , G_4 , G_5 , G_6 , and G_7 are as defined for Formula (A), or any variation thereof detailed herein.

[0225] In some variations of the foregoing Scheme A-3, compounds of the Formula (A) may be synthesized according to Scheme A-3-A.

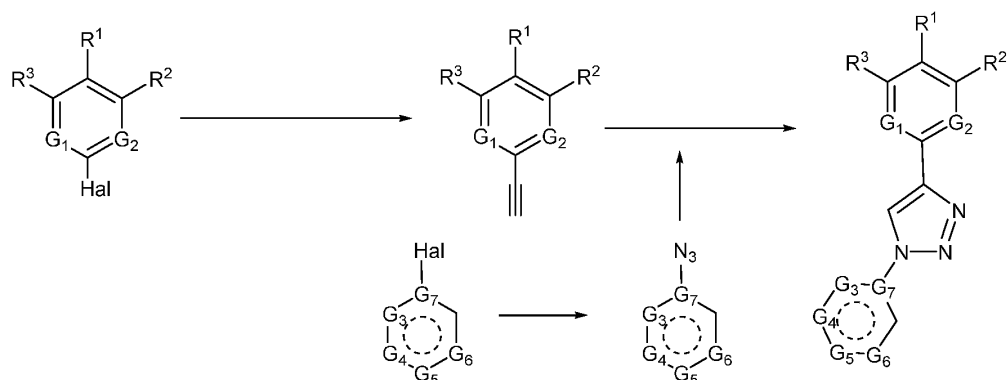
Scheme A-3-A.



wherein R^j is as defined for Formula (A), or any variation thereof detailed herein.

[0226] In some embodiments, compounds of the Formula (A) may be synthesized according to Scheme A-4.

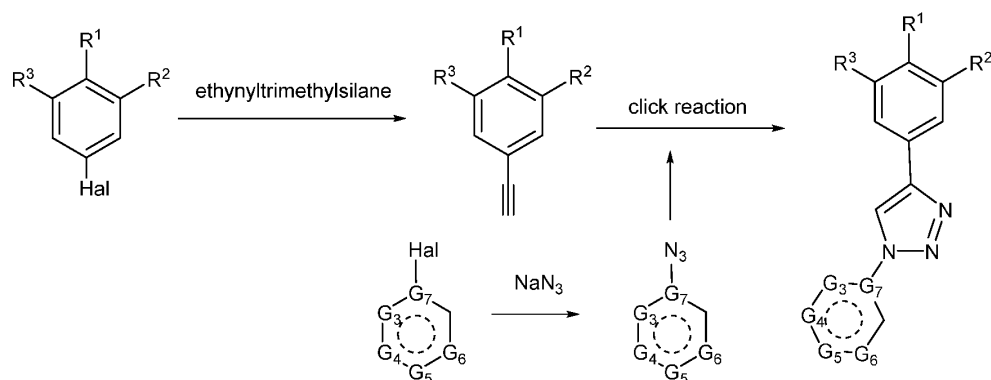
Scheme A-4.



wherein R^1 , R^2 , R^3 , G_1 , G_2 , G_3 , G_4 , G_5 , G_6 , and G_7 are as defined for Formula (A), or any variation thereof detailed herein, and Hal is a halogen.

[0227] In some variations of the foregoing Scheme A-4, compounds of the Formula (A) may be synthesized according to Scheme A-4-A.

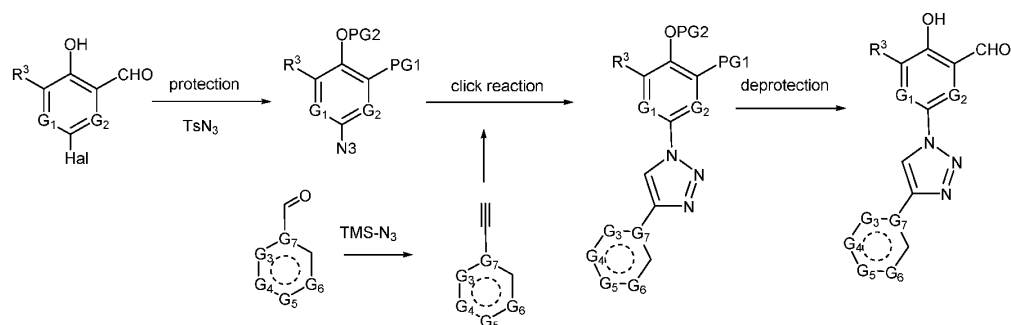
Scheme A-4-A.



wherein R^1 , R^2 , R^3 , G_3 , G_4 , G_5 , G_6 , and G_7 are as defined for Formula (A), or any variation thereof detailed herein, and Hal is a halogen.

[0228] In some embodiments, compounds of the Formula (A) may be synthesized according to Scheme A-5.

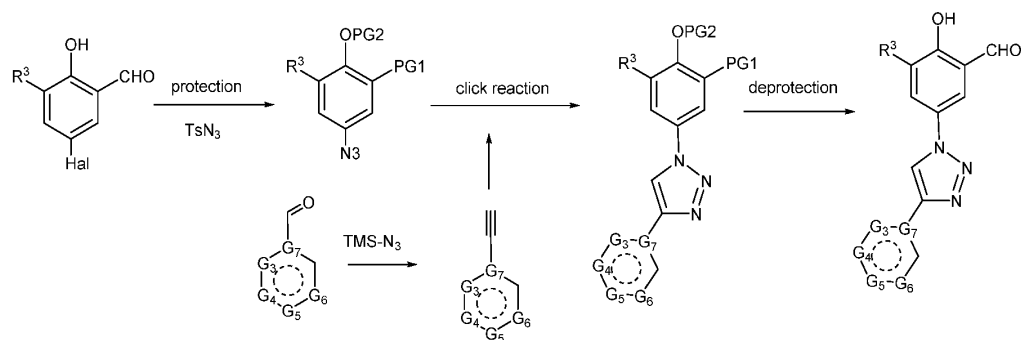
Scheme A-5.



wherein R^3 , G_1 , G_2 , G_3 , G_4 , G_5 , G_6 , and G_7 are as defined for Formula (A), or any variation thereof detailed herein, Hal is a halogen, and PG1 and PG2 are suitable protecting groups.

[0229] In some variations of the foregoing Scheme A-5, compounds of the Formula (A) may be synthesized according to Scheme A-5-A.

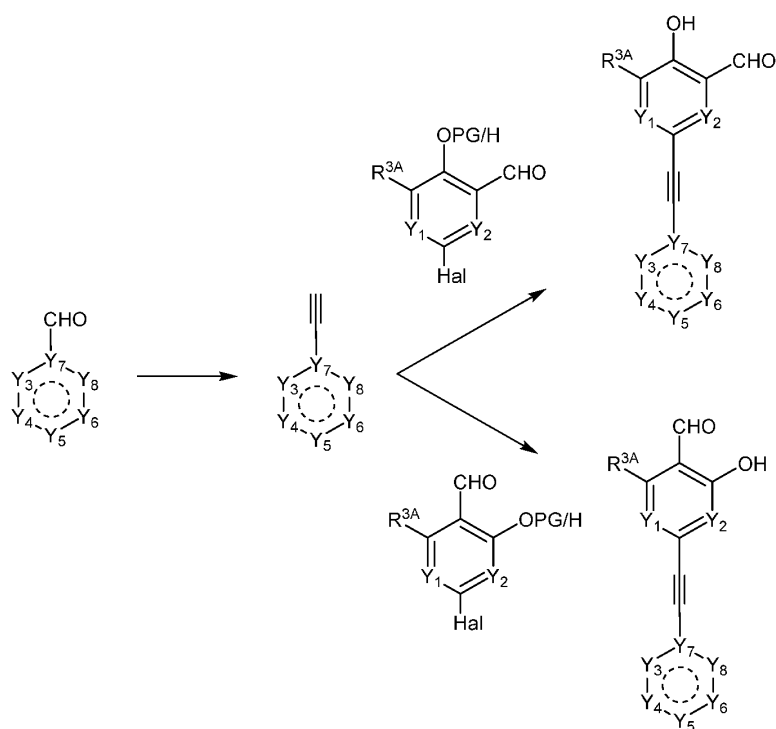
Scheme A-5-A.



wherein R^3 , G_3 , G_4 , G_5 , G_6 , and G_7 are as defined for Formula (A), or any variation thereof detailed herein, Hal is a halogen, and PG1 and PG2 are suitable protecting groups.

[0230] In some embodiments, compounds of the Formula (B) may be synthesized according to Scheme B-1.

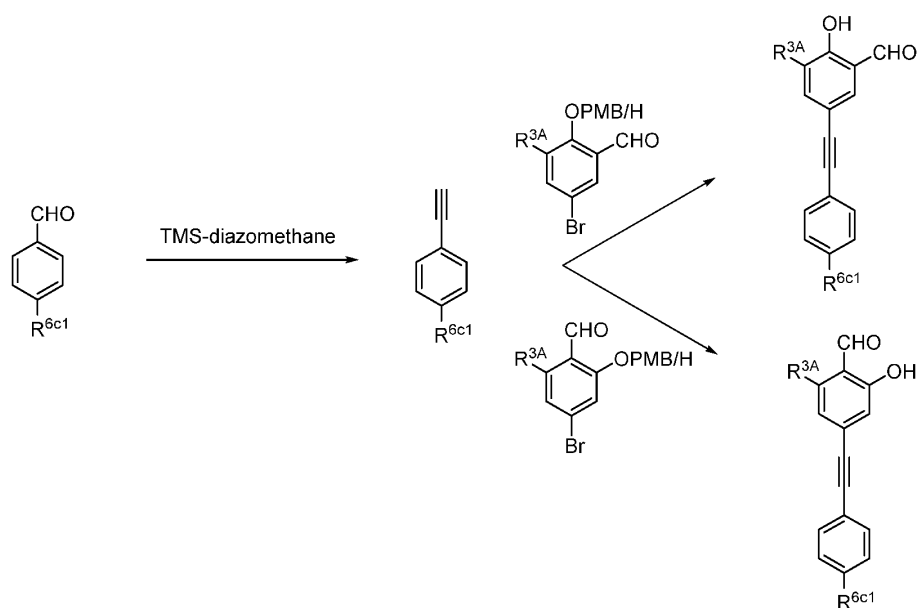
Scheme B-1.



wherein R^{3A}, Y₁, Y₂, Y₃, Y₄, Y₅, Y₆, Y₇, and Y₈ are as defined for Formula (B), or any variation thereof detailed herein; Hal is a halogen; and PG is any suitable protecting group. In some variations, a suitable protecting group is not necessary, and no protecting group is present on the phenolic group. In other variations, the suitable protecting group is a PMB (4-methoxybenzyl) group.

[0231] In some variations of the foregoing Scheme B-1, compounds of the Formula (B) may be synthesized according to Scheme B-1a.

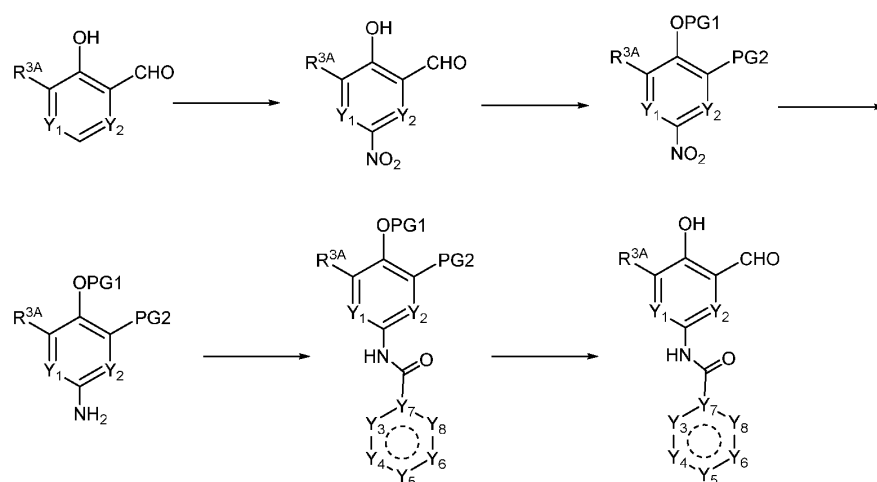
Scheme B-1a.



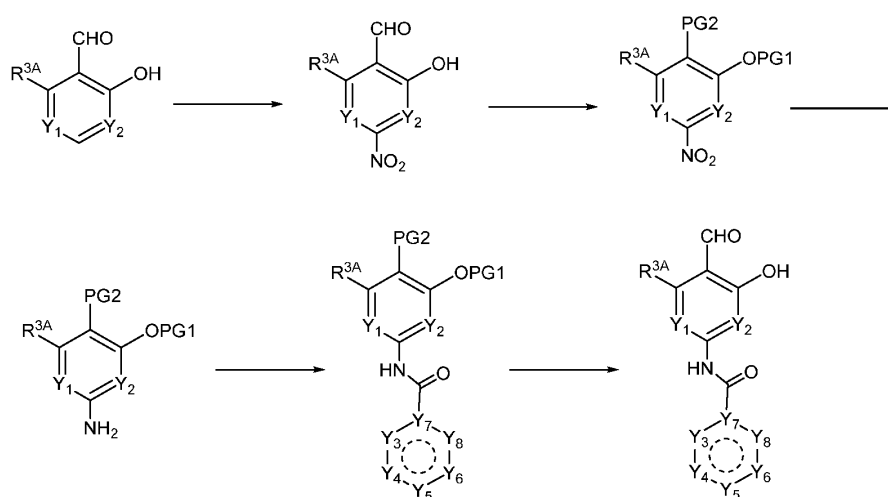
wherein R^{3A} and R^{6c1} are as defined for Formula (B), or any variation thereof detailed herein. In some variations, PMP is a suitable protecting group for an aromatic alcohol. In some variations, a suitable protecting group is not necessary, and no protecting group is present on the phenolic group.

[0232] In some embodiments, compounds of the Formula (B) may be synthesized according to Scheme B-2A or Scheme B-2B.

Scheme B-2A.



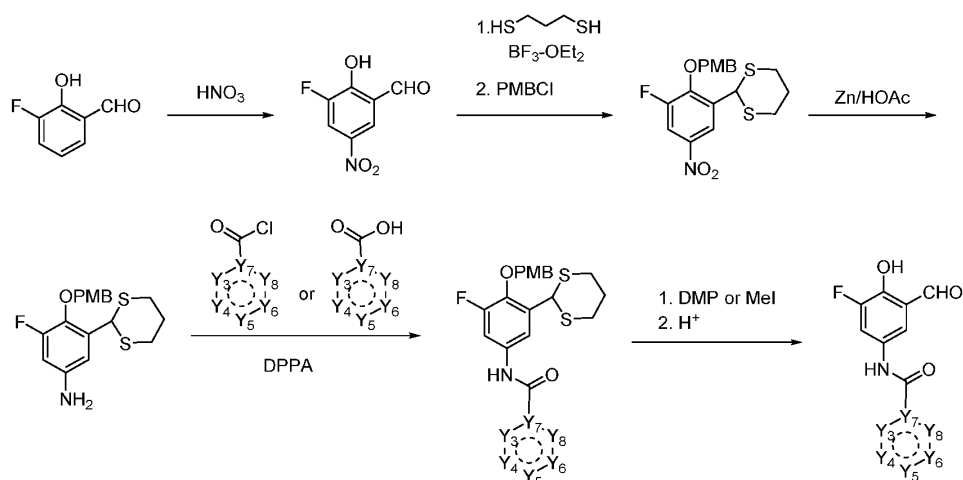
Scheme B-2B.



wherein R^{3A} , Y_1 , Y_2 , Y_3 , Y_4 , Y_5 , Y_6 , Y_7 , and Y_8 are as defined for Formula (B), or any variation thereof detailed herein; and PG1 and PG2 are suitable protecting groups.

[0233] In some variations of the foregoing Scheme B-2A, compounds of the Formula (B) may be synthesized according to Scheme B-2Aa.

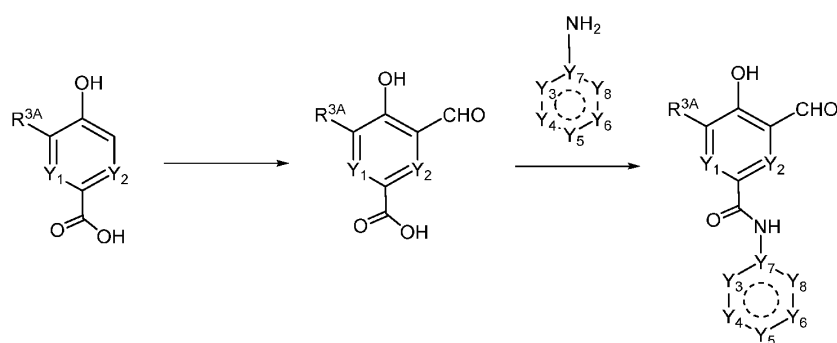
Scheme B-2Aa.



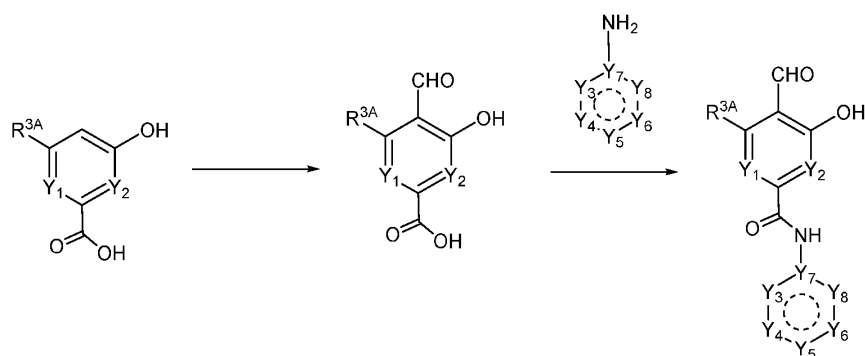
wherein Y₃, Y₄, Y₅, Y₆, Y₇, and Y₈ are as defined for Formula (B), or any variation thereof detailed herein.

[0234] In some embodiments, compounds of the Formula (B) may be synthesized according to Scheme B-3A or Scheme B-3B.

Scheme B-3A.



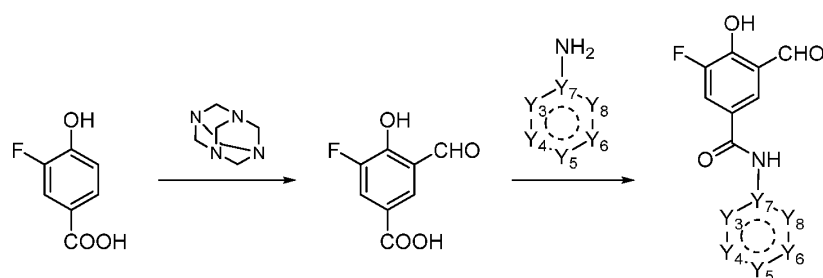
Scheme B-3B.



wherein R^{3A} , Y_1 , Y_2 , Y_3 , Y_4 , Y_5 , Y_6 , Y_7 , and Y_8 are as defined for Formula (B), or any variation thereof detailed herein.

[0235] In some variations of the foregoing Scheme B-3A, compounds of the Formula (B) may be synthesized according to Scheme B-3Aa.

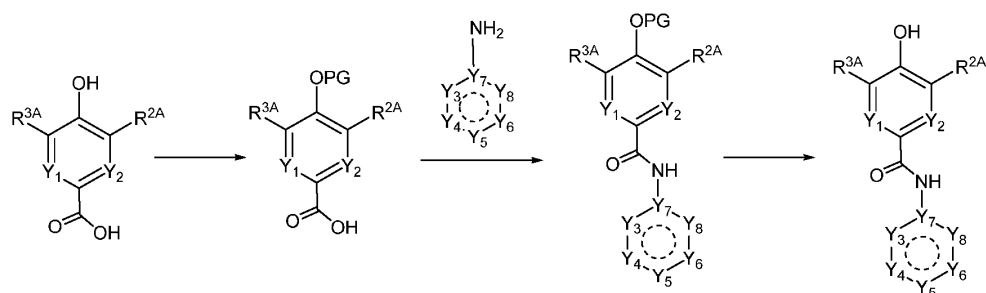
Scheme B-3Aa.



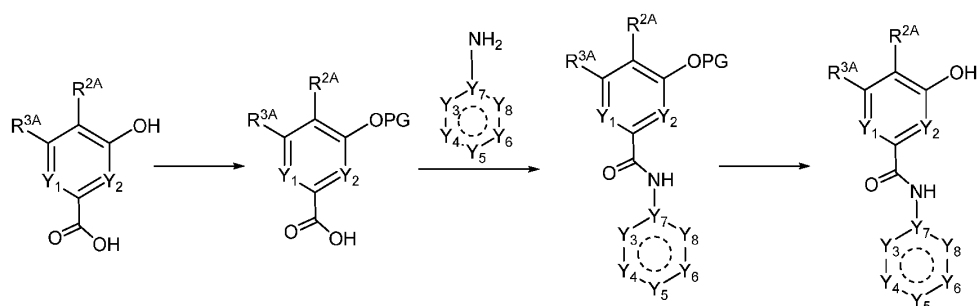
wherein Y_3 , Y_4 , Y_5 , Y_6 , Y_7 , and Y_8 are as defined for Formula (B), or any variation thereof detailed herein.

[0236] In some embodiments, compounds of the Formula (B) may be synthesized according to Scheme B-4A or Scheme B-4B.

Scheme B-4A.



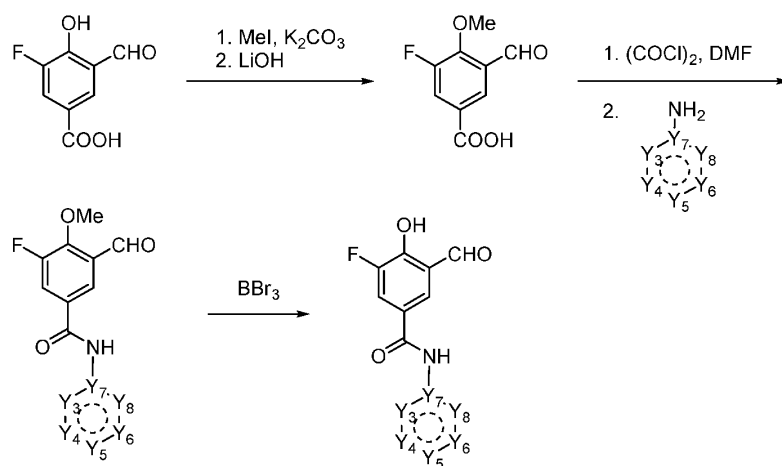
Scheme B-4B.



wherein R^{2A} , R^{3A} , Y_1 , Y_2 , Y_3 , Y_4 , Y_5 , Y_6 , Y_7 , and Y_8 are as defined for Formula (B), or any variation thereof detailed herein, and PG is a suitable protecting group.

[0237] In some variations of the foregoing Scheme B-4A, compounds of the Formula (B) may be synthesized according to Scheme B-4Aa.

Scheme B-4Aa.



wherein Y₃, Y₄, Y₅, Y₆, Y₇, and Y₈ are as defined for Formula (B), or any variation thereof detailed herein.

Chemical Synthesis

[0238] Exemplary chemical entities useful in methods of the present disclosure will now be described by reference to the specific examples that follow. Artisans will recognize that, to obtain the various compounds herein, starting materials may be suitably selected so that the ultimately desired substituents will be carried through the reaction scheme with or without protection as appropriate to yield the desired product. Alternatively, it may be necessary or desirable to employ, in the place of the ultimately desired substituent, a suitable group that may be carried through the reaction scheme and replaced as appropriate with the desired substituent. Furthermore, one of skill in the art will recognize that the transformations shown in the schemes below may be performed in any order that is compatible with the functionality of the particular pendant groups. Each of the reactions depicted in the general schemes may be run at a temperature from about 0 °C to the reflux temperature of the organic solvent used. Isotopically labeled compounds as described herein are prepared according to the methods described below, using suitably labeled starting materials. Such materials are generally available from commercial suppliers of radiolabeled chemical reagents.

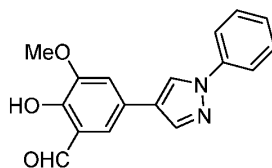
Examples

[0239] The following examples are offered to illustrate but not to limit the present disclosure. One of skill in the art will recognize that the following synthetic reactions and schemes may be modified by choice of suitable starting materials and reagents in order to access other compounds of Formula (A) and Formula (B). The compounds are prepared using the general methods described above.

[0240] The following abbreviations are used throughout the Examples: BuLi (butyl lithium), DCM (dichloromethane), DMF (N,N-dimethylformamide), DMSO (dimethyl sulfoxide), EA or EtOAc (Ethyl acetate), MeOH (methanol), PdCl₂(dppf) ((1,1'-bis(diphenylphosphino)ferrocene))palladium(II) dichloride), dppf (1,1'-

bis(diphenylphosphino)ferrocene), Pd(PPh₃)₂Cl₂ (bis(triphenylphosphine)palladium(II) dichloride), Pd(PPh₃)₄ (tetrakis(triphenylphosphine)palladium(0)), PMB (4-methoxybenzyl), PPh₃ (triphenylphosphane), Ruphos (2-Dicyclohexylphosphino-2',6'-diisopropoxybiphenyl), RuPhos Pd G3 ((2-Dicyclohexylphosphino-2',6'-diisopropoxy-1,1'-biphenyl)[2-(2'-amino-1,1'-biphenyl)]palladium(II) methanesulfonate), TBAF (tetrabutylammonium fluoride), TFA (trifluoroacetic acid), THF (tetrahydrofuran), TMS-diazomethane (tetramethylsilyldiazomethane), TLC (thin layer chromatography), XantPhos (4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene), XantPhos Pd G3 ([4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene]-2-(2'-amino-1,1'-biphenyl)]palladium(II) methanesulfonate), Xphos (2-Dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl), and XPhos Pd G3 ((2-Dicyclohexylphosphino-2',4',6'-triisopropyl-1,1'-biphenyl)[2-(2'-amino-1,1'-biphenyl)]palladium(II) methanesulfonate).

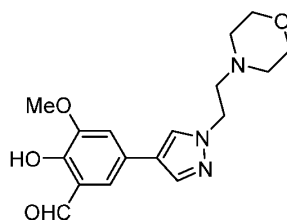
Example A1: 2-hydroxy-3-methoxy-5-(1-phenyl-1H-pyrazol-4-yl)benzaldehyde (Compound No. A1)



[0241] In a 30 mL sealed cap glass vial, 5-bromo-2-hydroxy-3-methoxybenzaldehyde (231 mg, 1.0 mmol), 1-phenyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (324 mg, 1.2 mmol) and Na₂CO₃ (666 mg, 6.0 mmol) were suspended in DMF-water (10 mL). Then bubbled Argon gas for one minute and added Pd(PPh₃)₄ (63 mg, 0.05 mmol) to the reaction vial and closed with sealed cap and continued at 105°C for 16 hours on a stirrer plate with metallic beads contained dish. Then cooled to room temperature and diluted with water (10 mL) and transferred into a separating funnel using dichloromethane. Acidified the aqueous layer with 1.0 N HCl to pH~3.0-4.0 and extracted with additional dichloromethane (2 x 50 mL). The combined organic layer washed with brine, dried over sodium sulfate and evaporated. The resulted crude product purified using silica gel column chromatography (hexane through hexane-EtOAc (0-100%)) to give the title compound as a light yellow solid (63 mg, 21% yield). ¹H NMR (500 MHz, Chloroform-*d*) δ 11.01 (s, 1H), 9.99 (s, 1H), 8.14 (s, 1H), 7.96 (s, 1H), 7.78 – 7.70 (m,

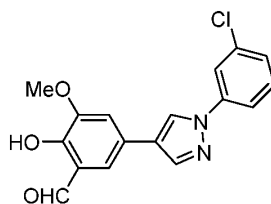
2H), 7.49 (t, $J = 7.9$ Hz, 2H), 7.39 – 7.30 (m, 2H), 7.27 (m, 1H) 4.01 (s, 3H); LC-MS m/z [M+H]⁺ calc'd for C₁₇H₁₄N₂O₃, 295; found, 295.

Example A2: 2-hydroxy-3-methoxy-5-(1-(2-morpholinoethyl)-1H-pyrazol-4-yl)benzaldehyde
(Compound No. A2)



[0242] The title compound was prepared from 5-bromo-2-hydroxy-3-methoxybenzaldehyde (231 mg, 1.0 mmol) and 4-(2-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazol-1-yl)ethyl)morpholine (369 mg, 1.2 mmol) as described in Example A1 to give the title compound as a yellow gummy solid (108 mg, 33% yield). ¹H NMR (500 MHz, Chloroform-*d*) δ 10.95 (s, 1H), 9.95 (s, 1H), 7.68 (s, 1H), 7.50 (s, 1H), 7.46 (d, $J = 2.3$ Hz, 1H), 7.18 (d, $J = 2.0$ Hz, 1H), 4.27 (m, 2H), 3.97 (s, 3H), 3.69 (m, 6H), 2.81 (m, 2H), 2.48 – 2.41 (m, 4H); LC-MS m/z [M+H]⁺ calc'd for C₁₇H₂₁N₃O₄, 332; found, 332.

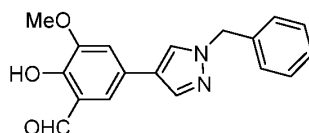
Example A3: 5-(1-(3-chlorophenyl)-1H-pyrazol-4-yl)-2-hydroxy-3-methoxybenzaldehyde
(Compound No. A3)



[0243] The title compound was prepared from 5-bromo-2-hydroxy-3-methoxybenzaldehyde (231 mg, 1.0 mmol) and 1-(3-chlorophenyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (267 mg, 1.2 mmol) as described in Example A1 to give the title compound cis/trans mixture as a yellow solid (53 mg, 16% yield). ¹H NMR (500 MHz, Chloroform-*d*) δ 11.01 (s, 1H), 9.99 (s, 1H), 8.13 (s, 1H), 7.96 (s, 1H), 7.79 (t, $J = 2.1$ Hz, 1H), 7.64 (dd, $J = 8.3$,

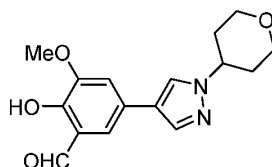
2.1 Hz, 1H), 7.42 (t, $J = 8.1$ Hz, 1H), 7.35 (d, $J = 1.9$ Hz, 1H), 7.33 – 7.28 (m, 1H), 7.25 (d, $J = 1.9$ Hz, 1H), 4.01 (s, 3H); LC-MS m/z $[M+H]^+$ calc'd for $C_{17}H_{13}ClN_2O_3$, 330; found, 330.

Example A4: 5-(1-benzyl-1H-pyrazol-4-yl)-2-hydroxy-3-methoxybenzaldehyde (Compound No. A4)



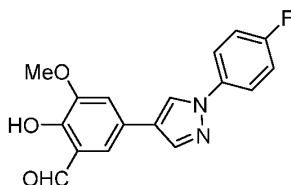
[0244] The title compound was prepared from 5-bromo-2-hydroxy-3-methoxybenzaldehyde (231 mg, 1.0 mmol) and 1-benzyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (341 mg, 1.2 mmol) as described in Example A1 to give the title compound as a brown solid (115 mg, 37% yield). 1H NMR (500 MHz, Chloroform- d) δ 10.94 (s, 1H), 9.93 (s, 1H), 7.78 (s, 1H), 7.59 (d, $J = 3.9$ Hz, 1H), 7.43 – 7.31 (m, 3H), 7.30 – 7.26 (m, 2H), 7.24 (d, $J = 2.0$ Hz, 1H), 7.16 (d, $J = 1.9$ Hz, 1H), 5.32 (s, 2H), 3.95 (s, 3H); LC-MS m/z $[M+H]^+$ calc'd for $C_{18}H_{16}N_2O_3$, 309; found, 309.

Example A5: 2-hydroxy-3-methoxy-5-(1-(tetrahydro-2H-pyran-4-yl)-1H-pyrazol-4-yl)benzaldehyde (Compound No. A5)



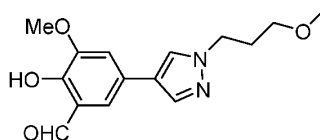
[0245] The title compound was prepared from 5-bromo-2-hydroxy-3-methoxybenzaldehyde (231 mg, 1.0 mmol) and 1-(tetrahydro-2H-pyran-4-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (334 mg, 1.2 mmol) as described in Example A1 to give the title compound as a brown solid (68 mg, 23% yield). 1H NMR (500 MHz, Chloroform- d) δ 10.95 (s, 1H), 9.95 (s, 1H), 7.75 (s, 1H), 7.69 (m, 1H), 7.27 (d, $J = 2.0$ Hz, 1H), 7.19 (d, $J = 2.0$ Hz, 1H), 4.39 (tt, $J = 10.4, 4.9$ Hz, 1H), 4.21 – 4.08 (m, 2H), 3.97 (s, 3H), 3.57 (td, $J = 11.6, 2.9$ Hz, 2H), 2.22 – 2.01 (m, 4H); LC-MS m/z $[M+H]^+$ calc'd for $C_{16}H_{18}N_2O_4$, 303; found, 303.

Example A6: 5-(1-(4-fluorophenyl)-1H-pyrazol-4-yl)-2-hydroxy-3-methoxybenzaldehyde
(Compound No. A6)



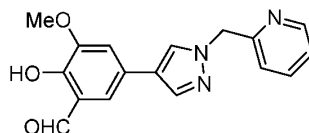
[0246] The title compound was prepared from 5-bromo-2-hydroxy-3-methoxybenzaldehyde (231 mg, 1.0 mmol) and (1-(4-fluorophenyl)-1H-pyrazol-4-yl)boronic acid (247 mg, 1.2 mmol) as described in Example A1 to give the title compound as a yellow solid (52 mg, 17% yield). ¹H NMR (500 MHz, Chloroform-*d*) δ 11.00 (s, 1H), 9.99 (s, 1H), 8.07 (d, *J* = 0.7 Hz, 1H), 7.95 (d, *J* = 0.7 Hz, 1H), 7.73 – 7.68 (m, 2H), 7.35 (d, *J* = 2.1 Hz, 1H), 7.25 (d, *J* = 2.0 Hz, 1H), 7.21 – 7.16 (m, 2H), 4.00 (s, 3H); LC-MS *m/z* [M+H]⁺ calc'd for C₁₇H₁₃FN₂O₃, 313; found, 313.

Example A7: 2-hydroxy-3-methoxy-5-(1-(3-methoxypropyl)-1H-pyrazol-4-yl)benzaldehyde
(Compound No. A7)



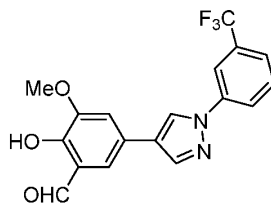
[0247] The title compound was prepared from 5-bromo-2-hydroxy-3-methoxybenzaldehyde (231 mg, 1.0 mmol) and 1-(3-methoxypropyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (319 mg, 1.2 mmol) as described in Example A1 to give the title compound as a black gummy solid (132 mg, 45% yield). ¹H NMR (500 MHz, Chloroform-*d*) δ 10.95 (s, 1H), 9.95 (s, 1H), 7.74 (d, *J* = 0.9 Hz, 1H), 7.62 (d, *J* = 0.9 Hz, 1H), 7.26 (d, *J* = 1.9 Hz, 1H), 7.19 (d, *J* = 2.1 Hz, 1H), 4.26 (t, *J* = 6.9 Hz, 2H), 3.97 (s, 3H), 3.37 (t, *J* = 5.9 Hz, 2H), 3.35 (s, 3H), 2.16 (ddd, *J* = 12.8, 7.0, 5.9 Hz, 2H); LC-MS *m/z* [M+H]⁺ calc'd for C₁₅H₁₈N₂O₄, 291; found, 291.

Example A8: 2-hydroxy-3-methoxy-5-(1-(pyridin-2-ylmethyl)-1H-pyrazol-4-yl)benzaldehyde (Compound No. A8)



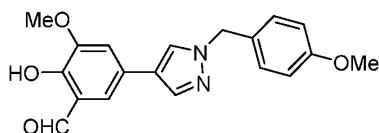
[0248] The title compound was prepared from 5-bromo-2-hydroxy-3-methoxybenzaldehyde (231 mg, 1.0 mmol) and 2-((4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazol-1-yl)methyl)pyridine (342 mg, 1.2 mmol) as described in Example A1 to give the title compound as an off-white solid (76 mg, 25% yield). ¹H NMR (500 MHz, Chloroform-*d*) δ 10.96 (s, 1H), 9.94 (s, 1H), 8.60 (dt, *J* = 4.8, 1.4 Hz, 1H), 7.79 (d, *J* = 8.2 Hz, 2H), 7.67 (qd, *J* = 7.5, 1.7 Hz, 1H), 7.27 (d, *J* = 2.0 Hz, 1H), 7.25 – 7.22 (m, 1H), 7.19 (d, *J* = 1.9 Hz, 1H), 7.15 (dt, *J* = 7.9, 1.1 Hz, 1H), 5.47 (s, 2H), 3.96 (s, 3H); LC-MS *m/z* [M+H]⁺ calc'd for C₁₇H₁₅N₃O₃, 310; found, 310.

Example A9: 2-hydroxy-3-methoxy-5-(1-(3-(trifluoromethyl)phenyl)-1H-pyrazol-4-yl)benzaldehyde (Compound No. A9)



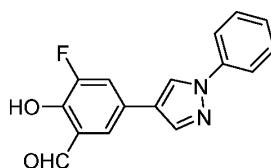
[0249] The title compound was prepared from 5-bromo-2-hydroxy-3-methoxybenzaldehyde (231 mg, 1.0 mmol) and (1-(3-(trifluoromethyl)phenyl)-1H-pyrazol-4-yl)boronic acid (307 mg, 1.2 mmol) as described in Example A1 to give the title compound as a yellow solid (97 mg, 27% yield). ¹H NMR (500 MHz, Chloroform-*d*) δ 11.01 (s, 1H), 9.99 (s, 1H), 8.19 (s, 1H), 8.02 (d, *J* = 1.9 Hz, 1H), 7.99 (s, 1H), 7.96 (dt, *J* = 7.9, 1.6 Hz, 1H), 7.62 (t, *J* = 7.9 Hz, 1H), 7.58 (d, *J* = 7.8 Hz, 1H), 7.37 (d, *J* = 2.0 Hz, 1H), 7.26 (s, 1H), 4.01 (s, 3H); LC-MS *m/z* [M+H]⁺ calc'd for C₁₈H₁₃F₃N₂O₃, 363; found, 363.

Example A10: 2-hydroxy-3-methoxy-5-(1-(4-methoxybenzyl)-1H-pyrazol-4-yl)benzaldehyde (Compound No. A10)



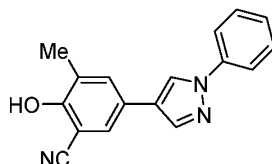
[0250] The title compound was prepared from 5-bromo-2-hydroxy-3-methoxybenzaldehyde (231 mg, 1.0 mmol) and 1-(4-methoxybenzyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (377 mg, 1.2 mmol) as described in Example A1 to give the title compound as a yellow solid (90 mg, 27% yield). ¹H NMR (500 MHz, Chloroform-*d*) δ 10.94 (s, 1H), 9.93 (s, 1H), 7.76 (s, 1H), 7.54 (s, 1H), 7.26 – 7.22 (m, 3H), 7.15 (d, *J* = 1.9 Hz, 1H), 6.94 – 6.89 (m, 2H), 5.28 (s, 2H), 3.95 (s, 3H), 3.80 (s, 3H); LC-MS *m/z* [M+H]⁺ calc'd for C₁₉H₁₈N₂O₄, 339; found, 339.

Example A11: 3-fluoro-2-hydroxy-5-(1-phenyl-1H-pyrazol-4-yl)benzaldehyde (Compound No. A11)



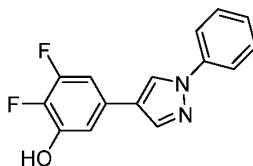
[0251] The title compound was prepared from 5-bromo-3-fluoro-2-hydroxybenzaldehyde (219 mg, 1.0 mmol) and 1-phenyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (324 mg, 1.2 mmol) as described in Example A1 to give the title compound as a yellow solid (86 mg, 30% yield). ¹H NMR (500 MHz, Chloroform-*d*) δ 10.89 (s, 1H), 10.00 (d, *J* = 1.9 Hz, 1H), 8.13 (s, 1H), 7.95 (s, 1H), 7.76 – 7.70 (m, 2H), 7.58 – 7.52 (m, 2H), 7.49 (dt, *J* = 8.4, 7.0 Hz, 2H), 7.38 – 7.29 (m, 1H); LC-MS *m/z* [M+H]⁺ calc'd for C₁₆H₁₁FN₂O₂, 283; found, 283.

Example A12: 2-hydroxy-3-methyl-5-(1-phenyl-1H-pyrazol-4-yl)benzonitrile (Compound No. A12)

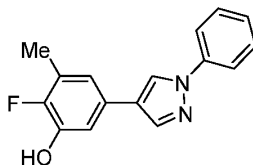


[0252] The title compound was prepared from 5-bromo-2-hydroxy-3-methylbenzonitrile (216 mg, 1.0 mmol) and 1-phenyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (324 mg, 1.2 mmol) as described in Example A1 to give the title compound as an off-white solid (98 mg, 36% yield). ¹H NMR (500 MHz, Chloroform-*d*) δ 8.10 (s, 1H), 7.92 (s, 1H), 7.74 – 7.69 (m, 2H), 7.55 – 7.52 (m, 1H), 7.52 – 7.49 (m, 1H), 7.49 – 7.45 (m, 2H), 7.33 (td, *J* = 7.3, 1.0 Hz, 1H), 5.87 (s, 1H), 2.34 (s, 3H); LC-MS *m/z* [M+H]⁺ calc'd for C₁₇H₁₃N₃O, 276; found, 276.

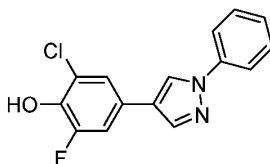
Example A13: 2,3-difluoro-5-(1-phenyl-1H-pyrazol-4-yl)phenol (Compound No. A13)



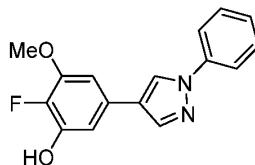
[0253] The title compound was prepared from 5-bromo-2,3-difluorophenol (209 mg, 1.0 mmol) and 1-phenyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (324 mg, 1.2 mmol) as described in Example A1 to give the title compound as an off-white solid (172 mg, 63% yield). ¹H NMR (500 MHz, Chloroform-*d*) δ 8.08 (s, 1H), 7.90 (s, 1H), 7.76 – 7.66 (m, 2H), 7.53 – 7.43 (m, 2H), 7.39 – 7.28 (m, 1H), 6.97 (dt, *J* = 7.1, 2.0 Hz, 1H), 6.91 (ddd, *J* = 10.7, 6.6, 2.2 Hz, 1H), 5.55 (s, 1H); LC-MS *m/z* [M+H]⁺ calc'd for C₁₅H₁₀F₂N₂O, 273; found, 273.

Example A14: 2-fluoro-3-methyl-5-(1-phenyl-1H-pyrazol-4-yl)phenol (Compound No. A14)

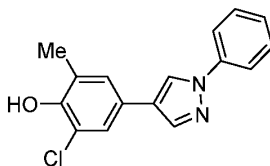
[0254] The title compound was prepared from 5-bromo-2-fluoro-3-methylphenol (205 mg, 1.0 mmol) and 1-phenyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (324 mg, 1.2 mmol) as described in Example A1 to give the title compound as a white solid (102 mg, 38% yield). ¹H NMR (500 MHz, Chloroform-*d*) δ 8.07 (s, 1H), 7.91 (s, 1H), 7.77 – 7.64 (m, 2H), 7.51 – 7.40 (m, 2H), 7.36 – 7.29 (m, 1H), 7.02 (dd, *J* = 7.9, 2.3 Hz, 1H), 6.90 (dd, *J* = 6.5, 2.2 Hz, 1H), 5.40 (s, 1H), 2.32 (d, *J* = 2.1 Hz, 3H); LC-MS *m/z* [M+H]⁺ calc'd for C₁₆H₁₃FN₂O, 269; found, 269.

Example A15: 2-chloro-6-fluoro-4-(1-phenyl-1H-pyrazol-4-yl)phenol (Compound No. A15)

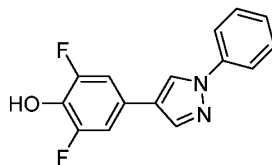
[0255] The title compound was prepared from 4-bromo-2-chloro-6-fluorophenol (225 mg, 1.0 mmol) and 1-phenyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (324 mg, 1.2 mmol) as described in Example A1 to give the title compound as an off-white solid (196 mg, 68% yield). ¹H NMR (500 MHz, Chloroform-*d*) δ 8.08 (s, 1H), 7.89 (d, *J* = 4.1 Hz, 1H), 7.79 – 7.65 (m, 2H), 7.51 – 7.44 (m, 2H), 7.36 – 7.30 (m, 2H), 7.20 (dd, *J* = 11.0, 2.1 Hz, 1H), 5.90 (s, 1H); LC-MS *m/z* [M+H]⁺ calc'd for C₁₅H₁₀ClFN₂O, 290; found, 290.

Example A16: 2-fluoro-3-methoxy-5-(1-phenyl-1H-pyrazol-4-yl)phenol (Compound No. A16)

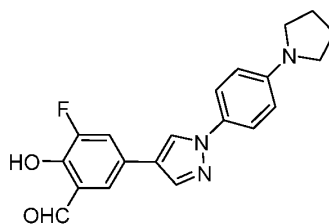
[0256] The title compound was prepared from 5-bromo-2-fluoro-3-methoxyphenol (221 mg, 1.0 mmol) and 1-phenyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (324 mg, 1.2 mmol) as described in Example A1 to give the title compound as a brown solid (205 mg, 72% yield). ¹H NMR (500 MHz, Chloroform-*d*) δ 8.09 (s, 1H), 7.92 (s, 1H), 7.82 – 7.67 (m, 2H), 7.56 – 7.42 (m, 2H), 7.36 – 7.28 (m, 1H), 6.82 (dd, *J* = 7.2, 2.1 Hz, 1H), 6.69 (dd, *J* = 7.2, 2.1 Hz, 1H), 5.41 (d, *J* = 3.9 Hz, 1H), 3.95 (s, 3H); LC-MS *m/z* [M+H]⁺ calc'd for C₁₆H₁₃FN₂O₂, 285; found, 285.

Example A17: 2-chloro-6-methyl-4-(1-phenyl-1H-pyrazol-4-yl)phenol (Compound No. A17)

[0257] The title compound was prepared from 4-bromo-2-chloro-6-methylphenol (222 mg, 1.0 mmol) and 1-phenyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (324 mg, 1.2 mmol) as described in Example A1 to give the title compound as a brown solid (179 mg, 63% yield). ¹H NMR (500 MHz, Chloroform-*d*) δ 8.07 (s, 1H), 7.90 (s, 1H), 7.75 – 7.69 (m, 2H), 7.51 – 7.44 (m, 2H), 7.36 (d, *J* = 2.1 Hz, 1H), 7.31 (td, *J* = 7.4, 1.3 Hz, 1H), 7.23 (d, *J* = 2.0 Hz, 1H), 5.60 (s, 1H), 2.33 (s, 3H); LC-MS *m/z* [M+H]⁺ calc'd for C₁₆H₁₃ClN₂O, 286; found, 286.

Example A18: 2,6-difluoro-4-(1-phenyl-1H-pyrazol-4-yl)phenol (Compound No. A18)

[0258] The title compound was prepared from 4-bromo-2,6-difluorophenol (209 mg, 1.0 mmol) and 1-phenyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (324 mg, 1.2 mmol) as described in Example A1 to give the title compound as a white solid (195 mg, 72% yield). ¹H NMR (500 MHz, Chloroform-*d*) δ 8.08 (s, 1H), 7.89 (s, 1H), 7.76 – 7.66 (m, 2H), 7.55 – 7.41 (m, 2H), 7.39 – 7.29 (m, 1H), 7.17 – 7.03 (m, 2H), 5.34 (s, 1H); LC-MS *m/z* [M+H]⁺ calc'd for C₁₅H₁₀F₂N₂O, 273; found, 273.

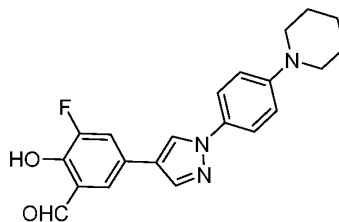
Example A19: 3-fluoro-2-hydroxy-5-(1-(4-(pyrrolidin-1-yl)phenyl)-1H-pyrazol-4-yl)benzaldehyde (Compound No. A19)

[0259] Step 1: 4-Bromo-1-(4-(pyrrolidin-1-yl)phenyl)-1H-pyrazole

[0260] A mixture of 4-bromo-1H-pyrazole (1.75 g, 12 mmol.), 1-(4-bromophenyl)pyrrolidine (2.25 g, 10 mmol) potassium carbonate (4.14 g, 30 mmol), CuI (190 mg, 1.0 mmol), and (1S,2S)-*N,N'*-dimethyl-1,2-cyclohexanediamine (284 mg, 2 mmol) in toluene (100 mL) was refluxed overnight under nitrogen protection. The mixture was cooled to room temperature and filtered. The cake was washed with ethyl acetate. The filtrate and wash were combined and concentrated. The residue was purified by silica gel column to give the desired title product (910 mg, 31% yield). LC-MS *m/z* [M+H]⁺ calc'd for C₁₃H₁₄BrN₃, 292; found, 292.

[0261] Step 2: A mixture of 4-Bromo-1-(4-(pyrrolidin-1-yl)phenyl)-1H-pyrazole (292 mg, 1.0 mmol), 3-fluoro-2-hydroxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzaldehyde (532 mg, 2.0 mmol), potassium carbonate (414 mg, 3.0 mmol), PdCl₂(dppf) (74 mg, 0.1 mmol) in dioxane/water (3:1) (12 mL) was heated at 95 °C for 2 hours under nitrogen atmosphere. The mixture was cooled to room temperature and filtered. The cake was washed with ethyl acetate. The filtrate and wash were combined, washed with water, dried over anhydrous sodium sulfate, and concentrated. The residue was purified by silica gel column chromatography to give the title product as a yellow solid (49 mg, 14% yield). ¹H NMR (*DMSO-d*₆, 400 MHz) δ : 10.87 (br, 1H), 10.32 (s, 1H), 8.83 (s, 1H), 8.12 (s, 1H), 7.92 (d, *J*=12.0 Hz, 1H), 7.79 (s, 1H), 7.64 (d, *J*=8.4 Hz, 2H), 6.64 (d, *J*=8.4 Hz, 2H), 3.27 (m, 4H), 1.97 (m, 4H); LC-MS *m/z* [M+H]⁺ calc'd for C₂₀H₁₈FN₃O₂, 352; found, 352.

Example A20: 3-fluoro-2-hydroxy-5-(1-(4-(piperidin-1-yl)phenyl)-1H-pyrazol-4-yl)benzaldehyde (Compound No. A20)



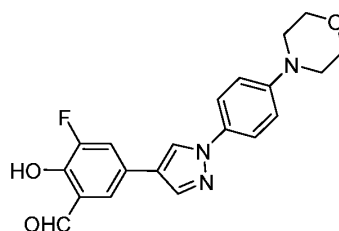
[0262] Step 1: 1-(4-(4-bromo-1H-pyrazol-1-yl)phenyl)piperidine

[0263] The title compound was prepared from 4-bromo-1H-pyrazole (1.75 g, 12 mmol), 1-(4-bromophenyl)piperidine (2.40 g, 10 mmol) as described in Step 1 of Example A19 to give the title compound (1.16 g, 38% yield). LC-MS *m/z* [M+H]⁺ calc'd for C₁₄H₁₆BrN₃, 306; found, 306.

[0264] Step 2: The title compound was prepared from 1-(4-(4-bromo-1H-pyrazol-1-yl)phenyl)piperidine (306 mg, 1.0 mmol) and 3-fluoro-2-hydroxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzaldehyde (532 mg, 2.0 mmol) as described in Step 2 of Example A19 to give the title compound as a yellow solid (128 mg, 35% yield). ¹H NMR (*DMSO-d*₆, 400 MHz) δ : 10.88 (s, 1H), 10.32 (s, 1H), 8.90 (s, 1H), 8.15 (s, 1H), 7.92 (d, *J*=12.0 Hz, 1H), 7.80 (s, 1H),

7.67 (d, $J=8.8$ Hz, 2H), 7.05 (d, $J=8.8$ Hz, 2H), 3.18 (m, 4H), 1.63 (m, 4H), 1.55 (m, 2H); LC-MS m/z $[M+H]^+$ calc'd for $C_{21}H_{20}FN_3O_2$, 366; found, 366.

Example A21: 3-fluoro-2-hydroxy-5-(1-(4-morpholinophenyl)-1H-pyrazol-4-yl)benzaldehyde (Compound No. A21)

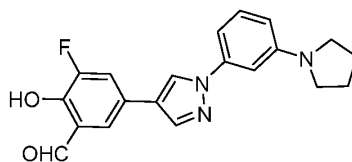


[0265] Step 1: 4-(4-(4-bromo-1H-pyrazol-1-yl)phenyl)morpholine

[0266] The title compound was prepared from 4-bromo-1H-pyrazole (1.75 g, 12 mmol), 4-(4-bromophenyl)morpholine (2.42 g, 10 mmol) as described in Step 1 of Example A19 to give the title compound (1.14 g, 37% yield). LC-MS m/z $[M+H]^+$ calc'd for $C_{13}H_{14}BrN_3O$, 308; found, 308.

[0267] Step 2: The title compound was prepared from 4-(4-(4-bromo-1H-pyrazol-1-yl)phenyl)morpholine (308 mg, 1.0 mmol) and 3-fluoro-2-hydroxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzaldehyde (532 mg, 2.0 mmol) as described in Step 2 of Example A19 to give the title compound as a yellow solid (63 mg, 17% yield). 1H NMR ($DMSO-d_6$, 400 MHz) δ : 10.89 (s, 1H), 10.32 (s, 1H), 8.93 (s, 1H), 8.17 (s, 1H), 7.93 (d, $J=12.0$ Hz, 1H), 7.81 (s, 1H), 7.72 (d, $J=8.8$ Hz, 2H), 7.08 (d, $J=9.2$ Hz, 2H), 3.76 (m, 4H), 3.16 (m, 4H); LC-MS m/z $[M+H]^+$ calc'd for $C_{20}H_{18}FN_3O_3$, 368; found, 368.

Example A22: 3-fluoro-2-hydroxy-5-(1-(3-(pyrrolidin-1-yl)phenyl)-1H-pyrazol-4-yl)benzaldehyde (Compound No. A22)

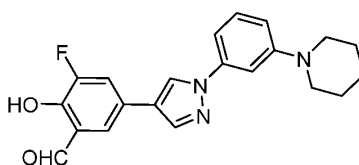


[0268] Step 1: 4-bromo-1-(3-(pyrrolidin-1-yl)phenyl)-1H-pyrazole

[0269] The title compound was prepared from 4-bromo-1H-pyrazole (1.75 g, 12 mmol.), 1-(3-bromophenyl)pyrrolidine (2.26 g, 10 mmol) as described in Step 1 of Example A19 to give the title compound (876 mg, 30% yield). LC-MS m/z $[M+H]^+$ calc'd for $C_{13}H_{14}BrN_3$, 292; found, 292.

[0270] Step 2: The title compound was prepared from 4-bromo-1-(3-(pyrrolidin-1-yl)phenyl)-1H-pyrazole (292 mg, 1.0 mmol) and 3-fluoro-2-hydroxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzaldehyde (532 mg, 2.0 mmol) as described in Step 2 of Example A19 to give the title compound as light yellow solid (81 mg, 23% yield). 1H NMR ($DMSO-d_6$, 400 MHz) δ : 10.91 (s, 1H), 10.33 (s, 1H), 9.02 (s, 1H), 8.20 (s, 1H), 7.96 (d, $J=12.0$ Hz, 1H), 7.83 (s, 1H), 7.26 (m, 1H), 7.07 (m, 1H), 7.00 (s, 1H), 6.48 (d, $J=7.6$ Hz, 1H), 3.31 (m, 4H), 1.99 (m, 4H); LC-MS m/z $[M+H]^+$ calc'd for $C_{20}H_{18}FN_3O_2$, 352; found, 352.

Example A23: 3-fluoro-2-hydroxy-5-(1-(3-(piperidin-1-yl)phenyl)-1H-pyrazol-4-yl)benzaldehyde (Compound No. A23)



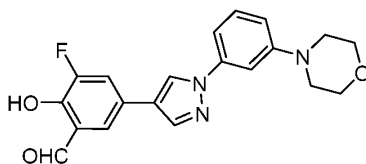
[0271] Step 1: 1-(3-(4-bromo-1H-pyrazol-1-yl)phenyl)piperidine

[0272] The title compound was prepared from 4-bromo-1H-pyrazole (1.75 g, 12 mmol.), 1-(3-bromophenyl)piperidine (2.40 g, 10 mmol) as described in Step 1 of Example A19 to give the title compound (1.28 g, 42% yield). LC-MS m/z $[M+H]^+$ calc'd for $C_{14}H_{16}BrN_3$, 306; found, 306.

[0273] Step 2: The title compound was prepared from 1-(3-(4-bromo-1H-pyrazol-1-yl)phenyl)piperidine (306 mg, 1.0 mmol) and 3-fluoro-2-hydroxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzaldehyde (532 mg, 2.0 mmol) as described in Step 2 of Example A19 to

give the title compound as a yellow solid (110 mg, 30% yield). ^1H NMR ($\text{DMSO}-d_6$, 400 MHz) δ : 10.91 (s, 1H), 10.33 (s, 1H), 9.05 (s, 1H), 8.21 (s, 1H), 7.95 (d, $J=12.0$ Hz, 1H), 7.83 (s, 1H), 7.38 (s, 1H), 7.28 (m, 1H), 7.23 (m, 1H), 6.87 (d, $J=8.0$ Hz, 1H), 3.25 (m, 4H), 1.65 (m, 4H), 1.58 (m, 2H); LC-MS m/z $[\text{M}+\text{H}]^+$ calc'd for $\text{C}_{21}\text{H}_{20}\text{FN}_3\text{O}_2$, 366; found, 366.

Example A24: 3-fluoro-2-hydroxy-5-(1-(3-morpholinophenyl)-1H-pyrazol-4-yl)benzaldehyde (Compound No. A24)

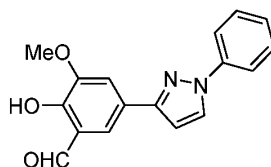


[0274] Step 1: 4-(3-(4-bromo-1H-pyrazol-1-yl)phenyl)morpholine

[0275] The title compound was prepared from 4-bromo-1H-pyrazole (1.75 g, 12 mmol.), 4-(3-bromophenyl)morpholine (2.42 g, 10 mmol) as described in Step 1 of Example A19 to give the title compound (524 mg, 17% yield). LC-MS m/z $[\text{M}+\text{H}]^+$ calc'd for $\text{C}_{13}\text{H}_{14}\text{BrN}_3\text{O}$, 308; found, 308.

[0276] Step 2: The title compound was prepared from 4-(3-(4-bromo-1H-pyrazol-1-yl)phenyl)morpholine (308 mg, 1.0 mmol) and 3-fluoro-2-hydroxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzaldehyde (532 mg, 2.0 mmol) as described in Step 2 of Example A19 to give the title compound as a yellow solid (144 mg, 39% yield). ^1H NMR ($\text{DMSO}-d_6$, 400 MHz) δ : 10.92 (s, 1H), 10.33 (s, 1H), 9.06 (s, 1H), 8.22 (s, 1H), 7.95 (d, $J=12.0$ Hz, 1H), 7.83 (s, 1H), 7.40 (s, 1H), 7.33 (m, 2H), 6.90 (d, $J=7.6$ Hz, 1H), 3.78 (m, 4H), 3.22 (m, 4H); LC-MS m/z $[\text{M}+\text{H}]^+$ calc'd for $\text{C}_{20}\text{H}_{18}\text{FN}_3\text{O}_3$, 368; found, 368.

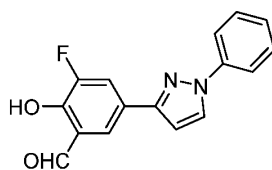
Example A25: 2-hydroxy-3-methoxy-5-(1-phenyl-1H-pyrazol-3-yl)benzaldehyde (Compound No. A25)



[0277] The title compound was prepared from 5-bromo-2-hydroxy-3-methoxybenzaldehyde (231 mg, 1.0 mmol) and 1-phenyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole

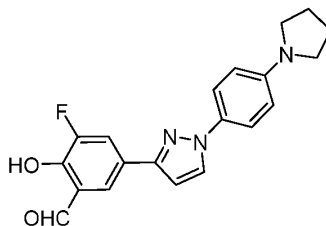
(324 mg, 1.2 mmol) as described in Example A1 to give the title compound as a yellow solid (163 mg, 55% yield). ^1H NMR (500 MHz, Chloroform-*d*) δ 11.13 (s, 1H), 10.01 (s, 1H), 7.98 (d, J = 2.5 Hz, 1H), 7.80 – 7.73 (m, 3H), 7.68 (d, J = 1.9 Hz, 1H), 7.49 (dd, J = 8.6, 7.4 Hz, 2H), 7.32 (td, J = 7.4, 1.1 Hz, 1H), 6.75 (d, J = 2.5 Hz, 1H), 4.03 (s, 3H); LC-MS m/z $[\text{M}+\text{H}]^+$ calc'd for $\text{C}_{17}\text{H}_{14}\text{N}_2\text{O}_3$, 295; found, 295.

Example A26: 3-fluoro-2-hydroxy-5-(1-phenyl-1H-pyrazol-3-yl)benzaldehyde (Compound No. A26)



[0278] The title compound was prepared from 5-bromo-3-fluoro-2-hydroxybenzaldehyde (219 mg, 1.0 mmol) and 1-phenyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (324 mg, 1.2 mmol) as described in Example A1 to give the title compound as a yellow solid (168 mg, 59% yield). ^1H NMR (500 MHz, Chloroform-*d*) δ 10.98 (s, 1H), 10.02 (d, J = 1.9 Hz, 1H), 7.98 (d, J = 2.5 Hz, 1H), 7.92 (d, J = 10.9 Hz, 2H), 7.79 – 7.74 (m, 2H), 7.53 – 7.45 (m, 2H), 7.38 – 7.29 (m, 1H), 6.73 (d, J = 2.5 Hz, 1H); LC-MS m/z $[\text{M}+\text{H}]^+$ calc'd for $\text{C}_{16}\text{H}_{11}\text{FN}_2\text{O}_2$, 283; found, 283.

Example A27: 3-fluoro-2-hydroxy-5-(1-(4-(pyrrolidin-1-yl)phenyl)-1H-pyrazol-3-yl)benzaldehyde (Compound No. A27)



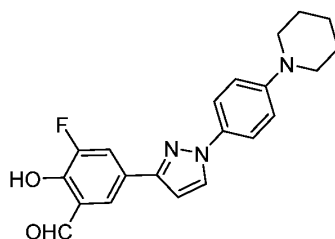
[0279] Step 1: 3-bromo-1-(4-(pyrrolidin-1-yl)phenyl)-1H-pyrazole

[0280] The title compound was prepared from 3-bromo-1H-pyrazole (1.75 g, 12 mmol.), 1-(4-bromophenyl)pyrrolidine (2.26 g, 10 mmol) as described in Step 1 of Example A19 to give

the title compound (379 mg, 13% yield). LC-MS m/z $[M+H]^+$ calc'd for $C_{13}H_{14}BrN_3$, 292; found, 292.

[0281] Step 2: The title compound was prepared from 3-bromo-1-(4-(pyrrolidin-1-yl)phenyl)-1H-pyrazole (292 mg, 1.0 mmol) and 3-fluoro-2-hydroxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzaldehyde (532 mg, 2.0 mmol) as described in Step 2 of Example A19 to give the title compound as a yellow solid (77 mg, 22% yield). 1H NMR ($DMSO-d_6$, 400 MHz) δ : 11.05 (br, 1H), 10.34 (s, 1H), 8.34 (s, 1H), 8.02 (m, 2H), 7.66 (m, 2H), 6.98 (s, 1H), 6.63 (m, 2H), 3.27 (m, 4H), 1.98 (m, 4H); LC-MS m/z $[M+H]^+$ calc'd for $C_{20}H_{18}FN_3O_2$, 352; found, 352.

Example A28: 3-fluoro-2-hydroxy-5-(1-(4-(piperidin-1-yl)phenyl)-1H-pyrazol-3-yl)benzaldehyde (Compound No. A28)

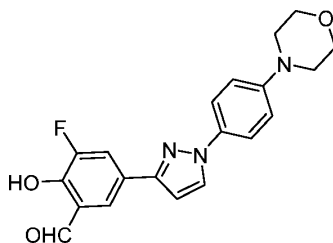


[0282] Step 1: 1-(4-(3-bromo-1H-pyrazol-1-yl)phenyl)piperidine

[0283] The title compound was prepared from 3-bromo-1H-pyrazole (1.75 g, 12 mmol.), 1-(4-bromophenyl)piperidine (2.40 g, 10 mmol) as described in Step 1 of Example A19 to give the title compound (1.01 g, 33% yield). LC-MS m/z $[M+H]^+$ calc'd for $C_{14}H_{16}BrN_3$, 306; found, 306.

[0284] Step 2: The title compound was prepared from 1-(4-(3-bromo-1H-pyrazol-1-yl)phenyl)piperidine (306 mg, 1.0 mmol) and 3-fluoro-2-hydroxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzaldehyde (532 mg, 2.0 mmol) as described in Step 2 of Example A19 to give the title compound as a yellow solid (92 mg, 25% yield). 1H NMR ($DMSO-d_6$, 400 MHz) δ : 11.06 (br, 1H), 10.34 (s, 1H), 8.40 (s, 1H), 8.02 (m, 2H), 7.70 (d, $J=8.8$ Hz, 2H), 7.03 (m, 3H), 3.18 (m, 4H), 1.64 (m, 4H), 1.55 (m, 2H); LC-MS m/z $[M+H]^+$ calc'd for $C_{21}H_{20}FN_3O_2$, 366; found, 366.

Example A29: 3-fluoro-2-hydroxy-5-(1-(4-morpholinophenyl)-1H-pyrazol-3-yl)benzaldehyde
(Compound No. A29)

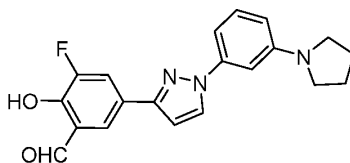


[0285] Step 1: 4-(4-(3-bromo-1H-pyrazol-1-yl)phenyl)morpholine

[0286] The title compound was prepared from 3-bromo-1H-pyrazole (1.75 g, 12 mmol.), 4-(4-bromophenyl)morpholine (2.42 g, 10 mmol) as described in Step 1 of Example A19 to give the title compound (585 mg, 19% yield). LC-MS m/z $[M+H]^+$ calc'd for $C_{13}H_{14}BrN_3O$, 308; found, 308.

[0287] Step 2: The title compound was prepared from 4-(4-(3-bromo-1H-pyrazol-1-yl)phenyl)morpholine (308 mg, 1.0 mmol) and 3-fluoro-2-hydroxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzaldehyde (532 mg, 2.0 mmol) as described in Step 2 of Example A19 to give the title compound as a yellow solid (118 mg, 32% yield). 1H NMR ($DMSO-d_6$, 400 MHz) δ : 11.07 (br, 1H), 10.33 (s, 1H), 8.43 (s, 1H), 8.02 (m, 2H), 7.74 (d, $J=8.8$ Hz, 2H), 7.07 (d, $J=8.8$ Hz, 2H), 7.01 (s, 1H), 3.76 (m, 4H), 3.16 (m, 4H); LC-MS m/z $[M+H]^+$ calc'd for $C_{20}H_{18}FN_3O_3$, 368; found, 368.

Example A30: 3-fluoro-2-hydroxy-5-(1-(3-(pyrrolidin-1-yl)phenyl)-1H-pyrazol-3-yl)benzaldehyde (Compound No. A30)

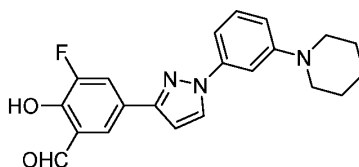


[0288] Step 1: 3-bromo-1-(3-(pyrrolidin-1-yl)phenyl)-1H-pyrazole

[0289] The title compound was prepared from 3-bromo-1H-pyrazole (1.75 g, 12 mmol.), 1-(3-bromophenyl)pyrrolidine (2.26 g, 10 mmol) as described in Step 1 of Example A19 to give the title compound (584 mg, 20% yield). LC-MS m/z $[M+H]^+$ calc'd for $C_{13}H_{14}BrN_3$, 292; found, 292.

[0290] Step 2: The title compound was prepared from 3-bromo-1-(3-(pyrrolidin-1-yl)phenyl)-1H-pyrazole (292 mg, 1.0 mmol) and 3-fluoro-2-hydroxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzaldehyde (532 mg, 2.0 mmol) as described in Step 2 of Example A19 to give the title compound as a light yellow solid (67 mg, 19% yield). ¹H NMR (*CDCl*₃, 400 MHz) δ : 10.99 (s, 1H), 10.02 (s, 1H), 7.94 (m, 3H), 7.31 (m, 1H), 6.97 (m, 2H), 6.70 (s, 1H), 6.55 (m, 1H), 3.39 (m, 4H), 2.07 (m, 4H); LC-MS *m/z* [M+H]⁺ calc'd for C₂₀H₁₈FN₃O₂, 352; found, 352.

Example A31: 3-fluoro-2-hydroxy-5-(1-(3-(piperidin-1-yl)phenyl)-1H-pyrazol-3-yl)benzaldehyde (Compound No. A31)

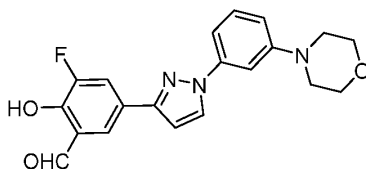


[0291] Step 1: 1-(3-(3-bromo-1H-pyrazol-1-yl)phenyl)piperidine

[0292] The title compound was prepared from 3-bromo-1H-pyrazole (1.75 g, 12 mmol), 1-(3-bromophenyl)piperidine (2.40 g, 10 mmol) as described in Step 1 of Example A19 to give the title compound (370 mg, 12% yield). LC-MS *m/z* [M+H]⁺ calc'd for C₁₄H₁₆BrN₃, 306; found, 306.

[0293] Step 2: The title compound was prepared from 1-(3-(3-bromo-1H-pyrazol-1-yl)phenyl)piperidine (306 mg, 1.0 mmol) and 3-fluoro-2-hydroxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzaldehyde (532 mg, 2.0 mmol) as described in Step 2 of Example A19 to give the title compound as a light yellow solid (83 mg, 27% yield). ¹H NMR (*DMSO-d*₆, 400 MHz) δ : 11.10 (br, 1H), 10.34 (s, 1H), 8.57 (s, 1H), 8.04 (m, 2H), 7.39 (s, 1H), 7.28 (m, 2H), 7.05 (s, 1H), 6.89 (m, 1H), 3.24 (m, 4H), 1.65 (m, 4H), 1.57 (m, 2H); LC-MS *m/z* [M+H]⁺ calc'd for C₂₁H₂₀FN₃O₂, 366; found, 366.

Example A32: 3-fluoro-2-hydroxy-5-(1-(3-morpholinophenyl)-1H-pyrazol-3-yl)benzaldehyde (Compound No. A32)

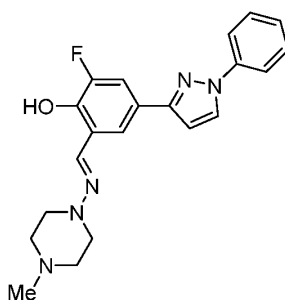


[0294] Step 1: 4-(3-(3-bromo-1H-pyrazol-1-yl)phenyl)morpholine

[0295] The title compound was prepared from 3-bromo-1H-pyrazole (1.75 g, 12 mmol.), 4-(3-bromophenyl)morpholine (2.42 g, 10 mmol) as described in Step 1 of Example A19 to give the title compound (524 mg, 17% yield). LC-MS m/z $[M+H]^+$ calc'd for $C_{13}H_{14}BrN_3O$, 308; found, 308.

[0296] Step 2: The title compound was prepared from 4-(3-(3-bromo-1H-pyrazol-1-yl)phenyl)morpholine (308 mg, 1.0 mmol) and 3-fluoro-2-hydroxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzaldehyde (532 mg, 2.0 mmol) as described in Step 2 of Example A19 to give the title compound as a white solid (114 mg, 31% yield). 1H NMR ($CDCl_3$, 400 MHz) δ : 11.01 (br, 1H), 10.03 (s, 1H), 7.98 (s, 1H), 7.93 (m, 2H), 7.55 (m, 1H), 7.40 (m, 1H), 7.29 (m, 1H), 7.02 (m, 1H), 6.73 (s, 1H), 3.99 (m, 4H), 3.33 (m, 4H); LC-MS m/z $[M-H]^-$ calc'd for $C_{20}H_{18}FN_3O_3$, 366; found, 366.

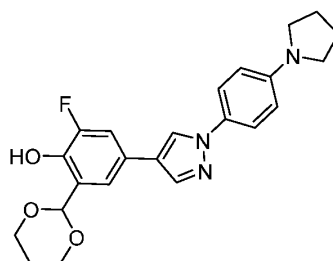
Example A33: (E)-2-fluoro-6-(((4-methylpiperazin-1-yl)imino)methyl)-4-(1-phenyl-1H-pyrazol-3-yl)phenol (Compound No. A33)



[0297] In a 20 mL sealed cap glass vial 3-fluoro-2-hydroxy-5-(1-phenyl-1H-pyrazol-3-yl)benzaldehyde (85 mg, 0.3 mmol) and 4-methylpiperazin-1-amine (65 mg, 0.3 mmol) were suspended in ethanol (5 mL) and added trifluoroacetic acid (3 drops) and warmed the mixture to get a clear solution. Then stirred at room temp for 2 hours, the resulting crashed product

collected by vacuum filtration and washed the product with small amount of ethanol to give the title product as white solid (85 mg, 75% yield). ^1H NMR (500 MHz, Chloroform-*d*) δ 11.86 (s, 1H), 7.94 (d, $J = 2.5$ Hz, 1H), 7.77 – 7.70 (m, 3H), 7.53 (d, $J = 2.7$ Hz, 1H), 7.50 – 7.42 (m, 3H), 7.29 (td, $J = 7.3, 1.3$ Hz, 2H), 6.67 (d, $J = 2.5$ Hz, 1H), 3.23 (t, $J = 5.1$ Hz, 4H), 2.77 – 2.50 (m, 4H), 2.37 (s, 3H); LC-MS m/z $[\text{M}-\text{H}]^-$ calc'd for $\text{C}_{21}\text{H}_{22}\text{FN}_5\text{O}$, 380; found, 380.

Example A34: 2-(1,3-dioxan-2-yl)-6-fluoro-4-(1-(4-(pyrrolidin-1-yl)phenyl)-1H-pyrazol-4-yl)phenol (Compound No. A34)

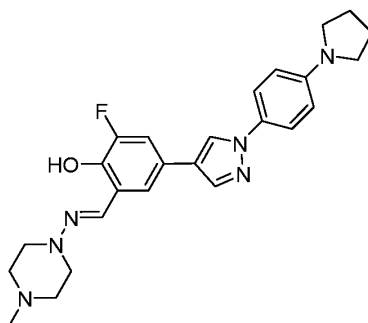


[0298] A solution of 3-fluoro-2-hydroxy-5-(1-(4-(pyrrolidin-1-yl)phenyl)-1H-pyrazol-4-yl)benzaldehyde (35 mg, 0.1 mmol), propane-1,3-diol (30 mg, 0.4 mmol), and TsOH (5 mg, 0.03 mmol) in toluene was refluxed for 2 hours. The solvent was removed mostly and the residue purified by prep-TLC to give desired product as white solid (13 mg, 32% yield). ^1H NMR (CDCl_3 , 300 MHz) δ : 7.95 (s, 1H), 7.86 (s, 1H), 7.74 (m, 1H), 7.55 (d, $J=9.0$ Hz, 2H), 7.22 (m, 1H), 6.71 (m, 2H), 4.36 (m, 2H), 4.08 (m, 2H), 3.37 (m, 4H), 2.23 (m, 1H), 2.08 (m, 5H); LC-MS m/z $[\text{M}+\text{H}]^+$ calc'd for $\text{C}_{23}\text{H}_{24}\text{FN}_3\text{O}_3$, 411; found, 411.

General procedure for Example A35 to Example A41:

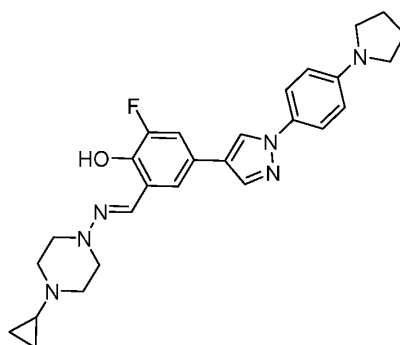
[0299] 3-fluoro-2-hydroxy-5-(1-(4-(pyrrolidin-1-yl)phenyl)-1H-pyrazol-4-yl)benzaldehyde (1 eq.) and amine compound (2 eq.) were dissolved in ethanol or methanol. The reaction was refluxed for 2 hours. The solvent was removed mostly and the residue was filtered. The cake was washed with ethanol and dried in *vacuo* to give desired product.

Example A35: (E)-2-fluoro-6-(((4-methylpiperazin-1-yl)imino)methyl)-4-(1-(4-(pyrrolidin-1-yl)phenyl)-1H-pyrazol-4-yl)phenol (Compound No. A35)



[0300] The title compound was prepared from 3-fluoro-2-hydroxy-5-(1-(4-(pyrrolidin-1-yl)phenyl)-1H-pyrazol-4-yl)benzaldehyde (100 mg, 0.28 mmol) and 4-methylpiperazin-1-amine (64 mg, 0.56 mmol) as described in above general procedure to give the title compound as white solid (80 mg, 63% yield). ^1H NMR (CDCl_3 , 400 MHz) δ : 11.60 (br, 1H), 7.93 (s, 1H), 7.85 (s, 1H), 7.72 (s, 1H), 7.52 (d, $J=8.4$ Hz, 2H), 7.21 (d, $J=11.6$ Hz, 1H), 7.12 (s, 1H), 6.61 (d, $J=8.4$ Hz, 2H), 3.33 (m, 8H), 2.80 (m, 4H), 2.49 (s, 3H), 2.04 (m, 4H); LC-MS m/z $[\text{M}+\text{H}]^+$ calc'd for $\text{C}_{25}\text{H}_{29}\text{FN}_6\text{O}$, 449; found, 449.

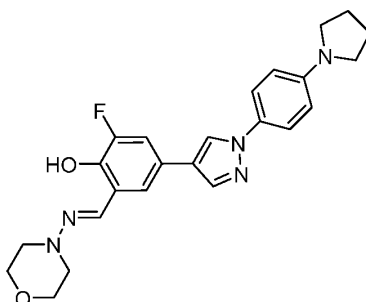
Example A36: (E)-2-(((4-cyclopropylpiperazin-1-yl)imino)methyl)-6-fluoro-4-(1-(4-(pyrrolidin-1-yl)phenyl)-1H-pyrazol-4-yl)phenol (Compound No. A36)



[0301] The title compound was prepared from 3-fluoro-2-hydroxy-5-(1-(4-(pyrrolidin-1-yl)phenyl)-1H-pyrazol-4-yl)benzaldehyde (20 mg, 0.06 mmol) and 4-cyclopropylpiperazin-1-amine dihydrochloride (12 mg, 0.06 mmol) as described in above general procedure except that sodium acetate (5 mg, 0.06 mmol) base added to the reaction mixture and finally washed the residue with water and ethanol to give the title compound as off-white solid (11 mg, 41% yield). ^1H NMR ($\text{DMSO}-d_6$, 400 MHz) δ : 11.52 (br, 1H), 8.69 (s, 1H), 8.01 (s, 1H), 7.90 (m, 1H), 7.62

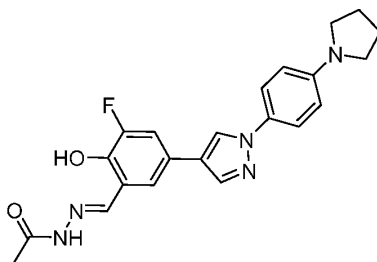
(d, $J=8.8$ Hz, 2H), 7.51 (m, 2H), 6.63 (d, $J=8.8$ Hz, 2H), 3.27 (m, 4H), 3.13 (m, 4H), 2.75 (m, 4H), 1.98 (m, 4H), 1.73 (m, 1H), 0.45 (m, 2H), 0.36 (m, 2H); LC-MS m/z $[M+H]^+$ calc'd for $C_{27}H_{31}FN_6O$, 475; found, 475.

Example A37: (*E*)-2-fluoro-6-((morpholinoimino)methyl)-4-(1-(4-(pyrrolidin-1-yl)phenyl)-1H-pyrazol-4-yl)phenol (Compound No. A37)



[0302] The title compound was prepared from 3-fluoro-2-hydroxy-5-(1-(4-(pyrrolidin-1-yl)phenyl)-1H-pyrazol-4-yl)benzaldehyde (100 mg, 0.28 mmol) and morpholin-4-amine (57 mg, 0.56 mmol) as described in above general procedure to give the title compound as white solid (85 mg, 69% yield). 1H NMR ($DMSO-d_6$, 400 MHz) δ : 11.42 (br, 1H), 8.70 (s, 1H), 8.00 (m, 2H), 7.62 (m, 2H), 7.53 (m, 2H), 6.63 (d, $J=8.8$ Hz, 2H), 3.80 (m, 4H), 3.27 (m, 4H), 3.16 (m, 4H), 1.97 (m, 4H); LC-MS m/z $[M+H]^+$ calc'd for $C_{24}H_{26}FN_5O_2$, 436; found, 436.

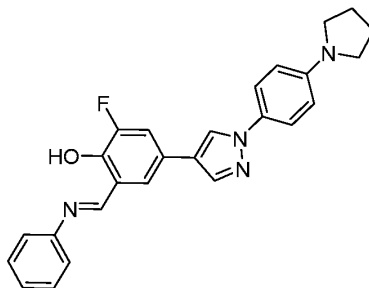
Example A38: N'-(3-fluoro-2-hydroxy-5-(1-(4-(pyrrolidin-1-yl)phenyl)-1H-pyrazol-4-yl)benzylidene)acetohydrazide (Compound No. A38)



[0303] The title compound was prepared from 3-fluoro-2-hydroxy-5-(1-(4-(pyrrolidin-1-yl)phenyl)-1H-pyrazol-4-yl)benzaldehyde (100 mg, 0.28 mmol) and acetohydrazide (41 mg, 0.56 mmol) as described in above general procedure to give the title compound as white solid (55 mg, 47% yield). 1H NMR ($DMSO-d_6$, 400 MHz) δ : 11.87 (br, 0.6H), 11.56 (br, 0.6H), 11.45

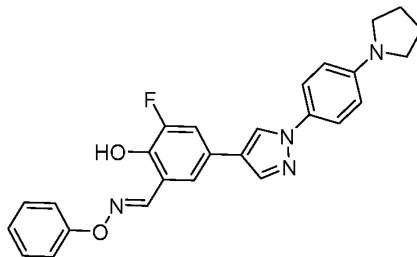
(br, 0.4H), 10.34 (br, 0.4H), 8.75 (s, 1H), 8.36 (s, 0.6H), 8.29 (s, 0.4H), 8.08 (s, 1H), 7.64 (m, 4H), 6.64 (d, $J=8.4$ Hz, 2H), 3.27 (m, 4H), 2.25 (s, 1H), 1.97-2.02 (m, 6H); LC-MS m/z $[M+H]^+$ calc'd for $C_{22}H_{22}FN_5O_2$, 408; found, 408.

Example A39: (E)-2-fluoro-6-((phenylimino)methyl)-4-(1-(4-(pyrrolidin-1-yl)phenyl)-1H-pyrazol-4-yl)phenol (Compound No. A39)



[0304] The title compound was prepared from 3-fluoro-2-hydroxy-5-(1-(4-(pyrrolidin-1-yl)phenyl)-1H-pyrazol-4-yl)benzaldehyde (100 mg, 0.28 mmol) and aniline (52 mg, 0.56 mmol) as described in above general procedure to give the title compound as white solid (57 mg, 47% yield). 1H NMR ($CDCl_3$, 400 MHz) δ : 13.62 (br, 1H), 8.71 (s, 1H), 8.02 (s, 1H), 7.91 (s, 1H), 7.62 (d, $J=7.6$ Hz, 2H), 7.32-7.49 (m, 9H), 3.44 (m, 4H), 2.14 (m, 4H); LC-MS m/z $[M+H]^+$ calc'd for $C_{26}H_{23}FN_4O$, 427; found, 427.

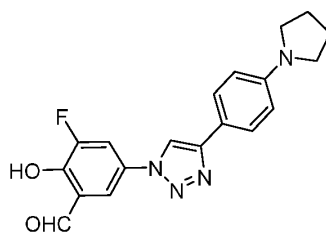
Example A40: (E)-3-fluoro-2-hydroxy-5-(1-(4-(pyrrolidin-1-yl)phenyl)-1H-pyrazol-4-yl)benzaldehyde O-phenyl oxime (Compound No. A40)



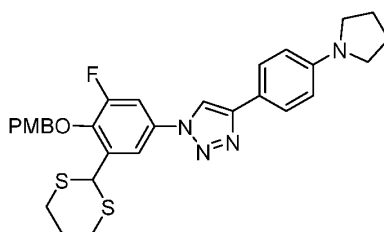
[0305] The title compound was prepared from 3-fluoro-2-hydroxy-5-(1-(4-(pyrrolidin-1-yl)phenyl)-1H-pyrazol-4-yl)benzaldehyde (50 mg, 0.14 mmol) and O-phenylhydroxylamine hydrochloride (31 mg, 0.21 mmol) as described in above general procedure except that TEA (29 mg, 0.28 mmol) base added to the reaction mixture and stirred overnight at room temperature to give the title compound as green solid (27 mg, 44% yield). 1H NMR ($DMSO-d_6$, 400 MHz) δ :

10.40 (br, 1H), 8.83 (d, $J=5.2$ Hz, 2H), 8.13 (s, 1H), 7.87 (s, 1H), 7.73 (d, $J=12.0$ Hz, 1H), 7.65 (d, $J=8.8$ Hz, 2H), 7.39 (m, 2H), 7.32 (m, 2H), 7.08 (m, 1H), 6.64 (d, $J=8.8$ Hz, 2H), 3.27 (m, 4H), 1.98 (m, 4H); LC-MS m/z $[M+H]^+$ calc'd for $C_{26}H_{23}FN_4O_2$, 443; found, 443.

Example A41: 3-fluoro-2-hydroxy-5-(4-(4-(pyrrolidin-1-yl)phenyl)-1H-1,2,3-triazol-1-yl)benzaldehyde (Compound No. A42)



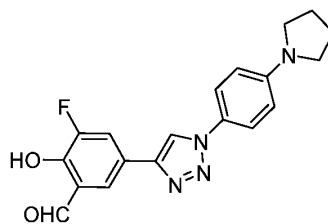
[0306] Step 1: 1-(3-(1,3-Dithian-2-yl)-5-fluoro-4-(4-methoxybenzyloxy)phenyl)-4-(4-(pyrrolidin-1-yl)phenyl)-1H-1,2,3-triazole



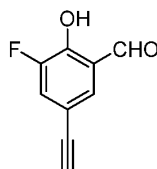
[0307] A mixture of 2-(5-azido-3-fluoro-2-(4-methoxybenzyloxy)phenyl)-1,3-dithiane (0.3 g, 0.77 mmol) (prepared as in Example A43), $CuSO_4$ (21 mg, 0.13 mmol), and L-ascorbic acid sodium salt (65 mg, 0.39 mmol) in MeOH/water (20 mL/2 mL) was purged with nitrogen for three times, then added 1-(4-Ethynylphenyl)pyrrolidine (112 mg, 0.77 mmol) to the reaction mixture. The reaction was heated at 50 °C for 1 hour. The mixture was cooled to room temperature, diluted with water (40 mL), and extracted with ethyl acetate (40 mLx3). The organic extracts were combined, washed with brine (40 mLx2), dried over anhydrous sodium sulfate, and concentrated. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate=20:1 to 2:1) to give the desired titled product (203 mg, 47% yield). LC-MS m/z $[M+H]^+$ calc'd for $C_{30}H_{31}FN_4O_2S_2$, 563; found, 563.

[0308] Step 2: A solution of above obtained step 1 product (150 mg, 0.27 mmol), MeI (3.8 g, 26.8 mmol), and NaHCO₃ (448 mg, 5.3 mmol) in acetonitrile/ water (15 mL/3 mL) was stirred overnight at 40 °C. The solution was diluted with water and extracted with ethyl acetate for three times. The organic extracts were combined, washed with brine, dried over anhydrous sodium sulfate, and concentrated. The residue was dissolved in 4N HCl (5 mL) and the reaction was stirred for 1 hour at room temperature. The solution was poured into ice-cold sat. sodium bicarbonate and extracted with ethyl acetate for three times. The organic extracts were combined, washed with brine, dried over anhydrous sodium sulfate, and concentrated. The residue was purified by prep-TLC (DCM/MeOH=20:1) to give the desired product as yellow solid (7 mg, 7% yield). ¹H NMR (CDCl₃, 400 MHz) δ : 11.07 (s, 1H), 10.03 (s, 1H), 8.01 (s, 1H), 7.84 (m, 2H), 7.75 (m, 2H), 6.68 (m, 2H), 3.36 (m, 4H), 2.05 (m, 4H); LC-MS m/z [M+H]⁺ calc'd for C₁₉H₁₇FN₄O₂, 353; found, 353.

Example A42: 3-fluoro-2-hydroxy-5-(1-(4-(pyrrolidin-1-yl)phenyl)-1H-1,2,3-triazol-4-yl)benzaldehyde (Compound No. A43)



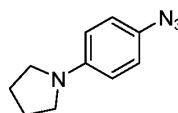
[0309] Step 1: 5-Ethynyl-3-fluoro-2-hydroxybenzaldehyde



[0310] Starting materials PdCl₂(PPh)₂ (0.3 g, 0.25 mmol), CuI (0.03 g, 0.1 mmol), and ethynyltrimethylsilane (1.47 g, 15.0 mmol) were added to a solution of 5-bromo-3-fluoro-2-hydroxybenzaldehyde (2.19 g, 10.0 mmol), triethylamine (2.02 g, 20.0 mmol), and triphenylphosphine (0.045 g, 0.125 mmol) in THF (20 mL) under nitrogen protection was refluxed for 60 hours. The mixture was cooled to room temperature, diluted with water/ethyl acetate, and filtered. The cake was washed with ethyl acetate. The filtrate and wash was

combined, separated, and the water phase was re-extracted with ethyl acetate for two more times. The organic extracts were combined, washed with brine, dried over anhydrous sodium sulfate, and concentrated. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate=500:1 to 300:1) to give 3-fluoro-2-hydroxy-5-((trimethylsilyl)ethynyl)benzaldehyde (1.1 g, 47% yield). The 3-fluoro-2-hydroxy-5-((trimethylsilyl)ethynyl)benzaldehyde (1.0 g, 4.2 mmol) was dissolved in THF (15 mL) and TBAF (2.2 g, 8.4 mmol) was added. The reaction was stirred for 1 hour at room temperature. The solvent was removed in vacuo and the residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate=500:1 to 300:1) to give the title product (0.31 g, 45% yield). ^1H NMR (CDCl_3 , 400 MHz) δ : 10.96 (br, 1H), 9.89 (d, $J=8.4$ Hz, 1H), 7.49 (m, 2H), 3.08 (s, 1H).

[0311] Step 2: 1-(4-Azidophenyl)pyrrolidine

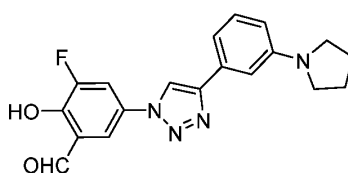


[0312] In a 50 mL dry round bottom flask, BuLi (4 mL, 10.0 mmol, 2.5 M in THF) was added to a solution of 1-(4-bromophenyl)pyrrolidine (0.5 g, 2.2 mmol) in THF (5 mL) at -78 °C. The reaction was stirred for 30 min. TsN_3 (1.3 g, 6.7 mmol) was added. The reaction was stirred for 5 hours at room temperature. The reaction was quenched with sat. ammonium chloride (20 mL) and extracted with EtOAc (20 mL x 3). The organic layers were combined, washed with brine (20 mL), dried over anhydrous sodium sulfate, and concentrated. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate=500:1 to 400:1) to give title product (150 mg, 36% yield). LC-MS m/z $[\text{M}+\text{H}]^+$ calc'd for $\text{C}_{10}\text{H}_{12}\text{N}_4$, 189; found, 189.

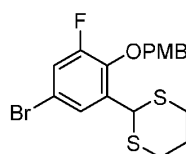
[0313] Step 3: A mixture of 1-(4-Azidophenyl)pyrrolidine (100 mg, 0.53 mmol), CuSO_4 (8.5 mg, 0.053 mmol), and L-ascorbic acid sodium salt (52.7 mg, 0.27 mmol) in t-BuOH/water (5 mL/5 mL) was purged with nitrogen for three times and 5-Ethynyl-3-fluoro-2-hydroxybenzaldehyde (131 mg, 0.80 mmol) was added to the reaction mixture. The reaction was heated overnight at 40 °C. The mixture was cooled to room temperature, diluted with water (20 mL), and extracted with ethyl acetate (20 mL x 3). The organic extracts were combined, washed with brine (20 mL x 2), dried over anhydrous sodium sulfate, and concentrated. The residue was

purified by silica gel column chromatography (petroleum ether/ethyl acetate=20:1 to 5:1) and prep-HPLC to give the desired final product as light yellow solid (12 mg, 6% yield). ^1H NMR ($\text{DMSO}-d_6$, 400 MHz) δ : 11.17 (br, 1H), 10.37 (s, 1H), 9.15 (s, 1H), 8.04 (m, 2H), 7.68 (d, $J=8.8$ Hz, 2H), 6.70 (d, $J=9.2$ Hz, 2H), 3.30 (m, 4H), 2.00 (m, 4H); LC-MS m/z $[\text{M}+\text{H}]^+$ calc'd for $\text{C}_{19}\text{H}_{17}\text{FN}_4\text{O}_2$, 353; found, 353.

Example A43: 3-fluoro-2-hydroxy-5-(4-(3-(pyrrolidin-1-yl)phenyl)-1H-1,2,3-triazol-1-yl)benzaldehyde (Compound No. A44)

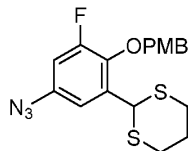


[0314] Step 1: 2-(5-Bromo-3-fluoro-2-(4-methoxybenzyloxy)phenyl)-1,3-dithiane



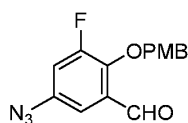
[0315] In a 100 mL dry round bottom flask, $\text{BF}_3 \cdot \text{OEt}_2$ (3.41 g, 24.0 mmol) was added to a solution of 5-bromo-3-fluoro-2-hydroxybenzaldehyde (4.36 g, 20.0 mmol) and propane-1,3-dithiol (2.6 g, 24.0 mmol) in DCM (20 mL) under nitrogen protection. The reaction was stirred for 3 hours at room temperature. The solution was poured into ice-water and extracted with ethyl acetate (50 mL x 3). The organic extracts were combined, washed with brine (30 mL), dried over anhydrous sodium sulfate, and concentrated. The crude was dissolved in DMF (20 mL) then PMBCl (6.24 g, 40.0 mmol) and potassium carbonate (8.28 g, 60 mmol) were added. The reaction was stirred for was 2 h at 90 °C. The mixture was cooled to room temperature, diluted with water (100 mL), and extracted with ethyl acetate (100 mL x 3). The organic extracts were combined, washed with brine (50 mL x 2), dried over anhydrous sodium sulfate, and concentrated. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate=500:1 to 400:1) to give titled product (6.37 g, 74% yield). ^1H NMR (CDCl_3 , 400 MHz) δ : 7.51 (s, 1H), 7.42 (m, 2H), 7.24 (m, 1H), 6.94 (m, 2H), 5.48 (s, 1H), 5.07 (s, 2H), 3.84 (s, 3H), 2.98 (m, 2H), 2.88 (m, 2H), 2.15 (m, 1H), 1.90 (m, 1H).

[0316] Step 2: 2-(5-Azido-3-fluoro-2-(4-methoxybenzyloxy)phenyl)-1,3-dithiane



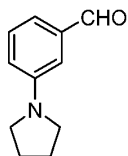
[0317] In a 100 mL dry round bottom flask, BuLi (6.6 mL, 10.5 mmol, 1.6 M in THF) was added to a solution of 2-(5-Bromo-3-fluoro-2-(4-methoxybenzyloxy)phenyl)-1,3-dithiane (1.0 g, 2.3 mmol) and TsN₃ (1.38 g, 7.0 mmol) in THF (10 mL) at -78 °C. The reaction was stirred for 2.5 hours at room temperature. The reaction was quenched with sat. ammonium chloride (30 mL) and extracted with EtOAc (30 mL x 3). The organic layers were combined, washed with brine (30 mL), dried over anhydrous sodium sulfate, and concentrated. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate=100:1 to 50:1) to give the titled product (0.71 g, 78% yield, containing ~55% debrominated side product inside). LC-MS m/z [M+H]⁺ calc'd for C₁₈H₁₈FN₃O₂S₂, 392; found, 392.

[0318] Step 3: 5-Azido-3-fluoro-2-(4-methoxybenzyloxy)benzaldehyde



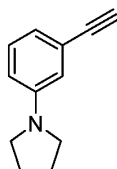
[0319] DMP (2.4 g, 5.6 mmol) was added to a solution of 2-(5-Azido-3-fluoro-2-(4-methoxybenzyloxy)phenyl)-1,3-dithiane (1.1 g, 2.8 mmol) in acetonitrile/DCM/water (16 mL/2 mL/2 mL). The reaction was stirred overnight at 45 °C. The mixture was diluted with ethyl acetate (50 mL) and filtered. The filtrate was washed with sat. sodium bicarbonate (50 mL). The organic layer was dried over anhydrous sodium sulfate and concentrated. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate=100:1 to 50:1) to give the titled product (0.79 g, 93% yield containing ~55% debromo-byproduct inside). LC-MS m/z [M+H]⁺ calc'd for C₁₅H₁₂FN₃O₃, 302; found, 302.

[0320] Step 4: 3-(Pyrrolidin-1-yl)benzaldehyde



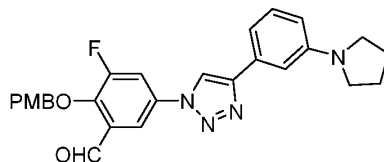
[0321] BuLi (20.6 mL, 33.2 mmol, 1.6 M in THF) was added to a solution of 1-(3-bromophenyl)pyrrolidine (5 g, 22.1 mmol) in THF (25 mL) at -78 °C. The reaction was stirred for 1 hour at this temperature. A solution of DMF (2.4 g, 33.2 mmol) in THF (5 mL) was added. The reaction was stirred for 2 hours at room temperature. The reaction was quenched with sat. ammonium chloride (50 mL) and extracted with EtOAc (50 mL x 3). The organic layers were combined, washed with brine (50 mL), dried over anhydrous sodium sulfate, and concentrated. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate=500:1 to 300:1) to give the desired product (2.85 g, 74% yield). ¹H NMR (CDCl₃, 400 MHz) δ : 9.97 (s, 1H), 7.79 (t, *J*=8.0 Hz, 1H), 7.16 (d, *J*=7.2 Hz, 1H), 7.04 (s, 1H), 6.83 (dd, *J*=8.4 Hz, 2.0 Hz, 1H), 3.36 (m, 4H), 2.06 (m, 4H).

[0322] Step 5: 1-(3-Ethynylphenyl)pyrrolidine



[0323] BuLi (4.3 mL, 6.9 mmol, 1.6 M in THF) was added to a solution of 3-(Pyrrolidin-1-yl)benzaldehyde (1.0 g, 5.7 mmol) in THF (10 mL) at -78 °C. The reaction was stirred for 30 min. TMSN₂ (3.4 mL, 6.9 mmol, 2 M in THF) was added. The reaction was stirred for 1 h at -78 °C. The reaction was quenched with sat. ammonium chloride (30 mL) and extracted with EtOAc (30 mLx3). The organic layers were combined, washed with brine (30 mL), dried over anhydrous sodium sulfate, and concentrated. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate=500:1 to 400:1) to give the desired 1-(3-Ethynylphenyl)pyrrolidine (0.63 g, 64% yield).

[0324] Step 6: 3-Fluoro-2-(4-methoxybenzyloxy)-5-(4-(3-(pyrrolidin-1-yl)phenyl)-1H-1,2,3-triazol-1-yl)benzaldehyde

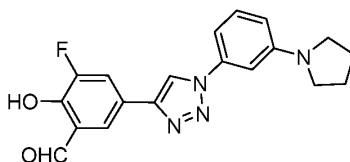


[0325] A mixture of 5-Azido-3-fluoro-2-(4-methoxybenzyloxy)benzaldehyde (0.4 g, 1.3 mmol), CuSO₄ (20 mg, 0.13 mmol), and L-ascorbic acid sodium salt (150 mg, 0.75 mmol) in t-

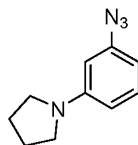
BuOH/water (5 mL/5 mL) was purged with nitrogen for three times then added 1-(3-Ethynylphenyl)pyrrolidine (0.2 g, 1.2 mmol) to the reaction mixture. The reaction was heated at 40 °C overnight. The mixture was cooled to room temperature, diluted with water (20 mL), and extracted with ethyl acetate (20 mL x 3). The organic extracts were combined, washed with brine (20 mL x 2), dried over anhydrous sodium sulfate, and concentrated. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate=20:1 to 2:1) to give PMB-protected desired product (120 mg, 22% yield). LC-MS m/z [M+H]⁺ calc'd for C₂₇H₂₅FN₄O₃, 473; found, 473.

[0326] Step 7: A solution of 3-Fluoro-2-(4-methoxybenzyloxy)-5-(4-(3-(pyrrolidin-1-yl)phenyl)-1H-1,2,3-triazol-1-yl)benzaldehyde (120 mg, 0.25 mmol) and TFA (86 mg, 0.76 mmol) in DCM (5 mL) was stirred overnight at rt. The solution was diluted with DCM (10 mL) and washed with sat. sodium bicarbonate (10 mL). The organic layer was dried over anhydrous sodium sulfate and concentrated. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate/DCM=20:1:1 to 5:1:1) to give the final desired product as light yellow solid (30 mg, 34% yield). ¹H NMR (DMSO-*d*₆, 400 MHz) δ : 11.51 (s, 1H), 10.40 (s, 1H), 9.31 (s, 1H), 8.21 (dd, *J*=11.2 Hz, 2.8 Hz, 1H), 8.03 (m, 1H), 7.26 (m, 1H), 7.17 (m, 1H), 7.11 (m, 1H), 6.56 (m, 1H), 3.31 (m, 4H), 2.00 (m, 4H); LC-MS m/z [M+H]⁺ calc'd for C₁₉H₁₇FN₄O₂, 353; found, 353.

Example A44: 3-fluoro-2-hydroxy-5-(1-(3-(pyrrolidin-1-yl)phenyl)-1H-1,2,3-triazol-4-yl)benzaldehyde (Compound No. A45)



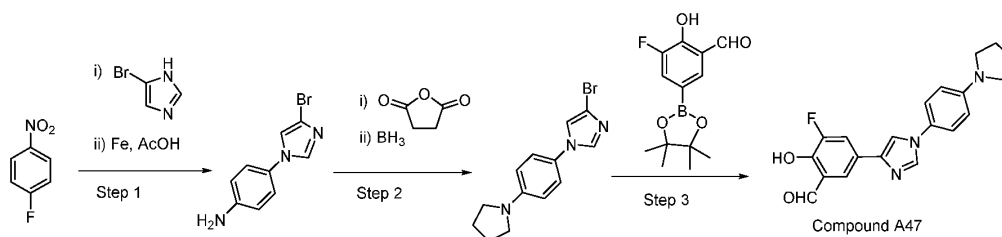
[0327] Step 1: 1-(3-Azidophenyl)pyrrolidine



[0328] A solution of 3-(pyrrolidin-1-yl)aniline (0.5 g, 3.1 mmol) in acetonitrile (10 mL) was cooled to 0 °C. Tert-Butyl nitrite (0.96 g, 9.3 mmol) and TMSN₃ (0.86 g, 7.4 mmol) were added. The reaction was stirred overnight at rt. The reaction was diluted with water (20 mL) and extracted with EtOAc (20 mL x 3). The organic layers were combined, washed with brine (20 mL), dried over anhydrous sodium sulfate, and concentrated. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate=300:1 to 100:1) to give the desired product (190 mg, 33% yield). LC-MS m/z [M+H]⁺ calc'd for C₁₀H₁₂N₄, 189; found, 189.

[0329] Step 2: A mixture of 1-(3-Azidophenyl)pyrrolidine (100 mg, 0.53 mmol), CuSO₄ (8.5 mg, 0.053 mmol), and L-ascorbic acid sodium salt (52.7 mg, 0.27 mmol) in t-BuOH/water (5 mL/5 mL) was purged with nitrogen for three times then added 5-Ethynyl-3-fluoro-2-hydroxybenzaldehyde (131 mg, 0.80 mmol) (from example A43) to the reaction mixture. The reaction was heated overnight at 40 °C. The mixture was cooled to room temperature, diluted with water (20 mL), and extracted with ethyl acetate (20 mL x 3). The organic extracts were combined, washed with brine (20 mL x 2), dried over anhydrous sodium sulfate, and concentrated. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate=20:1 to 5:1) and prep-TLC to give the final product as white solid (15 mg, 7% yield). ¹H NMR (CDCl₃, 400 MHz) δ: 11.05 (br, 1H), 10.03 (s, 1H), 8.21 (s, 1H), 8.01 (s, 1H), 7.88 (d, J=11.2 Hz, 1H), 7.44 (m, 1H), 7.34 (m, 1H), 7.19 (m, 1H), 6.92 (d, J=7.2 Hz, 1H), 3.48 (m, 4H), 2.16 (m, 4H); LC-MS m/z [M+H]⁺ calc'd for C₁₉H₁₇FN₄O₂, 353; found, 353.

Example A45: 3-fluoro-2-hydroxy-5-(1-(4-(pyrrolidin-1-yl)phenyl)-1H-imidazol-4-yl)benzaldehyde (Compound A47)



[0330] Step 1: 4-(4-bromo-1H-imidazol-1-yl)aniline

[0331] A mixture of 1-fluoro-4-nitrobenzene (1.16 g, 8.2 mmol, 1.2 eq.), 5-bromo-1H-imidazole (1 g, 6.8 mmol, 1.0 eq.), and potassium carbonate (2.84 g, 20.4 mmol, 3.0 eq.) in

DMF (15 mL) was heated at 80 °C for 2 hours under N₂ protection. The mixture was cooled to room temperature, poured into water, and extracted with ethyl acetate for three times. The organic extracts were combined, washed with brine, dried over anhydrous sodium sulfate, and concentrated to give crude 4-bromo-1-(4-nitrophenyl)-1H-imidazole (1.77 g, 6.63 mmol, 98% yield). LC-MS: 268.0, 270.0 (M+H)⁺, C₉H₆BrN₃O₂. In a 100 mL glass vial, iron powder (2.71 g, 48.32 mmol, 10.0 eq.) was added to a solution of 4-bromo-1-(4-nitrophenyl)-1H-imidazole (1.3 g, 4.83 mmol, 1.0 eq.) in AcOH (20 mL). The reaction was heated for 2 hours at 60°C. The reaction mixture was cooled to room temperature, poured into sat. NaHCO₃ and extracted with ethyl acetate for three times. The organic extracts were combined, washed with brine, dried over anhydrous sodium sulfate, and concentrated to give 4-(4-bromo-1H-imidazol-1-yl)aniline (790 mg, 3.31mmol, 68% yield).

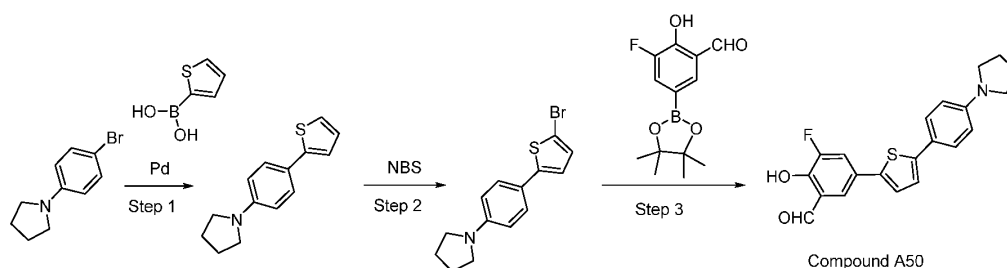
[0332] Step 2: 4-bromo-1-(4-(pyrrolidin-1-yl)phenyl)-1H-imidazole

[0333] A solution of 4-(4-bromo-1H-imidazol-1-yl)aniline (500 mg, 2.1 mmol, 1.0 eq.) and dihydrofuran-2,5-dione (422 mg, 4.2 mmol, 2.0 eq.) in toluene (15 mL) was stirred overnight at room temperature. The solution was poured into water and extracted with ethyl acetate for three times. The organic extracts were combined, washed with brine, dried over anhydrous sodium sulfate, and concentrated to give crude intermediate (710 mg). This intermediate was then refluxed in thionyl chloride (10 mL) for 1 hour and concentrated in vacuo to get the penultimate intermediate (690 mg). This intermediate (600 mg, 1.88 mmol, 1.0 eq.) was dissolved in THF (10 mL) and the solution was cooled to 0°C. Borane-dimethylsulfide (1.68 mL, 10 M, 9.0 eq.) was added. The reaction was stirred for 2 hours at 50°C. The system was cooled to room temperature, poured into ice water, and extracted with ethyl acetate for three times. The organic extracts were combined, washed with brine, dried over anhydrous sodium sulfate, and concentrated. The residue was purified by silica gel column chromatography (petroleum ether/EtOAc=20:1 to 10:1) to give 4-bromo-1-(4-(pyrrolidin-1-yl)phenyl)-1H-imidazole (240 mg, 0.82 mmol, 44% yield). LC-MS m/z [M+H]⁺ calc'd for C₁₃H₁₄BrN₃, 292; found, 292.

[0334] Step 3: A mixture of 4-bromo-1-(4-(pyrrolidin-1-yl)phenyl)-1H-imidazole (200 mg, 0.69 mmol, 1.0 eq.), 3-fluoro-2-hydroxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzaldehyde (459 mg, 1.73 mmol, 2.5 eq.), potassium carbonate (286 mg, 2.07 mmol, 3.0 eq.), PdCl₂(dppf) (85 mg, 0.07 mmol, 0.1 eq.) in dioxane/water (10 mL/3 mL) was heated at 100 °C for 3 hours under nitrogen atmosphere. The mixture was cooled to room temperature and poured

into water. Then pH of the system was adjusted to 4-5 and extracted with ethyl acetate for three times. The organic extracts were combined, washed with brine, dried over anhydrous sodium sulfate, and concentrated. The residue was purified by silica gel column (petroleum ether/EtOAc=50:1 to 20:1) to give 3-fluoro-2-hydroxy-5-(1-(4-(pyrrolidin-1-yl)phenyl)-1H-imidazol-4-yl)benzaldehyde (42 mg, 0.12 mmol, 17% yield) as a yellow solid. ¹H NMR (*DMSO-d*₆, 400 MHz) δ : 10.87 (br, 1H), 10.33 (s, 1H), 8.14 (d, *J*=10.4 Hz, 2H), 7.97-7.92 (m, 2H), 7.45 (d, *J*=8.8 Hz, 2H), 6.64 (d, *J*=8.4 Hz, 2H), 3.27 (m, 4H), 1.98 (m, 4H); LC-MS *m/z* [M+H]⁺ calc'd for C₂₀H₁₈FN₃O₂, 352; found, 352.

Example A46: 3-fluoro-2-hydroxy-5-(5-(4-(pyrrolidin-1-yl)phenyl)thiophen-2-yl)benzaldehyde (Compound A50)



[0335] Step 1: 1-(4-(thiophen-2-yl)phenyl)pyrrolidine

A mixture of thiophen-2-ylboronic acid (1.7 g, 13.3 mmol, 1.5 eq.), 1-(4-bromophenyl)pyrrolidine (2 g, 8.89 mmol, 1.0 eq.), potassium carbonate (3.7 g, 26.8 mmol, 3.0 eq.), and PdCl₂(dppf) (0.7 g, 0.89 mmol, 0.1 eq.) in dioxane/water (9 mL/3 mL) was heated at 95 °C for 2 hours under nitrogen atmosphere. The mixture was cooled to room temperature and filtered. The cake was washed with ethyl acetate. The filtrate and wash were combined, washed with water, dried over anhydrous sodium sulfate, and concentrated. The residue was purified by silica gel column (petroleum ether/EtOAc=100 to 300:1) to give 1-(4-(thiophen-2-yl)phenyl)pyrrolidine (1.2 g, 5.24 mmol, 59% yield).

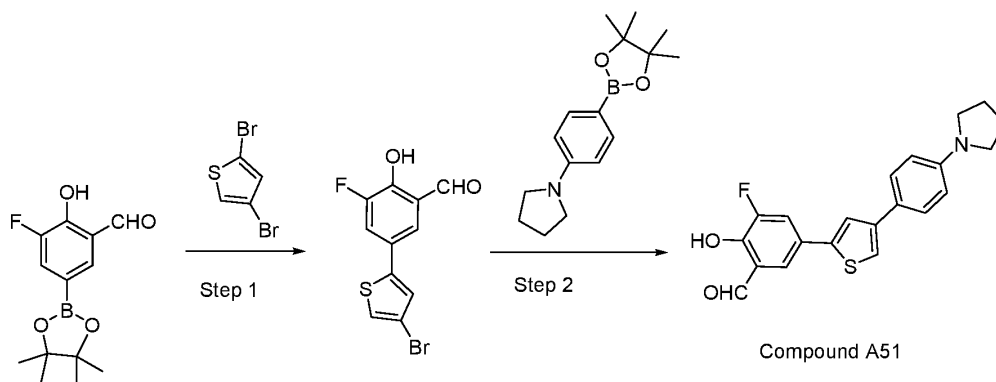
[0336] Step 2: 1-(4-(5-bromothiophen-2-yl)phenyl)pyrrolidine

A solution of 1-(4-(thiophen-2-yl)phenyl)pyrrolidine (950 mg, 4.15 mmol, 1 eq.) and NBS (1.11 g, 6.23 mmol, 1.5 eq.) in CHCl₃ (20 mL) was stirred for 2 h. The solution was poured into sat. sodium bicarbonate and extracted with CH₂Cl₂ for three times. The organic extracts were

combined, washed with water, dried over anhydrous sodium sulfate, and concentrated. The residue was purified by silica gel column (pure petroleum ether) to give 1-(4-(5-bromothiophen-2-yl)phenyl)pyrrolidine (350 mg, 1.13 mmol, 27% yield). ^1H NMR ($\text{DMSO}-d_6$, 400 MHz) δ : 7.39 (dd, $J=6.8$ Hz, 2.0 Hz, 2H), 7.14 (d, $J=4.0$ Hz, 1H), 7.08 (d, $J=4.0$ Hz, 1H), 6.54 (d, $J=8.8$ Hz, 2H), 3.25 (m, 4H), 1.96 (m, 4H).

[0337] Step 3: A mixture of 1-(4-(5-bromothiophen-2-yl)phenyl)pyrrolidine (340 mg, 1.10 mmol, 1.0 eq.), 3-fluoro-2-hydroxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzaldehyde (322 mg, 1.21 mmol, 1.1 eq.), potassium carbonate (456 mg, 3.30 mmol, 3.0 eq.), and $\text{PdCl}_2(\text{dppf})$ (90 mg, 0.11 mmol, 0.1 eq.) in dioxane/water (9 mL/3 mL) was heated at 95 °C for 2 hours under nitrogen atmosphere. The mixture was cooled to room temperature and poured into water. Then pH of the system was adjusted to 4-5 and extracted with ethyl acetate. The organic extracts were combined, washed with water, dried over anhydrous sodium sulfate, and concentrated. The residue was purified by silica gel column (petroleum ether/EtOAc=100:1 to 20:1) to give 3-fluoro-2-hydroxy-5-(5-(4-(pyrrolidin-1-yl)phenyl)thiophen-2-yl)benzaldehyde (110 mg, 0.30 mmol, 27% yield). ^1H NMR ($\text{DMSO}-d_6$, 400 MHz) δ : 11.10 (br, 1H), 10.31 (s, 1H), 7.90 (dd, $J=12.0$ Hz, 1.6 Hz, 1H), 7.65 (s, 1H), 7.47 (m, 3H), 7.26 (d, $J=3.6$ Hz, 1H), 6.57 (d, $J=8.8$ Hz, 2H), 3.36 (m, 4H), 1.96 (m, 4H). LC-MS m/z $[\text{M}+\text{H}]^+$ calc'd for $\text{C}_{21}\text{H}_{18}\text{FNO}_2\text{S}$, 368; found, 368.

Example A47: 3-fluoro-2-hydroxy-5-(4-(4-(pyrrolidin-1-yl)phenyl)thiophen-2-yl)benzaldehyde (Compound A51)

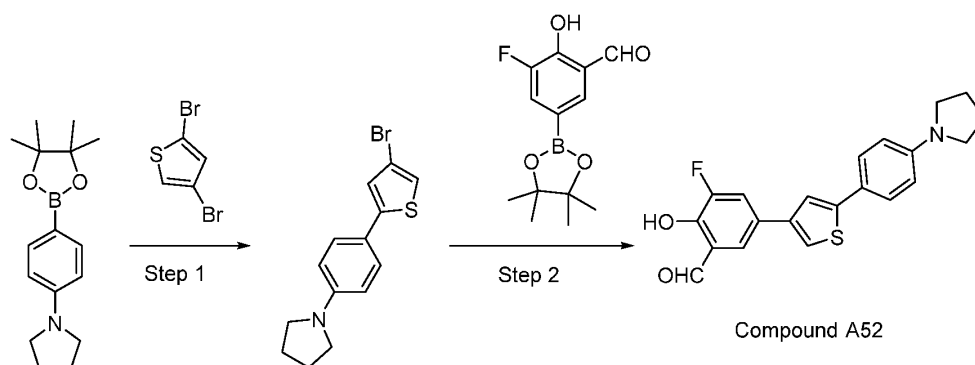


[0338] Step 1: 5-(4-bromothiophen-2-yl)-3-fluoro-2-hydroxybenzaldehyde

[0339] A mixture of 2,4-dibromothiophene (1 g, 4.1 mmol, 1.0 eq.), 3-fluoro-2-hydroxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzaldehyde (1.2 g, 4.51 mmol, 1.08 eq.), potassium phosphate (4.4 g, 20.8 mmol, 5.0 eq.), Pd(PPh₃)₄ (0.48 g, 0.41 mmol, 0.1 eq.) in dioxane/water (20 mL/6 mL) was heated at 100 °C for 3 hours under nitrogen atmosphere. The mixture was cooled to room temperature and poured into water. Then pH of the system was adjusted to 4-5 and extracted with ethyl acetate for three times. The organic extracts were combined, washed with brine, dried over anhydrous sodium sulfate, and concentrated. The residue was purified by silica gel column (petroleum ether/EtOAc=100:1 to 20:1) to give 5-(4-bromothiophen-2-yl)-3-fluoro-2-hydroxybenzaldehyde (390 mg, 1.29 mmol, 31% yield). LC-MS m/z [M+H]⁺ calc'd for C₁₁H₆BrFO₂S, 301; found, 301.

[0340] Step 2: A mixture of 5-(4-bromothiophen-2-yl)-3-fluoro-2-hydroxybenzaldehyde (302 mg, 1 mmol, 1.0 eq.), 1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)pyrrolidine (295 mg, 1.08 mmol, 1.08 eq.), potassium phosphate (1.06 g, 5.0 mmol, 5.0 eq.), Pd(PPh₃)₄ (116 mg, 0.1 mmol, 0.1 eq.) in dioxane/water (10 mL/3 mL) was heated at 100 °C for 3 hours under nitrogen atmosphere. The mixture was cooled to room temperature and poured into water. Then pH of the system was adjusted to 4-5 and extracted with ethyl acetate for three times. The organic extracts were combined, washed with brine, dried over anhydrous sodium sulfate, and concentrated. The residue was purified by silica gel column (petroleum ether/EtOAc=100:1 to 20:1) to give 3-fluoro-2-hydroxy-5-(4-(4-(pyrrolidin-1-yl)phenyl)thiophen-2-yl)benzaldehyde (60 mg, 0.16 mmol, 16% yield) as a yellow solid. ¹H NMR (DMSO-*d*₆, 400 MHz) δ : 11.13 (br, 1H), 10.32 (s, 1H), 8.00 (dd, *J*=12.4 Hz, 2.4 Hz, 1H), 7.93 (d, *J*=1.2 Hz, 1H), 7.72 (s, 1H), 7.61-7.55 (m, 3H), 6.57 (d, *J*=8.8 Hz, 2H), 3.26 (m, 4H), 1.97 (m, 4H). LC-MS m/z [M+H]⁺ calc'd for C₂₁H₁₈FNO₂S, 368; found, 368.

Example A48: 3-fluoro-2-hydroxy-5-(5-(4-(pyrrolidin-1-yl)phenyl)thiophen-3-yl)benzaldehyde (Compound A52)

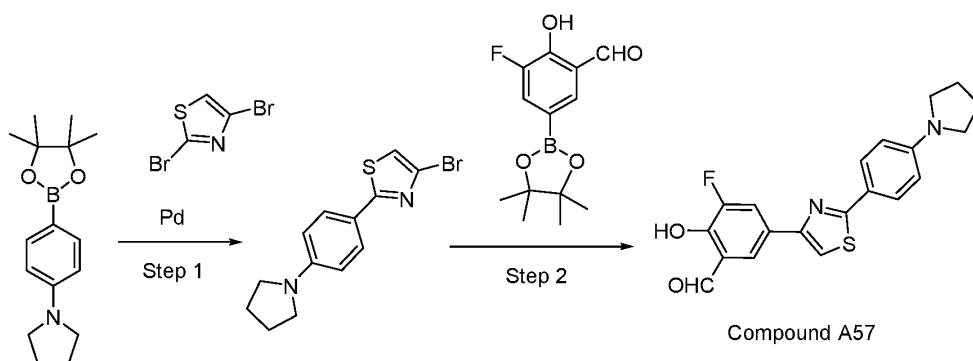


[0341] Step 1: 1-(4-(4-bromothiophen-2-yl)phenyl)pyrrolidine

A mixture of 2,4-dibromothiophene (1 g, 4.1 mmol, 1.0 eq.), 1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)pyrrolidine (1.22 g, 4.51 mmol, 1.08 eq.), potassium phosphate (4.4 g, 20.8 mmol, 5.0 eq.), Pd(PPh₃)₄ (0.48 g, 0.41 mmol, 0.1 eq.) in dioxane/water (20 mL/6 mL) was heated at 100 °C for 3 hours under nitrogen atmosphere. The mixture was cooled to room temperature and poured into water. Then pH of the system was adjusted to 4-5 and extracted with ethyl acetate for three times. The organic extracts were combined, washed with brine, dried over anhydrous sodium sulfate, and concentrated. The residue was purified by silica gel column (petroleum ether/EtOAc=100 to 500:1) to give 1-(4-(4-bromothiophen-2-yl)phenyl)pyrrolidine (260 mg, 0.84 mmol, 21% yield), used in next step.

[0342] Step 2: The title compound was prepared from 1-(4-(4-bromothiophen-2-yl)phenyl)pyrrolidine (230 mg, 0.74 mmol, 1.0 eq.) and 3-fluoro-2-hydroxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzaldehyde (214 mg, 0.80 mmol, 1.08 eq.) using a method similar to that as described in Example A47 to give the final title compound (110 mg, 0.30 mmol, 41% yield) as a yellow solid. ¹H NMR (*DMSO-d*₆, 400 MHz) δ: 10.98 (br, 1H), 10.32 (s, 1H), 8.00 (dd, *J*=12.4 Hz, 2.0 Hz, 1H), 7.87 (d, *J*=1.2 Hz, 1H), 7.75 (d, *J*=1.2 Hz, 1H), 7.70 (d, *J*=1.2 Hz, 1H), 7.54 (d, *J*=8.8 Hz, 2H), 6.58 (d, *J*=8.8 Hz, 2H), 3.27 (m, 4H), 1.97 (m, 4H). LC-MS *m/z* [M+H]⁺ calc'd for C₂₁H₁₈FNO₂S, 368; found, 368.

Example A49: 3-fluoro-2-hydroxy-5-(2-(4-(pyrrolidin-1-yl)phenyl)thiazol-4-yl)benzaldehyde (Compound A57)

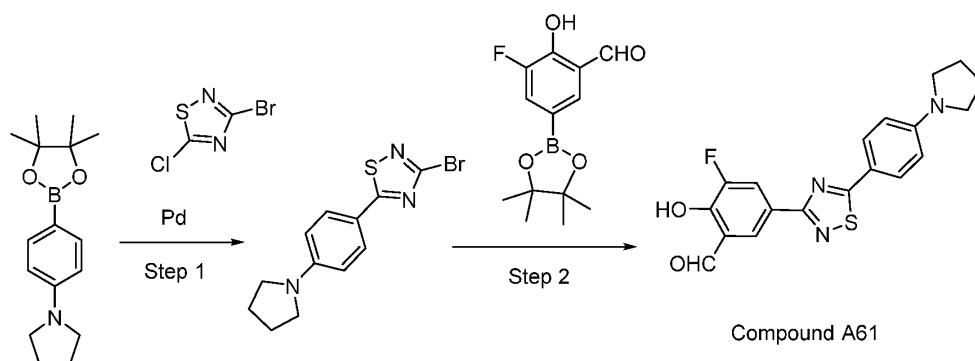


[0343] Step 1: 4-bromo-2-(4-(pyrrolidin-1-yl)phenyl)thiazole

[0344] A mixture of 2,4-dibromothiazole (500 mg, 2.06 mmol, 1.0 eq.), 1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)pyrrolidine (620 mg, 2.26 mmol, 1.1 eq.), potassium carbonate (850 mg, 6.18 mmol, 3.0 eq.), and PdCl₂(dppf) (170 mg, 0.21 mmol, 0.1 eq.) in dioxane/water (10 mL/5 mL) was heated at 100 °C for 1 hour under nitrogen protection. The mixture was cooled to room temperature, poured into water, and extracted with ethyl acetate for three times. The organic extracts were combined, washed with brine, dried over anhydrous sodium sulfate, and concentrated. The residue was purified by silica gel column (petroleum ether/EtOAc=100 to 500:1) to give 4-bromo-2-(4-(pyrrolidin-1-yl)phenyl)thiazole (397 mg, 1.29 mmol, 63% yield). LC-MS m/z [M+H]⁺ calc'd for C₁₃H₁₃BrN₂S, 311; found, 311.

[0345] Step 2: The title compound was prepared from 3-fluoro-2-hydroxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzaldehyde (415 mg, 1.56 mmol, 1.2 eq.) and 4-bromo-2-(4-(pyrrolidin-1-yl)phenyl)thiazole (400 mg, 1.30 mmol, 1.0 eq.) using a method similar to that as described in Example A47 to give the final title compound (110 mg, 0.30 mmol, 41% yield) as a yellow solid. ¹H NMR (DMSO-*d*₆, 400 MHz) δ: 11.12 (br, 1H), 10.35 (s, 1H), 8.14 (dd, *J*=10.0 Hz, 2.4 Hz, 2H), 7.97 (s, 1H), 7.82 (d, *J*=8.8 Hz, 2H), 6.63 (d, *J*=8.8 Hz, 2H), 3.31(m, 4H), 1.98 (m, 4H). LC-MS m/z [M-H]⁻ calc'd for C₂₀H₁₇FN₂O₂S, 367; found, 367.

Example A50: 3-fluoro-2-hydroxy-5-(5-(4-(pyrrolidin-1-yl)phenyl)-1,2,4-thiadiazol-3-yl)benzaldehyde (Compound A61)

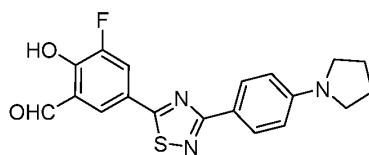


[0346] Step 1: 3-bromo-5-(4-(pyrrolidin-1-yl)phenyl)-1,2,4-thiadiazole

[0347] A mixture of 3-bromo-5-chloro-1,2,4-thiadiazole (0.5 g, 2.5 mmol, 1.0 eq.), 1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)pyrrolidine (0.75 g, 2.75 mmol, 1.1 eq.), potassium phosphate (1.59 g, 7.5 mmol, 3.0 eq.), PdCl₂(dppf) (204 mg, 0.25 mmol, 0.1 eq.) in DMF/water (6 mL/2 mL) was heated at 80 °C for 2.5 hours under nitrogen atmosphere. The mixture was cooled to room temperature and poured into water. Then pH of the system was adjusted to 4-5 and extracted with ethyl acetate for three times. The organic extracts were combined, washed with brine, dried over anhydrous sodium sulfate, and concentrated. The residue was purified by silica gel column (petroleum ether/EtOAc=20:1 to 50:1) to give 3-bromo-5-(4-(pyrrolidin-1-yl)phenyl)-1,2,4-thiadiazole (203 mg, 0.66 mmol, 26% yield). LC-MS *m/z* [M+H]⁺ calc'd for C₁₂H₁₂BrN₃S, 312; found, 312.

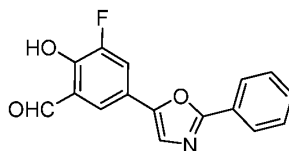
[0348] Step 2: The title compound was prepared from 3-fluoro-2-hydroxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzaldehyde (133 mg, 0.50 mmol, 1.1 eq.) and 3-bromo-5-(4-(pyrrolidin-1-yl)phenyl)-1,2,4-thiadiazole (140 mg, 0.45 mmol, 1.0 eq.) using a method similar to that as described in Example A47 to give the final title compound (30 mg, 0.08 mmol, 18% yield) as a yellow solid. ¹H NMR (DMSO-*d*₆, 400 MHz) δ: 11.54 (br, 1H), 10.37 (s, 1H), 8.38 (d, *J*=1.2 Hz, 1H), 8.24 (dd, *J*=11.6 Hz, 2.0 Hz, 1H), 7.89 (d, *J*=8.8 Hz, 2H), 6.67 (d, *J*=8.8 Hz, 2H), 3.35 (m, 4H), 1.99 (t, *J*=6.6 Hz, 4H). LC-MS *m/z* [M+H]⁺ calc'd for C₁₉H₁₆FN₃O₂S, 370; found, 370.

Example A51: 3-fluoro-2-hydroxy-5-(3-(4-(pyrrolidin-1-yl)phenyl)-1,2,4-thiadiazol-5-yl)benzaldehyde (Compound A62)



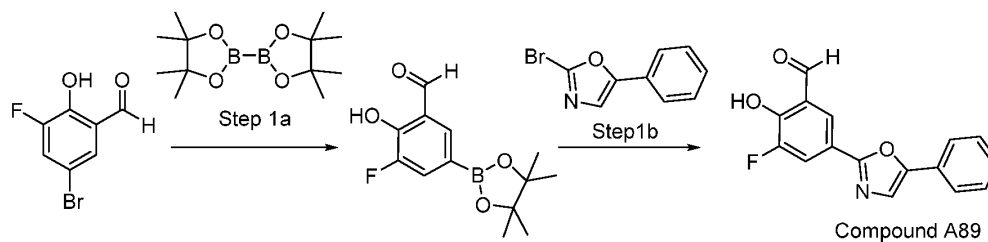
[0349] The title compound was prepared from 1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)pyrrolidine (258 mg, 0.94 mmol, 1.1 eq.) and 5-(3-bromo-1,2,4-thiadiazol-5-yl)-3-fluoro-2-hydroxybenzaldehyde (260 mg, 0.86 mmol, 1 eq.) (prepared as in Example A47) using a method similar to that as described in Example A47 to give the final title compound (87 mg, 0.24 mmol, 27% yield) as a yellow solid. ^1H NMR ($\text{DMSO}-d_6$, 400 MHz) δ : 11.88 (br, 1H), 10.36 (s, 1H), 8.22 (dd, $J=11.2$ Hz, 2.4 Hz, 1H), 8.15 (s, 1H), 8.13 (d, $J=8.8$ Hz, 2H), 6.65 (d, $J=9.2$ Hz, 2H), 3.32 (t, $J=6.8$ Hz, 4H), 1.98 (m, 4H). LC-MS m/z $[\text{M}+\text{H}]^+$ calc'd for $\text{C}_{19}\text{H}_{16}\text{FN}_3\text{O}_2\text{S}$, 370; found, 370.

Example A52: 3-fluoro-2-hydroxy-5-(2-phenyloxazol-5-yl)benzaldehyde (Compound A88)



[0350] The title compound was prepared from 5-bromo-2-phenyloxazole (223 mg, 1 mmol, 1 eq.) and 3-fluoro-2-hydroxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzaldehyde (244 mg, 1.08 mmol, 1.08 eq.) using a method similar to that as described in Example A47 to give the final title compound (120 mg, 0.42 mmol, 42% yield) as a yellow solid. ^1H NMR ($\text{DMSO}-d_6$, 400 MHz) δ : 11.35 (br, 1H), 10.35 (s, 1H), 8.12-8.06 (m, 3H), 7.92 (s, 1H), 7.86 (s, 1H), 7.57 (m, 3H). LC-MS m/z $[\text{M}+\text{H}]^+$ calc'd for $\text{C}_{16}\text{H}_{10}\text{FNO}_3$, 284; found, 284.

Example A53: 3-fluoro-2-hydroxy-5-(5-phenyloxazol-2-yl)benzaldehyde (Compound A89)

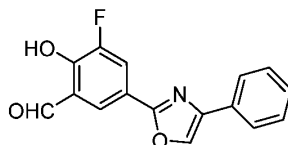


[0351] 3-fluoro-2-hydroxy-5-(5-phenyloxazol-2-yl)benzaldehyde was synthesized in a manner similar to that described by Ji et al. (*RSC Adv.*, 2018, 8, 13643-13648.)

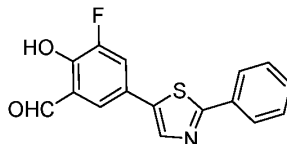
[0352] Step 1a: 5-bromo-3-fluoro-2-hydroxybenzaldehyde (131 mg, 0.6 mmol), bis(pinacolato)diboron, (253 mg, 0.66 mmol), potassium phosphate tribasic (254.7 mg), XPhos Pd G3 (50.8 mg) and XPhos (28.6 mg) were placed in a 5 mL microwave vial with a stir bar. Dioxane (2.4 mL) was added and the vial was degassed with argon and sealed. The reaction was heated to 130°C in a Biotage microwave for 60 minutes.

[0353] Step 1b: An aliquot (0.8 mL) of the reaction mixture from step 1a was added to a microwave vial containing 2-bromo-5-phenyloxazole (44.8 mg, 0.2 mmol), XPhos Pd G3 (8.5 mg) and XPhos (4.8 mg). The reaction was degassed with argon and heated to 130°C in a microwave for 30 minutes. The reaction mixture was diluted with DCM, acidified to pH=3 with citric acid and extracted 3 times with DCM. The combined organic phases were washed with brine and dried over anhydrous Na₂SO₄, filtered and evaporated. The crude product was purified by flash column chromatography 0-10% MeOH/DCM. Yield (6.6 mg, 12%). ¹H NMR (500 MHz, CDCl₃) δ 11.22 (s, 1H), 10.04 (d, J = 1.7 Hz, 1H), 8.19 (dd, J = 2.0, 1.2 Hz, 1H), 8.10 (dd, J = 11.0, 2.0 Hz, 1H), 7.98 (s, 1H), 7.85 – 7.77 (m, 2H), 7.48 – 7.41 (m, 2H), 7.40 – 7.33 (m, 1H). MS m/z [M+H]⁺ calc'd for C₁₆H₁₀FO₃, 284; found 284.

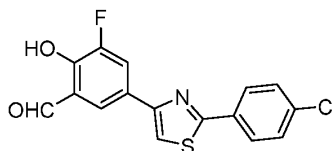
Example A54: 3-fluoro-2-hydroxy-5-(4-phenyloxazol-2-yl)benzaldehyde (Compound A90)



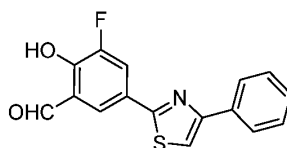
[0354] The title compound was prepared using a method similar to that as described in Example A53, using commercially available 2-bromo-4-phenyloxazole. Yield: 14%. ¹H NMR (500 MHz, CDCl₃) δ 11.22 (s, 1H), 10.04 (d, J = 1.7 Hz, 1H), 8.19 (dd, J = 2.0, 1.2 Hz, 1H), 8.10 (dd, J = 11.0, 2.0 Hz, 1H), 7.98 (s, 1H), 7.84 – 7.78 (m, 2H), 7.49 – 7.41 (m, 2H), 7.40 – 7.32 (m, 1H). MS m/z [M+H]⁺ calc'd for C₁₆H₁₀FO₃, 284; found 284.

Example A55: 3-fluoro-2-hydroxy-5-(2-phenylthiazol-5-yl)benzaldehyde (Compound A91)

[0355] The title compound was prepared using a method similar to that as described in Example A53, using commercially available 5-bromo-2-phenylthiazole. Yield 9%. ^1H NMR (500 MHz, CDCl_3) δ 11.15 (s, 1H), 10.03 (d, J = 1.8 Hz, 1H), 8.03 (dd, J = 2.1, 1.2 Hz, 1H), 8.01 (s, 1H), 7.97 (dd, J = 11.1, 2.1 Hz, 1H), 7.62 – 7.59 (m, 2H), 7.47 – 7.43 (m, 2H), 7.40 – 7.35 (m, 1H). MS m/z $[\text{M}+\text{H}]^+$ calc'd for $\text{C}_{16}\text{H}_{10}\text{FNO}_2\text{S}$, 300; found 300.

Example A56: 5-(2-(4-chlorophenyl)thiazol-4-yl)-3-fluoro-2-hydroxybenzaldehyde (Compound A92)

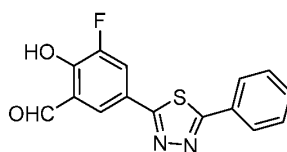
[0356] The title compound was prepared using a method similar to that as described in Example A53, using commercially available 4-bromo-2-(4-chlorophenyl)thiazole. Yield: 14%. ^1H NMR (500 MHz, Chloroform- d) δ 11.03 (s, 1H), 10.04 (d, J = 1.8 Hz, 1H), 8.06 (dd, J = 2.1, 1.2 Hz, 1H), 8.00 – 7.95 (m, 3H), 7.47 – 7.43 (m, 3H). MS m/z $[\text{M}+\text{H}]^+$ calc'd for $\text{C}_{16}\text{H}_9\text{ClFNO}_2\text{S}$, 334; found 334.

Example A57: 3-fluoro-2-hydroxy-5-(4-phenylthiazol-2-yl)benzaldehyde (Compound A93)

[0357] The title compound was prepared using a method similar to that as described in Example A53, using commercially available 2-bromo-4-phenylthiazole. Yield: 30%. ^1H NMR (500 MHz, CDCl_3) δ 11.16 (s, 1H), 10.04 (d, J = 1.8 Hz, 1H), 8.08 – 8.04 (m, 1H), 8.07 (s, 1H),

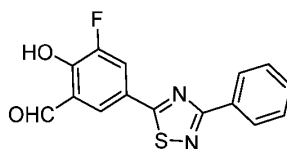
7.99 – 7.97 (m, 2H), 7.50 (s, 1H), 7.49 – 7.44 (m, 2H), 7.40 – 7.36 (m, 1H). MS m/z [M+H]⁺ calc'd for C₁₆H₁₀FN₂O₂S 300; found 300.

Example A58: 3-fluoro-2-hydroxy-5-(5-phenyl-1,3,4-thiadiazol-2-yl)benzaldehyde (Compound A94)



[0358] The title compound was prepared using a method similar to that as described in Example A53, using commercially available 2-bromo-5-phenyl-1,3,4-thiadiazole. Yield: 20%. ¹H NMR (500 MHz, Chloroform-*d*) δ 11.26 (s, 1H), 10.04 (d, *J* = 1.7 Hz, 1H), 8.08 (dd, *J* = 2.0, 1.2 Hz, 1H), 8.02 (tt, *J* = 7.4, 2.1 Hz, 3H), 7.55 – 7.49 (m, 3H). MS m/z [M+H]⁺ calc'd for C₁₅H₉FN₂O₂S 301; found 301.

Example A59: 3-fluoro-2-hydroxy-5-(3-phenyl-1,2,4-thiadiazol-5-yl)benzaldehyde (New Compound A95)



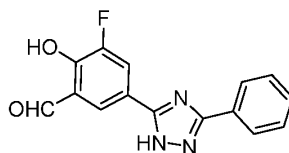
[0359] The title compound was prepared using a method similar to that as described in Example A53. However, the intermediate 3-fluoro-2-hydroxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzaldehyde, was synthesized and isolated according to the procedure by DiMauro et al. (*J. Org. Chem.*, 2006, 71(10), 359-3962.)

[0360] Step 1: To a 5mL microwave vial was added 5-bromo-3fluoro-salicaldehyde (329mg, 1.5 mmol), bis(pinacolato)diboron (419 mg, 1.65 mmol), potassium acetate (295 mg, 3 mmol) and Pd(dppf)Cl₂ (109 mg, 0.15 mmol) followed by 5mL of dioxane. The mixture was purged with argon and heated in the microwave for 45 minutes at 140°C. The mixture was cooled, tranfered to a round bottom flask, concentrated to dryness and resuspended in DCM. After filtering through celite and concentrating again, the product was purified by flash column

chromatography using 0-100% DCM in Hexanes as an eluent to provide 3-fluoro-2-hydroxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzaldehyde as a colorless oil that solidified upon standing (237 mg, 59% yield). ¹H NMR (500 MHz, DMSO-d₆) δ 11.35 (s, 1H), 10.27 (s, 1H), 7.82 (dd, J = 1.6, 0.7 Hz, 1H), 7.59 (dd, J = 11.1, 1.5 Hz, 1H), 1.29 (s, 12H).

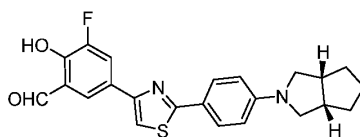
[0361] Step 2: To a 2mL microwave vial was added 3-fluoro-2-hydroxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzaldehyde (40 mg, 0.15 mmol) from step 1a, 5-bromo-3-phenyl-1,2,4-thiadiazole (36 mg, 0.15 mmol), XPhos Pd G3 (6.4 mg, 0.05 eq.) and XPhos (3.6 mg, 0.05 eq.) dioxane (0.6 mL) and degassed 0.5M K₃PO₄ (0.6 mL). The microwave vessel was purged with argon and heated to 130°C in the microwave for 30 minutes. The reaction mixture was diluted with DCM, acidified to pH=3 with citric acid and extracted 3 times with DCM. The combined organic phases were washed with brine and dried over anhydrous Na₂SO₄, filtered and evaporated. The crude product was purified by flash column chromatography 0-10% MeOH/DCM. Yield (8 mg, 17%). ¹H NMR (500 MHz, DMSO-d₆) δ 12.02 (bs, 1H), 10.36 (s, 1H), 8.36 – 8.24 (m, 3H), 8.24 – 8.15 (m, 1H), 7.64 – 7.47 (m, 3H). MS m/z [M+H]⁺ calc'd for C₁₅H₉FN₂O₂S, 301; found 301.

Example A60: 3-fluoro-2-hydroxy-5-(3-phenyl-1H-1,2,4-triazol-5-yl)benzaldehyde (New Compound A96)



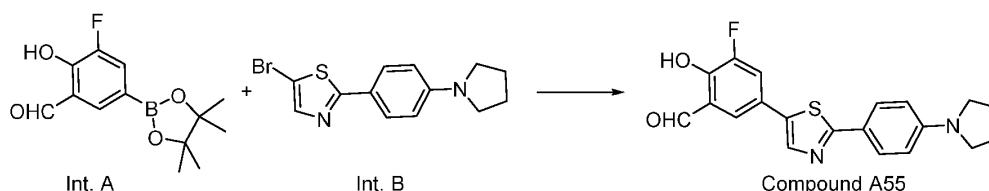
[0362] The title compound was prepared using a method similar to that as described in Example A53, using commercially available 5-bromo-3-phenyl-1H-1,2,4-triazole. Yield: 8%. ¹H NMR (500 MHz, DMSO-d₆) δ 14.59 (s, 1H), 11.3 (bs, 1H), 10.37 (s, 1H), 8.21 (d, J = 1.9 Hz, 1H), 8.07 (d, J = 8.9 Hz, 3H), 7.66 – 7.37 (m, 3H). MS m/z [M+H]⁺ calc'd for C₁₅H₁₀FN₃O₂, 284; found 284.

Example A61: 3-fluoro-5-(2-(4-((3aR,6aS)-hexahydrocyclopenta[c]pyrrol-2(1H)-yl)phenyl)thiazol-4-yl)-2-hydroxybenzaldehyde (Compound A97)



[0363] 3-fluoro-5-(2-(4-((3aR,6aS)-hexahydrocyclopenta[c]pyrrol-2(1H)-yl)phenyl)thiazol-5-yl)-2-hydroxybenzaldehyde was synthesized from Compound A92 by a similar method described by Maiti et al. (*Chem. Sci.*, 2011, **2**, 57-68.) 5-(2-(4-chlorophenyl)thiazol-4-yl)-3-fluoro-2-hydroxybenzaldehyde (24 mg, 0.09 mmol), was added to a 2 mL microwave vial with (3aR,6aS)-octahydrocyclopenta[c]pyrrole hydrochloride (16 mg, 0.11 mmol), RuPhos Pd G3 (3.67 mg, 0.05 eq.) and RuPhos (2.05 mg, 0.05eq.). The vial was sealed and evacuated and backfilled with argon three times. THF (0.3 mL) and 1M LiHMDS in THF (0.3 mL) was added via syringe. The reaction mixture was heated to 65°C with stirring overnight. The reaction mixture was then diluted with dichloromethane, washed with water, dried over Na₂SO₄, filtered and evaporated. The crude material was purified by flash column chromatography using 0-30% ethyl acetate in hexanes. Yield: 8 mg, 22%. ¹H NMR (499 MHz, Chloroform-d) δ 10.99 (s, 1H), 10.03 (d, J = 1.9 Hz, 1H), 8.06 (dd, J = 2.1, 1.1 Hz, 1H), 7.95 (dd, J = 11.7, 2.1 Hz, 1H), 7.90 – 7.85 (m, 2H), 6.60 (dd, J = 8.8, 6.7 Hz, 3H), 3.55 (dd, J = 9.7, 7.9 Hz, 2H), 3.12 (dd, J = 9.7, 3.9 Hz, 2H), 2.82 (m, 2H), 1.89 (m, 2H), 1.83 – 1.73 (m, 1H), 1.69 – 1.59 (m, 1H), 1.55 (m, 2H). MS m/z [M+H]⁺ calc'd for C₂₃H₂₁FN₂O₂S, 409; found 409.

Example A62: 3-fluoro-2-hydroxy-5-(2-(4-(pyrrolidin-1-yl)phenyl)thiazol-5-yl)benzaldehyde (Compound A55)

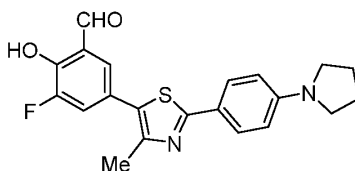


[0364] The synthesis of Intermediate B, 5-bromo-2-(4-(pyrrolidin-1-yl)phenyl)thiazole, was accomplished by adding 1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)pyrrolidine (476 mg, 1.7 mmol), 2,5-dibromothiazole (508 mg, 2.1 mmol), XantPhos Pd G3 (83 mg, 0.09 mmol) and Xantphos (50.4 mg, 0.09 mmol) to a 40 mL screw top pressure relief vial. Dioxane (8.7 mL) and degassed 0.5M K₃PO₄ (8.7 mL) were added and the vial was degassed with argon.

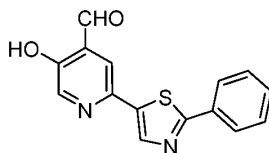
The sealed reaction vessel was heated to 140°C for 4 hours, cooled, diluted with DCM and extracted with a water and saturated aqueous NaHCO₃. The combined aqueous layers were extracted 2 times more with DCM. The combined organic layers were washed with brine, dried over Na₂SO₄, filtered and evaporated. Purified using 0-70% DCM/ Hexanes to provide 5-bromo-2-(4-(pyrrolidin-1-yl)phenyl)thiazole (274 mg, 51% yield). ¹H NMR (500 MHz, DMSO-d₆) δ 7.79 (s, 1H), 7.74 – 7.61 (m, 2H), 6.67 – 6.52 (m, 2H), 3.29 – 3.22 (m, 4H), 2.08 – 1.87 (m, 4H).

[0365] Compound A55, 3-Fluoro-2-hydroxy-5-(2-(4-(pyrrolidin-1-yl)phenyl)thiazol-5-yl)benzaldehyde, was synthesized by coupling Int. A, 3-fluoro-2-hydroxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzaldehyde (94 mg, 0.35 mmol), with Intermediate B, 5-bromo-2-(4-(pyrrolidin-1-yl)phenyl)thiazole (109 mg, 0.35 mmol), in a method similar to that as described in Example A59. Yield: 32 mg, 25%. ¹H NMR (500 MHz, DMSO-d₆) δ 11.20 (bs, 1H), 10.31 (s, 1H), 8.14 (s, 1H), 7.96 (dd, J = 11.9, 2.3 Hz, 1H), 7.82 – 7.72 (m, 2H), 7.64 (dd, J = 2.3, 1.0 Hz, 1H), 6.66 – 6.57 (m, 2H), 3.31 – 3.28 (m, 4H), 2.02 – 1.94 (m, 4H). MS m/z [M+H]⁺ calc'd for C₂₀H₁₇FN₂O₂S, 369; found 369.

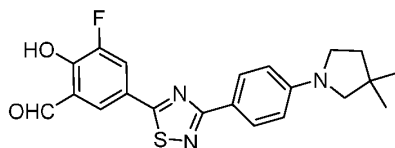
Example A63: 3-fluoro-2-hydroxy-5-(4-methyl-2-(4-(pyrrolidin-1-yl)phenyl)thiazol-5-yl)benzaldehyde (Compound A98)



[0366] The title compound was prepared using a method similar to that as described in Example A62 using 3-fluoro-2-hydroxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzaldehyde (50 mg, 0.19 mmol) and 5-bromo-4-methyl-2-(4-(pyrrolidin-1-yl)phenyl)thiazole (58 mg, 0.19 mmol), made a method similar to that as described for Int. B in Example A62, was used to make 3-fluoro-2-hydroxy-5-(4-methyl-2-(4-(pyrrolidin-1-yl)phenyl)thiazol-5-yl)benzaldehyde (28 mg, 40% yield). ¹H NMR (500 MHz, Chloroform-d) δ 10.98 (s, 1H), 9.97 (d, J = 1.8 Hz, 1H), 7.88 – 7.73 (m, 2H), 7.50 – 7.43 (m, 2H), 6.57 (dd, J = 9.1, 2.6 Hz, 2H), 3.41 – 3.32 (m, 4H), 2.51 (s, 3H), 2.04 (ddd, J = 6.7, 4.2, 2.9 Hz, 4H). MS m/z [M+H]⁺ calc'd for C₂₁H₁₉FN₂O₂S, 383; found 383.

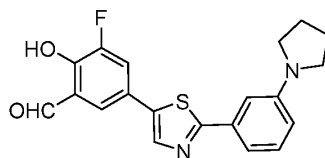
Example A64: 5-hydroxy-2-(2-phenylthiazol-5-yl)isonicotinaldehyde (Compound A99)

[0367] 5-Hydroxy-2-(2-phenylthiazol-5-yl)isonicotinaldehyde was synthesized by coupling 2-bromo-5-hydroxyisonicotinaldehyde (50 mg, 0.25 mmol) with commercially available 2-phenyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)thiazole (71 mg, 0.25 mmol) using a method similar to that as described in Example A59. Yield: 8 mg, 11%. ¹H NMR (499 MHz, Chloroform-d) δ 10.35 (s, 1H), 10.11 (d, J = 0.6 Hz, 1H), 8.55 (d, J = 0.7 Hz, 1H), 8.22 (s, 1H), 8.04 – 7.96 (m, 2H), 7.83 (d, J = 0.7 Hz, 1H), 7.52 – 7.42 (m, 3H). MS m/z $[M+H]^+$ calc'd for C₁₅H₁₀N₂O₂S, 283; found 283.

Example A65: 5-(3-(4-(3,3-dimethylpyrrolidin-1-yl)phenyl)-1,2,4-thiadiazol-5-yl)-3-fluoro-2-hydroxybenzaldehyde (Compound A100)

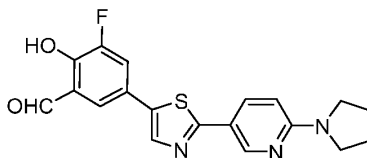
[0368] The title compound was prepared from 3,3-dimethyl-1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)pyrrolidine (176 mg, 0.58 mmol, 1.1 eq) and 5-(3-bromo-1,2,4-thiadiazol-5-yl)-3-fluoro-2-hydroxybenzaldehyde (162 mg, 0.53 mmol, 1.0 eq.) (prepared as in Example A47) using a method similar to that as described in Example A46 to give the final title compound (22 mg, 0.06 mmol, 10% yield) as a yellow solid. ¹H NMR (DMSO-*d*₆, 400 MHz) δ : 11.87 (br, 1H), 10.36 (s, 1H), 8.23 (m, 1H), 8.16 (s, 1H), 8.10 (d, J =8.8 Hz, 2H), 6.61 (d, J =8.8 Hz, 2H), 3.41 (t, J =6.8 Hz, 2H), 3.11 (s, 2H), 1.80 (t, J =6.8 Hz, 2H), 1.13 (s, 6H). LC-MS m/z $[M+H]^+$ calc'd for C₂₁H₂₀FN₃O₂S, 398; found, 398.

Example A66: 3-fluoro-2-hydroxy-5-(2-(3-(pyrrolidin-1-yl)phenyl)thiazol-5-yl)benzaldehyde (Compound A101)



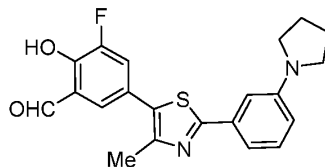
[0369] 3-Fluoro-2-hydroxy-5-(2-(3-(pyrrolidin-1-yl)phenyl)thiazol-5-yl)benzaldehyde was synthesized using a method similar to that as described in Example A62 with 3-fluoro-2-hydroxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzaldehyde (11 mg, 0.04 mmol) and 5-bromo-2-(3-(pyrrolidin-1-yl)phenyl)thiazole (14 mg, 0.17 mmol), made by a method similar to that as described for Int. B in Example A62, as the starting materials. Yield: 8 mg, 51%. ¹H NMR (500 MHz, DMSO-d₆) δ 11.28 (s, 1H), 10.32 (s, 1H), 8.28 (s, 1H), 8.02 (dd, J = 11.8, 2.3 Hz, 1H), 7.78 – 7.67 (m, 1H), 7.29 (t, J = 7.9 Hz, 1H), 7.15 (dt, J = 7.6, 1.1 Hz, 1H), 7.07 (t, J = 2.1 Hz, 1H), 6.67 (dd, J = 8.2, 2.5 Hz, 1H), 3.30 – 3.27 (m, 4H), 2.03 – 1.95 (m, 4H). MS m/z [M+H]⁺ calc'd for C₂₀H₁₇FN₂O₂S, 369; found 369.

Example A67: 3-fluoro-2-hydroxy-5-(2-(6-(pyrrolidin-1-yl)pyridin-3-yl)thiazol-5-yl)benzaldehyde (New Compound A102)



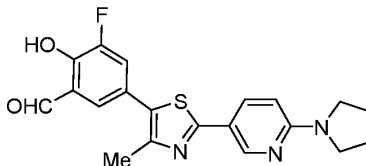
[0370] The title compound was made using a method similar to that as described in Example A62 Starting from 3-fluoro-2-hydroxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzaldehyde (25 mg, 0.09 mmol) and 5-bromo-2-(6-(pyrrolidin-1-yl)pyridin-3-yl)thiazole (29 mg, 0.09 mmol), made by a method similar to that as described for Int. B in Example A62. Yield: 31 mg, 89%. ¹H NMR (500 MHz, DMSO-d₆) δ 11.24 (s, 1H), 10.31 (s, 1H), 8.65 (dd, J = 2.5, 0.7 Hz, 1H), 8.19 (s, 1H), 8.01 – 7.94 (m, 2H), 7.65 (dd, J = 2.4, 1.0 Hz, 1H), 6.56 (dd, J = 9.0, 0.8 Hz, 1H), 3.45 (d, J = 6.4 Hz, 4H), 2.01 – 1.93 (m, 4H). MS m/z [M+H]⁺ calc'd for C₁₉H₁₆FN₃O₂S, 370; found 370.

Example A68: 3-fluoro-2-hydroxy-5-(4-methyl-2-(3-(pyrrolidin-1-yl)phenyl)thiazol-5-yl)benzaldehyde (Compound A103)



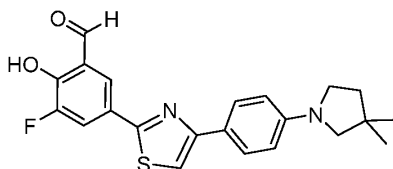
[0371] The title compound was made using a method similar to that as described in Example A62 using 3-fluoro-2-hydroxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzaldehyde (46 mg, 0.17 mmol) and 5-bromo-4-methyl-2-(3-(pyrrolidin-1-yl)phenyl)thiazole (55 mg, 0.17 mmol), made in a similar manner to Int. B in Example A62. Yield: 31 mg, 47%. ¹H NMR (500 MHz, DMSO-d₆) δ 11.26 (s, 1H), 10.32 (s, 1H), 7.74 (dd, J = 11.7, 2.3 Hz, 1H), 7.59 (dd, J = 2.3, 1.0 Hz, 1H), 7.31 – 7.22 (m, 1H), 7.14 – 7.07 (m, 1H), 7.03 (t, J = 2.1 Hz, 1H), 6.65 (ddd, J = 8.3, 2.5, 0.9 Hz, 1H), 3.31 – 3.25 (m, 4H), 2.48 (s, 3H), 2.02 – 1.93 (m, 4H). MS m/z [M+H]⁺ calc'd for C₂₁H₁₉FN₂O₂S, 383; found 383.

Example A69: 3-fluoro-2-hydroxy-5-(4-methyl-2-(6-(pyrrolidin-1-yl)pyridin-3-yl)thiazol-5-yl)benzaldehyde (Compound A104)



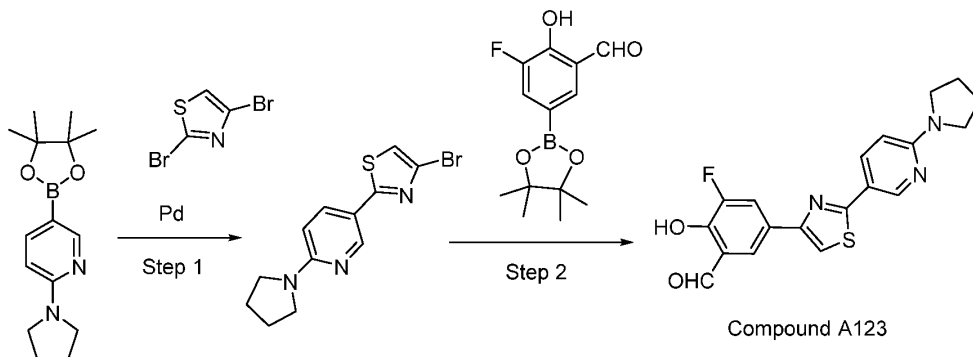
[0372] The title compound was made using a method similar to that as described in Example A62 starting from 3-fluoro-2-hydroxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzaldehyde (49 mg, 0.18 mmol) and 5-bromo-4-methyl-2-(6-(pyrrolidin-1-yl)pyridin-3-yl)thiazole (59 mg, 0.18mmol), made in a similar manner to Int. B in Example A62. Yield: 62 mg, 89%. ¹H NMR (499 MHz, DMSO-d₆) δ 11.23 (s, 1H), 10.32 (s, 1H), 8.61 (d, J = 2.4 Hz, 1H), 7.96 (dd, J = 8.9, 2.5 Hz, 1H), 7.71 (dd, J = 11.7, 2.3 Hz, 1H), 7.56 (dd, J = 2.3, 1.0 Hz, 1H), 6.54 (dd, J = 11.2, 8.9 Hz, 1H), 3.45 (d, J = 6.5 Hz, 4H), 2.44 (s, 3H), 1.96 (h, J = 3.3 Hz, 4H). MS m/z [M+H]⁺ calc'd for C₂₀H₁₈FN₃O₂S, 384; found 384.

Example A70: 5-(4-(4-(3,3-dimethylpyrrolidin-1-yl)phenyl)thiazol-2-yl)-3-fluoro-2-hydroxybenzaldehyde (Compound A105)



[0373] The title compound was prepared from 3,3-Dimethyl-1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)pyrrolidine (153 mg, 0.51 mmol, 1.1 eq.) and 5-(4-bromothiazol-2-yl)-3-fluoro-2-hydroxybenzaldehyde (140 mg, 0.46 mmol, 1.0 eq.) (prepared as in Example A47) using a method similar to that as described in Example A46 to give the final title compound (48 mg, 0.12 mmol, 26% yield) as a yellow solid. ^1H NMR ($\text{DMSO}-d_6$, 400 MHz) δ : 11.51 (br, 1H), 10.35 (s, 1H), 8.11 (dd, $J=11.2$ Hz, 2.0 Hz, 1H), 8.05 (s, 1H), 7.84 (d, $J=8.8$ Hz, 2H), 7.79 (s, 1H), 6.56 (d, $J=8.8$ Hz, 2H), 3.38 (m, 2H), 3.07 (s, 2H), 1.78 (d, $J=6.8$ Hz, 2H), 1.12 (s, 6H). LC-MS m/z $[\text{M}-\text{H}]^-$ calc'd for $\text{C}_{22}\text{H}_{21}\text{FN}_2\text{O}_2\text{S}$, 395; found, 395.

Example A71: 3-fluoro-2-hydroxy-5-(2-(6-(pyrrolidin-1-yl)pyridin-3-yl)thiazol-4-yl)benzaldehyde (Compound A123)



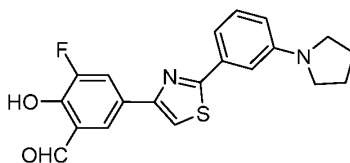
[0374] Step 1: 4-bromo-2-(6-(pyrrolidin-1-yl)pyridin-3-yl)thiazole

[0375] A mixture of 2,4-dibromothiazole (486 mg, 2.0 mmol, 1.0 eq.), 2-(pyrrolidin-1-yl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (603 mg, 2.2 mmol, 1.1 eq.), potassium carbonate (828 mg, 6.0 mmol, 3.0 eq.), and $\text{PdCl}_2(\text{dppf})$ (146 mg, 0.2 mmol, 0.1 eq.) in dioxane/water (10 mL/5 mL) was heated at 100 °C for 1 hour under nitrogen protection. The

mixture was cooled to room temperature, poured into water, and extracted with ethyl acetate for three times. The organic extracts were combined, washed with brine, dried over anhydrous sodium sulfate, and concentrated. The residue was purified by silica gel column using hexane-EtOAc (0-100%) to give 4-bromo-2-(6-(pyrrolidin-1-yl)pyridin-3-yl)thiazole (520 mg, 84% yield). LC-MS m/z $[M+H]^+$ calc'd for $C_{12}H_{12}BrN_3S$, 311; found, 311.

[0376] Step 2: In a 30 mL sealed cap glass vial, 3-fluoro-2-hydroxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzaldehyde (266 mg, 1.0 mmol, 1.0 eq.), 4-bromo-2-(6-(pyrrolidin-1-yl)pyridin-3-yl)thiazole (310 mg, 1.30 mmol, 1.0 eq.), sodium carbonate (318 mg, 3.0 mmol, 3.0 eq.) combined in 1:1 dioxane-water (10 mL) then passed nitrogen for 2 min through the mixture and added $Pd(PPh_3)_4$ (112 mg, 0.1 mmol, 0.1 eq) and sealed the cap and continued at 105 °C for 8 hours. Then cooled room temperature and added water and extracted with EtOAc (2 x 25 mL) and washed with brine and dried over sodium sulfate and evaporated. The resulting crude product purified by column chromatography using hexane-EtOAc (0-100%) eluent to give the final title compound (108 mg, 29% yield) as a yellow solid. 1H NMR (500 MHz, Chloroform- d) δ 11.00 (s, 1H), 10.02 (d, J = 1.8 Hz, 1H), 8.77 (d, J = 2.4 Hz, 1H), 8.11 – 8.02 (m, 2H), 7.94 (dd, J = 11.7, 2.0 Hz, 1H), 7.29 (s, 1H), 6.43 (d, J = 8.9 Hz, 1H), 3.54 (m, 4H), 2.10 – 2.01 (m, 4H). LC-MS m/z $[M+H]^+$ calc'd for $C_{19}H_{16}FN_3O_2S$, 370; found, 370.

Example A72: 3-fluoro-2-hydroxy-5-(2-(3-(pyrrolidin-1-yl)phenyl)thiazol-4-yl)benzaldehyde (Compound A124)



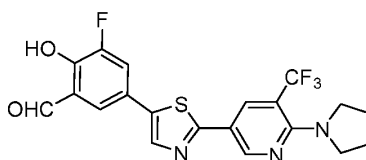
[0377] Step1: 4-bromo-2-(3-(pyrrolidin-1-yl)phenyl)thiazole

[0378] The title compound was prepared from 1-(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)pyrrolidine (601 mg, 2.2 mmol, 1.1 eq.) and 2,4-dibromothiazole (486 mg, 2.0 mmol, 1.0 eq.) using a method similar to that as described in Example A71 to give the desired

product (540 mg, 87% yield) as off-white solid. LC-MS m/z $[M+H]^+$ calc'd for $C_{13}H_{13}BrN_2S$, 310; found, 310.

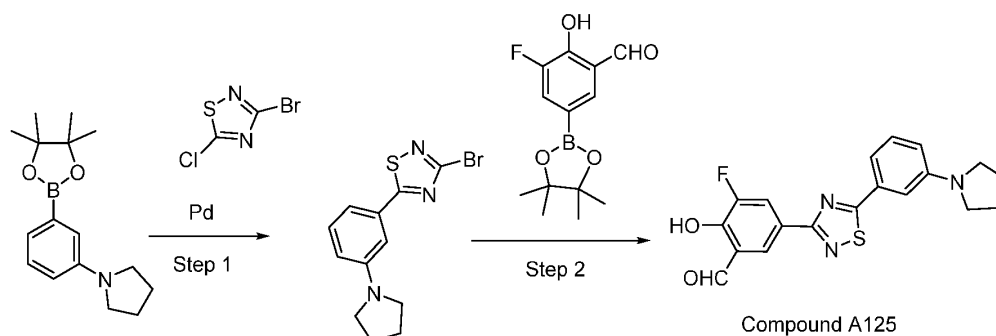
[0379] Step 2: The title compound was prepared from 3-fluoro-2-hydroxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzaldehyde (133 mg, 0.5 mmol, 1.0 eq.) and 4-bromo-2-(3-(pyrrolidin-1-yl)phenyl)thiazole (155 mg, 0.5 mmol, 1.0 eq.) using a method similar to that as described in Example A46 to give the final title compound (110 mg, 41% yield) as a yellow solid. 1H NMR (500 MHz, Chloroform- d) δ 11.01 (s, 1H), 10.04 (d, J = 1.9 Hz, 1H), 8.06 (t, J = 1.6 Hz, 1H), 7.97 (dd, J = 11.6, 2.1 Hz, 1H), 7.40 (s, 1H), 7.33 – 7.27 (m, 2H), 7.20 (t, J = 2.0 Hz, 1H), 6.66 (dt, J = 8.2, 1.6 Hz, 1H), 3.39 m, 4H), 2.15 – 1.96 (m, 4H). LC-MS m/z $[M+H]^+$ calc'd for $C_{20}H_{17}FN_2O_2S$, 369; found, 369.

Example A73: 3-fluoro-2-hydroxy-5-(2-(6-(pyrrolidin-1-yl)-5-(trifluoromethyl)pyridin-3-yl)thiazol-5-yl)benzaldehyde (Compound A114)



[0380] 3-Fluoro-2-hydroxy-5-(2-(6-(pyrrolidin-1-yl)-5-(trifluoromethyl)pyridin-3-yl)thiazol-5-yl)benzaldehyde was synthesized using a method similar to that as described in Example A62 using 3-fluoro-2-hydroxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzaldehyde (69 mg, 0.35 mmol) with 5-bromo-2-(6-(pyrrolidin-1-yl)-5-(trifluoromethyl)pyridin-3-yl)thiazole (97 mg, 0.35 mmol), synthesized using a similar method as that described for Int. B in Example A62. Yield: 50 mg, 45%. 1H NMR (499 MHz, DMSO- d_6) δ 11.28 (s, 1H), 10.31 (s, 1H), 8.85 (d, J = 2.3 Hz, 1H), 8.33 (d, J = 2.3 Hz, 1H), 8.27 (s, 1H), 8.00 (dd, J = 11.9, 2.3 Hz, 1H), 7.67 (dd, J = 2.3, 1.0 Hz, 1H), 3.60 (d, J = 6.3 Hz, 4H), 1.98 – 1.88 (m, 4H). LC-MS m/z $[M-H]^+$ calc'd for $C_{20}H_{15}F_4N_3O_2S$, 438, found 438.

Example A74: 3-fluoro-2-hydroxy-5-(5-(3-(pyrrolidin-1-yl)phenyl)-1,2,4-thiadiazol-3-yl)benzaldehyde (Compound A125)

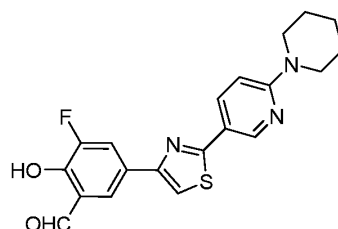


[0381] Step1: 3-bromo-5-(3-(pyrrolidin-1-yl)phenyl)-1,2,4-thiadiazole

[0382] The title compound was prepared from 1-(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)pyrrolidine (601 mg, 2.2 mmol, 1.1 eq.) and 3-bromo-5-chloro-1,2,4-thiadiazole (310 mg, 2.0 mmol, 1.0 eq.) using a method similar to that as described in Example A71 to give the desired product (351 mg, 57% yield) as yellow solid. LC-MS m/z $[M+H]^+$ calc'd for $C_{12}H_{12}BrN_3S$, 311; found, 311.

[0383] Step 2: The title compound was prepared from 3-fluoro-2-hydroxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzaldehyde (200 mg, 0.75 mmol, 1.5 eq.) and 3-bromo-5-(3-(pyrrolidin-1-yl)phenyl)-1,2,4-thiadiazole (155 mg, 0.5 mmol, 1.0 eq.) using a method similar to that as described in Example A46 to give the final title compound (42 mg, 49% yield) as a yellow solid. 1H NMR (500 MHz, Chloroform- d) δ 11.21 (s, 1H), 10.06 (d, J = 1.8 Hz, 1H), 8.46 (t, J = 1.6 Hz, 1H), 8.39 (dd, J = 11.4, 2.0 Hz, 1H), 7.34 (t, J = 7.9 Hz, 1H), 7.28 – 7.23 (m, 1H), 7.17 (t, J = 2.1 Hz, 1H), 6.74 (dd, J = 8.3, 2.5 Hz, 1H), 3.45 – 3.28 (m, 4H), 2.07 (m, 4H). LC-MS m/z $[M+H]^+$ calc'd for $C_{19}H_{16}FN_3O_2S$, 370; found, 370.

Example A75: 3-fluoro-2-hydroxy-5-(2-(6-(piperidin-1-yl)pyridin-3-yl)thiazol-4-yl)benzaldehyde (Compound A126)

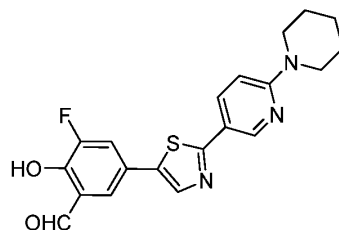


[0384] Step1: 4-bromo-2-(6-(piperidin-1-yl)pyridin-3-yl)thiazole

[0385] The title compound was prepared from 2-(piperidin-1-yl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (634 mg, 2.2 mmol, 1.1 eq.) and 2,4-dibromothiazole (486 mg, 2.0 mmol, 1.0 eq.) using a method similar to that as described in Example A71 to give the desired product (352 mg, 54% yield) as yellow solid. LC-MS m/z $[M+H]^+$ calc'd for $C_{13}H_{14}BrN_3S$, 325; found, 325.

[0386] Step 2: The title compound was prepared from 3-fluoro-2-hydroxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzaldehyde (200 mg, 0.75 mmol, 1.5 eq.) and 4-bromo-2-(6-(piperidin-1-yl)pyridin-3-yl)thiazole (162 mg, 0.5 mmol, 1.0 eq.) using a method similar to that as described in Example A46 to give the final title compound (21 mg, 11% yield) as a yellow solid. 1H NMR (500 MHz, Chloroform-*d*) δ 11.00 (s, 1H), 10.03 (d, $J = 1.9$ Hz, 1H), 8.76 (d, $J = 2.5$ Hz, 1H), 8.07 (dd, $J = 9.0, 2.5$ Hz, 1H), 8.04 (t, $J = 1.6$ Hz, 1H), 7.94 (dd, $J = 11.7, 2.1$ Hz, 1H), 7.30 (s, 1H), 6.69 (d, $J = 9.0$ Hz, 1H), 3.74 – 3.40 (m, 4H), 1.74 – 1.63 (m, 6H). LC-MS m/z $[M+H]^+$ calc'd for $C_{20}H_{18}FN_3O_2S$, 384; found, 384.

Example A76: 3-fluoro-2-hydroxy-5-(2-(6-(piperidin-1-yl)pyridin-3-yl)thiazol-5-yl)benzaldehyde (Compound A127)

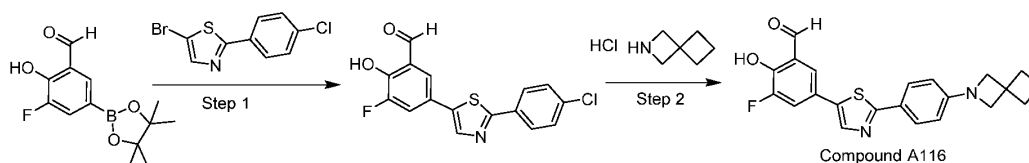


[0387] Step1: 5-bromo-2-(6-(piperidin-1-yl)pyridin-3-yl)thiazole

[0388] The title compound was prepared from 2-(piperidin-1-yl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (634 mg, 2.2 mmol, 1.1 eq.) and 2,5-dibromothiazole (486 mg, 2.0 mmol, 1.0 eq.) using a method similar to that as described in Example A71 to give the desired product (225 mg, 35% yield) as yellow solid. LC-MS m/z $[M+H]^+$ calc'd for $C_{13}H_{14}BrN_3S$, 325; found, 325.

[0389] Step 2: The title compound was prepared from 3-fluoro-2-hydroxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzaldehyde (80 mg, 0.3 mmol, 1.2 eq.) and 5-bromo-2-(6-(piperidin-1-yl)pyridin-3-yl)thiazole (81 mg, 0.25 mmol, 1.0 eq.) using a method similar to that as described in Example A46 to give the final title compound (78 mg, 81% yield) as a yellow solid. ¹H NMR (500 MHz, Chloroform-*d*) δ 10.98 (s, 1H), 9.99 (d, *J* = 1.8 Hz, 1H), 8.70 (d, *J* = 2.5 Hz, 1H), 8.00 (dd, *J* = 9.0, 2.5 Hz, 1H), 7.87 (s, 1H), 7.62 – 7.53 (m, 2H), 6.69 (d, *J* = 9.0 Hz, 1H), 3.77 – 3.48 (m, 4H), 1.75 – 1.63 (m, 6H). LC-MS *m/z* [M+H]⁺ calc'd for C₂₀H₁₈FN₃O₂S, 384; found, 384.

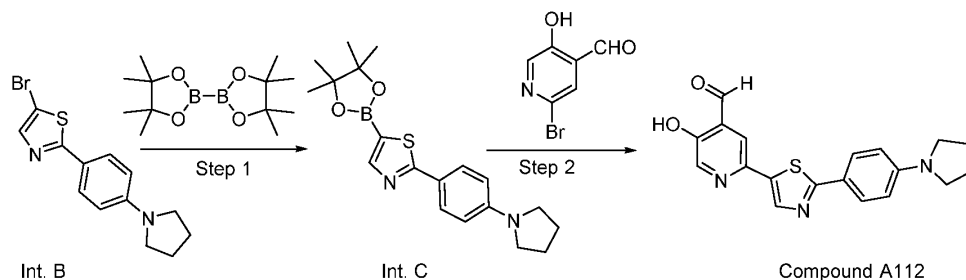
Example A77: 5-(2-(4-(2-azaspiro[3.3]heptan-2-yl)phenyl)thiazol-5-yl)-3-fluoro-2-hydroxybenzaldehyde (Compound A116)



[0390] Step 1: Starting from 3-fluoro-2-hydroxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzaldehyde (175 mg, 0.66 mmol) and commercially available 5-bromo-2-(4-chlorophenyl)thiazole (181 mg, 0.66 mmol) the procedure from Example A95 was used to make 5-(2-(4-chlorophenyl)thiazol-5-yl)-3-fluoro-2-hydroxybenzaldehyde, Compound A130 (68 mg, 31% yield). LC-MS *m/z* [M-H]⁺ calc'd for C₁₆H₉ClFNO₂S, 334; found, 334.

[0391] Step 2: A method similar to that as described in Example A61 was used to make 5-(2-(4-(2-azaspiro[3.3]heptan-2-yl)phenyl)thiazol-5-yl)-3-fluoro-2-hydroxybenzaldehyde in 11% yield. ¹H NMR (500 MHz, DMSO-*d*₆) δ 11.22 (s, 1H), 10.31 (d, *J* = 3.0 Hz, 1H), 8.15 (s, 1H), 7.97 – 7.92 (m, 1H), 7.74 (d, *J* = 6.7 Hz, 1H), 7.73 (s, 1H), 7.64 (dd, *J* = 2.3, 1.0 Hz, 1H), 6.50 – 6.44 (m, 2H), 3.87 (s, 4H), 2.19 (t, *J* = 7.6 Hz, 4H), 1.87 – 1.75 (m, 2H). LC-MS *m/z* [M-H]⁺ calc'd for C₂₂H₁₉FN₂O₂S, 395; found, 395.

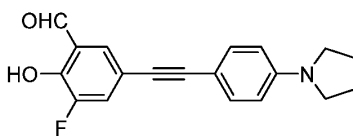
Example A78: 5-hydroxy-2-(2-(4-(pyrrolidin-1-yl)phenyl)thiazol-5-yl)isonicotinaldehyde (Compound A112)



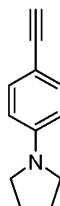
[0392] Step 1: The starting material, Int. B, was synthesized using a similar method as described in Example A62. Int. C, 2-(4-(pyrrolidin-1-yl)phenyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)thiazole, was made using a similar method used to make 3-fluoro-2-hydroxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzaldehyde in Example A59. However, the Int. C was not purified before using in the next reaction. After completion of the reaction, the crude mixture was taken up in DCM filtered through celite and concentrated to dryness.

[0393] Step 2: Using a similar method as described in Example A59, crude 2-(4-(pyrrolidin-1-yl)phenyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)thiazole (123 mg), Int. C, and 2-bromo-5-hydroxyisonicotinaldehyde (70 mg, 0.35 mmol) were used to make 5-hydroxy-2-(2-(4-(pyrrolidin-1-yl)phenyl)thiazol-5-yl)isonicotinaldehyde (12 mg, Yield: 10%). ¹H NMR (500 MHz, DMSO-d₆) δ 11.29 (bs, 1H), 10.39 (s, 1H), 8.44 (s, 1H), 8.31 (s, 1H), 7.99 (s, 1H), 7.83 – 7.73 (m, 2H), 6.67 – 6.55 (m, 2H), 3.32-3.29 (m, 4H), 2.36 – 1.61 (m, 4H). LC-MS m/z [M+H]⁺ calc'd for C₁₉H₁₇N₃O₂S, 352; found 352.

Example B1: 3-fluoro-2-hydroxy-5-((4-(pyrrolidin-1-yl)phenyl)ethynyl)benzaldehyde
(Compound No. B1)



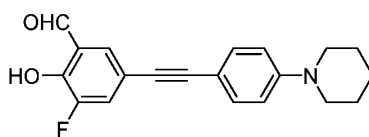
[0394] Step 1: 1-(4-ethynylphenyl)pyrrolidine



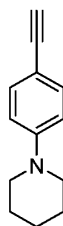
[0395] To a solution of TMS-diazomethane (17.14 mL, 34.29 mmol) in THF (50 mL) was added BuLi (13.72 mL, 34.29 mmol, 2 M in THF) at -78 °C. The reaction was stirred for 30 min at -78 °C. Then 4-(pyrrolidin-1-yl)benzaldehyde (5 g, 28.57 mmol) was added. The reaction was stirred for another 1 h at -78 °C. The mixture was quenched with sat. NH₄Cl (150 mL) and then extracted with ethyl acetate (100 mLx3). The organic extracts were combined, dried over anhydrous sodium sulfate, and concentrated. The crude was purified by silica gel column chromatography (petroleum ether/ethyl acetate=200:1 to 100:1) to give the desired product as a white solid (2.1 g, 43% yield). ¹H NMR (CDCl₃, 400 MHz) δ: 7.35 (d, *J*=8.4 Hz, 2H), 6.46 (d, *J*=8.4 Hz, 2H), 3.29 (t, *J*=6.2 Hz, 4H), 2.98 (s, 1H), 2.01 (t, *J*=6.2 Hz, 4H).

[0396] Step 2: A mixture of 5-bromo-3-fluoro-2-(4-methoxybenzyloxy)benzaldehyde (988 mg, 2.92 mmol), 1-(4-ethynylphenyl)pyrrolidine (600 mg, 3.51 mmol), TBAF.3H₂O (5.5 g, 17.54 mmol), and Pd(PPh₃)₂Cl₂ (62 mg, 0.09 mmol) in THF (20 mL) was heated at 80 °C for 2 h. The mixture was cooled to room temperature, diluted with water (100 mL), and then extracted with ethyl acetate (100 mLx3). The organic extracts were combined, washed with brine (80 mL), dried over anhydrous sodium sulfate, and concentrated. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate=20:1 to 10:1) to give the PMB-protected penultimate product (417 mg, 33% yield). The PMB-protected intermediate (100 mg, 0.23 mmol) was dissolved in dichloromethane (5 mL) and TFA (3 mL) was added. The reaction was stirred for 30 min at room temp. The solvent was removed *in vacuo* and the residue was purified by prep-TLC (petroleum ether/ethyl acetate=5:1) to afford the title compound as yellow solid (23 mg, 32% yield). ¹H NMR (CDCl₃, 400 MHz) δ: 11.00 (s, 1H), 9.90 (s, 1H), 7.52 (s, 1H), 7.46 (d, *J*=11.2 Hz, 1H), 7.37 (d, *J*=8.4 Hz, 2H), 6.51 (d, *J*=8.4 Hz, 2H), 3.31 (m, 4H), 2.02 (m, 4H); LC-MS *m/z* [M-H]⁻ calc'd for C₁₉H₁₆FNO₂, 308; found, 308.

Example B2: 3-fluoro-2-hydroxy-5-((4-(piperidin-1-yl)phenyl)ethynyl)benzaldehyde (Compound No. B2)



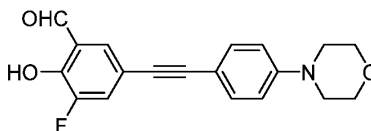
Step 1: 1-(4-ethynylphenyl)piperidine



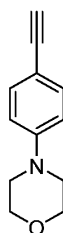
[0397] To a solution of TMS-diazomethane (6.3 mL, 12.6 mmol) in THF (20 mL) was added BuLi (6.3 mL, 12.6 mmol, 2 M in THF) at -78 °C. The reaction was stirred for 30 min at -78 °C. Then 4-(piperidin-1-yl)benzaldehyde (1.89 g, 10 mmol) was added in THF. The reaction was stirred for another 1 h at -78 °C. The mixture was quenched with sat. NH₄Cl (100 mL) and then extracted with ethyl acetate (100 mLx3). The organic extracts were combined, dried over anhydrous sodium sulfate, and concentrated. The crude was purified by silica gel column chromatography to give the desired product (1.42 g, 77% yield).

[0398] Step 2: The title compound was prepared from 5-bromo-3-fluoro-2-hydroxybenzaldehyde (219 mg, 1.0 mmol) and 1-(4-ethynylphenyl)piperidine (185 mg, 1.0 mmol) using a method similar to that as described in Example B1 to give the title compound as yellow solid (91 mg, 28% yield). ¹H NMR (*DMSO-d*₆, 400 MHz) δ 11.33 (br, 1H), 10.26 (s, 1H), 7.67 (d, *J*=11.2 Hz, 1H), 7.57 (s, 1H), 7.35 (d, *J*=8.4 Hz, 2H), 6.93 (d, *J*=8.4 Hz, 2H), 3.24 (m, 4H), 1.57 (m, 6H); LC-MS *m/z* [M+H]⁺ calc'd for C₂₀H₁₈FNO₂, 324; found, 324.

Example B3: 3-fluoro-2-hydroxy-5-((4-morpholinophenyl)ethynyl)benzaldehyde (Compound No. B3)



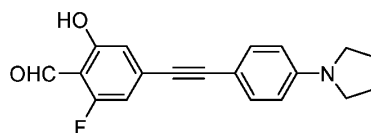
Step 1: 4-(4-ethynylphenyl)morpholine



[0399] To a solution of TMS-diazomethane (6.3 mL, 12.6 mmol) in THF (20 mL) was added BuLi (6.3 mL, 12.6 mmol, 2 M in THF) at -78 °C. The reaction was stirred for 30 min at -78 °C. Then 4-morpholinobenzaldehyde (2 g, 10.5 mmol) was added. The reaction was stirred for another 1 h at -78 °C. The mixture was quenched with sat. NH₄Cl (100 mL) and then extracted with ethyl acetate (100 mLx3). The organic extracts were combined, dried over anhydrous sodium sulfate, and concentrated. The crude was purified by silica gel column chromatography (petroleum ether/ethyl acetate=200:1 to 100:1) to give the desired product as a white solid (1.1 g, 56% yield).

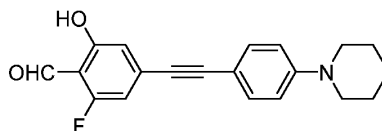
[0400] Step 2: A mixture of 5-bromo-3-fluoro-2-(4-methoxybenzyloxy)benzaldehyde (561 mg, 3.0 mmol), 4-(4-ethynylphenyl)morpholine (1.01 g, 3.0 mmol), TBAF·3H₂O (5.68 g, 18.0 mmol), and Pd(PPh₃)₂Cl₂ (63 mg, 0.09 mmol) in THF (20 mL) was heated at 80 °C for 3 h. The mixture was cooled to rt, diluted with water (100 mL), and then extracted with ethyl acetate (100 mLx3). The organic extracts were combined, washed with brine (80 mL), dried over anhydrous sodium sulfate, and concentrated. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate=5:1 to 1:1) to give PMB-protected penultimate product as yellow solid (410 mg, 31% yield). PMB-protected intermediate (100 mg, 0.22 mmol) was dissolved in dichloromethane (5 mL) and TFA (3 mL) was added. The reaction was stirred for 30 min at rt. The solvent was removed *in vacuo* and the residue was purified by prep-TLC (petroleum ether/ethyl acetate=1:1) to afford the title product as a yellow solid (27 mg, 37% yield). ¹H NMR (*DMSO-d*₆, 400 MHz) δ : 10.20 (s, 1H), 7.43-7.46 (m, 2H), 7.36 (d, *J*=8.4 Hz, 2H), 6.95 (d, *J*=8.4 Hz, 2H), 3.73 (m, 4H), 3.17 (m, 4H); LC-MS *m/z* [M+H]⁺ calc'd for C₁₉H₁₆FN₂O₃, 326; found, 326.

Example B4: 2-fluoro-6-hydroxy-4-((4-(pyrrolidin-1-yl)phenyl)ethynyl)benzaldehyde
(Compound No. B4)



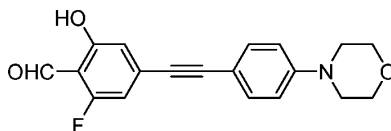
[0401] A mixture of 4-bromo-2-fluoro-6-hydroxybenzaldehyde (900 mg, 4.1 mmol), 1-(4-ethynylphenyl)pyrrolidine (847 mg, 5.0 mmol), $\text{PdCl}_2(\text{PPh}_3)_2$ (290 mg, 0.4 mmol), and $\text{TBAF} \cdot 3\text{H}_2\text{O}$ (7.8 g, 24.8 mmol) in THF (30 mL) was refluxed for 3 hours under nitrogen atmosphere. The mixture was cooled to room temperature, diluted with water (100 mL), and extracted with ethyl acetate (100 mLx3). The organic extracts were combined, washed with brine (50 mLx2), dried over anhydrous sodium sulfate, and concentrated. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate=100:1 to 20:1) to give the title product as a yellow solid (900 mg, 71% yield). ^1H NMR (CDCl_3 , 400 MHz) δ : 11.53 (s, 1H), 10.18 (s, 1H), 7.40 (d, $J=8.8$ Hz, 2H), 6.83 (s, 1H), 6.71 (m, 1H), 6.51 (d, $J=8.4$ Hz, 2H), 3.32 (m, 4H), 2.03 (m, 4H); LC-MS m/z $[\text{M}+\text{H}]^+$ calc'd for $\text{C}_{19}\text{H}_{16}\text{FNO}_2$, 310; found, 310.

Example B5: 2-fluoro-6-hydroxy-4-((4-(piperidin-1-yl)phenyl)ethynyl)benzaldehyde
(Compound No. B5)



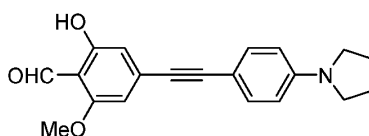
[0402] The title compound was prepared from 4-bromo-2-fluoro-6-hydroxybenzaldehyde (219 mg, 1.0 mmol) and 1-(4-ethynylphenyl)piperidine (185 mg, 1.0 mmol) using a method similar to that as described in Example B1 to give the title compound as a yellow solid (181 mg, 56% yield). ^1H NMR ($\text{DMSO}-d_6$, 400 MHz) δ 11.37 (br, 1H), 10.22 (s, 1H), 7.39 (d, $J=8.8$ Hz, 2H), 6.93 (m, 2H), 6.88 (m, 2H), 3.28 (m, 4H), 1.58 (m, 6H); LC-MS m/z $[\text{M}+\text{H}]^+$ calc'd for $\text{C}_{20}\text{H}_{18}\text{FNO}_2$, 324; found, 324.

Example B6: 2-fluoro-6-hydroxy-4-((4-morpholinophenyl)ethynyl)benzaldehyde (Compound No. B6)



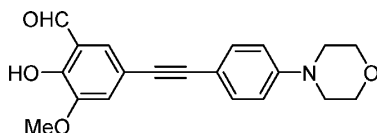
[0403] The title compound was prepared from 4-bromo-2-fluoro-6-hydroxybenzaldehyde (219 mg, 1.0 mmol) and 4-(4-ethynylphenyl)morpholine (187 mg, 1.0 mmol) using a method similar to that as described in Example B1 to give the title compound as a yellow solid (134 mg, 41% yield). ¹H NMR (*DMSO-d*₆, 400 MHz) δ 11.38 (br, 1H), 10.22 (s, 1H), 7.45 (d, *J*=8.4 Hz, 2H), 6.99 (d, *J*=8.4 Hz, 2H), 6.91 (m, 2H), 3.73 (m, 4H), 3.22 (m, 4H); LC-MS *m/z* [M+H]⁺ calc'd for C₁₉H₁₆FNO₃, 326; found, 326.

Example B7: 2-hydroxy-6-methoxy-4-((4-(pyrrolidin-1-yl)phenyl)ethynyl)benzaldehyde (Compound No. B7)



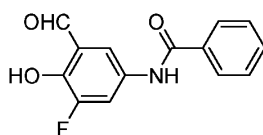
[0404] A mixture of 4-bromo-2-hydroxy-6-methoxybenzaldehyde (462 mg, 2.0 mmol), 1-(4-ethynylphenyl)pyrrolidine (340 mg, 2.0 mmol), PdCl₂(PPh₃)₂ (140 mg, 0.2 mmol), and TBAF·3H₂O (3.78 g, 12.0 mmol) in THF (30 mL) was refluxed for 2 hours under nitrogen atmosphere. The mixture was cooled to room temperature, diluted with water (100 mL), and extracted with ethyl acetate (100 mLx3). The organic extracts were combined, washed with brine (50 mLx2), dried over anhydrous sodium sulfate, and concentrated. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate/dichloromethane=300:1:1 to 200:1:20) to give the title product as a yellow solid (320 mg, 50% yield). ¹H NMR (*CDCl*₃, 400 MHz) δ 12.03 (s, 1H), 10.26 (s, 1H), 7.41 (d, *J*=8.0 Hz, 2H), 6.64 (s, 1H), 6.47-6.53 (m, 3H), 3.60 (s, 3H), 3.31 (m, 4H), 2.03 (m, 4H); LC-MS *m/z* [M+H]⁺ calc'd for C₂₀H₁₉NO₃, 322; found, 322.

Example B8: 2-hydroxy-3-methoxy-5-((4-morpholinophenyl)ethynyl)benzaldehyde (Compound No. B8)



[0405] A mixture of 5-bromo-3-methoxy-2-(4-methoxybenzyloxy)benzaldehyde (1.3 g, 3.74 mmol), 4-(4-ethynylphenyl)morpholine (700 mg, 3.74 mmol), TBAF·3H₂O (7 g, 22.44 mmol), and Pd(PPh₃)₂Cl₂ (79 mg, 0.11 mmol) in THF (20 mL) was heated at 80 °C for 2 h. The mixture was cooled to rt, diluted with water (100 mL), and then extracted with ethyl acetate (100 mLx3). The organic extracts were combined, washed with brine (80 mL), dried over anhydrous sodium sulfate, and concentrated. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate=5:1 to 1:1) to give a PMB-protected penultimate product (880 mg, 51% yield). The PMB-protected intermediate (100 mg, 0.22 mmol) was dissolved in dichloromethane (5 mL), and TFA (3 mL) was added. The reaction was stirred for 30 min at room temperature. The solvent was removed *in vacuo*, and the residue was purified by prep-TLC (petroleum ether/ethyl acetate=1:1) to afford the title product as a yellow solid (31 mg, 42% yield). ¹H NMR (CDCl₃, 400 MHz) δ : 11.23 (s, 1H), 9.90 (s, 1H), 7.44 (m, 2H), 7.38 (s, 1H), 7.22 (s, 1H), 6.89 (m, 2H), 3.93 (s, 3H), 3.88 (m, 4H), 3.23 (m, 4H); LC-MS m/z [M+H]⁺ calc'd for C₂₀H₁₉NO₄, 338; found, 338.

Example B9: N-(3-fluoro-5-formyl-4-hydroxyphenyl)benzamide (Compound No. B9)



Step 1: 3-fluoro-2-hydroxy-5-nitrobenzaldehyde

[0406] In a 125 mL round bottom flask, HNO₃ (2.23 mL, 50.0 mmol) in TFA (20 mL) was added to a solution of 3-fluoro-2-hydroxybenzaldehyde (2 g, 14.3 mmol) in acetic acid (10 mL) at 0 °C. The reaction was stirred for 1 hour at 0 °C. The solution was poured into ice-water, and the resulting precipitate was filtered and washed with petroleum ether to give 3-fluoro-2-

hydroxy-5-nitrobenzaldehyde (1.8 g, 68% yield), which was used for next reaction without further purification. ^1H NMR (CDCl_3 , 400 MHz) δ : 11.67 (s, 1H), 10.05 (s, 1H), 8.45 (s, 1H), 8.27 (dd, $J=10.0$ Hz, 2.8 Hz, 1H).

Step 2: 2-(3-fluoro-2-(4-methoxybenzyloxy)-5-nitrophenyl)-1,3-dithiane

[0407] $\text{BF}_3 \cdot \text{Et}_2\text{O}$ (4.9 mL, 18.2 mmol) was added to a mixture of 3-fluoro-2-hydroxy-5-nitrobenzaldehyde (2.8 g, 15.1 mmol) and propane-1,3-dithiol (1.82 mL, 18.2 mmol) in dichloromethane (30 mL). The reaction was stirred overnight at room temperature. The mixture was poured into ice water and the resulting precipitate was filtered and washed with petroleum ether/dichloromethane (10:1). The cake was dried to give intermediate (3.9 g, 94% yield) as a yellow solid. ^1H NMR ($\text{DMSO}-d_6$, 400 MHz) δ : 12.01 (br, 1H), 8.09 (m, 2H), 5.73 (s, 1H), 3.17 (m, 2H), 2.91 (m, 2H), 2.13 (m, 1H), 1.77 (m, 1H). The intermediate (2.75 g, 10.0 mmol) was dissolved in DMF (20 mL) then added PMBCl (3.12 g, 20.0 mmol) and potassium carbonate (4.1 g, 30.0 mmol, 3 eq.) to the reaction mixture. The reaction was heated at 90 °C for 3 hours. The mixture was poured into water and extracted with ethyl acetate for three times. The organic extracts were combined, washed with brine, dried over anhydrous sodium sulfate, and concentrated to give crude 2-(3-fluoro-2-(4-methoxybenzyloxy)-5-nitrophenyl)-1,3-dithiane (3.3 g, 84% yield), which was used for the next reaction without further purification.

Step 3: 3-(1,3-dithian-2-yl)-5-fluoro-4-(4-methoxybenzyloxy)aniline

[0408] A mixture of 2-(3-fluoro-2-(4-methoxybenzyloxy)-5-nitrophenyl)-1,3-dithiane (2.1 g, 5.3 mmol) and iron (3 g, 53.2 mmol) in acetic acid (20 mL) was heated at 60 °C for 3 hours. The mixture was diluted with ethyl acetate and filtered. The filtrate was neutralized with sodium bicarbonate to pH 8-9, and the organic layer was separated. The water phase was re-extracted with ethyl acetate for two more times. The organic extracts were combined, washed with brine, dried over anhydrous sodium sulfate, and concentrated to give crude 3-(1,3-dithian-2-yl)-5-fluoro-4-(4-methoxybenzyloxy)aniline (1.2 g, 62% yield), which was used for the next reaction without further purification. ^1H NMR ($\text{DMSO}-d_6$, 400 MHz) δ : 7.38 (d, $J=8.4$ Hz, 2H), 6.96 (d, $J=8.0$ Hz, 2H), 6.50 (s, 1H), 6.34 (d, $J=13.2$ Hz, 1H), 5.42 (s, 1H), 5.31 (br, 2H), 4.81 (s, 2H), 3.77 (s, 3H), 3.02 (m, 2H), 2.89 (m, 2H), 2.12 (m, 1H), 1.69 (m, 1H).

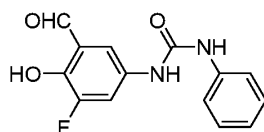
Step 4: N-(3-(1,3-dithian-2-yl)-5-fluoro-4-(4-methoxybenzyloxy)phenyl)benzamide

[0409] A solution of 3-(1,3-dithian-2-yl)-5-fluoro-4-(4-methoxybenzyloxy)aniline (500 mg, 1.37 mmol), benzoyl chloride (289 mg, 2.05 mmol), and triethylamine (415 mg, 4.11 mmol) in dichloromethane (20 mL) was stirred overnight at room temperature. The solvent was removed, and the residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate=20:1 to 5:1) to give N-(3-(1,3-dithian-2-yl)-5-fluoro-4-(4-methoxybenzyloxy)phenyl)benzamide (620 mg, 96% yield). LC-MS m/z [M+H]⁺ calc'd for C₂₅H₂₄FNO₃S₂, 470; found, 470.

Step 5: N-(3-fluoro-5-formyl-4-hydroxyphenyl)benzamide

[0410] A mixture of N-(3-(1,3-dithian-2-yl)-5-fluoro-4-(4-methoxybenzyloxy)phenyl)benzamide (620 mg, 1.32 mmol) and DMP (1.12 g, 2.64 mmol) in acetonitrile/dichloromethane/water (16 mL/2 mL/2 mL) was stirred overnight at 45 °C. The mixture was filtered and the cake was washed with dichloromethane. The filtrate and wash were washed with 5% sodium bicarbonate solution. The water phase was re-extracted with dichloromethane for two more times. The organic extracts were combined, washed with brine, dried over anhydrous sodium sulfate, and concentrated. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate/dichloromethane=50:1:1 to 20:1:1) to give PMB-protected N-(3-fluoro-5-formyl-4-hydroxyphenyl)benzamide (250 mg, 50% yield). The PMB-protected N-(3-fluoro-5-formyl-4-hydroxyphenyl)benzamide (250 mg, 0.66 mmol) was dissolved in dichloromethane (5 mL) and added TFA (230 mg, 1.98 mmol) to the mixture. The reaction was stirred for 1 hour at room temperature. The solvent was removed in vacuo and the residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate/dichloromethane=20:1:1 to 10:1:1) to give N-(3-fluoro-5-formyl-4-hydroxyphenyl)benzamide (60 mg, 0.23 mmol, 35% yield) as a white solid. ¹H NMR (DMSO-*d*₆, 400 MHz) δ: 10.74 (s, 1H), 10.39 (s, 1H), 10.32 (s, 1H), 7.90-8.04 (m, 4H), 7.52-7.61 (m, 3H); LC-MS m/z [M+H]⁺ calc'd for C₁₄H₁₀FNO₃, 260; found, 260.

Example B10: 1-(3-fluoro-5-formyl-4-hydroxyphenyl)-3-phenylurea (Compound No. B10)

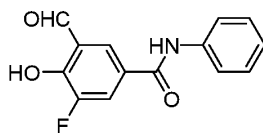


Step 1: 1-(3-(1,3-dithian-2-yl)-5-fluoro-4-(4-methoxybenzyloxy)phenyl)-3-phenylurea

[0411] DPPA (1.1 g, 4 mmol) and triethylamine (0.42 g, 4 mmol) were added to a solution of benzoic acid (0.35 g, 2.9 mmol) in dioxane (10 mL). The reaction was stirred for 30 min at room temperature. Then, 3-(1,3-dithian-2-yl)-5-fluoro-4-(4-methoxybenzyloxy)aniline (0.5 g, 1.4 mmol, 1 eq.) was added to the reaction mixture and the reaction was heated at 90 °C for 3 hours. The solvent was removed and the residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate/dichloromethane=30:1:1 to 10:1:1) to give 1-(3-(1,3-dithian-2-yl)-5-fluoro-4-(4-methoxybenzyloxy)phenyl)-3-phenylurea (610 mg, 92% yield). LC-MS m/z $[M+H]^+$ calc'd for $C_{25}H_{25}FN_2O_3S_2$, 485; found, 485.

Step 2: 1-(3-fluoro-5-formyl-4-hydroxyphenyl)-3-phenylurea

[0412] A solution of 1-(3-(1,3-dithian-2-yl)-5-fluoro-4-(4-methoxybenzyloxy)phenyl)-3-phenylurea (300 mg, 0.62 mmol), MeI (1.76 g, 12.4 mmol), and $NaHCO_3$ (1 g, 12.4 mmol) in acetonitrile/ water (15 mL/3 mL) was stirred overnight at 50 °C. The solution was diluted with water and extracted with ethyl acetate for three times. The organic extracts were combined, washed with brine, dried over anhydrous sodium sulfate, and concentrated. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate/dichloromethane=10:1:1 to 5:1:1) to give PMB-protected 1-(3-fluoro-5-formyl-4-hydroxyphenyl)-3-phenylurea (170 mg, 70% yield). The PMB-protected 1-(3-fluoro-5-formyl-4-hydroxyphenyl)-3-phenylurea (80 mg, 0.20 mmol) was dissolved in 6 N HCl/dioxane (5 mL) and the reaction was stirred for 30 min at room temperature. The solution was poured into ice-cold sat. sodium bicarbonate and extracted with ethyl acetate for three times. The organic extracts were combined, washed with brine, dried over anhydrous sodium sulfate, and concentrated. The residue was purified by prep-TLC ($CH_2Cl_2/MeOH=20:1$) to give 1-(3-fluoro-5-formyl-4-hydroxyphenyl)-3-phenylurea (30 mg, 0.23 mmol, 54% yield) as an off-white solid. 1H NMR ($DMSO-d_6$, 400 MHz) δ : 10.50 (s, 1H), 10.28 (s, 1H), 8.78 (s, 1H), 8.70 (s, 1H), 7.74 (m, 1H), 7.46 (m, 3H), 7.27 (m, 2H), 6.97 (m, 1H); LC-MS m/z $[M+H]^+$ calc'd for $C_{14}H_{11}FN_2O_3$, 275; found, 275.

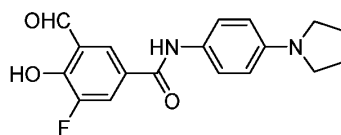
Example B11: 3-fluoro-5-formyl-4-hydroxy-N-phenylbenzamide (Compound No. B11)Step 1: 3-fluoro-5-formyl-4-hydroxybenzoic acid

[0413] A solution of HMPA (28 g, 0.2 mol, 2 eq.) in TFA (20 mL) was added to a solution of 3-fluoro-4-hydroxybenzoic acid (15.6 g, 0.1 mol) in TFA (30 mL). The reaction was stirred overnight at 100 °C. The solution was cooled to room temperature and poured into 3 M HCl (200 mL). The mixture was stirred for 30 min and the resulting precipitate was filtered and dried to give 3-fluoro-5-formyl-4-hydroxybenzoic acid, which was used for the next reaction without further purification. LC-MS m/z $[M-H]^-$ calc'd for $C_8H_5FO_4$, 183; found, 183.

Step 2: 3-fluoro-5-formyl-4-hydroxy-N-phenylbenzamide

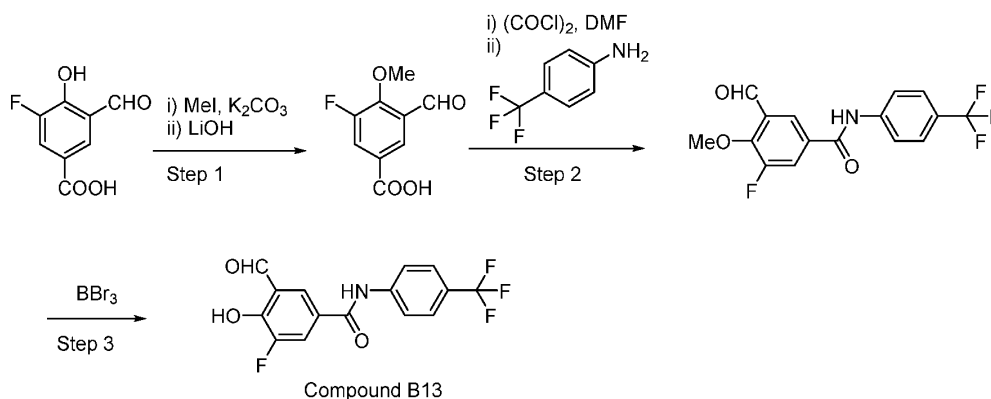
[0414] HATU (0.63 g, 1.7 mmol) and N-Methylmorpholine (0.67 g, 6.6 mmol) were added to a mixture of 3-fluoro-5-formyl-4-hydroxybenzoic acid (0.2 g, 1.1 mmol) and aniline hydrochloride (0.43 g, 3.3 mmol) in dichloromethane (30 mL). The mixture was stirred overnight at room temperature. The solvent was removed and the residue dissolved in a mixture of ether (6 mL) and 4 M HCl (6 mL). The mixture was stirred overnight at room temperature. The mixture was diluted with water (20 mL) and extracted with ethyl acetate (20 mLx3). The organic extracts were combined, washed with brine (20 mL), dried over anhydrous sodium sulfate, and concentrated. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate/dichloromethane=10:1:1 to 2:1:1) to give the desired 3-fluoro-5-formyl-4-hydroxy-N-phenylbenzamide product as light yellow solid (4% yield). 1H NMR ($DMSO-d_6$, 400 MHz) δ : 11.67 (br, 1H), 10.36 (s, 1H), 10.30 (s, 1H), 8.20 (s, 1H), 8.11 (dd, $J=12.0$ Hz, 2.4 Hz, 1H), 7.75 (d, $J=7.2$ Hz, 1H), 7.35 (m, 2H), 7.11 (m, 1H); LC-MS m/z $[M-H]^-$ calc'd for $C_{14}H_{10}FNO_3$, 258; found, 258.

Example B12: 3-fluoro-5-formyl-4-hydroxy-N-(4-(pyrrolidin-1-yl)phenyl)benzamide (Compound No. B12)



[0415] The title compound was synthesized in a similar manner as described for 3-fluoro-5-formyl-4-hydroxy-N-phenylbenzamide in Example B11 to obtain the desired product as a green solid (67% yield). ^1H NMR ($\text{DMSO}-d_6$, 400 MHz) δ : 11.57 (br, 1H), 10.35 (s, 1H), 10.03 (br, 1H), 8.18 (s, 1H), 8.09 (dd, $J=12.0$ Hz, 2.4 Hz, 1H), 7.53 (d, $J=8.8$ Hz, 2H), 6.55 (d, $J=8.0$ Hz, 2H), 3.22 (m, 4H), 1.95 (m, 4H); LC-MS m/z $[\text{M}+\text{H}]^+$ calc'd for $\text{C}_{18}\text{H}_{17}\text{FN}_2\text{O}_3$, 329; found, 329.

Example B13: 3-fluoro-5-formyl-4-hydroxy-N-(4-(trifluoromethyl)phenyl)benzamide
(Compound No. B13)



Step 1: 3-fluoro-5-formyl-4-methoxybenzoic acid

[0416] A mixture of 3-fluoro-5-formyl-4-hydroxybenzoic acid (0.5 g, 2.7 mmol), MeI (1.16 g, 8.2 mmol), and potassium carbonate (1.13 g, 8.2 mmol) in DMF (5 mL) was heated at 50 °C for 3 hours. The mixture was cooled to room temperature, diluted with water (20 mL), and extracted with ethyl acetate (20 mLx3). The organic extracts were combined, washed with brine (10 mLx2), dried over anhydrous sodium sulfate, and concentrated. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate=100:1 to 20:1) to give methyl ether intermediate (0.58 g, quantitative yield). The methyl ether intermediate (0.58 g, 2.7 mmol) was dissolved in THF/water (2 mL/2 mL), and $\text{LiOH}\cdot\text{H}_2\text{O}$ (0.57 g, 13.5 mmol) was added. The reaction was stirred for 1 hour at room temperature. The pH of the reaction system was adjusted

to 4-5 and extracted three times with ethyl acetate. The organic extracts were combined, washed with brine, dried over anhydrous sodium sulfate, and concentrated to give crude 3-fluoro-5-formyl-4-methoxybenzoic acid (0.5 g, 94% yield), which was used for the next reaction without further purification.

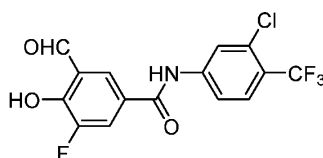
Step 2: 3-fluoro-5-formyl-4-methoxy-N-(4-(trifluoromethyl)phenyl)benzamide

[0417] A drop of DMF was added to a solution of 3-fluoro-5-formyl-4-methoxybenzoic acid (0.2 g, 1.0 mmol) and oxalyl chloride (0.39 g, 3.0 mmol) in DCM (5 mL). The reaction was stirred for 1 hour at room temperature. The solvent was removed *in vacuo* and the residue was co-evaporated two times with dichloromethane. The residue was then dissolved in dichloromethane (5 mL). 4-Trifluoromethylaniline (0.5 g, 3.0 mmol), DMAP (0.02 g, 0.1 mmol), and triethylamine (0.5 g, 5.0 mmol) were added. The reaction was stirred for 1 hour. LC-MS showed formation of the desired product. The solvent was removed and the residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate/dichloromethane=20:1:1 to 5:1:1) to give 3-fluoro-5-formyl-4-methoxy-N-(4-(trifluoromethyl)phenyl)benzamide (130 mg, 38% yield), containing 4-trifluoromethylaniline inside at the same spot. LC-MS m/z $[M+H]^+$ calc'd for $C_{16}H_{11}F_4NO_3$, 342; found, 342.

Step 3: 3-fluoro-5-formyl-4-hydroxy-N-(4-(trifluoromethyl)phenyl)benzamide

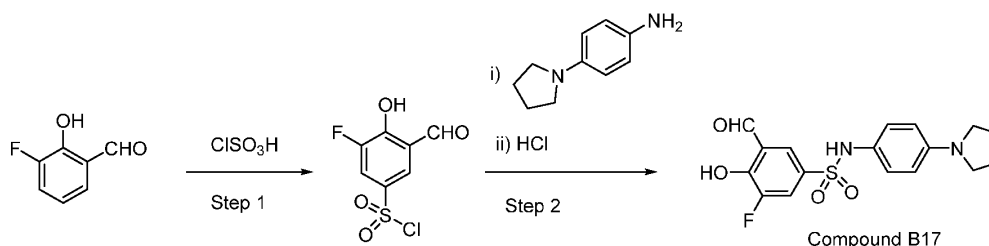
[0418] BBr_3 (191 mg, 0.76 mmol) was added to a solution of 3-fluoro-5-formyl-4-methoxy-N-(4-(trifluoromethyl)phenyl)benzamide (130 mg, 0.38 mmol) in dichloromethane (5 mL) at $-78^\circ C$. The reaction was stirred for 30 min at room temperature. The solution was diluted with dichloromethane and washed with sat. sodium bicarbonate. The organic layer was separated, dried over anhydrous sodium sulfate, and concentrated. The residue was removed *in vacuo* and the residue was co-evaporated two times with dichloromethane. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate/dichloromethane=20:1:1 to 5:1:1) to give 3-fluoro-5-formyl-4-hydroxy-N-(4-(trifluoromethyl)phenyl)benzamide (50 mg, 40% yield). 1H NMR ($DMSO-d_6$, 400 MHz) δ : 11.77 (br, 1H), 10.62 (s, 1H), 10.36 (s, 1H), 8.22 (s, 1H), 8.13 (dd, $J=12.0$ Hz, 2.0 Hz, 1H), 8.00 (d, $J=8.8$ Hz, 2H), 7.74 (d, $J=8.4$ Hz, 2H); LC-MS m/z $[M+H]^+$ calc'd for $C_{15}H_9F_4NO_3$, 328; found, 328.

Example B14: N-(3-Chloro-4-(trifluoromethyl)phenyl)-3-fluoro-5-formyl-4-hydroxybenzamide
(Compound No. B14)



[0419] The title product was synthesized in a similar manner as described for 3-fluoro-5-formyl-4-hydroxy-N-(4-(trifluoromethyl)phenyl)benzamide in Example B13. Yield for step 3: 22%, brown solid. ^1H NMR ($\text{DMSO}-d_6$, 400 MHz) δ : 11.84 (br, 1H), 10.74 (s, 1H), 10.37 (s, 1H), 8.20 (m, 2H), 8.11 (dd, $J=11.6$ Hz, 2.0 Hz, 1H), 7.92 (m, 2H); LC-MS m/z $[\text{M}+\text{H}]^+$ calc'd for $\text{C}_{15}\text{H}_8\text{ClF}_4\text{NO}_3$, 362; found, 362.

Example B15: 3-fluoro-5-formyl-4-hydroxy-N-(4-(pyrrolidin-1-yl)phenyl)benzenesulfonamide
(Compound B17)

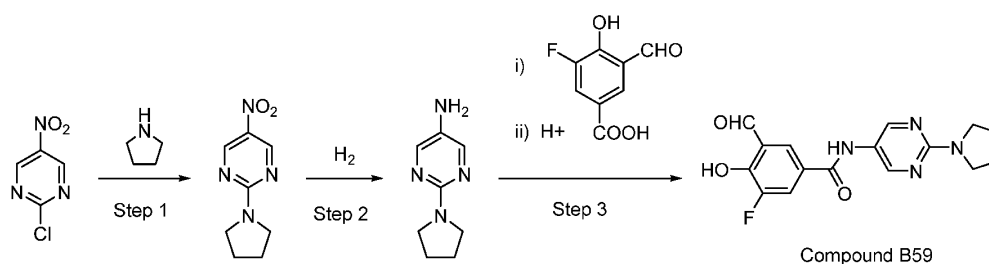


Step 1: 3-fluoro-5-formyl-4-hydroxybenzene-1-sulfonyl chloride

[0420] Chlorosulfonic acid (1.66 g, 14.3 mmol, 10 eq.) was added dropwise to a solution of 3-fluoro-2-hydroxybenzaldehyde (200 mg, 1.4 mmol, 1.0 eq.) in dichloromethane (10 mL) at 0°C . The reaction was stirred overnight at room temperature. The reaction mixture was poured into ice-water (30 mL) and extracted with dichloromethane for three times. The organic extracts were combined, washed with brine, dried over anhydrous sodium sulfate and concentrated to give crude 3-fluoro-5-formyl-4-hydroxybenzene-1-sulfonyl chloride (390 mg, quantitative yield), which was used in next reaction without further purification. LC-MS m/z $[\text{M}-\text{HCl}]^-$ calc'd for $\text{C}_7\text{H}_4\text{ClFO}_4\text{S}$, 219; found, 219.

[0421] Step 2: A solution of 3-fluoro-5-formyl-4-hydroxybenzene-1-sulfonyl chloride (390 mg, 1.64 mmol, 1.0 eq.), 4-(pyrrolidin-1-yl)aniline (664 mg, 4.10 mmol, 2.5 eq.), and N-methyl morpholine (497 mg, 4.92 mmol, 3.0 eq.) in dichloromethane (10 mL) was stirred for 5 hours. The reaction mixture was poured into 4 N HCl. The reaction was stirred for 3 hours and then extracted with ethyl acetate for three times. The organic extracts were combined, washed with brine, dried over anhydrous sodium sulfate, and concentrated. The residue was purified by silica gel column chromatography and prep-TLC to give 3-fluoro-5-formyl-4-hydroxy-N-(4-(pyrrolidin-1-yl)phenyl)benzenesulfonamide (23 mg, 0.06 mmol, 4% yield) as a yellow solid. ^1H NMR ($\text{DMSO}-d_6$, 400 MHz) δ : 12.03 (br, 1H), 10.26 (br, 1H), 9.57 (s, 1H), 7.75 (s, 1H), 7.62 (dd, $J=10.4$ Hz, 2.4 Hz, 1H), 6.82 (d, $J=8.8$ Hz, 2H), 6.38 (d, $J=8.0$ Hz, 2H), 3.13 (m, 4H), 1.90 (m, 4H). LC-MS m/z $[\text{M}+\text{H}]^+$ calc'd for $\text{C}_{17}\text{H}_{17}\text{FN}_2\text{O}_4\text{S}$, 365; found, 365.

Example B16: 3-fluoro-5-formyl-4-hydroxy-N-(2-(pyrrolidin-1-yl)pyrimidin-5-yl)benzamide (Compound B59)



Step 1: 5-nitro-2-(pyrrolidin-1-yl)pyrimidine

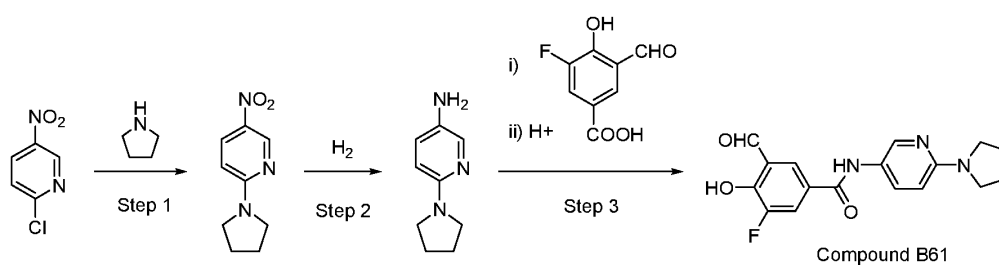
[0422] A mixture of 2-chloro-5-nitropyrimidine (2 g, 12.6 mmol, 1.0 eq.), pyrrolidine (1.3 g, 18.9 mmol, 1.5 eq.), and potassium carbonate (3.5 g, 25.2 mmol, 2.0 eq.) in DMF (10 mL) was stirred for 5 hours at room temperature. The mixture was poured into water (100 mL) and extracted with ethyl acetate for three times. The organic extracts were combined, washed with brine, dried over anhydrous sodium sulfate, and concentrated to give 5-nitro-2-(pyrrolidin-1-yl)pyrimidine (2.3 g, 94% yield), which was used for next reaction without further purification. LC-MS m/z $[\text{M}+\text{H}]^+$ calc'd for $\text{C}_8\text{H}_{10}\text{N}_4\text{O}_2$, 195; found, 195.

Step 2: 2-(pyrrolidin-1-yl)pyrimidin-5-amine

[0423] A mixture of 5-nitro-2-(pyrrolidin-1-yl)pyrimidine (2.3 g, 11.9 mmol, 1.0 eq.) and Pd/C (0.2 g) in methanol (10 mL) was hydrogenated for 2 hours. Pd/C was filtered off and washed with methanol. The filtrate and wash were combined and concentrated to give 2-(pyrrolidin-1-yl)pyrimidin-5-amine (1.63 g, 84% yield), which was used for next reaction without further purification. LC-MS m/z $[M+H]^+$ calc'd for $C_8H_{12}N_4$, 165; found, 165.

[0424] Step 3: HATU (0.71 g, 1.87 mmol, 1.5 eq.) and N-methyl morpholine (0.4 g, 3.74 mmol, 3.0 eq.) were added to a mixture of 3-fluoro-5-formyl-4-hydroxybenzoic acid (0.23 g, 1.25 mmol, 1.0 eq.) and 2-(pyrrolidin-1-yl)pyrimidin-5-amine (0.5 g, 3.05 mmol, 2.5 eq.) in dichloromethane (30 mL). The mixture was stirred overnight at 30°C. The solvent was removed and the residue dissolved in a mixture of dioxane (6 mL) and 4 N HCl (6 mL). The mixture was stirred for 2 hours at 55°C. The mixture was diluted with water (20 mL) and washed with ethyl acetate (30 mL). The wash was discarded. The water phase was neutralized with sodium bicarbonate and extracted with ethyl acetate for three times. The organic extracts were combined, washed with brine (20 mL), dried over anhydrous sodium sulfate, and concentrated. The residue was purified by silica gel column chromatography (petroleum ether/acetone=20:1 to 5:1) to give 3-fluoro-5-formyl-4-hydroxy-N-(2-(pyrrolidin-1-yl)pyrimidin-5-yl)benzamide (15 mg, 0.05 mmol, 4% yield) as a pale yellow solid. 1H NMR ($DMSO-d_6$, 400 MHz) δ : 11.70 (br, 1H), 10.35 (s, 1H), 10.22 (br, 1H), 8.59 (s, 2H), 8.20 (s, 1H), 8.07 (dd, $J=11.6$ Hz, 2.0 Hz, 1H), 3.48 (m, 4H), 1.94 (m, 4H). LC-MS m/z $[M+H]^+$ calc'd for $C_{16}H_{15}FN_4O_3$, 331; found, 331.

Example B17: 3-fluoro-5-formyl-4-hydroxy-N-(6-(pyrrolidin-1-yl)pyridin-3-yl)benzamide (Compound B61)



Step 1: 5-nitro-2-(pyrrolidin-1-yl)pyridine

[0425] A mixture of 2-chloro-5-nitropyridine (2 g, 12.6 mmol, 1.0 eq.), pyrrolidine (1.3 g, 18.9 mmol, 1.5 eq.), and potassium carbonate (3.5 g, 25.2 mmol, 2.0 eq.) in DMF (10 mL) was

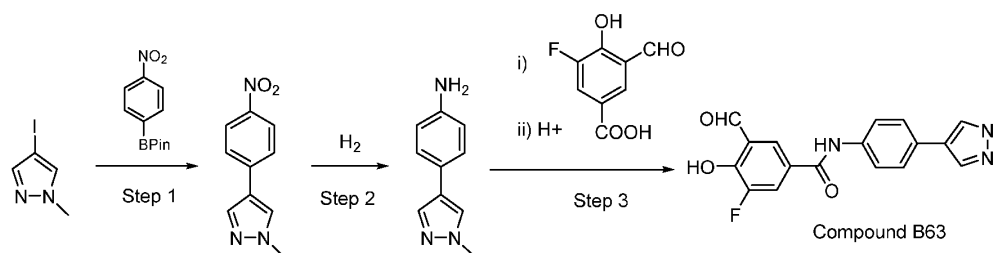
stirred for 5 hours at room temperature. The mixture was poured into water (100 mL) and extracted with ethyl acetate for three times. The organic extracts were combined, washed with brine, dried over anhydrous sodium sulfate, and concentrated to give 5-nitro-2-(pyrrolidin-1-yl)pyridine (2.4 g, 99% yield), which was used for next reaction without further purification. LC-MS m/z $[M+H]^+$ calc'd for $C_9H_{11}N_3O_2$, 194; found, 194.

Step 2: 6-(pyrrolidin-1-yl)pyridin-3-amine

[0426] A mixture of 5-nitro-2-(pyrrolidin-1-yl)pyridine (2 g, 10.4 mmol, 1.0 eq.) and Pd/C (0.2 g) in methanol (10 mL) was hydrogenated for 2 h. Pd/C was filtered off and washed with methanol. The filtrate and wash were combined and concentrated to give 6-(pyrrolidin-1-yl)pyridin-3-amine (1.38 g, 82% yield), which was used for next reaction without further purification. LC-MS m/z $[M+H]^+$ calc'd for $C_9H_{13}N_3$, 164; found, 164.

[0427] Step 3: HATU (1.24 g, 3.26 mmol, 1.5 eq.) and N-methyl morpholine (0.66 g, 6.51 mmol, 3.0 eq.) were added to a mixture of 3-fluoro-5-formyl-4-hydroxybenzoic acid (0.4 g, 2.17 mmol, 1.0 eq.) and 6-(pyrrolidin-1-yl)pyridin-3-amine (0.89 g, 5.43 mmol, 2.5 eq.) in DCM (30 mL). The mixture was stirred overnight at 30°C. The solvent was removed and the residue dissolved in a mixture of dioxane (6 mL) and 4 N HCl (6 mL). The mixture was stirred for 3 h at 55°C. The mixture was neutralized with lithium hydroxide to pH 9-10 and washed with dichloromethane and ethyl acetate each for two times. The water phase was then treated with HCl to pH~3 then to pH~7-8 with sodium bicarbonate. The mixture was then extracted with ethyl acetate for three times. The organic extracts were combined, washed with brine (20 mL), dried over anhydrous sodium sulfate, and concentrated. The residue was purified by silica gel column chromatography (petroleum ether/acetone=20:1 to 5:1) to give 3-fluoro-5-formyl-4-hydroxy-N-(6-(pyrrolidin-1-yl)pyridin-3-yl)benzamide (75 mg, 0.23 mmol, 11% yield) as a pale yellow solid. 1H NMR ($DMSO-d_6$, 400 MHz) δ : 11.69 (br, 1H), 10.35 (br, 1H), 10.11 (br, 1H), 8.34 (s, 1H), 8.18 (s, 1H), 8.07 (d, $J=10.8$ Hz, 1H), 7.82 (m, 1H), 6.47 (d, $J=9.2$ Hz, 1H), 3.45 (m, 4H), 1.94 (m, 4H). LC-MS m/z $[M+H]^+$ calc'd for $C_{17}H_{16}FN_3O_3$, 330; found, 330.

Example B18: 3-fluoro-5-formyl-4-hydroxy-N-(4-(1-methyl-1H-pyrazol-4-yl)phenyl)benzamide (Compound B63)



Step 1: 1-methyl-4-(4-nitrophenyl)-1H-pyrazole

[0428] A mixture of 4-iodo-1-methyl-1H-pyrazole (0.7 g, 3.4 mmol, 1.0 eq.), 4,4,5,5-tetramethyl-2-(4-nitrophenyl)-1,3,2-dioxaborolane (1.1 g, 5.0 mmol, 1.5 eq.), potassium carbonate (1.4 g, 10.1 mmol, 3.0 eq.) and Pd(dppf)Cl₂ (0.2 g, 0.34 mmol, 0.1 eq.) in dioxane/water (30 mL/10 mL) was heated for 3 hours at 90°C. The mixture was concentrated, diluted with water (30 mL), and then extracted with ethyl acetate for three times. The organic extracts were combined, washed with brine, dried over anhydrous sodium sulfate, and concentrated. The residue was purified by silica gel column chromatography (petroleum ether/EtOAc/DCM=50:1:1 to 5:1:1) to give 1-methyl-4-(4-nitrophenyl)-1H-pyrazole (0.6 g, 88% yield). LC-MS m/z [M+H]⁺ calc'd for C₁₀H₉N₃O₂, 204; found, 204.

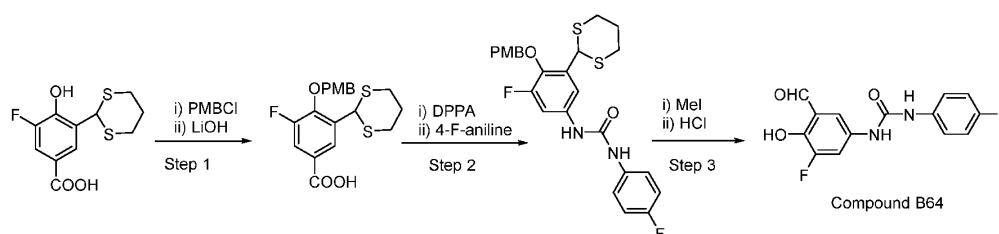
Step 2: 4-(1-methyl-1H-pyrazol-4-yl)aniline

[0429] A mixture of 1-methyl-4-(4-nitrophenyl)-1H-pyrazole (0.6 g, 3.0 mmol, 1.0 eq.) and Pd/C (0.1 g) in methanol (10 mL) was hydrogenated for 2 hours. Pd/C was filtered off and washed with methanol. The filtrate and wash were combined and concentrated to give 4-(1-methyl-1H-pyrazol-4-yl)aniline (0.48 g, 94% yield) as a grey solid, which was used for next reaction without further purification. LC-MS m/z [M+H]⁺ calc'd for C₁₀H₁₁N₃, 174; found, 174.

[0430] Step 3: HATU (0.66 g, 1.74 mmol, 1.5 eq.) and N-methyl morpholine (0.35 g, 3.48 mmol, 3.0 eq.) were added to a mixture of 3-fluoro-5-formyl-4-hydroxybenzoic acid (0.21 g, 1.16 mmol, 1.0 eq.) and 4-(1-methyl-1H-pyrazol-4-yl)aniline (0.4 g, 2.31 mmol, 2.0 eq.) in dichloromethane (30 mL). The reaction was stirred overnight at rt. The resulting precipitate was filtered and dissolved in a mixture of dioxane (6 mL) and 3 N HCl (6 mL). The mixture was stirred for 2 hours at room temperature and extracted with ethyl acetate for three times. The organic extracts were combined, washed with brine, dried over anhydrous sodium sulfate, and concentrated. The solid was stirred in dichloromethane (10 mL) for 10 min and filtered. The

filtrate was concentrated, dissolved in dichloromethane (5 mL), and petroleum ether was added slowly. The resulting precipitate was collected and dried to give 3-fluoro-5-formyl-4-hydroxy-N-(4-(1-methyl-1H-pyrazol-4-yl)phenyl)benzamide (45 mg, 0.13mmol, 11% yield) as a yellow solid. ^1H NMR ($\text{DMSO}-d_6$, 400 MHz) δ : 11.65 (br, 1H), 10.35 (s, 1H), 10.27 (s, 1H), 8.19 (s, 1H), 8.09 (m, 2H), 7.83 (s, 1H), 7.74 (d, $J=8.8$ Hz, 2H), 7.54 (d, $J=8.4$ Hz, 2H), 3.86 (s, 3H). LC-MS m/z $[\text{M}+\text{H}]^+$ calc'd for $\text{C}_{18}\text{H}_{14}\text{FN}_3\text{O}_3$, 340; found, 340.

Example B19: 1-(3-(1,3-dithian-2-yl)-5-fluoro-4-(4-methoxybenzyloxy)phenyl)-3-(4-fluorophenyl)urea (Compound B64)



Step 1: 3-(1,3-dithian-2-yl)-5-fluoro-4-(4-methoxybenzyloxy)benzoic acid

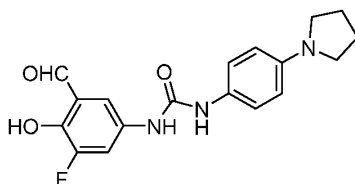
[0431] A mixture of 3-(1,3-dithian-2-yl)-5-fluoro-4-hydroxybenzoic acid (1 g, 3.6 mmol, 1.0 eq.), PMBCl (1.2 g, 7.6 mmol, 2.1 eq.), and potassium carbonate (1 g, 7.2 mmol, 2.0 eq.) in DMF (5 mL) was heated for 3 hours at 90°C. The mixture was poured into water (30 mL) and extracted with ethyl acetate for three times. The organic extracts were combined, washed with brine, dried over anhydrous sodium sulfate, and concentrated to give crude intermediate (1.9 g, quantitative yield), which was used for next reaction without further purification. The crude intermediate (1.9 g, 3.6 mmol, 1.0 eq.) was dissolved in water/THF (5 mL/5 mL) and $\text{LiOH}\cdot\text{H}_2\text{O}$ (0.76 g, 18.0 mmol, 5.0 eq.) was added. The reaction was stirred for 5 hours at 80°C. pH of the system was adjusted to 3-4 with 5% KHSO_4 . The resulting mixture was extracted with ethyl acetate for three times. The organic extracts were combined, washed with brine, dried over anhydrous sodium sulfate, and concentrated to give crude 3-(1,3-dithian-2-yl)-5-fluoro-4-(4-methoxybenzyloxy)benzoic acid (1.4 g, quantitative yield), which was used for next reaction without further purification. LC-MS m/z $[\text{M}-\text{H}]^-$ calc'd for $\text{C}_{19}\text{H}_{19}\text{FO}_4\text{S}_2$, 393; found, 393.

Step 2: 1-(3-(1,3-dithian-2-yl)-5-fluoro-4-(4-methoxybenzyloxy)phenyl)-3-(4-fluorophenyl)urea

[0432] A solution of 3-(1,3-dithian-2-yl)-5-fluoro-4-(4-methoxybenzyloxy)benzoic acid (0.3 g, 0.76 mmol, 1.0 eq.), DPPA (251 mg, 0.91 mmol, 1.2 eq.), and TEA (231 mg, 2.28 mmol, 3.0 eq.) in dioxane (10 mL) was stirred for 30 min at room temperature and 4-fluoroaniline (169 mg, 1.52 mmol, 2.0 eq.) was added. The reaction was then heated overnight at 90°C. The reaction mixture was cooled to room temperature, poured into water, and extracted with ethyl acetate for three times. The organic extracts were combined, washed with brine, dried over anhydrous sodium sulfate, and concentrated. The residue was purified by silica gel column chromatography (petroleum ether/EtOAc = 20:1 to 3:1) to give 1-(3-(1,3-dithian-2-yl)-5-fluoro-4-(4-methoxybenzyloxy)phenyl)-3-(4-fluorophenyl)urea (240 mg, 63% yield). LC-MS m/z $[M+H]^+$ calc'd for $C_{25}H_{24}F_2N_2O_3S_2$, 503; found, 503.

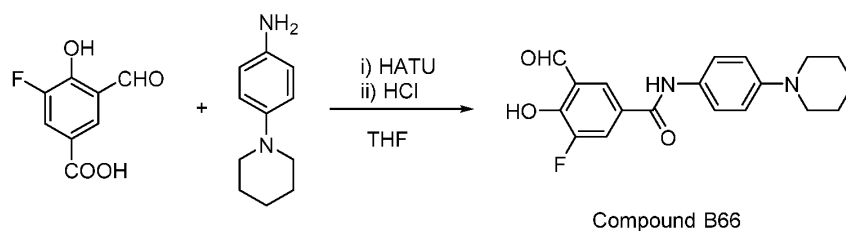
[0433] Step 3: MeI (6.5 g, 45.8 mmol, 100 eq.) was added to a mixture of 1-(3-(1,3-dithian-2-yl)-5-fluoro-4-(4-methoxybenzyloxy)phenyl)-3-(4-fluorophenyl)urea (230 mg, 0.46 mmol, 1.0 eq.) and $NaHCO_3$ (770 mg, 9.17 mmol, 20.0 eq.) in acetonitrile/water (30 mL/6 mL). The reaction was heated for 6 hours at 40°C. The reaction mixture was cooled to room temperature, poured into water, and extracted with ethyl acetate for three times. The organic extracts were combined, washed with brine, dried over anhydrous sodium sulfate, and concentrated. The residue was stirred in dichloromethane (3 mL) and the solid was collected to give the intermediate (~100 mg). The intermediate (~100 mg) was dissolved in dioxane (2 mL) and 6 N HCl/dioxane (3 mL) was added. The reaction was stirred for 1 hour at room temperature. The solution was poured into ice-cold sat. $NaHCO_3$ and extracted with ethyl acetate for three times. The organic extracts were combined, washed with brine, dried over anhydrous sodium sulfate, and concentrated. The solid was stirred in dichloromethane (3 mL) for 10 min and filtered. The cake was collected and dried to give 1-(3-fluoro-5-formyl-4-hydroxyphenyl)-3-(4-fluorophenyl)urea (45 mg, 0.15 mmol, 34% yield) as an off-white solid. 1H NMR ($DMSO-d_6$, 400 MHz) δ : 10.51 (br, 1H), 10.27 (s, 1H), 8.77 (d, $J=14.4$ Hz, 2H), 8.69 (dd, $J=12.8$ Hz, 2.4 Hz, 1H), 7.45 (m, 3H), 7.12 (m, 2H). LC-MS m/z $[M+H]^+$ calc'd for $C_{14}H_{10}F_2N_2O_3$, 293; found, 293.

Example B20: 1-(3-fluoro-5-formyl-4-hydroxyphenyl)-3-(4-(pyrrolidin-1-yl)phenyl)urea (Compound B65)



[0434] 4-(Pyrrolidin-1-yl)aniline (176 mg, 1.09 mmol, 1.0 eq.) was added to a solution of 3-fluoro-5-formyl-4-hydroxybenzoic acid (200 mg, 1.09 mmol, 1.0 eq.) in dioxane (5 mL). The reaction was stirred for 10 min at room temperature. The resulting mixture was concentrated and the residue was stirred in dichloromethane (20 mL) for 10 min, and then filtered. The cake was dried and re-suspended in dioxane (30 mL). DPPA (448 mg, 1.63 mmol, 1.5 eq.) and TEA (329 mg, 3.26 mmol, 3.0 eq.) were added. The reaction was stirred for 30 min at room temperature. Then 4-(pyrrolidin-1-yl)aniline (176 mg, 1.09 mmol, 1.0 eq.) was added and the reaction was heated for 3 hours at 90°C. The mixture was cooled to room temperature and poured into 4 N HCl/water (50 mL). After stirring for 1 hour at room temperature, the mixture was extracted with ethyl acetate for three times and dichloromethane for 4 times. The organic extracts were combined, dried over anhydrous sodium sulfate, and concentrated. The residue was purified by silica gel column chromatography (petroleum ether/EtOAc=20:1 to 3:1) and prep-TLC to give 1-(3-fluoro-5-formyl-4-hydroxyphenyl)-3-(4-(pyrrolidin-1-yl)phenyl)urea (25 mg, 0.07 mmol, 7% yield) as a green solid. ¹H NMR (*DMSO-d*₆, 400 MHz) δ : 10.45 (br, 1H), 10.27 (s, 1H), 8.63 (br, 1H), 8.57 (br, 1H), 7.71 (dd, *J*=13.2 Hz, 2.4 Hz, 1H), 7.46 (s, 1H), 7.31 (m, 2H), 6.74 (m, 2H), 3.93 (m, 4H), 1.99 (m, 4H). LC-MS *m/z* [*M*+*H*]⁺ calc'd for C₁₈H₁₈FN₃O₃, 344; found, 344.

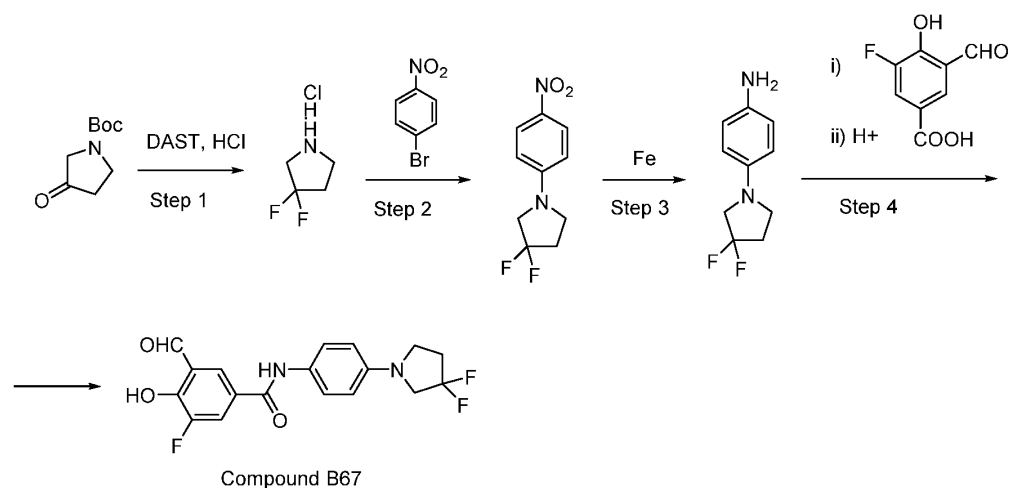
Example B21: 3-fluoro-5-formyl-4-hydroxy-N-(4-(piperidin-1-yl)phenyl)benzamide (New Compound B66)



[0435] In a 50 mL glass vial, a solution of 3-fluoro-5-formyl-4-hydroxybenzoic acid (200 mg, 1.09 mmol, 1.0 eq.), 4-(piperidin-1-yl)aniline (478mg, 2.73 mmol, 2.5 eq.), HATU (619 mg,

1.63 mmol, 1.5 eq.), and N-methyl morpholine (329 mg, 3.26 mmol, 3.0 eq.) in THF (10 mL) was stirred overnight at room temperature. The reaction mixture was poured into 4 N HCl. The reaction was stirred for 30 min and then extracted with ethyl acetate for three times. The organic extracts were combined, washed with brine, dried over anhydrous sodium sulfate, and concentrated. The residue was purified by silica gel column chromatography and prep-TLC to give 3-fluoro-5-formyl-4-hydroxy-N-(4-(piperidin-1-yl)phenyl)benzamide (23 mg, 0.04 mmol, 4% yield) as a yellow solid. ^1H NMR (CDCl_3 , 400 MHz) δ : 11.30 (br, 1H), 10.02 (s, 1H), 8.03 (s, 1H), 7.89 (d, $J=10.0$ Hz, 1H), 7.74 (br, 1H), 7.51 (m, 2H), 7.02 (m, 2H), 3.16 (m, 4H), 1.76 (m, 6H). LC-MS m/z $[\text{M}+\text{H}]^+$ calc'd for $\text{C}_{19}\text{H}_{19}\text{FN}_2\text{O}_3$, 343; found, 343.

Example B22: N-(4-(3,3-difluoropyrrolidin-1-yl)phenyl)-3-fluoro-5-formyl-4-hydroxybenzamide (Compound B67)



Step 1: 3,3-difluoropyrrolidine hydrochloride

[0436] DAST (4.03 g, 67.6 mmol, 2.5 eq.) was added to a solution of tert-butyl 3-oxopyrrolidine-1-carboxylate (5 g, 27.0 mmol, 1.0 eq.) in dichloromethane (30 mL). The reaction was stirred for 5 hours at room temperature. The reaction mixture was poured into ice cold sat. NaHCO_3 solution (100 mL) and extracted with dichloromethane for three times. The organic extracts were combined, washed with brine, dried over anhydrous sodium sulfate, and concentrated to give crude Boc-3,3-difluoropyrrolidine (5.9 g, quantitative yield), which was

then treated with 6 N HCl in dioxane to give 3,3-difluoropyrrolidine hydrochloride (4.1 g, quantitative yield). LC-MS m/z $[M+H]^+$ calc'd for $C_4H_8ClF_2N$, 110; found, 110.

Step 2: 3,3-difluoro-1-(4-nitrophenyl)pyrrolidine

[0437] A mixture of 3,3-difluoropyrrolidine hydrochloride (1.43 g, 1.0 mmol, 1.0 eq.) 1-bromo-4-nitrobenzene (2.01 g, 1.0 mmol, 1 eq.), BINAP (0.94 g, 0.15 mmol, 0.15 eq.), Cs_2CO_3 (8.15 g, 2.5 mmol, 2.5 eq.), and $Pd(OAc)_2$ (0.23 g, 0.1 mmol, 0.1 eq.) in toluene (20 mL) was heated overnight at 95°C. The reaction mixture was cooled to room temperature, poured into water (100 mL) and extracted with ethyl acetate for three times. The organic extracts were combined, washed with brine, dried over anhydrous sodium sulfate, and concentrated. The residue was purified by silica gel column chromatography to give 3,3-difluoro-1-(4-nitrophenyl)pyrrolidine (1.5 g, 66% yield). LC-MS m/z $[M+H]^+$ calc'd for $C_{10}H_{10}F_2N_2O_2$, 229; found, 229.

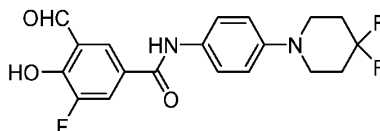
Step 3: 4-(3,3-difluoropyrrolidin-1-yl)aniline

[0438] Iron powder (3.7 g, 66.1 mmol, 10.0 eq.) was added to a solution of 3,3-difluoro-1-(4-nitrophenyl)pyrrolidine (1.5 g, 6.6 mmol, 1.0 eq.) in AcOH (30 mL). The reaction was heated for 2 hours at 60°C. The reaction mixture was cooled to room temperature, poured into sat. $NaHCO_3$ and extracted with ethyl acetate for three times. The organic extracts were combined, washed with brine, dried over anhydrous sodium sulfate, and concentrated to give crude 4-(3,3-difluoropyrrolidin-1-yl)aniline (1.1 g, 84% yield), which was used for next reaction without further purification. LC-MS m/z $[M+H]^+$ calc'd for $C_{10}H_{12}F_2N_2$, 199; found, 199.

[0439] Step 4: A solution of 3-fluoro-5-formyl-4-hydroxybenzoic acid (200 mg, 1.09 mmol, 1.0 eq.), 4-(3,3-difluoropyrrolidin-1-yl)aniline (430 mg, 2.17 mmol, 2.0 eq.), HATU (619 mg, 1.63 mmol, 1.5 eq.), and N-methyl morpholine (329 mg, 3.26 mmol, 3.0 eq.) in THF (10 mL) was stirred overnight at room temperature. The reaction mixture was poured into 4 N HCl. The reaction was stirred for 30 min and then extracted with ethyl acetate for three times. The organic extracts were combined, washed with brine, dried over anhydrous sodium sulfate, and concentrated. The residue was purified by silica gel column chromatography and prep-TLC to give N-(4-(3,3-difluoropyrrolidin-1-yl)phenyl)-3-fluoro-5-formyl-4-hydroxybenzamide (50 mg, 0.13 mmol, 12% yield) as a yellow solid. 1H NMR ($DMSO-d_6$, 400 MHz) δ : 11.61 (br, 1H), 10.35 (s, 1H), 10.10 (br, 1H), 8.18 (s, 1H), 8.09 (dd, $J=12.0$ Hz, 2.0 Hz, 1H), 7.59 (d, $J=8.8$ Hz,

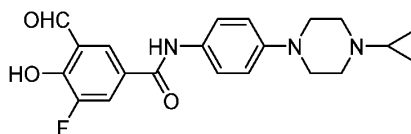
2H), 6.63 (d, $J=9.2$ Hz, 2H), 3.68 (t, $J=9.6$ Hz, 2H), 3.43 (m, 4H). LC-MS m/z $[M+H]^+$ calc'd for $C_{18}H_{15}F_3N_2O_3$, 365; found, 365.

Example B23: N-(4-(4,4-difluoropiperidin-1-yl)phenyl)-3-fluoro-5-formyl-4-hydroxybenzamide (New Compound B68)



[0440] A solution of 3-fluoro-5-formyl-4-hydroxybenzoic acid (200 mg, 1.09 mmol, 1.0 eq.), 4-(4,4-difluoropiperidin-1-yl)aniline (460 mg, 2.17 mmol, 2.0 eq.) (prepared as in Example B22), HATU (619 mg, 1.63 mmol, 1.5 eq.), and N-methyl morpholine (329 mg, 3.26 mmol, 3.0 eq.) in THF (10 mL) was stirred overnight at room temperature. The reaction mixture was poured into 4 N HCl. The reaction was stirred for 30 min and then extracted with ethyl acetate for three times. The organic extracts were combined, washed with brine, dried over anhydrous sodium sulfate, and concentrated. The residue was purified by silica gel column chromatography and prep-TLC to give N-(4-(4,4-difluoropiperidin-1-yl)phenyl)-3-fluoro-5-formyl-4-hydroxybenzamide (13 mg, 0.03 mmol, 3% yield) as a yellow solid. 1H NMR ($DMSO-d_6$, 400 MHz) δ : 11.63 (br, 1H), 10.35 (s, 1H), 10.15 (br, 1H), 8.18 (s, 1H), 8.09 (d, $J=11.6$ Hz, 1H), 7.61 (d, $J=8.8$ Hz, 2H), 7.01 (d, $J=8.8$ Hz, 2H), 3.29 (m, 4H), 2.05 (m, 4H). LC-MS m/z $[M+H]^+$ calc'd for $C_{19}H_{17}F_3N_2O_3$, 379; found, 379.

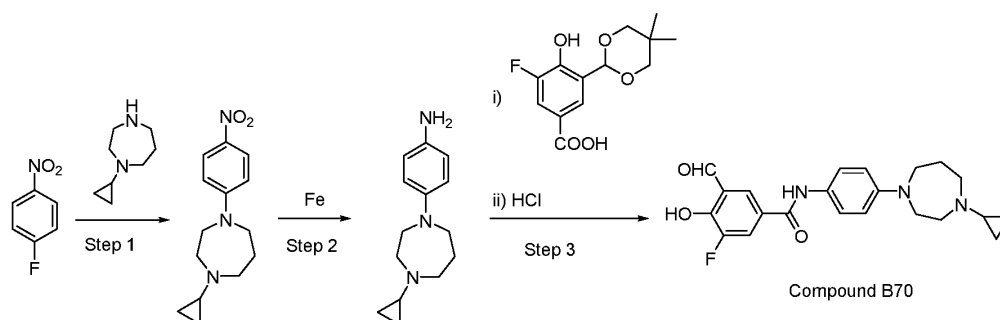
Example B24: N-(4-(4-cyclopropylpiperazin-1-yl)phenyl)-3-fluoro-5-formyl-4-hydroxybenzamide (Compound B69)



[0441] A solution of 3-fluoro-5-formyl-4-hydroxybenzoic acid (200 mg, 1.09 mmol, 1.0 eq.), 4-(4-cyclopropylpiperazin-1-yl)aniline (590 mg, 2.73 mmol, 2.5 eq.) (prepared as in Example B22), HATU (619 mg, 1.63 mmol, 1.5 eq.), and N-methyl morpholine (329 mg, 3.26

mmol, 3.0 eq.) in THF (10 mL) was stirred overnight at room temperature. The reaction mixture was poured into 4 N HCl. The reaction was stirred for 30 min and then extracted with ethyl acetate for three times. The organic extracts were combined, washed with brine, dried over anhydrous sodium sulfate, and concentrated. The residue was purified by silica gel column chromatography and prep-TLC to give N-(4-(4-cyclopropylpiperazin-1-yl)phenyl)-3-fluoro-5-formyl-4-hydroxybenzamide (25 mg, 0.03 mmol, 6% yield) as a pale yellow solid. ^1H NMR ($\text{DMSO-}d_6$, 400 MHz) δ : 11.65 (br, 1H), 10.36 (s, 1H), 10.21 (s, 1H), 8.19 (s, 1H), 8.10 (dd, $J=11.6$ Hz, 2.0 Hz, 1H), 7.65 (d, $J=9.2$ Hz, 2H), 7.01 (d, $J=8.8$ Hz, 2H), 3.77 (m, 2H), 3.54 (m, 2H), 3.36 (m, 2H), 3.06 (m, 2H), 2.93 (m, 1H), 1.10 (m, 2H), 0.82 (m, 2H). LC-MS m/z $[\text{M}+\text{H}]^+$ calc'd for $\text{C}_{21}\text{H}_{22}\text{FN}_3\text{O}_3$, 384; found, 384.

Example B25: N-(4-(4-cyclopropyl-1,4-diazepan-1-yl)phenyl)-3-fluoro-5-formyl-4-hydroxybenzamide (New Compound B70)



Step 1: 1-cyclopropyl-4-(4-nitrophenyl)-1,4-diazepane

[0442] In a 100 mL glass vial, a mixture of 1-fluoro-4-nitrobenzene (1.1 g, 7.80 mmol, 1.1 eq.), 1-cyclopropyl-1,4-diazepane (1 g, 7.14 mmol, 1.0 eq.), and K_2CO_3 (4.9 g, 35.5 mmol, 5.0 eq.) in DMF (20 mL) was heated for 7 hours at 50°C . The mixture was poured into water and extracted with ethyl acetate for three times. The organic extracts were combined, washed with brine, dried over anhydrous sodium sulfate, and concentrated. The residue was purified by silica gel column chromatography (pure DCM) to give 1-cyclopropyl-4-(4-nitrophenyl)-1,4-diazepane (1.57 g, 6.01 mmol, 84% yield) as a yellow oil. LC-MS m/z $[\text{M}+\text{H}]^+$ calc'd for $\text{C}_{14}\text{H}_{19}\text{N}_3\text{O}_2$, 262; found, 262.

Step 2: 4-(4-cyclopropyl-1,4-diazepan-1-yl)aniline

[0443] In a 100 mL glass vial, iron powder (794 mg, 14.18 mmol, 10 eq.) was added to a solution of 1-cyclopropyl-4-(4-nitrophenyl)-1,4-diazepane (370 mg, 1.42 mmol, 1.0 eq.) in AcOH (10 mL). The reaction was heated for 2 hours at 60°C. The reaction mixture was cooled to room temperature, poured into sat. NaHCO₃ and extracted with ethyl acetate for three times. The organic extracts were combined, washed with brine, dried over anhydrous sodium sulfate, and concentrated to give 4-(4-cyclopropyl-1,4-diazepan-1-yl)aniline (290 mg, 1.26 mmol, 88% yield). LC-MS m/z [M+H]⁺ calc'd for C₁₄H₂₁N₃, 232; found, 232.

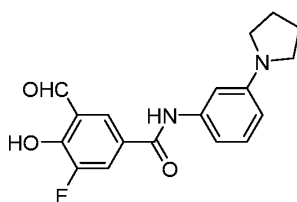
Step 3a: 3-(5,5-dimethyl-1,3-dioxan-2-yl)-5-fluoro-4-hydroxybenzoic acid

[0444] In a 100 mL glass vial, a solution of 3-fluoro-5-formyl-4-hydroxybenzoic acid (2 g, 10.9 mmol, 1.0 eq.), 2,2-dimethylpropane-1,3-diol (2.26 g, 21.8 mmol, 2.0 eq.), and p-TsOH.H₂O (414 mg, 2.18 mmol, 0.2 eq.) in toluene (30 mL) was heated for 3 hours at 90°C. The solvent was removed in vacuo and the residue was dissolved in water/EtOAc. The mixture was then extracted with ethyl acetate for three times. The organic extracts were combined, washed with brine, dried over anhydrous sodium sulfate, and concentrated to give crude 3-(5,5-dimethyl-1,3-dioxan-2-yl)-5-fluoro-4-hydroxybenzoic acid (2.97 g, quantitative yield). LC-MS m/z [M+H]⁺ calc'd for C₁₃H₁₅FO₅, 271; found, 271.

[0445] Step 3: In a 100 mL glass vial, a solution of 3-(5,5-dimethyl-1,3-dioxan-2-yl)-5-fluoro-4-hydroxybenzoic acid (193 mg, 0.71 mmol, 1.0 eq.), 4-(4-cyclopropyl-1,4-diazepan-1-yl)aniline (180 mg, 0.79 mmol, 1.1 eq.), HATU (324 mg, 0.85 mmol, 1.2 eq.), and NMM (215 mg, 2.13 mmol, 3.0 eq.) in THF (10 mL) was stirred for 4 hours at room temperature. The solution was poured into sat. NaHCO₃ and extracted with ethyl acetate for three times. The organic extracts were combined, washed with brine, dried over anhydrous sodium sulfate, and concentrated. The residue was purified by silica gel column chromatography (CH₂Cl₂/MeOH=300:1 to 150:1) and prep-TLC to give the intermediate (40 mg, 0.08 mmol, 12% yield). The intermediate (30 mg, 0.06 mmol, 1.0 eq.) was dissolved in THF/4 N HCl (2 mL/4 mL) and the reaction was stirred for 30 min at room temperature. pH of the system was adjusted to 7-7.5 and extracted with ethyl acetate for three times. The organic extracts were combined, washed with brine, dried over anhydrous sodium sulfate, and concentrated. The residue was purified by prep-TLC to give N-(4-(4-cyclopropyl-1,4-diazepan-1-yl)phenyl)-3-fluoro-5-formyl-4-hydroxybenzamide (7 mg, 0.02 mmol, 29% yield) as a yellow solid. ¹H NMR (DMSO-*d*₆, 400 MHz) δ: 10.32 (s, 1H), 9.96 (s, 1H), 8.14 (s, 1H), 8.00 (d, *J*=12.0 Hz, 1H), 7.50

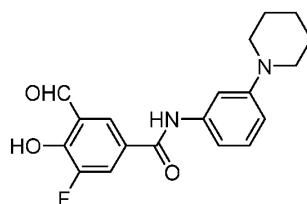
(d, $J=8.8$ Hz, 2H), 6.68 (d, $J=9.2$ Hz, 2H), 3.49 (m, 4H), 2.92 (m, 2H), 2.75 (m, 2H), 2.01 (m, 1H), 1.89 (m, 2H), 0.47 (m, 2H), 0.38 (m, 2H). LC-MS m/z $[M+H]^+$ calc'd for $C_{22}H_{24}FN_3O_3$, 398; found, 398.

Example B26: 3-fluoro-5-formyl-4-hydroxy-N-(3-(pyrrolidin-1-yl)phenyl)benzamide
(Compound B71)



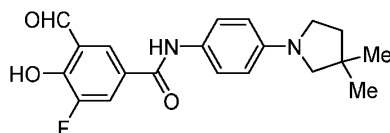
[0446] In a 100 mL glass vial, a solution of 3-(5,5-dimethyl-1,3-dioxan-2-yl)-5-fluoro-4-hydroxybenzoic acid (300 mg, 1.11 mmol, 1.0 eq.), 3-(pyrrolidin-1-yl)aniline (180 mg, 1.11 mmol, 1.0 eq.), HATU (633 mg, 1.67 mmol, 1.5 eq.), and NMM (336 mg, 3.33 mmol, 3.0 eq.) in THF (10 mL) was stirred overnight at rt. The solution was poured into sat. $NaHCO_3$ and extracted with ethyl acetate for three times. The organic extracts were combined, washed with brine, dried over anhydrous sodium sulfate, and concentrated. The residue was purified by silica gel column chromatography (Petroleum ether/EtOAc=20:1 to 5:1) to give an intermediate (110 mg, 0.27 mmol, 24% yield). The intermediate (100 mg, 0.24 mmol, 1.0 eq.) was dissolved in THF/4 N HCl (2 mL/4 mL) and the reaction was stirred for 30 min at room temperature. The mixture was extracted with ethyl acetate for three times. The organic extracts were combined, washed with brine, dried over anhydrous sodium sulfate, and concentrated. The residue was purified by silica gel column chromatography (Petroleum ether/EtOAc =10:1 to 5:1) to give 3-fluoro-5-formyl-4-hydroxy-N-(3-(pyrrolidin-1-yl)phenyl)benzamide (65 mg, 0.20 mmol, 83% yield) as a yellow solid. 1H NMR ($DMSO-d_6$, 400 MHz) δ : 11.62 (br, 1H), 10.35 (s, 1H), 10.07 (s, 1H), 8.19 (s, 1H), 8.10 (dd, $J=11.6$ Hz, 1.6 Hz, 1H), 7.08 (m, 2H), 7.00 (d, $J=2.0$ Hz, 1H), 6.29 (m, 1H), 3.22 (m, 4H), 1.97 (m, 4H). LC-MS m/z $[M+H]^+$ calc'd for $C_{18}H_{17}FN_2O_3$, 329; found, 329.

Example B27: 3-fluoro-5-formyl-4-hydroxy-N-(3-(piperidin-1-yl)phenyl)benzamide
(Compound B72)



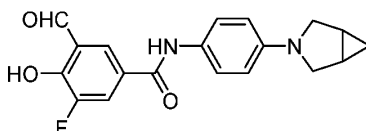
[0447] The title compound was prepared from 3-(5,5-dimethyl-1,3-dioxan-2-yl)-5-fluoro-4-hydroxybenzoic acid (250 mg, 0.93 mmol, 1 eq.) and 3-(piperidin-1-yl)aniline (163 mg, 0.93 mmol, 1 eq.) using a method similar to that as described in Example B25 to give the title compound 3-fluoro-5-formyl-4-hydroxy-N-(3-(piperidin-1-yl)phenyl)benzamide (7 mg, 0.02 mmol, 11% yield) as a light yellow solid. ^1H NMR ($\text{DMSO}-d_6$, 400 MHz) δ : 11.66 (br, 1H), 10.35 (s, 1H), 10.11 (s, 1H), 8.19 (s, 1H), 8.10 (dd, $J=11.6$ Hz, 2.0 Hz, 1H), 7.36 (m, 1H), 7.22 (m, 1H), 7.15 (m, 1H), 6.69 (m, 1H), 3.14 (m, 4H), 1.62 (m, 4H), 1.55 (m, 2H). LC-MS m/z $[\text{M}+\text{H}]^+$ calc'd for $\text{C}_{19}\text{H}_{19}\text{FN}_2\text{O}_3$, 343; found, 343.

Example B28: N-(4-(3,3-dimethylpyrrolidin-1-yl)phenyl)-3-fluoro-5-formyl-4-hydroxybenzamide (Compound B73)



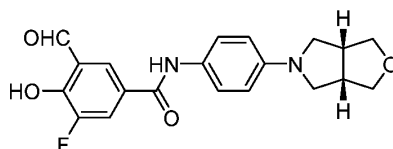
[0448] The title compound was prepared from 3-(5,5-dimethyl-1,3-dioxan-2-yl)-5-fluoro-4-hydroxybenzoic acid (270 mg, 1.0 mmol, 1.0 eq.) and 4-(3,3-dimethylpyrrolidin-1-yl)aniline (190 mg, 1 mmol, 1.0 eq.) (prepared as in Example B25) using a method similar to that as described in Example B25 to give the title compound (130 mg, 0.37 mmol, 74% yield) as a yellow solid. ^1H NMR ($\text{DMSO}-d_6$, 400 MHz) δ : 11.60 (br, 1H), 10.34 (s, 1H), 9.99 (s, 1H), 8.16 (d, $J=1.2$ Hz, 1H), 8.06 (dd, $J=11.6$ Hz, 2.0 Hz, 1H), 7.50 (d, $J=8.8$ Hz, 2H), 6.47 (d, $J=9.2$ Hz, 2H), 3.35-3.28 (m, 2H), 3.00 (s, 2H), 1.75 (t, $J=10.8$ Hz, 2H), 1.11 (s, 6H). LC-MS m/z $[\text{M}+\text{H}]^+$ calc'd for $\text{C}_{20}\text{H}_{21}\text{FN}_2\text{O}_3$, 357; found, 357.

Example B29: N-(4-(3-azabicyclo[3.1.0]hexan-3-yl)phenyl)-3-fluoro-5-formyl-4-hydroxybenzamide (Compound B74)



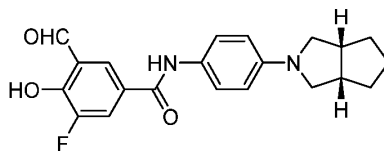
[0449] The title compound was prepared from 3-(5,5-dimethyl-1,3-dioxan-2-yl)-5-fluoro-4-hydroxybenzoic acid (310 mg, 1.15 mmol, 1.0 eq.) and 4-(3-azabicyclo[3.1.0]hexan-3-yl)aniline (200 mg, 1.15 mmol, 1.0 eq.) (prepared as in Example B25) using a method similar to that as described in Example B25 to give the title compound (60 mg, 0.18 mmol, 39% yield). ^1H NMR ($\text{DMSO}-d_6$, 400 MHz) δ : 11.62 (br, 1H), 10.34 (s, 1H), 10.01 (s, 1H), 8.16 (d, $J=1.6$ Hz, 1H), 8.06 (dd, $J=12.0$ Hz, 2.0 Hz, 1H), 7.50 (d, $J=8.8$ Hz, 2H), 6.53 (d, $J=9.2$ Hz, 2H), 3.48 (d, $J=9.2$ Hz, 2H), 3.12 (m, 2H), 1.67 (m, 2H), 0.70 (m, 1H), 0.27 (m, 1H). LC-MS m/z $[\text{M}+\text{H}]^+$ calc'd for $\text{C}_{19}\text{H}_{17}\text{FN}_2\text{O}_3$, 341; found, 341.

Example B30: 3-fluoro-5-formyl-4-hydroxy-N-(4-((3aR,6aS)-tetrahydro-1H-furo[3,4-c]pyrrol-5(3H)-yl)phenyl)benzamide (Compound B75)



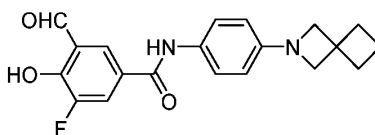
[0450] The title compound was prepared from 3-(5,5-dimethyl-1,3-dioxan-2-yl)-5-fluoro-4-hydroxybenzoic acid (270 mg, 1.0 mmol, 1.0 eq.) and 4-((3aR,6aS)-dihydro-1H-furo[3,4-c]pyrrol-5(3H,6H,6aH)-yl)aniline (204 mg, 1.0 mmol, 1.0 eq.) (prepared as in Example B25) using a method similar to that as described in Example B25 to give the title compound (60 mg, 0.16 mmol, 36% yield). ^1H NMR ($\text{DMSO}-d_6$, 400 MHz) δ : 11.59 (br, 1H), 10.34 (s, 1H), 10.06 (s, 1H), 8.17 (s, 1H), 8.08 (dd, $J=12.0$ Hz, 2.0 Hz, 1H), 7.54 (d, $J=8.8$ Hz, 2H), 6.63 (d, $J=8.8$ Hz, 2H), 3.85 (m, 2H), 3.54 (m, 2H), 3.31 (m, 2H), 3.15 (m, 2H), 2.98 (m, 2H). LC-MS m/z $[\text{M}+\text{H}]^+$ calc'd for $\text{C}_{20}\text{H}_{19}\text{FN}_2\text{O}_4$, 371; found, 371.

Example B31: 3-fluoro-5-formyl-N-(4-((3aR,6aS)-hexahydrocyclopenta[c]pyrrol-2(1H)-yl)phenyl)-4-hydroxybenzamide (Compound B76)



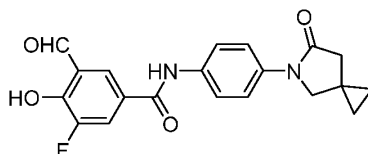
[0451] The title compound was prepared from 3-(5,5-dimethyl-1,3-dioxan-2-yl)-5-fluoro-4-hydroxybenzoic acid (270 mg, 1.0 mmol, 1.0 eq.) and 4-((3aR,6aS)-hexahydrocyclopenta[c]pyrrol-2(1H)-yl)aniline (202 mg, 1.0 mmol, 1.0 eq.) (prepared as in Example B25) using a method similar to that as described in Example B25 to give the title compound (220 mg, 0.60 mmol, 62% yield). ¹H NMR (*DMSO-d*₆, 400 MHz) δ : 11.60 (br, 1H), 10.34 (s, 1H), 10.04 (s, 1H), 8.17 (d, *J*=1.6 Hz, 1H), 8.08 (dd, *J*=12.0 Hz, 2.0 Hz, 1H), 7.52 (d, *J*=9.2 Hz, 2H), 6.60 (d, *J*=9.2 Hz, 2H), 3.36 (m, 2H), 2.94 (m, 2H), 2.74 (m, 2H), 1.79 (m, 2H), 1.54 (m, 1H), 1.49 (m, 1H), 1.45 (m, 2H). LC-MS *m/z* [*M*+*H*]⁺ calc'd for C₂₁H₂₁FN₂O₃, 369; found, 369.

Example B32: N-(4-(2-azaspiro[3.3]heptan-2-yl)phenyl)-3-fluoro-5-formyl-4-hydroxybenzamide (Compound B77)



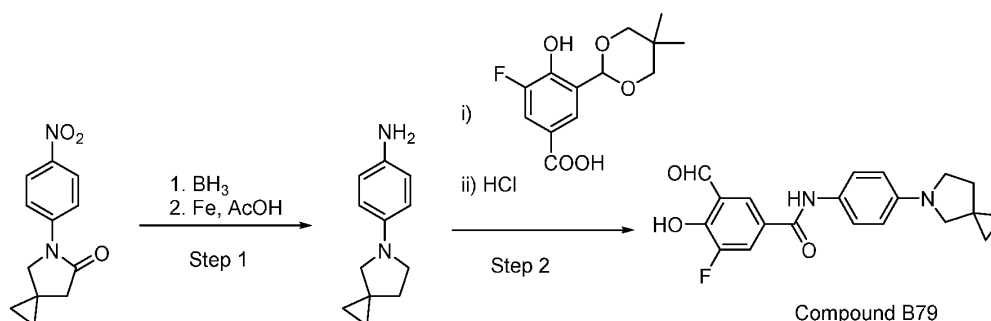
[0452] The title compound was prepared from 3-(5,5-dimethyl-1,3-dioxan-2-yl)-5-fluoro-4-hydroxybenzoic acid (270 mg, 1.0 mmol, 1.0 eq.) and 4-(2-azaspiro[3.3]heptan-2-yl)aniline (188 mg, 1 mmol, 1.0 eq.) (Ref: 2-Azaspiro[3.3]heptane, hydrochloride prepared as in Zhang, Hui et al., PCT Int. Appl., 2013013504, 31 Jan 2013) (prepared as in Example B25) using a method similar to that as described in Example B25 to give the title compound (140 mg, 0.40 mmol, 53% yield) as a yellow solid. ¹H NMR (*DMSO-d*₆, 400 MHz) δ : 11.60 (br, 1H), 10.34 (s, 1H), 10.05 (s, 1H), 8.16 (d, *J*=1.6 Hz, 1H), 8.07 (dd, *J*=11.6 Hz, 2.0 Hz, 1H), 7.51 (d, *J*=8.8 Hz, 2H), 6.39 (d, *J*=8.8 Hz, 2H), 3.74 (s, 4H), 2.16 (t, *J*=5.0 Hz, 4H), 1.84-1.80 (m, 2H). LC-MS *m/z* [*M*+*H*]⁺ calc'd for C₂₀H₁₉FN₂O₃, 355; found, 355.

Example B33: 3-fluoro-5-formyl-4-hydroxy-N-(4-(6-oxo-5-azaspiro[2.4]heptan-5-yl)phenyl)benzamide (Compound B78)



[0453] The title compound was prepared from 3-(5,5-dimethyl-1,3-dioxan-2-yl)-5-fluoro-4-hydroxybenzoic acid (281 mg, 1.04 mmol, 1.0 eq.) and 5-(4-aminophenyl)-5-azaspiro[2.4]heptan-6-one (210 mg, 1.04 mmol, 1.0 eq.) (prepared as in Example B22) using a method similar to that as described in Example B25 to give the title compound (100 mg, 0.27 mmol, 49% yield) as a white solid. ^1H NMR ($\text{DMSO}-d_6$, 400 MHz) δ : 11.68 (br, 1H), 10.36 (s, 1H), 10.33 (s, 1H), 8.20 (s, 1H), 8.11 (dd, $J=11.6$ Hz, 2.0 Hz, 1H), 7.75 (d, $J=8.8$ Hz, 2H), 7.62 (d, $J=9.2$ Hz, 2H), 3.75 (s, 2H), 2.56 (s, 2H), 0.70 (s, 4H). LC-MS m/z $[\text{M}+\text{H}]^+$ calc'd for $\text{C}_{20}\text{H}_{17}\text{FN}_2\text{O}_4$, 369; found, 369.

Example B34: N-(4-(5-azaspiro[2.4]heptan-5-yl)phenyl)-3-fluoro-5-formyl-4-hydroxybenzamide (Compound B79)



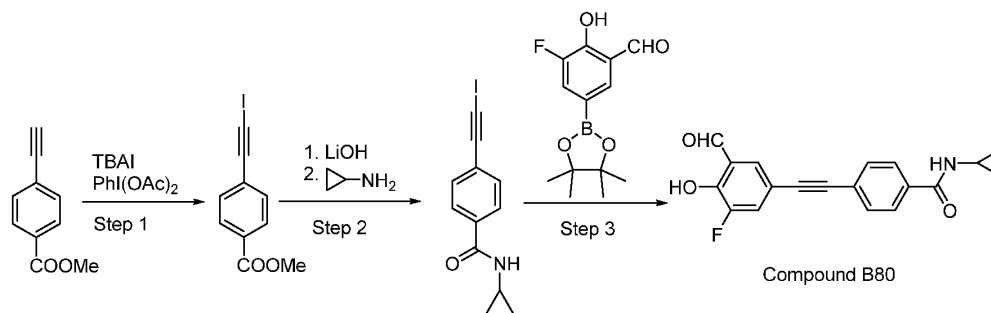
Step 1: 4-(5-azaspiro[2.4]heptan-5-yl)aniline

[0454] 5-(4-Nitrophenyl)-5-azaspiro[2.4]heptan-6-one (300 mg, 1.29 mmol, 1.0 eq.) was dissolved in THF (10 ml) and the solution was cooled to 0°C . Borane-dimethylsulfide (0.26 mL, 10 M in DMS, 2.58 mmol, 2.0 eq.) was added. The reaction was stirred for 1 hour at 50°C . The system was cooled to room temperature, poured into ice water, and extracted with ethyl acetate

for three times. The organic extracts were combined, washed with brine, dried over anhydrous sodium sulfate, and concentrated to give crude 5-(4-nitrophenyl)-5-azaspiro[2.4]heptane (305 mg, quantitative yield). In a 100 mL glass vial, iron powder (770 mg, 13.75 mmol, 10 eq.) was added to a solution of 5-(4-nitrophenyl)-5-azaspiro[2.4]heptane (305 mg, 1.29 mmol, 1.0 eq.) in AcOH (20 mL). The reaction was heated for 2 hours at 60°C. The reaction mixture was cooled to room temperature, poured into sat. NaHCO₃ and extracted with ethyl acetate for three times. The organic extracts were combined, washed with brine, dried over anhydrous sodium sulfate, and concentrated to give crude 4-(5-azaspiro[2.4]heptan-5-yl)aniline (180 mg, 0.96 mmol, 74% yield), which was used for next reaction without further purification.

[0455] Step 2: The title compound was prepared from 3-(5,5-dimethyl-1,3-dioxan-2-yl)-5-fluoro-4-hydroxybenzoic acid (284 mg, 1.05 mmol, 1.0 eq.) and 4-(5-azaspiro[2.4]heptan-5-yl)aniline (180 mg, 0.96 mmol, 1 eq.) using a method similar to that as described in Example B25 to give the title compound (70 mg, 0.20 mmol, 44% yield) as a yellow solid. ¹H NMR (DMSO-*d*₆, 400 MHz) δ : 10.34 (br, 1H), 10.00 (br, 1H), 8.16 (s, 1H), 8.06 (d, *J*=11.6 Hz, 1H), 7.53 (d, *J*=8.8 Hz, 2H), 6.49 (d, *J*=8.8 Hz, 2H), 3.36 (m, 2H), 3.15 (s, 2H), 1.91 (t, *J*=6.4 Hz, 2H), 0.62 (d, *J*=8.0 Hz, 4H). LC-MS *m/z* [M+H]⁺ calc'd for C₂₀H₁₉FN₂O₃, 355; found, 355.

Example B35: N-cyclopropyl-4-((3-fluoro-5-formyl-4-hydroxyphenyl)ethynyl)benzamide (Compound B80)



[0456] Step 1: methyl 4-(iodoethynyl)benzoate

In a 100 mL glass vial, PhI(OAc)₂ (3.66 g, 11.4 mmol, 1.0 eq.) was added to a solution of methyl 4-ethynylbenzoate (1.82 g, 11.4 mmol, 1.0 eq.) and TBAI (5.04 g, 13.7 mmol, 1.2 eq.) in acetonitrile (20 mL). The reaction was stirred for 5 hours at room temperature. The mixture was

poured into water (50 mL) and extracted with ethyl acetate for three times. The organic extracts were combined, washed with brine, dried over anhydrous sodium sulfate, and concentrated to give crude methyl 4-(iodoethynyl)benzoate (3.64 g, quantitative yield) as a yellow solid, which was used for next reaction without further purification.

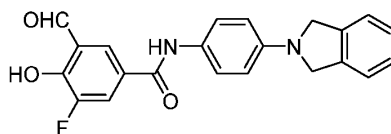
[0457] Step 2: N-cyclopropyl-4-(iodoethynyl)benzamide

In a 50 mL glass vial, LiOH.H₂O (1.34 g, 28.4 mmol, 2.5 eq.) was added to a solution of methyl 4-(iodoethynyl)benzoate (crude, 3.64 g, 11.4 mmol, 1.0 eq.) in water/THF (10 mL/10 mL). The reaction was stirred for 2 hours at room temperature. The solution was diluted with water and extracted with petroleum ether for two times. The petroleum ether layers were discarded. Then pH of the water phase was adjusted to 3-4 with 5% KHSO₄ and then the mixture was extracted with ethyl acetate for three times. The organic extracts were combined, washed with brine, dried over anhydrous sodium sulfate, and concentrated to give acid (2.36 g, 76% yield) as a white solid. The resulting acid (2.36 g, 8.7 mmol, 1.0 eq.) was dissolved in CH₂Cl₂ (10 mL) in a 50 mL glass vial. HATU (3.96 g, 10.4 mmol, 1.2 eq.), cyclopropanamine (1.24 g, 21.7 mmol, 2.5 eq.), and N-methyl morpholine (2.63 g, 26.0 mmol, 3.0 eq.) were added. The mixture was stirred for 2 hours at room temperature. The mixture was poured into water and extracted with CH₂Cl₂ for two times. The organic extracts were combined, washed with brine (20 mL), dried over anhydrous sodium sulfate, and concentrated. The residue was purified by silica gel column chromatography (petroleum ether/EtOAc=20:1 to 5:1) to give N-cyclopropyl-4-(iodoethynyl)benzamide (1.86 g, 6.0 mmol, 69% yield) as a yellow solid. LC-MS m/z [M+H]⁺ calc'd for C₁₂H₁₀NO, 312; found, 312.

[0458] Step 3: In a 100 mL glass vial, a mixture of N-cyclopropyl-4-(iodoethynyl)benzamide (520 mg, 1.67 mmol, 1.0 eq.), 3-fluoro-2-hydroxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzaldehyde (488 mg, 1.83 mmol, 1.1 eq.), K₂CO₃ (690 mg, 5.0 mmol, 3.0 eq.), and Pd(dppf)Cl₂ (136 mg, 0.17 mmol, 0.1 eq.) in dioxane/water (9 mL/3 mL) was stirred for 1 hour at room temperature. The mixture was poured into water, acidified to pH 4-5 with 5% KHSO₄, and extracted with ethyl acetate for three times. The organic extracts were combined, washed with brine, dried over anhydrous sodium sulfate, and concentrated. The residue was purified by silica gel column chromatography (CH₂Cl₂/MeOH=100 to 300:1) to give N-cyclopropyl-4-((3-fluoro-5-formyl-4-hydroxyphenyl)ethynyl)benzamide (13 mg, 0.04 mmol, 2% yield) as a yellow solid. ¹H NMR (DMSO-*d*₆, 400 MHz) δ : 11.52 (br, 1H), 10.28 (s,

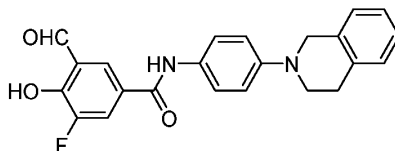
1H), 8.55 (d, $J=4.0$ Hz, 1H), 7.86 (d, $J=8.0$ Hz, 2H), 7.78 (dd, $J=11.2$ Hz, 2.0 Hz, 1H), 7.67-7.61 (m, 3H), 2.84 (m, 1H), 0.85 (m, 2H), 0.72 (m, 2H). LC-MS m/z $[M+H]^+$ calc'd for $C_{19}H_{14}FNO_3$, 324; found, 324.

Example B36: 3-fluoro-5-formyl-4-hydroxy-N-(4-(isoindolin-2-yl)phenyl)benzamide (New Compound B81)



[0459] The title compound was prepared from 3-(5,5-dimethyl-1,3-dioxan-2-yl)-5-fluoro-4-hydroxybenzoic acid (296 mg, 1.1 mmol, 1.0 eq.) and 4-(isoindolin-2-yl)aniline (230 mg, 1.10 mmol, 1.0 eq.) (prepared as in Example B25) using a method similar to that as described in Example B25 to give the title compound (190 mg, 0.51 mmol, 60% yield). 1H NMR ($DMSO-d_6$, 400 MHz) δ : 11.57 (br, 1H), 10.36 (s, 1H), 10.08 (s, 1H), 8.20 (s, 1H), 8.10 (d, $J=11.6$ Hz, 1H), 7.62 (d, $J=8.8$ Hz, 2H), 7.41 (m, 2H), 7.31 (m, 2H), 6.68 (d, $J=8.8$ Hz, 2H), 4.61 (s, 4H). LC-MS m/z $[M+H]^+$ calc'd for $C_{22}H_{17}FN_2O_3$, 377; found, 377.

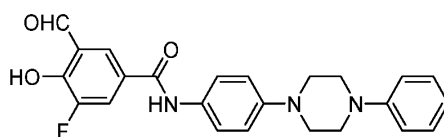
Example B37: N-(4-(3,4-dihydroisoquinolin-2(1H)-yl)phenyl)-3-fluoro-5-formyl-4-hydroxybenzamide (Compound B82)



[0460] The title compound was prepared from 3-(5,5-dimethyl-1,3-dioxan-2-yl)-5-fluoro-4-hydroxybenzoic acid (416 mg, 1.56 mmol, 1.0 eq.) and 4-(3,4-dihydroisoquinolin-2(1H)-yl)aniline (350 mg, 1.56 mmol, 1.0 eq.) (prepared as in Example B25) using a method similar to that as described in Example B25 to give the title compound (130 mg, 0.33 mmol, 51% yield). 1H NMR ($DMSO-d_6$, 400 MHz) δ : 11.66 (br, 1H), 10.35 (s, 1H), 10.10 (s, 1H), 8.17 (s, 1H), 8.07 (dd, $J=11.6$ Hz, 1.6 Hz, 1H), 7.61 (d, $J=8.8$ Hz, 2H), 7.23-7.16 (m, 4H), 7.01 (d, $J=8.8$ Hz,

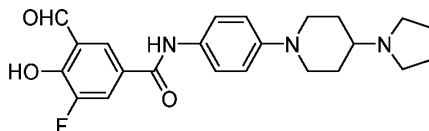
2H), 4.36 (s, 2H), 3.51 (t, $J=5.6$ Hz, 2H), 2.91 (d, $J=5.6$ Hz, 2H). LC-MS m/z $[M+H]^+$ calc'd for $C_{23}H_{19}FN_2O_3$, 391; found, 391.

Example B38: 3-fluoro-5-formyl-4-hydroxy-N-(4-(4-phenylpiperazin-1-yl)phenyl)benzamide (Compound B83)



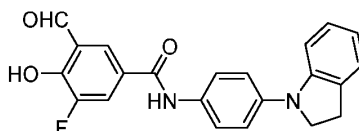
[0461] The title compound was prepared from 3-(5,5-dimethyl-1,3-dioxan-2-yl)-5-fluoro-4-hydroxybenzoic acid (373 mg, 1.38 mmol, 1.0 eq.) and 4-(4-phenylpiperazin-1-yl)aniline (350 mg, 1.38 mmol, 1.0 eq.) (prepared as in Example B25) using a method similar to that as described in Example B25 to give the title compound (4 mg, 0.01 mmol, 2% yield). 1H NMR ($DMSO-d_6$, 400 MHz) δ : 11.60 (br, 1H), 10.35 (br, 1H), 10.14 (br, 1H), 8.19 (s, 1H), 8.10 (d, $J=10.0$ Hz, 1H), 7.63 (m, 2H), 7.24 (m, 2H), 7.02 (m, 2H), 6.81 (m, 1H), 3.27 (m, 8H). LC-MS m/z $[M+H]^+$ calc'd for $C_{24}H_{22}FN_3O_3$, 420; found, 420.

Example B39: 3-fluoro-5-formyl-4-hydroxy-N-(4-(4-(pyrrolidin-1-yl)piperidin-1-yl)phenyl)benzamide (Compound B84)



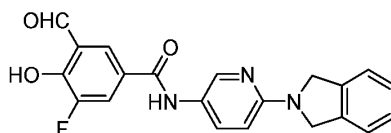
[0462] The title compound was prepared from 3-(5,5-dimethyl-1,3-dioxan-2-yl)-5-fluoro-4-hydroxybenzoic acid (170 mg, 0.63 mmol, 1.0 eq.) and 4-(4-(pyrrolidin-1-yl)piperidin-1-yl)aniline (140 mg, 0.57 mmol, 1.0 eq.) (prepared as in Example B25) using a method similar to that as described in Example B25 to give the title compound (47 mg, 0.11 mmol, 48% yield). 1H NMR ($DMSO-d_6$, 400 MHz) δ : 10.14 (s, 1H), 9.51 (s, 1H), 7.86 (d, $J=2.8$ Hz, 1H), 7.55 (d, $J=9.2$ Hz, 2H), 7.45 (d, $J=13.6$ Hz, 2.4 Hz, 1H), 6.88 (d, $J=9.2$ Hz, 2H), 3.60 (d, $J=12.4$ Hz, 2H), 2.75 (m, 4H), 2.641 (t, $J=11.6$ Hz, 2H), 2.54 (m, 1H), 1.97 (d, $J=12.0$ Hz, 2H), 1.75 (m, 4H), 1.55 (m, 2H). LC-MS m/z $[M+H]^+$ calc'd for $C_{23}H_{26}FN_3O_3$, 412; found, 412.

Example B40: 3-fluoro-5-formyl-4-hydroxy-N-(4-(4-(pyrrolidin-1-yl)piperidin-1-yl)phenyl)benzamide (Compound B85)



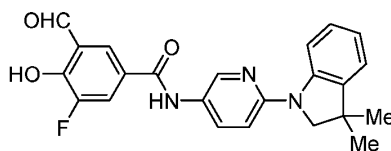
[0463] The title compound was prepared from 3-(5,5-dimethyl-1,3-dioxan-2-yl)-5-fluoro-4-hydroxybenzoic acid (283 mg, 1.05 mmol, 1.1 eq.) and 4-(indolin-1-yl)aniline (200 mg, 0.95 mmol, 1 eq.) (prepared as in Example B25) using a method similar to that as described in Example B25 to give the title compound (7 mg, 0.02 mmol, 7% yield). ^1H NMR ($\text{DMSO}-d_6$, 400 MHz) δ : 11.63 (br, 1H), 10.36 (s, 1H), 10.25 (s, 1H), 8.20 (d, $J=1.6$ Hz, 1H), 8.11 (dd, $J=12.0$ Hz, 2.0 Hz, 1H), 7.73 (d, $J=8.8$ Hz, 2H), 7.23 (dd, $J=8.8$ Hz, 2.8 Hz, 2H), 7.16 (d, $J=7.2$ Hz, 1H), 7.04 (m, 2H), 6.71 (m, 1H), 3.92 (d, $J=8.4$ Hz, 2H), 3.09 (d, $J=8.4$ Hz, 2H). LC-MS m/z $[\text{M}+\text{H}]^+$ calc'd for $\text{C}_{22}\text{H}_{17}\text{FN}_2\text{O}_3$, 377; found, 377.

Example B41: 3-fluoro-5-formyl-4-hydroxy-N-(6-(isoindolin-2-yl)pyridin-3-yl)benzamide (Compound B86)



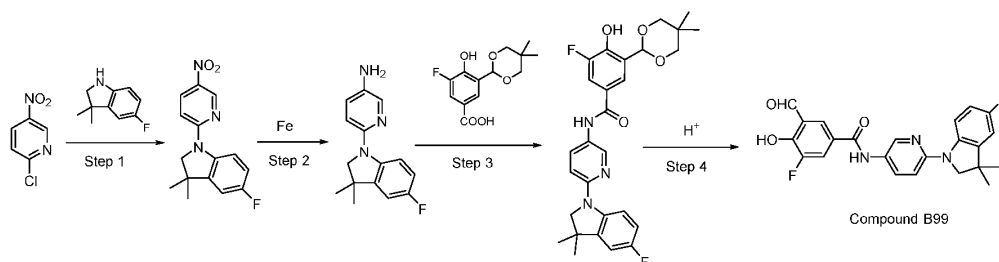
[0464] The title compound was prepared from 3-(5,5-dimethyl-1,3-dioxan-2-yl)-5-fluoro-4-hydroxybenzoic acid (637 mg, 2.37 mmol, 1.0 eq.) and 6-(isoindolin-2-yl)pyridin-3-amine (500 mg, 2.37 mmol, 1.0 eq.) (prepared as in Example B16) using a method similar to that as described in Example B25 to give the title compound (47 mg, 0.12 mmol, 15% yield). ^1H NMR ($\text{DMSO}-d_6$, 400 MHz) δ : 11.81 (br, 1H), 10.76 (br, 1H), 10.36 (s, 1H), 8.65 (s, 1H), 8.37 (d, $J=7.2$ Hz, 1H), 8.24-8.21 (m, 2H), 7.45 (m, 2H), 7.39 (m, 2H), 7.20 (d, $J=7.2$ Hz, 1H), 4.95 (s, 4H). LC-MS m/z $[\text{M}+\text{H}]^+$ calc'd for $\text{C}_{21}\text{H}_{16}\text{FN}_3\text{O}_3$, 378; found, 378.

Example B42: N-(6-(3,3-dimethylindolin-1-yl)pyridin-3-yl)-3-fluoro-5-formyl-4-hydroxybenzamide (Compound B87)



[0465] The title compound was prepared from 3-(5,5-dimethyl-1,3-dioxan-2-yl)-5-fluoro-4-hydroxybenzoic acid (475 mg, 1.76 mmol, 1.0 eq.) and 6-(3,3-dimethylindolin-1-yl)pyridin-3-amine (420 mg, 1.76 mmol, 1.0 eq.) (prepared as in Example B16) using a method similar to that as described in Example B25 to give the title compound (87 mg, 0.21 mmol, 25% yield). ¹H NMR (*DMSO-d*₆, 400 MHz) δ : 11.67 (br, 1H), 10.36 (s, 1H), 10.34 (s, 1H), 8.63 (d, *J*=2.8 Hz, 1H), 8.22 (d, *J*=1.6 Hz, 1H), 8.18-8.04 (m, 3H), 7.20 (dd, *J*=7.6 Hz, 1.2 Hz, 1H), 7.14 (m, 1H), 6.89 (m, 1H), 6.85 (m, 1H), 3.78 (s, 2H), 1.35 (s, 6H). LC-MS *m/z* [M+H]⁺ calc'd for C₂₃H₂₀FN₃O₃, 406; found, 406.

Example B43: 3-fluoro-N-(6-(5-fluoro-3,3-dimethylindolin-1-yl)pyridin-3-yl)-5-formyl-4-hydroxybenzamide (Compound B99)



[0466] Step 1: 5-fluoro-3,3-dimethyl-1-(5-nitropyridin-2-yl)indoline

A mixture of 5-fluoro-3,3-dimethylindoline (1 g, 6.1 mmol, 1.0 eq.), 2-chloro-5-nitropyridine (1.44 g, 9.1 mmol, 1.5 eq.), cesium carbonate (4.94 g, 15.2 mmol, 2.5 eq.), BINAP (566 mg, 0.91 mmol, 0.15 eq.), and Pd(OAc)₂ (136 mg, 0.61 mmol, 0.1 eq.) in toluene (30 mL) was heated at 95°C for 30 min. The mixture was cooled to room temperature, poured into water, and extracted with ethyl acetate for three times. The organic extracts were combined, washed with brine, dried over anhydrous sodium sulfate, and concentrated. The residue was purified by

silica gel column chromatography (petroleum ether/EtOAc=300:1 to 100:1) to give 5-fluoro-3,3-dimethyl-1-(5-nitropyridin-2-yl)indoline (910 mg, 52% yield), used in next step.

[0467] Step 2: 6-(5-fluoro-3,3-dimethylindolin-1-yl)pyridin-3-amine

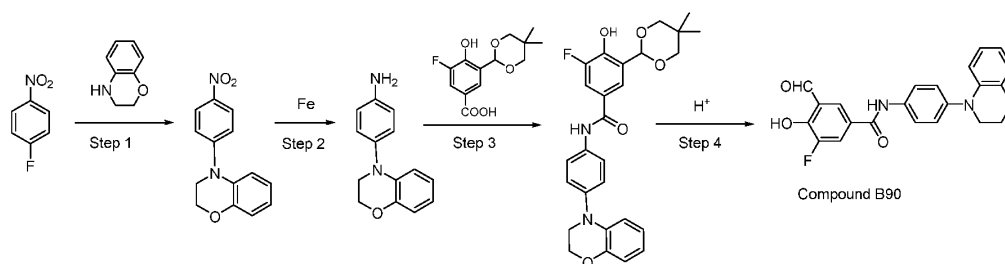
6-(5-Fluoro-3,3-dimethylindolin-1-yl)pyridin-3-amine (690 mg, 2.7 mmol, 87% yield) was prepared from 5-fluoro-3,3-dimethyl-1-(5-nitropyridin-2-yl)indoline (900 mg, 3.1 mmol, 1.0 eq.) and Fe (1.76 g, 31.4 mmol, 10 eq.) following the similar procedure for 4-(3,3-dimethylpyrrolidin-1-yl)aniline in Example B25. LC-MS m/z [M+H]⁺ calc'd for C₁₅H₁₆FN₃, 258; found, 258.

[0468] Step 3: 3-(5,5-dimethyl-1,3-dioxan-2-yl)-5-fluoro-N-(6-(5-fluoro-3,3-dimethylindolin-1-yl)pyridin-3-yl)-4-hydroxybenzamide

3-(5,5-Dimethyl-1,3-dioxan-2-yl)-5-fluoro-N-(6-(5-fluoro-3,3-dimethylindolin-1-yl)pyridin-3-yl)-4-hydroxybenzamide (550 mg, 47% yield) was prepared from 6-(5-fluoro-3,3-dimethylindolin-1-yl)pyridin-3-amine (600 mg, 2.3 mmol, 1.0 eq.) and 3-(5,5-dimethyl-1,3-dioxan-2-yl)-5-fluoro-4-hydroxybenzoic acid (630 mg, 2.3 mmol, 1.0 eq.) following the similar procedure for 3-(5,5-dimethyl-1,3-dioxan-2-yl)-N-(4-(3,3-dimethylpyrrolidin-1-yl)phenyl)-5-fluoro-4-hydroxybenzamide in Example B25. LC-MS m/z [M+H]⁺ calc'd for C₂₈H₂₉F₂N₃O₄, 510; found, 510.

[0469] Step 4: 3-Fluoro-N-(6-(5-fluoro-3,3-dimethylindolin-1-yl)pyridin-3-yl)-5-formyl-4-hydroxybenzamide (80 mg, 18% yield) was prepared as a yellow solid from 3-(5,5-dimethyl-1,3-dioxan-2-yl)-5-fluoro-N-(6-(5-fluoro-3,3-dimethylindolin-1-yl)pyridin-3-yl)-4-hydroxybenzamide (550 mg, 1.08 mmol, 1.0 eq.) following the similar procedure as in Example B25. Pos. LC-MS: 423.9 (M+H)⁺, C₂₃H₁₉F₂N₃O₃. ¹H NMR (DMSO-d₆, 400 MHz) δ: 11.67 (br, 1H), 10.36 (br, 1H), 10.33 (br, 1H), 8.62 (br, 1H), 8.22 (m, 2H), 8.13-8.06 (m, 2H), 7.11 (m, 1H), 6.95-6.89 (m, 2H), 3.80 (s, 2H), 1.35 (s, 6H). LC-MS m/z [M+H]⁺ calc'd for C₂₃H₁₉F₂N₃O₃, 424; found, 424.

Example B44: N-(4-(2,3-dihydro-4H-benzo[b][1,4]oxazin-4-yl)phenyl)-3-fluoro-5-formyl-4-hydroxybenzamide (Compound B90)



[0470] Step 1: 4-(4-nitrophenyl)-3,4-dihydro-2H-benzo[b][1,4]oxazine

4-(4-Nitrophenyl)-3,4-dihydro-2H-benzo[b][1,4]oxazine (1.43 g, 5.6 mmol, 56% yield) was prepared from 3,4-dihydro-2H-benzo[b][1,4]oxazine (1.35 g, 10.0 mmol, 1.0 eq.) and 1-fluoro-4-nitrobenzene (1.7 g, 12.0 mmol, 1.1 eq.) following the similar procedure for 3,3-dimethyl-1-(4-nitrophenyl)pyrrolidine in Example B25. No LCMS was taken for this compound.

[0471] Step 2: 4-(2H-benzo[b][1,4]oxazin-4(3H)-yl)aniline

4-(2H-Benzo[b][1,4]oxazin-4(3H)-yl)aniline (847 mg, 3.75 mmol, 67% yield) was prepared from 4-(4-nitrophenyl)-3,4-dihydro-2H-benzo[b][1,4]oxazine (1.43 g, 5.59 mmol, 1.0 eq.) and Fe (3.13 g, 55.9 mmol, 10 eq.) following the similar procedure for 4-(3,3-dimethylpyrrolidin-1-yl)aniline in Example B25. LC-MS m/z $[M+H]^+$ calc'd for $C_{14}H_{14}N_2O$, 227; found, 227.

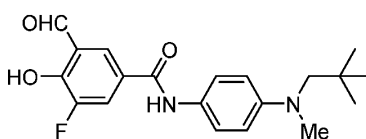
[0472] Step 3: N-(4-(2H-benzo[b][1,4]oxazin-4(3H)-yl)phenyl)-3-(5,5-dimethyl-1,3-dioxan-2-yl)-5-fluoro-4-hydroxybenzamide

N-(4-(2H-Benzo[b][1,4]oxazin-4(3H)-yl)phenyl)-3-(5,5-dimethyl-1,3-dioxan-2-yl)-5-fluoro-4-hydroxybenzamide (403 mg, 0.84 mmol, 45% yield) was prepared from 4-(2H-benzo[b][1,4]oxazin-4(3H)-yl)aniline (420 mg, 1.86 mmol, 1 eq.) and 3-(5,5-dimethyl-1,3-dioxan-2-yl)-5-fluoro-4-hydroxybenzoic acid (502 mg, 1.86 mmol, 1.0 eq.) following the similar procedure for 3-(5,5-dimethyl-1,3-dioxan-2-yl)-N-(4-(3,3-dimethylpyrrolidin-1-yl)phenyl)-5-fluoro-4-hydroxybenzamide in Example B25. LC-MS m/z $[M+H]^+$ calc'd for $C_{27}H_{27}FN_2O_5$, 479; found, 479.

[0473] Step 4: N-(4-(2H-Benzo[b][1,4]oxazin-4(3H)-yl)phenyl)-3-fluoro-5-formyl-4-hydroxybenzamide (110 mg, 0.28 mmol, 33% yield) was prepared as a yellow solid from N-(4-(2H-benzo[b][1,4]oxazin-4(3H)-yl)phenyl)-3-(5,5-dimethyl-1,3-dioxan-2-yl)-5-fluoro-4-hydroxybenzamide (400 mg, 0.84 mmol, 1.0 eq.) following the similar procedure for Example B25. 1H NMR ($DMSO-d_6$, 400 MHz) δ : 11.67 (br, 1H), 10.36 (s, 1H), 10.31 (s, 1H), 8.20 (d,

$J=1.6$ Hz, 1H), 8.10 (dd, $J=11.6$ Hz, 2.8 Hz, 1H), 7.76 (d, $J=8.8$ Hz, 2H), 7.24 (d, $J=8.8$ Hz, 2H), 6.81-6.69 (m, 4H), 4.25 (t, $J=4.0$ Hz, 2H), 3.67 (d, $J=4.0$ Hz, 2H). LC-MS m/z $[M+H]^+$ calc'd for $C_{22}H_{17}FN_2O_4$, 393; found, 393.

Example B45: 3-fluoro-5-formyl-4-hydroxy-N-(4-(methyl(neopentyl)amino)phenyl)benzamide (Compound B94)



[0474] Step 1: N-methyl-N-neopentyl-4-nitroaniline

N-Methyl-N-neopentyl-4-nitroaniline (670 mg, 3.02 mmol, 91% yield) was prepared from N,2,2-trimethylpropan-1-amine hydrochloride (500 mg, 3.64 mmol, 1.1 eq.) and 1-fluoro-4-nitrobenzene (466 mg, 3.30 mmol, 1.0 eq.) following the similar procedure for 3,3-dimethyl-1-(4-nitrophenyl)pyrrolidine in Example B25. No LCMS was taken for this compound.

[0475] Step 2: N1-methyl-N1-neopentylbenzene-1,4-diamine

N1-Methyl-N1-neopentylbenzene-1,4-diamine (320 mg, 1.66 mmol, 55% yield) was prepared from N-methyl-N-neopentyl-4-nitroaniline (670 mg, 3.02 mmol, 1.0 eq.) and Fe (1.69 g, 30.2 mmol, 10 eq.) following the similar procedure for 4-(3,3-dimethylpyrrolidin-1-yl)aniline in Example B25. LC-MS m/z $[M+H]^+$ calc'd for $C_{12}H_{20}N_2$, 193; found, 193.

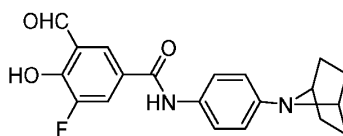
[0476] Step 3: 3-(5,5-dimethyl-1,3-dioxan-2-yl)-5-fluoro-4-hydroxy-N-(4-(methyl(neopentyl) amino)phenyl)benzamide

3-(5,5-Dimethyl-1,3-dioxan-2-yl)-5-fluoro-4-hydroxy-N-(4-(methyl(neopentyl)amino)phenyl)benzamide (170 mg, 0.38 mmol, 74% yield) was prepared from N1-methyl-N1-neopentylbenzene-1,4-diamine (100 mg, 0.52 mmol, 1 eq.) and 3-(5,5-dimethyl-1,3-dioxan-2-yl)-5-fluoro-4-hydroxybenzoic acid (155 mg, 0.57 mmol, 1.1 eq.) following the similar procedure for 3-(5,5-dimethyl-1,3-dioxan-2-yl)-N-(4-(3,3-dimethylpyrrolidin-1-yl)phenyl)-5-fluoro-4-hydroxybenzamide in Example B25. LC-MS m/z $[M+H]^+$ calc'd for $C_{25}H_{33}FN_2O_4$, 445; found, 445.

[0477] Step 4: 3-Fluoro-5-formyl-4-hydroxy-N-(4-(methyl(neopentyl)amino)phenyl)benzamide (60 mg, 0.17 mmol, 44% yield) was prepared as a

yellow solid from 3-(5,5-dimethyl-1,3-dioxan-2-yl)-5-fluoro-4-hydroxy-N-(4-(methyl(neopentyl)amino)phenyl)benzamide (170 mg, 0.38 mmol, 1 eq.) following the similar procedure for Example B25. ^1H NMR (CDCl_3 , 400 MHz) δ : 11.26 (br, 1H), 10.00 (br, 1H), 7.97 (s, 1H), 7.85 (d, $J=10.8$ Hz, 1H), 7.56 (br, 1H), 7.39 (d, $J=8.4$ Hz, 2H), 6.74 (br, 2H), 3.14 (s, 2H), 3.00 (s, 3H), 1.00 (s, 9H). LC-MS m/z $[\text{M}+\text{H}]^+$ calc'd for $\text{C}_{20}\text{H}_{23}\text{FN}_2\text{O}_3$, 359; found, 359.

Example B46: N-(4-(7-azabicyclo[2.2.1]heptan-7-yl)phenyl)-3-fluoro-5-formyl-4-hydroxybenzamide (Compound B95)



[0478] Step 1: (1s,4s)-7-(4-nitrophenyl)-7-azabicyclo[2.2.1]heptane

(1s,4s)-7-(4-Nitrophenyl)-7-azabicyclo[2.2.1]heptane (710 mg, 3.26 mmol, 96% yield) was prepared from (1s,4s)-7-azabicyclo[2.2.1]heptane hydrochloride (500 mg, 3.73 mmol, 1.1 eq.) and 1-fluoro-4-nitrobenzene (480 mg, 3.40 mmol, 1.1 eq.) following the similar procedure for 3,3-dimethyl-1-(4-nitrophenyl)pyrrolidine in Example B25. No LCMS was taken for this compound.

[0479] Step 2: 4-((1s,4s)-7-azabicyclo[2.2.1]heptan-7-yl)aniline

4-((1s,4s)-7-Azabicyclo[2.2.1]heptan-7-yl)aniline (490 mg, 2.61 mmol, 80% yield) was prepared from (1s,4s)-7-(4-nitrophenyl)-7-azabicyclo[2.2.1]heptane (710 mg, 3.26 mmol, 1 eq.) and Fe (1.8 g, 32.6 mmol, 10 eq.) following the similar procedure for 4-(3,3-dimethylpyrrolidin-1-yl)aniline in Example B25. LC-MS m/z $[\text{M}+\text{H}]^+$ calc'd for $\text{C}_{12}\text{H}_{16}\text{N}_2$, 189; found, 189.

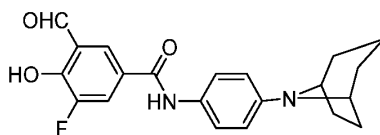
[0480] Step 3: N-(4-((1s,4s)-7-azabicyclo[2.2.1]heptan-7-yl)phenyl)-3-(5,5-dimethyl-1,3-dioxan-2-yl)-5-fluoro-4-hydroxybenzamide

N-(4-((1s,4s)-7-Azabicyclo[2.2.1]heptan-7-yl)phenyl)-3-(5,5-dimethyl-1,3-dioxan-2-yl)-5-fluoro-4-hydroxybenzamide (360 mg, 0.82 mmol, 37% yield) was prepared from 4-((1s,4s)-7-azabicyclo[2.2.1]heptan-7-yl)aniline (420 mg, 2.23 mmol, 1 eq.) and 3-(5,5-dimethyl-1,3-dioxan-2-yl)-5-fluoro-4-hydroxybenzoic acid (660 mg, 2.44 mmol, 1.1 eq.) following the similar

procedure for 3-(5,5-dimethyl-1,3-dioxan-2-yl)-N-(4-(3,3-dimethylpyrrolidin-1-yl)phenyl)-5-fluoro-4-hydroxybenzamide in Example B25. LC-MS m/z [M+H]⁺ calc'd for C₂₅H₂₉FN₂O₄, 441; found, 441.

[0481] Step 4: N-(4-((1s,4s)-7-Azabicyclo[2.2.1]heptan-7-yl)phenyl)-3-fluoro-5-formyl-4-hydroxybenzamide (75 mg, 0.21 mmol, 59% yield) was prepared as a light yellow solid from N-(4-((1s,4s)-7-azabicyclo[2.2.1]heptan-7-yl)phenyl)-3-(5,5-dimethyl-1,3-dioxan-2-yl)-5-fluoro-4-hydroxybenzamide (160 mg, 0.36 mmol, 1 eq.) following the similar procedure for Example B25. ¹H NMR (CDCl₃, 400 MHz) δ: 11.28 (br, 1H), 9.98 (d, J=1.2 Hz, 1H), 7.96 (s, 1H), 7.84 (d, J=10.8 Hz, 1H), 7.65 (s, 1H), 7.41 (d, J=8.4 Hz, 2H), 6.89 (d, J=8.8 Hz, 2H), 4.16 (t, J=2.0 Hz, 2H), 1.80 (t, J=3.2 Hz, 4H), 1.44 (d, J=6.8 Hz, 4H). LC-MS m/z [M+H]⁺ calc'd for C₂₀H₁₉FN₂O₃, 355; found, 355.

Example B47: N-(4-(8-azabicyclo[3.2.1]octan-8-yl)phenyl)-3-fluoro-5-formyl-4-hydroxybenzamide (Compound B96)



[0482] Step 1: (1R,5S)-8-(4-nitrophenyl)-8-azabicyclo[3.2.1]octane

(1R,5S)-8-(4-Nitrophenyl)-8-azabicyclo[3.2.1]octane (740 mg, 3.19 mmol, 98% yield) was prepared from (1R,5S)-8-azabicyclo[3.2.1]octane hydrochloride (500 mg, 3.39 mmol, 1.05 eq.) and 1-fluoro-4-nitrobenzene (455 mg, 3.23 mmol, 1.0 eq.) following the similar procedure for 3,3-dimethyl-1-(4-nitrophenyl)pyrrolidine in Example B25. No LCMS was taken for this compound.

[0483] Step 2: 4-((1R,5S)-8-azabicyclo[3.2.1]octan-8-yl)aniline

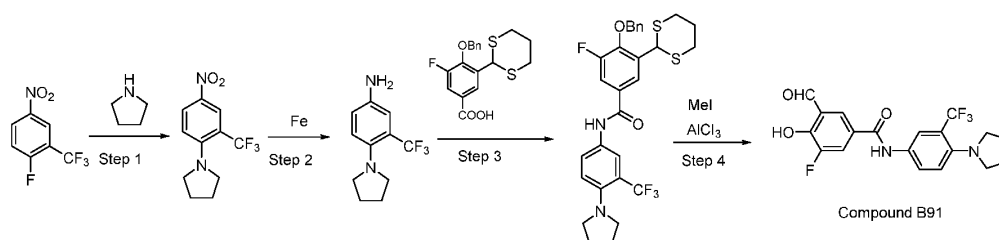
4-((1R,5S)-8-Azabicyclo[3.2.1]octan-8-yl)aniline (610 mg, 3.02 mmol, 95% yield) was prepared from (1R,5S)-8-(4-nitrophenyl)-8-azabicyclo[3.2.1]octane (740 mg, 3.19 mmol, 1.0 eq.) and Fe (1.8 g, 31.9 mmol, 10 eq.) following the similar procedure for 4-(3,3-dimethylpyrrolidin-1-yl)aniline in Example B25. No LCMS was taken for this compound.

[0484] Step 3: N-(4-((1R,5S)-8-azabicyclo[3.2.1]octan-8-yl)phenyl)-3-(5,5-dimethyl-1,3-dioxan-2-yl)-5-fluoro-4-hydroxybenzamide

N-(4-((1R,5S)-8-Azabicyclo[3.2.1]octan-8-yl)phenyl)-3-(5,5-dimethyl-1,3-dioxan-2-yl)-5-fluoro-4-hydroxybenzamide (420 mg, 0.93 mmol, 47% yield) was prepared from 4-((1R,5S)-8-azabicyclo[3.2.1]octan-8-yl)aniline (400 mg, 1.98 mmol, 1 eq.) and 3-(5,5-dimethyl-1,3-dioxan-2-yl)-5-fluoro-4-hydroxybenzoic acid (588 mg, 2.18 mmol, 1.1 eq.) following the similar procedure for 3-(5,5-dimethyl-1,3-dioxan-2-yl)-N-(4-(3,3-dimethylpyrrolidin-1-yl)phenyl)-5-fluoro-4-hydroxybenzamide in Example B25. LC-MS m/z $[M+H]^+$ calc'd for $C_{26}H_{31}FN_3O_4$, 455; found, 455.

[0485] Step 4: N-(4-((1R,5S)-8-Azabicyclo[3.2.1]octan-8-yl)phenyl)-3-fluoro-5-formyl-4-hydroxybenzamide (190 mg, 0.52 mmol, 56% yield) was prepared as a yellow solid from N-(4-((1R,5S)-8-azabicyclo[3.2.1]octan-8-yl)phenyl)-3-(5,5-dimethyl-1,3-dioxan-2-yl)-5-fluoro-4-hydroxybenzamide (420 mg, 0.93 mmol, 1 eq.) following the similar procedure for Example B25. Pos. LC-MS: 369.0 $(M+H)^+$, $C_{21}H_{21}FN_2O_3$. 1H NMR ($CDCl_3$, 400 MHz) δ : 11.26 (br, 1H), 10.00 (s, 1H), 7.96 (s, 1H), 7.98 (s, 1H), 7.86 (d, $J=10.8$ Hz, 1H), 7.63 (br, 1H), 7.43 (d, $J=8.0$ Hz, 2H), 7.77 (br, 2H), 4.18 (br, 2H), 2.09 (m, 2H), 1.98-1.81 (m, 4H), 1.56 (m, 2H), 1.23 (m, 2H). LC-MS m/z $[M+H]^+$ calc'd for $C_{21}H_{21}FN_2O_3$, 369; found, 369.

Example B48: 3-fluoro-5-formyl-4-hydroxy-N-(4-(pyrrolidin-1-yl)-3-(trifluoromethyl)phenyl)benzamide (Compound B91)



[0486] Step 1: 1-(4-nitro-2-(trifluoromethyl)phenyl)pyrrolidine

1-(4-Nitro-2-(trifluoromethyl)phenyl)pyrrolidine (930 mg, 3.6 mmol, 75% yield) was prepared from pyrrolidine (357 mg, 5.0 mmol, 1.05 eq.) and 1-fluoro-4-nitro-2-(trifluoromethyl)benzene (1 g, 4.8 mmol, 1.0 eq.) following the similar procedure for 3,3-dimethyl-1-(4-nitrophenyl)pyrrolidine in Example B25. No LCMS was taken for this compound.

[0487] Step 2: 4-(pyrrolidin-1-yl)-3-(trifluoromethyl)aniline

4-(Pyrrolidin-1-yl)-3-(trifluoromethyl)aniline (790 mg, 3.4 mmol, 98% yield) was prepared from 1-(4-nitro-2-(trifluoromethyl)phenyl)pyrrolidine (900 mg, 3.5 mmol, 1.0 eq.) and Fe (1.94 g, 34.6 mmol, 10 eq.) following the similar procedure for 4-(3,3-dimethylpyrrolidin-1-yl)aniline in Example B25. LC-MS m/z $[M+H]^+$ calc'd for $C_{11}H_{13}N_3O_2$, 231; found, 231.

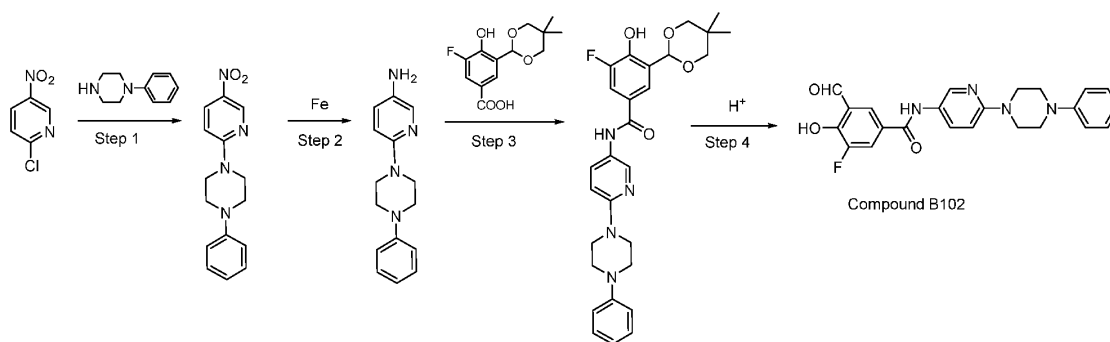
[0488] Step 3: 4-(benzyloxy)-3-(1,3-dithian-2-yl)-5-fluoro-N-(4-(pyrrolidin-1-yl)-3-(trifluoromethyl)phenyl)benzamide

[0489] Benzyl bromide (BnBr) (3.62 g, 21.2 mmol, 2.0 eq.) was added to a solution of 3-(1,3-dithian-2-yl)-5-fluoro-4-hydroxybenzoic acid (2.9 g, 10.6 mmol, 1.0 eq.) and potassium carbonate (2.9 g, 21.0 mmol, 2.0 eq.) in DMF (25 mL). The mixture was stirred for 3 hours at room temperature and poured into water. The mixture was then extracted with ethyl acetate for three times. The organic extracts were combined, washed with brine, dried over anhydrous sodium sulfate, and concentrated to give crude bis-Bn protected ester (3.1 g, 6.8 mmol, 64% yield) as light yellow solid. The ester (3.1 g, 6.8 mmol, 1.0 eq.) was mixed with LiOH.H₂O (833 mg, 20.5 mmol, 3 eq.) in THF/water (5 mL/5 mL). The reaction was stirred for 2 hours at room temperature. Then pH of the reaction system was acidified to 3-4 and the mixture was extracted with ethyl acetate for three times. The organic extracts were combined, washed with brine, dried over anhydrous sodium sulfate, and concentrated. The residue was crystallized in ethyl acetate/petroleum ether to give 4-(benzyloxy)-3-(1,3-dithian-2-yl)-5-fluorobenzoic acid (1.5 g, 4.1 mmol, 60% yield) as white solid. The resulting 4-(benzyloxy)-3-(1,3-dithian-2-yl)-5-fluorobenzoic acid (445 mg, 1.2 mmol, 1.0 eq.) was dissolved in dichloromethane (10 mL) and oxalyl chloride (311 mg, 2.4 mmol, 2.0 eq.) and DMF (1 drop) was added. The reaction was stirred for 2 hours at room temperature. The solvent was removed *in vacuo* and the residue was co-evaporated with dichloromethane for two times. The residue was then dissolved in dichloromethane and the solution was cooled to 0°C. Then, 4-(pyrrolidin-1-yl)-3-(trifluoromethyl)aniline (309 mg, 1.3 mmol, 1.1 eq.) and TEA (369 mg, 3.6 mmol, 3.0 eq.) were added successively. The reaction was stirred for 3 hours at room temperature. The solution was poured into water and extracted with dichloromethane for two times. The organic extracts were washed with 1% KHSO₄, dried over anhydrous sodium sulfate, and concentrated. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate=20:1 to 5:1) to give 4-(benzyloxy)-3-(1,3-dithian-2-yl)-5-fluoro-N-(4-(pyrrolidin-1-yl)-3-

(trifluoromethyl)phenyl)benzamide (370 mg, 0.64 mmol, 53% yield) as a yellow powder. LC-MS m/z $[M+H]^+$ calc'd for $C_{29}H_{28}F_4N_2O_2S_2$, 577; found, 577.

[0490] Step 4: A mixture of 4-(benzyloxy)-3-(1,3-dithian-2-yl)-5-fluoro-N-(4-(pyrrolidin-1-yl)-3-(trifluoromethyl)phenyl)benzamide (350 mg, 0.61 mmol, 1.0 eq.), MeI (12.3 g, 60.8 mmol, 100 eq.), and sodium bicarbonate (1.46 g, 12.2 mmol, 20 eq.) in acetonitrile/water (25 mL/5 mL) was heated at 40°C for 2 hours. The mixture was cooled to room temperature, poured into water, and extracted with ethyl acetate for three times. The organic extracts were combined, washed with brine, dried over anhydrous sodium sulfate, and concentrated. The residue was purified by silica gel column chromatography (petroleum ether/EtOAc=100:1 to 20:1) to give the intermediate (290 mg, 0.60 mmol, 98% yield) as a yellow solid. The intermediate (190 mg, 0.39 mmol, 1.0 eq.) was dissolved in dichloromethane (10 mL) and anhydrous $AlCl_3$ (208 mg, 1.56 mmol, 4.0 eq.) was added. The reaction was stirred overnight at room temperature. The mixture was poured into ice-water and dichloromethane. The insoluble stuff was filtered off and the filtrate was extracted with DCM for three times. The organic extracts were combined, dried over anhydrous sodium sulfate, and concentrated. The residue was purified by prep-TLC to give 4-(benzyloxy)-3-fluoro-5-formyl-N-(4-(pyrrolidin-1-yl)-3-(trifluoromethyl)phenyl)benzamide (80 mg, 0.20 mmol, 52% yield) as a yellow solid. 1H NMR ($DMSO-d_6$, 400 MHz) δ : 10.34 (s, 1H), 10.30 (s, 1H), 8.19 (s, 1H), 8.07 (m, 2H), 7.88 (dd, $J=9.2$ Hz, 2.0 Hz, 1H), 7.20 (d, $J=9.2$ Hz, 1H), 3.20 (m, 4H), 1.89 (m, 4H). LC-MS m/z $[M+H]^+$ calc'd for $C_{19}H_{16}F_4N_2O_3$, 397; found, 397.

Example B49: 3-fluoro-5-formyl-4-hydroxy-N-(6-(4-phenylpiperazin-1-yl)pyridin-3-yl)benzamide (Compound B102)



[0491] Step 1: 1-(5-nitropyridin-2-yl)-4-phenylpiperazine

1-(5-Nitropyridin-2-yl)-4-phenylpiperazine (2.1 g, 7.4 mmol, 74% yield) was prepared from 1-phenylpiperazine hydrochloride (1.78 g, 11.0 mmol, 1.1 eq.), potassium carbonate (4.4 g, 31.89 mmol, 3.0 eq.), and 2-chloro-5-nitropyridine (1.58 g, 10.0 mmol, 1.0 eq.) following the similar procedure for 3,3-dimethyl-1-(4-nitrophenyl)pyrrolidine in Example B25. No LCMS was taken for this compound.

[0492] Step 2: 6-(4-phenylpiperazin-1-yl)pyridin-3-amine

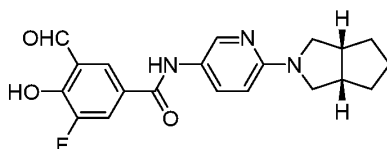
6-(4-Phenylpiperazin-1-yl)pyridin-3-amine (750 mg, 2.95 mmol, 84% yield) was prepared from 1-(5-nitropyridin-2-yl)-4-phenylpiperazine (1 g, 3.52 mmol, 1.0 eq.) and Fe (1.97 g, 35.2 mmol, 10 eq.) following the similar procedure for 4-(3,3-dimethylpyrrolidin-1-yl)aniline in Example B25. No LCMS was taken for this compound.

[0493] Step 3: 3-(5,5-dimethyl-1,3-dioxan-2-yl)-5-fluoro-4-hydroxy-N-(6-(4-phenylpiperazin-1-yl)pyridin-3-yl)benzamide

3-(5,5-Dimethyl-1,3-dioxan-2-yl)-5-fluoro-4-hydroxy-N-(6-(4-phenylpiperazin-1-yl)pyridin-3-yl)benzamide (270 mg, 0.53 mmol, 53% yield) was prepared from 6-(4-phenylpiperazin-1-yl)pyridin-3-amine (254 mg, 1.0 mmol, 1.0 eq.) and 3-(5,5-dimethyl-1,3-dioxan-2-yl)-5-fluoro-4-hydroxybenzoic acid (270 mg, 1.0 mmol, 1.0 eq.) following the similar procedure for 3-(5,5-dimethyl-1,3-dioxan-2-yl)-N-(4-(3,3-dimethylpyrrolidin-1-yl)phenyl)-5-fluoro-4-hydroxybenzamide in Example B25. LC-MS m/z [M+H]⁺ calc'd for C₂₈H₃₁FN₄O₄, 507; found, 507.

[0494] Step 4: 3-Fluoro-5-formyl-4-hydroxy-N-(6-(4-phenylpiperazin-1-yl)pyridin-3-yl)benzamide (120 mg, 0.29 mmol, 54% yield) was prepared as a yellow solid from 3-(5,5-dimethyl-1,3-dioxan-2-yl)-5-fluoro-4-hydroxy-N-(6-(4-phenylpiperazin-1-yl)pyridin-3-yl)benzamide (270 mg, 0.53 mmol, 1 eq.) following the similar procedure for Example B25. ¹H NMR (DMSO-*d*₆, 400 MHz) δ: 11.69 (br, 1H), 10.35 (br, 1H), 10.21 (s, 1H), 8.47 (d, *J*=2.0 Hz, 1H), 8.19 (s, 1H), 8.08 (dd, *J*=11.6 Hz, 1H), 7.93 (dd, *J*=8.8 Hz, 2.0 Hz, 1H), 7.24 (m, 2H), 6.99 (m, 2H), 6.96 (d, *J*=8.8 Hz, 1H), 6.81 (m, 1H), 3.61 (m, 4H), 3.25 (m, 4H). LC-MS m/z [M+H]⁺ calc'd for C₂₃H₂₁FN₄O₃, 421; found, 421.

Example B50: 3-fluoro-5-formyl-N-(6-((3aR,6aS)-hexahydrocyclopenta[c]pyrrol-2(1H)-yl)pyridin-3-yl)-4-hydroxybenzamide (Compound B103)



[0495] Step 1: (3aR,6aS)-2-(5-nitropyridin-2-yl)octahydrocyclopenta[c]pyrrole

(3aR,6aS)-2-(5-Nitropyridin-2-yl)octahydrocyclopenta[c]pyrrole (680 mg, 2.9 mmol, 86% yield) was prepared from (3aR,6aS)-octahydrocyclopenta[c]pyrrole hydrochloride (0.5 g, 3.4 mmol, 1.0 eq.), potassium carbonate (1.4 g, 10.2 mmol, 3.0 eq.), and 2-chloro-5-nitropyridine (0.53 g, 3.7 mmol, 1.1 eq.) following the similar procedure for 3,3-dimethyl-1-(4-nitrophenyl)pyrrolidine in Example B25. No LCMS was taken for this compound.

[0496] Step 2: 6-((3aR,6aS)-hexahydrocyclopenta[c]pyrrol-2(1H)-yl)pyridin-3-amine

6-((3aR,6aS)-Hexahydrocyclopenta[c]pyrrol-2(1H)-yl)pyridin-3-amine (410 mg, 2.0 mmol, 94% yield) was prepared from (3aR,6aS)-2-(5-nitropyridin-2-yl)octahydrocyclopenta[c]pyrrole (0.5 g, 2.1 mmol, 1.0 eq.) and Fe (1.2 g, 21.5 mmol, 10 eq.) following the similar procedure for 4-(3,3-dimethylpyrrolidin-1-yl)aniline in Example B25. No LCMS was taken for this compound.

[0497] Step 3: 3-(5,5-dimethyl-1,3-dioxan-2-yl)-5-fluoro-N-(6-((3aR,6aS)-hexahydrocyclopenta[c]pyrrol-2(1H)-yl)pyridin-3-yl)-4-hydroxybenzamide

3-(5,5-Dimethyl-1,3-dioxan-2-yl)-5-fluoro-N-(6-((3aR,6aS)-hexahydrocyclopenta[c]pyrrol-2(1H)-yl)pyridin-3-yl)-4-hydroxybenzamide (160 mg, 0.35 mmol, 33% yield) was prepared from 6-((3aR,6aS)-hexahydrocyclopenta[c]pyrrol-2(1H)-yl)pyridin-3-amine (240 mg, 1.18 mmol, 1.1 eq.) and 3-(5,5-dimethyl-1,3-dioxan-2-yl)-5-fluoro-4-hydroxybenzoic acid (290 mg, 1.07 mmol, 1.0 eq.) following the similar procedure for 3-(5,5-dimethyl-1,3-dioxan-2-yl)-N-(4-(3,3-dimethylpyrrolidin-1-yl)phenyl)-5-fluoro-4-hydroxybenzamide in Example B25. LC-MS m/z [M+H]⁺ calc'd for C₂₅H₃₀FN₃O₄, 456; found, 456.

[0498] Step 4: 3-Fluoro-5-formyl-N-(6-((3aR,6aS)-hexahydrocyclopenta[c]pyrrol-2(1H)-yl)pyridin-3-yl)-4-hydroxybenzamide (70 mg, 0.19 mmol, 54% yield) was prepared as a yellow solid from 3-(5,5-dimethyl-1,3-dioxan-2-yl)-5-fluoro-N-(6-((3aR,6aS)-hexahydrocyclopenta[c]pyrrol-2(1H)-yl)pyridin-3-yl)-4-hydroxybenzamide (160 mg, 0.35

mmol, 1 eq.) following the similar procedure for Example B25. ^1H NMR (CDCl_3 , 400 MHz) δ : 10.01 (br, 1H), 8.78 (br, 1H), 8.39 (s, 1H), 8.26 (s, 1H), 8.17 (m, 1H), 8.03 (d, $J=10.8$ Hz, 1H), 6.50 (d, $J=9.2$ Hz, 1H), 3.72 (m, 2H), 3.32 (m, 2H), 2.84 (m, 2H), 1.92 (m, 2H), 1.78 (m, 1H), 1.65 (m, 1H), 1.53 (m, 2H). LC-MS m/z $[\text{M}+\text{H}]^+$ calc'd for $\text{C}_{20}\text{H}_{20}\text{FN}_3\text{O}_3$, 370; found, 370.

Biological Example 1: In vitro Assay

i. TLR2 assays

[0499] Synthetic diacylated lipoprotein (Pam2CSK4, TLR2/6 agonist) and synthetic triacylated lipoprotein (Pam3CSK4, TLR1/2 agonist) were obtained from InvivoGen and were dissolved in endotoxin-free water to a concentration 1 mg/mL, vortexed until complete solubilization, and stored in aliquots at -20°C . Prior to addition to cells, an aliquot of the dissolved ligand was vortexed shortly and then was diluted in medium to 25 ng/mL Pam2CSK4 or 1000 ng/mL Pam3CSK4. The EC_{50} of the agonists for each assay run was determined by using 3-fold dilutions of each agonist from the following starting concentrations: 5 ng/mL for Pam2CSK4, and 200 ng/mL for Pam3CSK4.

[0500] Test compounds were solubilized fresh to 10 - 20 mM stocks in DMSO and sonicated for 5-10 minutes in a water bath sonicator. Serial dilutions were prepared in DMSO, and then diluted in medium. The final concentration of DMSO used in the assay was 1 %.

[0501] HEK-Blue hTLR2 reporter cells (InvivoGen) are HEK-293 cells stably expressing both the human TLR2 gene and a secreted embryonic alkaline phosphatase (SEAP) reporter construct downstream of NF κ B promotor sites. HEK-Blue hTLR2 reporters were cultured according to manufacturer's protocol using Dulbecco's Modified Eagle Medium (DMEM; Gibco) containing 1X GlutaMax (Gibco), 10% heat-inactivated Fetal Bovine Serum (Gibco), Pen-Strep (50 U/mL penicillin, 50 $\mu\text{g/mL}$ streptomycin, Gibco), 100 $\mu\text{g/mL}$ Normocin (InvivoGen), and the selective antibiotic, 1x HEK-Blue Selection (InvivoGen). Quanti-Blue reagent (InvivoGen) for detection and quantification of secreted alkaline phosphatase was dissolved in 100 mL of endotoxin-free water, warmed to 37°C for 30 minutes and then filtered using a 0.2 μm membrane.

ii. TLR9 assay

[0502] Synthetic ODNs (ODN 2006 (ODN7909), class B CpG oligonucleotide, TLR9 agonist) was obtained from InvivoGen and was dissolved in endotoxin-free water to a concentration 500 μ M, vortexed until complete solubilization, and stored in aliquots at -20 °C. Prior to addition to cells, an aliquot of the dissolved ligand was vortexed shortly and then was diluted in medium to 50 μ M. The EC₅₀ of the agonist for each assay run was determined by using 3-fold dilutions from the starting concentration 10 μ M.

[0503] Test compounds were solubilized fresh to 10 - 20 mM stocks in DMSO and sonicated for 5-10 minutes in a water bath sonicator. Serial dilutions were prepared in DMSO, and then diluted in medium. The final concentration of DMSO used in the assay was 1 %.

[0504] HEK-Blue hTLR9 reporter cells (InvivoGen) are HEK -293 cells stably expressing both the human TLR9 gene and a secreted embryonic alkaline phosphatase (SEAP) reporter construct downstream of NF κ B promotor sites. HEK-Blue hTLR9 cells were cultured according to manufacturer's protocol using Dulbecco's Modified Eagle Medium (DMEM; Gibco) containing 1X GlutaMax (Gibco), 10% heat-inactivated Fetal Bovine Serum (Gibco), Pen-Strep (50 U/mL penicillin, 50 μ g/mL streptomycin, Gibco), 100 μ g/mL Normocin (InvivoGen), and the selective antibiotics, 10 μ g/mL Blasticidin (InvivoGen), and 100 μ g/mL Zeocin (InvivoGen). Quanti-Blue reagent (InvivoGen) for detection and quantification of secreted alkaline phosphatase was dissolved in 100 mL of endotoxin-free water, warmed to 37 °C for 30 minutes and then filtered using a 0.2 μ m membrane.

Biological Example 2: HEK-Blue hTLR2 antagonism assay

i. TLR2 assays

[0505] On day 1, 50 μ L of each test compound dilution in duplicates or a vehicle control was added to each well of a 96-well plate followed by addition of 150 μ L of HEK-Blue hTLR2 cell suspension (1×10^5 cells/well) and incubated at 37 °C/5% CO₂ for 2 h. Next, 50 μ L of an approximate 3x EC₅₀ concentration of each agonist (Pam2CSK4 or Pam3CSK4) was added to the wells containing test compounds or the vehicle control. The plates were then incubated at 37 °C/5% CO₂ for 18 h. For each assay run, non-treated HEK-Blue hTLR2 cells were treated with serial dilutions of agonists to determine EC₅₀ values for the respective run.

[0506] On day 2, secreted alkaline phosphatase (SEAP) activity was detected in cell culture supernatants. In brief, 20 μ L was collected from each well and transferred to a 96-well plate. Next, 200 μ L of Quanti-Blue detection reagent was added to each well. Plates were incubated at room temperature for 15 min. and SEAP activity was assessed by spectrophotometer OD reading at 655 nm. Table A and Table B show the activities of the compounds tested in HEK cells using Pam2CSK4 and Pam3CSK4 as agonists. The activities of the compounds against Pam2CSK4 and Pam3CSK4 are presented as IC₅₀ values which were defined as concentrations of the compounds where percent inhibition of the signal induced by agonist is equal to 50. IC₅₀ values were calculated based on 8-point dilutions for each compound.

ii. TLR9 assay

[0507] On day 1, 50 μ L of each test compound dilution in duplicates or a vehicle control was added to each well of a 96-well plate followed by addition of 150 μ L of HEK-Blue hTLR9 cell suspension (1×10^5 cells/well) and incubated at 37 °C/5% CO₂ for 2 h. Next, 50 μ L of an approximate 3x EC₅₀ concentration of TLR9 agonist, ODN 2006, was added to the wells containing test compounds or the vehicle control. The plates were then incubated at 37 °C/5% CO₂ for 18 h. For each assay run, vehicle-treated HEK-Blue hTLR9 cells were treated with serial dilutions of agonist to determine EC₅₀ values for the respective run.

[0508] On day 2, secreted alkaline phosphatase (SEAP) activity was detected in cell culture supernatants. In brief, 30 μ L was collected from each well and transferred to a 96-well plate. Next, 200 μ L of Quanti-Blue detection reagent was added to each well. Plates were incubated at 37°C for 60 min. and SEAP activity was assessed by spectrophotometer OD reading at 655 nm. Table A and Table B show the activities of the compounds tested in HEK-Blue hTLR9 cells against ODN 2006. The activities of the compounds against ODN 2006 are presented as IC₅₀ values which were defined as concentrations of the compounds where percent inhibition of the signal induced by agonist is equal to 50. Exact IC₅₀ values were calculated based on 8-point dilutions for each compound. Approximate IC₅₀ values (~ or <) were calculated based on 4-point dilutions for each compound.

Table A.

Example No.	Compound No.	IC ₅₀ (μM) with Pam2CSK4	IC ₅₀ (μM) with Pam3CSK4	~IC ₅₀ (μM) with ODN2006
A1	A1	2.2	0.9	~2
A2	A2	>100	>100	>33
A3	A3	9.9	8.3	ND
A4	A4	8.5	10.5	ND
A5	A5	>100	>100	ND
A6	A6	14.1	12.0	ND
A7	A7	36.8	42.3	>33
A8	A8	85.5	>100	>33
A9	A9	3.8	5.1	ND
A10	A10	5.2	5.2	ND
A11	A11	2.3	2.0	ND
A12	A12	>100	>100	>33
A13	A13	45.7	39.7	>33
A14	A14	42.2	42.6	>33
A15	A15	>100	>100	>33
A16	A16	>100	>100	>33
A17	A17	52.6	43.4	ND
A18	A18	>100	>100	ND
A19	A19	0.5	0.5	<1.2
A20	A20	0.5	0.2	ND
A21	A21	2.6	1.1	ND
A22	A22	0.9	0.9	>10
A23	A23	0.8	0.9	ND
A24	A24	4.3	5.4	ND
A25	A25	1.9	1.2	~3
A26	A26	2.9	2.7	~3
A27	A27	0.9	0.8	<1.2
A28	A28	0.9	0.8	ND
A29	A29	6.4	7.6	ND
A30	A30	2.1	2.2	ND
A31	A31	3.4	6.2	ND
A32	A32	12.7	17.4	ND
A33	A33	4.0	3.6	~4
A34	A34	6.9	3.9	ND
A35	A35	1.6	0.7	ND
A36	A36	>100	>100	ND
A37	A37	>100	>100	ND
A38	A38	0.4	0.4	ND
A39	A39	0.5	0.5	ND
A40	A40	7.2	2.7	ND
A41	A42	0.4	0.3	0.1
A42	A43	1.1	1.1	<1.2

A43	A44	1.0	0.7	~1.2
A44	A45	1.3	1.3	ND
A45	A47	2.3	1.3	<1.2
A46	A50	4.1	0.9	ND
A47	A51	1.7	0.7	<1.2
A48	A52	0.7	0.2	<1.2
A49	A57	1.0	0.3	0.3
A50	A61	3.2	1.0	<1.2
A51	A62	0.7	0.4	0.2
A52	A88	2.1	1.3	~3
A53	A89	>100	>100	ND
A54	A90	6.5	4.5	ND
A55	A91	3.8	2.1	<1.2
A56	A92	3.5	0.9	ND
A57	A93	4.8	2.1	<1.2
A58	A94	14.8	9.2	<1.2
A59	A95	3.0	2.3	~1.4
A60	A96	12.1	8.8	~6.3
A61	A97	0.9	0.3	ND
A62	A55	0.6	0.4	0.2
A63	A98	1.4	1.0	ND
A64	A99	3.3	2.2	ND
A65	A100	1.4	0.6	ND
A66	A101	3.2	1.0	ND
A67	A102	1.9	1	ND
A68	A103	3.9	1.3	ND
A69	A104	6.8	3.9	ND
A70	A105	1.9	0.5	ND
A71	A123	1.7	1.5	ND
A72	A124	1.7	1.0	ND
A73	A114	0.7	0.4	ND
A74	A125	3.3	2.0	ND
A75	A126	1.1	0.6	ND
A76	A127	1.2	0.7	ND
A77	A116	1.3	0.6	ND
A78	A112	0.3	0.2	ND

ND = Not Determined

Table B.

Example No.	Compound No.	IC₅₀ (μM) with Pam2CSK4	IC₅₀ (μM) with Pam3CSK4	~IC₅₀ (μM) with ODN2006
B1	B1	1.1	0.7	<1.2
B2	B2	0.5	0.3	ND
B3	B3	3.7	2.2	<1.2

B4	B4	6.3	2.7	~1.5
B5	B5	1.9	1.1	ND
B6	B6	3.8	1.8	ND
B7	B7	35.7	20.8	>33
B8	B8	2.9	1.6	ND
B9	B9	8.1	6.8	ND
B10	B10	11.6	7.2	ND
B11	B11	12.0	10.6	<1.2
B12	B12	2.7	2.0	0.7
B13	B13	1.9	1.9	ND
B14	B14	1.3	1.5	>33
B15	B17	12.7	6.6	~2.9
B16	B59	32.7	19.8	ND
B17	B61	16.4	9.3	ND
B18	B63	30.1	11.3	ND
B19	B64	10.9	8.0	ND
B20	B65	8.7	3.7	<1.2
B21	B66	1.8	1.0	ND
B22	B67	3.3	1.2	<1.2
B23	B68	3.5	1.0	<1.2
B24	B69	7.6	2.3	ND
B25	B70	11.5	6.5	ND
B26	B71	2.6	1.7	~2.5
B27	B72	4.6	2.4	ND
B28	B73	0.6	0.3	0.3
B29	B74	1.6	0.8	<1.2
B30	B75	13.0	6.0	~4.7
B31	B76	1.2	0.6	<1.2
B32	B77	0.6	0.3	<1.2
B33	B78	34.4	18.5	ND
B34	B79	4.1	1.4	ND
B35	B80	15.5	35.9	ND
B36	B81	1.0	0.5	ND
B37	B82	1.2	0.7	ND
B38	B83	1.0	0.3	ND
B39	B84	33.9	14.3	ND
B40	B85	1.3	0.7	ND
B41	B86	4.3	1.8	ND
B42	B87	0.5	0.4	0.1
B43	B99	0.6	0.5	ND
B44	B90	2.9	1.9	ND
B45	B94	1.0	0.9	ND
B46	B95	3.7	2.8	ND
B47	B96	1.4	1.1	ND
B48	B91	2.2	1.6	ND

B49	B102	2.0	1.0	ND
B50	B103	1.7	1.0	ND

ND = Not Determined